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The Neurobiology and Pharmacotherapy of Posttraumatic Stress Disorder (PTSD)

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Abstract

New approaches to the neurobiology of posttraumatic stress disorder (PTSD) are needed to address the reported crisis in PTSD drug development. These new approaches may require the field to move beyond a narrow fear-based perspective, as fear-based medications have not yet demonstrated compelling efficacy. Antidepressants, particularly recent rapid-acting antidepressants, exert complex effects on brain function and structure that build on novel aspects of the biology of PTSD, including a role for stress-related synaptic dysconnectivity in the neurobiology and treatment of PTSD. Here, we integrate this perspective within a broader framework, i.e., a dual pathology model of (1) stress-related synaptic loss arising from amino acid-based pathology, and (2) stress-related synaptic gain related to monoamine-based pathology. Then, we summarize the standard and experimental (e.g., ketamine) pharmacotherapeutic options for PTSD, and discuss their putative mechanism of action and clinical efficacy.

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating, and often chronic, psychiatric disorder that develops following exposure to severe trauma. PTSD is associated with intrusive memories, distressing dreams, dissociative reactions, avoidance of trauma-related stimuli, negative cognition and mood, increased arousal and irritability, and clinically significant distress and impairment in functioning. It is estimated that 70% of the world population have been exposed to trauma and that approximately 6% of trauma-exposed individuals develop

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Conflict of Interest statement

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PTSD (1). The prevalence is even higher in select populations with high trauma exposure. For example, the prevalence of PTSD is close to 25% in combat-exposed Veterans (2). Yet, unfortunately, to date the neurobiology of the disorder is not fully understood and available treatment options are limited, with only two FDA approved medications – both of which are slow-acting antidepressants (SAAD) (3).

Perhaps the greatest advancement in understanding the neurobiology of PTSD has been in the field of fear regulation. PTSD was found to be associated with deficits in fear extinction, increased generalization of fear, and a negative bias of viewing threat from neutral stimuli and feeling danger in a safe environment. These fear conditioning disturbances are believed to underlie many of the symptoms of PTSD and to correlate with some of the biological abnormalities identified in patients with PTSD (4–6). However, the mechanisms through which trauma induces fear dysregulation and extinction deficits are not entirely clear. In addition, to date, the drug development of fear-based pharmacotherapeutic approaches (e.g. d-cycloserine or propranolol) has been challenging (7–9), raising concerns whether narrowly targeting fear memory is the optimal path for drug development. Moreover, the only PTSD drugs with reproducible efficacy are antidepressants. These drugs are believed to target the reversal of trauma- and stress-induced synaptic dysconnectivity and have shown efficacy across a number of stress-related disorders with no known prominent fear dysregulation (10–13).

Convergent evidence implicates stress in the pathophysiology of trauma-related impairment in fear extinction (4; 14). Moreover, accumulating literature increasingly implicates glutamate dysregulation and synaptic loss in the pathophysiology and treatment of PTSD (11; 12). Together, these findings have led to the proposition of a synaptic connectivity model of PTSD based on impairment in stress response, resulting in sustained threat paradigm and chronic stress pathology (CSP) (11–13). The synaptic dysconnectivity model provides a framework for investigating and understanding the biological predispositions, pathophysiology, and treatment of PTSD (Fig. 1). In the current review, we present a synaptic and a network-based models of PTSD, describe a “vicious cycle” of chronic stress pathology, and propose a dual pathology model associating (1) the stress-related synaptic loss in the prefrontal cortex and hippocampus with amino acid-based pathology, and (2) the stress-related synaptic gain in the nucleus accumbens, and presumably the basolateral amygdala, with monoamine-based pathology. Then, we summarize the standard and experimental (e.g., ketamine) pharmacotherapeutic options for PTSD, and discuss their putative mechanism of action and clinical efficacy.

2. Neurobiology of PTSD

2.a. Stress Response

Life threatening traumatic events, associated with PTSD psychopathology, typically induce a prolonged stress response, whether the stressor was acute (e.g., mass shooting) or chronic (e.g., combat). Thus, while transient (minutes to hours) stress responses may enhance plasticity, improve cognition, and promote resilience (15–17), traumatic stressors are often associated with chronic (days to weeks) stress responses that are detrimental to the brain and are often accompanied with behavioral disturbances (18; 19). In animals, stress-related

synaptic loss and the associated behavioral changes are evident within days to weeks of traumatic stress, and are reversible typically within 2–4 weeks after the stress (18; 20). In humans, most trauma-exposed individuals transiently experience symptoms associated with PTSD. However, individuals still symptomatic 4 weeks after the trauma may have lasting illness (1; 21).

The propensity to exhibit lasting stress responses is complex and reflects genetics, history of environmental exposures, stage of life, and features of the traumatic stress and post-traumatic social context (21). Psychopathology risk increases in proportion to the severity of the stressor. Inescapable, uncontrollable, unpredictable, repeated, and severe stressors pose an increased probability to initiate a sustained threat paradigm leading to chronic stress responses with subsequent biological and behavioral abnormalities (17; 18; 20; 22). Similarly, biopsychosocial vulnerabilities (e.g., female sex, history of early life stress, or predisposing neuronal disturbances) represent an increased risk for fear-related disturbances leading to sustained threat paradigm and prolonged stress responses following severe traumatic events (21; 23; 24).

This complexity contributes to variability in the reported rates of PTSD. On average, fewer than 10% of individuals exposed to extreme stress develop PTSD. But the PTSD rate is 20% following assaultive violence and up to 50% in rape victims (25). Among refugees, PTSD rates range from 4 to 86%, with higher rates associated with the severity of the trauma exposure (26). Among tattooed Auschwitz Holocaust survivors, 80% suffered intrusive recollections, 90% experienced recurrent nightmares, and 100% endured sleep disturbances (27). Together, the data suggest that, despite the level of resiliency of an individual, increasing the magnitude of the traumatic load would eventually precipitate psychopathology. Thus, the variability in posttraumatic outcomes could be due to an individualized threshold at which a person develops a prolonged stress response and subsequent psychopathology. In this context, resiliency could be conceptualized as not only whether a trauma victim would suffer from PTSD symptoms, but rather expressed as reduced PTSD severity, reduced duration of PTSD symptoms, or reduced impact of PTSD symptoms on overall quality of life (i.e., less disability, less disruption of social relationships, and less development of comorbid diagnoses such as addiction).

2.b. Synaptic Model of Chronic Stress Pathology (CSP)

Extreme stressors, particularly when repeated, induce neuronal remodeling associated with regional reductions and increases in synaptic density. In animal studies, the CSP reduction in synaptic connectivity has been mostly demonstrated in the prefrontal cortex (PFC) and the hippocampus, while the increases in synaptic connectivity were most evident in the nucleus accumbens (NAc) and the basolateral amygdala (18; 28).

In the PFC and hippocampus, prolonged stress responses have been associated with disruption in glucocorticoid signaling, increased neuroinflammation, reduced brain derived neurotrophic factor (BDNF), and astrocytic deficits along with reduced uptake of synaptically-released glutamate, leading to increased extracellular glutamate and excitotoxicity (10; 29–31). Particularly, prolonged stress response maintains a paradoxical increase in extracellular glutamate despite a considerable reduction in glutamate

neurotransmission, N-methyl-D-aspartate receptors (NMDARs), and α-amino-3-hydroxy-5-methyl-4-isoxazloepropionic acid receptors (AMPARs) (19; 32; 33). These molecular changes precipitate neuronal atrophy consistent with reduced dendritic length and arborization, and reduction in synaptic density and neurotransmission strength. In preclinical studies, this synaptic loss and hypoconnectivity is directly associated with behavioral abnormalities, including mood and anxiety dysregulation (18; 34). Moreover, these CSP behavioral disturbances are normalized following the reversal of the synaptic deficit, by both SAAD and rapid-acting antidepressants (RAAD; e.g. ketamine) (29; 35).

In the amygdala, CSP is associated with functional and structural changes consistent with reduced synaptic connectivity in the medial amygdala, but increased BDNF and synaptic connectivity in the basolateral amygdala (36–38). Notably, a single stressor is sufficient to upregulate BDNF in the basolateral amygdala, which is evident 1 day post-stress and lasts for at least 10 days (38). The single stressor also gradually increases basolateral amygdala synaptogenesis over the 10-day period, which is paralleled by a gradual increase in anxiety-like behavior (39). Similarly, a single large dose of corticosterone induces sustained anxiety-like behavior and increased basolateral amygdala hypertrophy, lasting more than 10 days (40). Moreover, after withholding the stressor, hippocampal/PFC synaptic loss, downregulation of BDNF, and related behavioral disturbances recover within 2–4 weeks, while the basolateral amygdala synaptic hyperconnectivity, upregulation of BDNF, and related anxiety-like behavior are not reversible within the same time period (38; 41–43). In the NAc, CSP is also associated with neuronal hypertrophy, including increased BDNF, dendritic length and branching, and synaptic density and strength (44–52). Similarly, the NAc hypertrophy is associated with behavioral impairment and is reversed by both SAAD and RAAD (28; 53; 54).

2.c. Dual Pathology Model: Amino Acid-Based vs. Monoamine-Based Pathology

A major challenge in PTSD, depression, and anxiety research is apparent “contradictory” biological findings across human studies. This is best exemplified in the reports of reduced hippocampal volume in some, but not all PTSD cohorts (55; 56). Similarly, increased amygdala volume was found in some, but not all PTSD patients (57; 58). Together, these seemingly contradictory findings raise the question whether trauma and stress psychopathology is associated with two distinct underlying pathophysiological processes, one related to synaptic loss and another related to synaptic gain.

Indeed, as described earlier, the synaptic model of CSP provides abundant evidence associating localized synaptic loss with Amino Acid-Based Pathology (ABP), consistent with glutamate dysregulation and excitotoxicity. Conversely, synaptic gain – particularly in the NAc – is associated with Monoamine-Based Pathology (MBP), consistent with disruption in catecholamine (i.e., adrenaline, noradrenaline, and dopamine) signaling (Fig. 1). Integrating these preclinical data along with accumulating clinical evidence, we recently described a dual pathology model proposing trauma and stress pathology is independently associated with both ABP and MBP (59). However, the characteristic of the stressor and the individual biopsychosocial predispositions may differentially lead to prominent amino acid

disruption and synaptic loss (i.e., ABP) or monoamine dysregulation and synaptic gain (i.e., MBP) (59).

In the dual pathology model, ABP would be more closely associated with prominent glutamate dysregulation and synaptic loss, as evident by treatment resistance to monoaminergic drugs, alterations in glutamate and GABA markers and signaling, and gross structural correlates of synaptic loss on magnetic resonance imaging (MRI) (59–61). In contrast, MBP would be more closely associated with monoamine dysregulation and synaptic gain, as evident by enhanced response to monoaminergic drugs, signs of autonomic dysregulation, and gray matter hypertrophy [reviewed in (29; 59)}]. Consistent with this model, animal studies have shown that the type and magnitude of a stressor determine the extent and nature of the dopaminergic response in the NAc (62; 63), and its related behavioral pathology (50; 64). Moreover, it has been also shown that only a subgroup of animals develops MBP NAc hypertrophy and related behavioral disturbances (65). Therefore, the stressor characteristics, along with individual predisposition, may dictate the pattern of biological injury (i.e., MBP vs. ABP) and related behavioral abnormalities (e.g., PTSD or depression). For example, certain stressors, such as single prolonged stress, are more likely to recapitulate key symptoms of PTSD (66; 67). Comparably, differing brain regions may have variable response to a unique stress, for example, brief uncontrollable stress was found to induce synaptic loss in the infralimbic (medial PFC, involved in extinction), but not prelimbic area (dorsal PFC, involved in fear acquisition) (68).

The dual pathology model was proposed initially for major depressive disorder (MDD) (29; 59; 61). However, various lines of evidence also support the applicability of this model for PTSD. First, traumatic stress may trigger either PTSD and/or depression, as well as increase the risk of several other stress-related disorders (69). Second, the preclinical CSP literature summarized earlier clearly implicates both ABP and MBP in PTSD. Third, in addition to the extensive human evidence relating synaptic loss and ABP to PTSD (70–75), there is strong evidence of catecholamine dysregulation and MBP in patients with PTSD (76–78) – where increases in catecholamine are believed to simultaneously weaken dorsolateral PFC (dlPFC) synaptic connectivity and strengthen neuronal activity in the amygdala and striatum (which includes the NAc) (50–52; 79). Notably, the “viscous cycle” of chronic stress pathology (Fig. 1) suggests that initial MBP behavioral disturbances further exacerbate the stress magnitude, which could eventually lead to ABP and synaptic loss. Thus, the discrepancy in the amygdala findings in PTSD (i.e., both hypertrophy and hypotrophy) may also reflect the time course of the disorder, with chronic suffering from severe PTSD leading to more prominent ABP and synaptic loss. This hypothesized time course effect of an MBP to ABP switch is supported by the fact that compiled data of multiple cohorts or meta-analyses often succeed in demonstrating the ABP-related biomarkers (e.g., gray matter deficits), but fails to show statistically significant structural evidence of synaptic gain (80–83).

Finally, considering the noticeable role of chronic stress pathology across many psychiatric disorders, the dual pathology model presented is unlikely to be limited to depression and PTSD, but rather common to several psychiatric disorders, including generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), panic disorder, and bipolar depression (60; 84–92). Together, the presented models hypothesize that CSP, and related

synaptic dysconnectivity (Fig. 1), are common across many psychiatric disorders. Most importantly, targeting synaptic connectivity is a convergent pathway across antidepressants – a class of medications that has shown efficacy in alleviating symptoms of major depression, PTSD, GAD, OCD, panic disorder, bipolar depression, and other disorders with a considerable chronic stress component. Therefore, while the synaptic pathology described by ABP and MBP is not specific to PTSD, it is increasingly evident that targeting these synaptic disturbances is essential for successful pharmacological treatment (e.g., both traditional and rapid acting antidepressants – drugs that show efficacy in PTSD Treatment – are believed to exert their effects by affecting neuroplasticity and synaptic restructuring (18; 29; 30; 93)). Moreover, there is well replicated evidence that markers of MBP (e.g., lack gray matter deficits) predicts better response to monoaminergic antidepressants, with some studies associating ABP biomarkers (e.g., smaller hippocampal volume) with enhanced response to amino acid-based antidepressants (e.g., ketamine or riluzole) (60; 94).

2.d. Network-Based Model of PTSD

Trauma-related structural and functional synaptic dysconnectivity has been demonstrated in animals and in humans within brain regions critical to anxiety, mood, and fear regulation (95). Thus, the question is raised how the pattern of CSP synaptic dysconnectivity may dictate the prominent clinical presentation, being it PTSD, depression, or another stress-related psychopathology.

In the PTSD literature, early models presented an elegant circuit-based hypothesis supported by a wealth of neuroimaging studies (95). It is believed that reduced hippocampal, but increased amygdala, synaptic connectivity might be predisposing factors that are exacerbated by the index traumatic event to induce disruption in fear memory function (96; 97). This pattern of synaptic dysconnectivity would favor striatal-dependent “habitual” over hippocampal-dependent “cognitive” memory (98–100). In patients with PTSD, it is thought that the heightened fear and arousal are correlates of underlying hyperactivity in the amygdala and dorsal anterior cingulate, putatively due to loss of top-down control from a hypoactive PFC, as well as due to fear extinction deficits driven by dysfunction in the medial PFC and hippocampus (95; 101).

Recently, a more comprehensive model – known as the *triple network model* – has been proposed (102; 103). Similar to the synaptic model of CSP, the triple network model is not specific to PTSD, but rather to a broad range of psychopathological presentations (102). This network-based model extends the circuit-based hypothesis in PTSD by incorporating the wide disruption in three large-scale intrinsic connectivity networks, that are the default mode network, the central executive network, and the salience network (Fig. 2) (104). The default mode network spatially spans important regions in the posterior cingulate cortex, medial PFC, and medial temporal lobe including the hippocampus (105). It is known to engage in self-referential, introspective processes, and autobiographical memory. Consistent with its function, it is most active at rest, and hypoactive during goal-oriented tasks. In individuals with PTSD, the default mode is known to be hypoactive and weakly interconnected (106; 107), which is thought to parallel symptoms of dissociation, avoidance, and intrusiveness (102; 103).

The central executive network, which is anchored primarily in the dlPFC, is known to engage in goal- directed behavior and top-down regulation of emotions. Here, evidence of dysconnectivity in PTSD is thought to mirror a loss of modulation over fear/threat-detection circuits, and deficits in cognition and executive function. In line with this hypothesis, enhanced connectivity between the central executive network and default mode network was found in individuals who respond to exposure therapy, suggesting a compensatory role (108; 109). The salience network, has important nodes in the insula, dorsal anterior cingulate cortex, and possibly the amygdala. The salience network is implicated to the response to subjective salience and arbitrates between central executive network (task-positive) and default mode network (task-negative) accordingly (103; 110). Dysconnectivity in the salience network is thought to impair this arbitration function, resulting in a low threshold for saliency and a hypervigilant state (107; 111). In summary, by extending the fronto-limbic fear circuitry model, the triple network model may better account for the varying endophenotypes in PTSD, as well as the symptomology of common comorbidities (102; 103). In addition, it provides a construct for better understanding of the interplay between the pattern of microstructural synaptic disturbances and the complexity of clinical psychopathological presentations.

3. Pharmacotherapy of PTSD

3.a. Complexity of PTSD symptomatology

PTSD is distinctive among psychiatric disorders because by definition it depends on a type of environmental exposure. Moreover, in adults, the PTSD diagnosis has higher test-retest reliability compared to most psychiatric disorders (112). While these characteristics foretell reproducible neurobiological and pharmacotherapeutic studies, the complexity of PTSD symptomatology and high comorbidity considerably hindered the consistency of most biological findings in PTSD, including the clinical efficacy of standard and investigational medications. In fact, the constellation of PTSD symptoms appears to recapitulate core symptomatology of most psychiatric disorders including anxiety, depression, addictive, impulsive, obsessive-compulsive (e.g., intrusive thoughts), and dissociative/psychotic disorders. Furthermore, the presence of “pure” PTSD in the absence of psychiatric comorbidities is often the exception rather than the rule (112). Together, this complexity has resulted in a pattern of PTSD drugs showing promise in early clinical trials, then later fail to show consistent efficacy in replication and/or larger trials (113; 114). Moreover, the efficacy of many of the most commonly prescribed medications for PTSD has never been tested adequately (e.g., trazodone, quetiapine, mirtazapine, gabapentin, etc.). This state of affairs has been described as a crisis requiring a national commitment to PTSD pharmacotherapy research (3).

Currently, PTSD focused psychotherapies are considered first line of treatment, with pharmacotherapy as first or second line in some guidelines (115). Here, we present a list of standard and investigational drugs that were studied in PTSD. Of these, only paroxetine and sertraline – both are serotonin reuptake inhibitors – are FDA approved for PTSD treatment. In addition, to date, meta-analyses have overall only supported the clinical efficacy of few drugs – all of which are antidepressants, which underscores the prospect of developing drugs

that target trauma- and stress-related pathology (e.g., ketamine targeting synaptic dysconnectivity) compared to PTSD specific abnormalities (e.g., D-cycloserine or propranolol targeting fear circuitry).

3.b. Traditional Drugs: Slow-Acting Antidepressants

In the 1950s, it was serendipitously discovered that iproniazid and imipramine have antidepressant effects, drugs that were being developed to treat tuberculosis and schizophrenia, respectively. Subsequently, other antidepressants that possess a common mechanism of increasing synaptic serotonin have been developed. Among these drugs are the serotonin reuptake inhibitors, the tricyclic antidepressants (e.g., imipramine), and monoamine oxidase inhibitors (e.g., iproniazid). These traditional drugs are SAAD requiring weeks to months to achieve full therapeutic benefit. SAAD have shown efficacy in several depressive, anxiety, and trauma-related disorders. The mechanisms through which SAAD exert their therapeutic effects are not fully known. The drug's *in vitro* pharmacodynamics of increasing synaptic serotonin, combined with laboratory studies associating serotonin depletion with depressive symptoms, have resulted in the rise of the "serotonin deficiency" hypothesis of depression (116). However, several lines of evidence have questioned this model, including the discrepancy between the acute increase in serotonin and the delayed therapeutic response following treatment with SAAD (117). More recently, accumulating evidence in animal models have shown that repeated, but not acute, treatment with SAAD reverses the depressive-like behavior by increasing BDNF in brain structures known to have stress-related synaptic loss (30; 118). Consistent with the synaptic model of CSP, the neurotrophic hypothesis of SAAD provides putative explanation for the delayed onset of treatment response, as well as for the efficacy of SAAD in several psychiatric disorders with a prominent stress-related pathology.

In PTSD, the highest evidence of clinical efficacy is mostly for trials investigating paroxetine, sertraline, and venlafaxine (119). Other SAAD have shown efficacy in some meta-analyses, but these SAAD were investigated mostly in small samples clinical trials (120). Although some SAAD are more effective than placebo in reducing PTSD symptoms, the effect size of these drugs is often small, with high treatment resistance in certain population – e.g., in Veterans (120–122).

3.c. Novel Drugs: Rapid-Acting Antidepressants

In the late 1990s, a study exploring the role of NMDARs in the pathology of depression unexpectedly found RAAD effects following infusion of a single subanesthetic dose of ketamine (123). This finding has since been replicated in several studies and other RAAD are being developed. Ketamine is typically administered intravenously over 40 minutes, with the antidepressant effects evident within few hours and lasting for approximately two weeks following single infusion. These effects are maintained by repeated 2–3 times per week administration in short-term studies (124; 125). Ketamine is believed to exert its RAAD effects by inducing a transient surge in post-synaptic glutamate activation, leading to upregulation of BDNF and increased synaptic formation (126). In animals, it was shown that ketamine reverses the stress-related synaptic loss/gain within 24h of administration (54; 127). Supportive evidence, paralleling the preclinical findings, have been reported in humans

suggesting a rapid structural and functional reversal of synaptic dysconnectivity within 24h of treatment of depressed patients (59; 128; 129). Consistent with the synaptic model of CSP, ketamine's therapeutic effects extend beyond depression and have been suggested in several stress-related disorders (130–133), particularly in tre2ating suicidal ideations (134; 135).

In PTSD, a pilot randomized controlled trial showed moderate to large effect size in reducing PTSD symptoms following administration of a single infusion of ketamine compared to an active placebo control (136). Other retrospective or case report studies have supported the potential utility of subanesthetic doses of ketamine in treating PTSD (124; 137). However, it remains to be seen whether these early reports would be replicated in future confirmatory randomized controlled trials (*clinicaltrials.gov/ct2/show/NCT02655692*). In addition, ketamine induces transient perceptual disturbances during infusion and is used as a recreational drug. Thus, the safety and efficacy of repeated ketamine administration would need to be confirmed prior to adopting it as standard treatment.

3.d. Other Drugs

In addition to SAAD and RAAD, several drugs have been tested in PTSD. Unfortunately, many of these drugs have failed to show reproducible therapeutic benefit. Despite the failure in confirmatory clinical trials and/or in meta-analyses, several of these drugs continue to be frequently used as augmentation in treating PTSD, particularly second-generation antipsychotics (e.g., risperidone), prazosin, and benzodiazepines. Risperidone is the most studied antipsychotic in PTSD, with early promising result, yet failed in a large confirmatory augmentation randomized controlled trial (113). Prazosin, an α1-adrenoreceptor antagonist, showed early promise in treating PTSD, particularly sleep-related symptoms. However, several studies have failed to reproduce these effects and a recent large randomized controlled trial has shown no differences between prazosin and placebo in treating overall PTSD or sleep-related symptoms (114). Benzodiazepine failed to show therapeutic effects in PTSD, with evidence that they may worsen symptoms or increase risk of developing PTSD (138). Other drugs that have been tested with limited to no evidence to support their use, include: topiramate, buproprion, divaloproex, NK1R antagonists, and ganaxolone (120; 121).

3.e. PTSD Prevention

Hydrocortisone and β-adrenergic receptor blockers (e.g., propranolol) are the main pharmacological approaches investigated to prevent the development of PTSD following trauma. Based on evidence of low cortisol in patient with PTSD (139), it was suggested that administering hydrocortisone shortly after the traumatic event may reduce the risk of developing PTSD. Similarly, preclinical evidence has shown that propranolol can block consolidation of traumatic memory, which raised the possibility that administering propranolol shortly after the trauma may reduce the risk of PTSD. To date, randomized controlled trials found no preventive effects following propranolol administration post trauma exposure, although these were mostly small trials with varied administration regimen and timing (8; 9). Conversely, there is preliminary evidence to suggest that hydrocortisone

may have beneficial effects in reducing PTSD risk (8; 9). Other pharmacological preventive approaches that were reported, but which currently have no strong evidence to support their use, include serotonin reuptake inhibitors, temazepam, gabapentin, albuterol, morphine, and oxytocin (9; 140; 141).

3.f. Psychotherapy Augmentation

Preclinical studies have shown that the partial NMDAR agonist D-cycloserine facilitates the excitation of fear (142). Considering the hypothesized extinction failure in PTSD, several studies have investigated whether administration of D-cycloserine would augment the therapeutic effect of fear exposure in psychotherapy for PTSD. To date, the results have been mixed, with some studies showing beneficial effects, while others showing worsening of symptoms (7; 11). It has been suggested that pretreatment with D-cycloserine might indiscriminately enhance the consolidation of memory, leading to improvement if the patient successfully achieved extinction during the fear exposure session or to inadvertently enhance reconsolidation of trauma memory and worsening of symptoms if the exposure session was unsuccessful (143). A recent small randomized controlled trial suggested beneficial effects combining propranolol with trauma reactivation, a pilot finding that awaits replication (144). Another approach for PTSD psychotherapy augmentation is the administration of 3,4-methylenedioxy-methamphetamine (MDMA), a recreational drug known as “ecstasy”, which induces transient serotonin and norepinephrine release (145; 146). MDMA is currently in phase 3 trials and has received an FDA breakthrough designation, which facilitates the approval of the drug if the randomized controlled trial results were confirmatory. Considering the addiction liability of the drug, strong evidence of safety and therapeutic benefit would be required.

4. Conclusions

Psychiatric illnesses are often conceptualized as entities with complex interaction between biological, psychological, and social components. Notably, chronic stress – as predisposing, triggering, or perpetuating factor – is a major component of most psychiatric disorders. Moreover, biomarkers suggestive of stress-related synaptic dysconnectivity (e.g., gray matter deficits) were reported across most severe psychiatric disorders. Furthermore, antidepressants, that are believed to exert their clinical benefit through the reversal of stress-related synaptic dysconnectivity, have shown clinical efficacy in several psychiatric disorders. Together, this converging evidence strongly suggests CSP is a common pathophysiological process across multiple disorders. In recent years, clinical neuroscience research has begun to unravel the unique dysconnectivity patterns through which CSP contribute to distinct clinical presentations, including PTSD – highlighting a triple network model of psychopathology. Finally, although pharmacotherapeutic options to alleviate PTSD are available, these drugs have minimal (e.g., serotonin reuptake inhibitors) or inconsistent efficacy (e.g., prazosin or risperidone). While SAAD have minimal effects on synaptic remodeling and PTSD symptoms, RAAD exert strong synaptic remodeling and pilot evidence suggest high efficacy in alleviating PTSD. It remains to be seen whether the initial promise of these novel drugs would eventually translate into robust and effective pharmacological treatment for millions of individuals suffering from PTSD.

References

1. Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, et al. 2017 Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med 47:2260–74 [PubMed: 28385165]
2. Fulton JJ, Calhoun PS, Wagner HR, Schry AR, Hair LP, et al. 2015 The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans: a meta-analysis. J Anxiety Disord 31:98–107 [PubMed: 25768399]
3. Krystal JH, Davis LL, Neylan TC, M AR, Schnurr PP, et al. 2017 It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry 82:e51–e9 [PubMed: 28454621]
4. Maeng LY, Milad MR. 2017 Post-Traumatic Stress Disorder: The Relationship Between the Fear Response and Chronic Stress. Chronic Stress 1:2470547017713297
5. VanElzakker MB, Dahlgren MK, Davis FC, Dubois S, Shin LM. 2014 From Pavlov to PTSD: the extinction of conditioned fear in rodents, humans, and anxiety disorders. Neurobiol Learn Mem 113:3–18 [PubMed: 24321650]
6. Maren S, Phan KL, Liberzon I. 2013 The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci 14:417–28 [PubMed: 23635870]
7. Baker JF, Cates ME, Luthin DR. 2017 D-cycloserine in the treatment of posttraumatic stress disorder. Mental Health Clinician 7:88–94 [PubMed: 29955504]
8. Sijbrandij M, Kleiboer A, Bisson JI, Barbui C, Cuijpers P. 2015 Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis. Lancet Psychiatry 2:413–21 [PubMed: 26360285]
9. Amos T, Stein DJ, Ipser JC. 2014 Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). Cochrane Database Syst Rev:CD006239
10. Abdallah CG, Sanacora G, Duman RS, Krystal JH. 2015 Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics. Annu Rev Med 66:509–23 [PubMed: 25341010]
11. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG. 2017 Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. Neurosci Lett 649:147–55 [PubMed: 27916636]
12. Abdallah CG, Southwick SM, Krystal JH. 2017 Neurobiology of posttraumatic stress disorder (PTSD): A path from novel pathophysiology to innovative therapeutics. Neurosci Lett 649:130–2 [PubMed: 28478864]
13. Krystal JH, Abdallah CG, Averill LA, Kelmendi B, Harpaz-Rotem I, et al. 2017 Synaptic Loss and the Pathophysiology of PTSD: Implications for Ketamine as a Prototype Novel Therapeutic. Curr Psychiatry Rep 19:74 [PubMed: 28844076]
14. Maren S, Holmes A. 2016 Stress and Fear Extinction. Neuropsychopharmacology 41:58–79 [PubMed: 26105142]
15. Yuen EY, Liu W, Karatsoreos IN, Feng J, McEwen BS, Yan Z. 2009 Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. Proc Natl Acad Sci U S A 106:14075–9 [PubMed: 19666502]
16. Yuen EY, Liu W, Karatsoreos IN, Ren Y, Feng J, et al. 2011 Mechanisms for acute stress-induced enhancement of glutamatergic transmission and working memory. Molecular Psychiatry 16:156–70 [PubMed: 20458323]
17. Averill LA, Averill CL, Kelmendi B, Abdallah CG, Southwick S. 2018 Stress Response Modulation Underlying the Psychobiology of Resilience. Curr Psychiatry Rep:In Press
18. McEwen BS. 2017 Neurobiological and Systemic Effects of Chronic Stress. Chronic Stress 1:1–11
19. Yuen EY, Wei J, Liu W, Zhong P, Li X, Yan Z. 2012 Repeated stress causes cognitive impairment by suppressing glutamate receptor expression and function in prefrontal cortex. Neuron 73:962–77 [PubMed: 22405206]
20. Popoli M, Yan Z, McEwen BS, Sanacora G. 2012 The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. Nat Rev Neurosci 13:22–37

21. Ozer EJ, Best SR, Lipsey TL, Weiss DS. 2003 Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. Psychol Bull 129:52–73 [PubMed: 12555794]
22. Sutanto W, de Kloet ER. 1994 The use of various animal models in the study of stress and stress-related phenomena. Lab Anim 28:293–306 [PubMed: 7830368]
23. Zoladz PR, Diamond DM. 2013 Current status on behavioral and biological markers of PTSD: a search for clarity in a conflicting literature. Neurosci Biobehav Rev 37:860–95 [PubMed: 23567521]
24. Admon R, Milad MR, Hendler T. 2013 A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. Trends Cogn Sci 17:337–47 [PubMed: 23768722]
25. Breslau N 2012 Epidemiology of posttraumatic stress disorder in adults The Oxford Handbook of Traumatic Stress Disorders. Oxford University Press: New York:84–97
26. Bogic M, Njoku A, Priebe S. 2015 Long-term mental health of war-refugees: a systematic literature review. BMC Int Health Hum Rights 15:29 [PubMed: 26510473]
27. Kuch K, Cox BJ. 1992 Symptoms of PTSD in 124 survivors of the Holocaust. Am J Psychiatry 149:337–40 [PubMed: 1536271]
28. Russo SJ, Nestler EJ. 2013 The brain reward circuitry in mood disorders. Nat Rev Neurosci 14:609–25 [PubMed: 23942470]
29. Abdallah CG, Sanacora G, Duman RS, Krystal JH. 2018 The neurobiology of depression, ketamine and rapid-acting antidepressants: Is it glutamate inhibition or activation? Pharmacol Ther
30. Duman RS, Aghajanian GK. 2012 Synaptic dysfunction in depression: potential therapeutic targets. Science 338:68–72 [PubMed: 23042884]
31. Sanacora G, Banasr M. 2013 From pathophysiology to novel antidepressant drugs: glial contributions to the pathology and treatment of mood disorders. Biol Psychiatry 73:1172–9 [PubMed: 23726152]
32. Li SX, Han Y, Xu LZ, Yuan K, Zhang RX, et al. 2018 Uncoupling DAPK1 from NMDA receptor GluN2B subunit exerts rapid antidepressant-like effects. Mol Psychiatry 23:597–608 [PubMed: 28439098]
33. Banasr M, Chowdhury GM, Terwilliger R, Newton SS, Duman RS, et al. 2010 Glial pathology in an animal model of depression: reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. Molecular Psychiatry 15:501–11 [PubMed: 18825147]
34. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. 2016 Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat Med 22:238–49 [PubMed: 26937618]
35. Hare B, Ghosal S, Duman R. 2017 Rapid acting antidepressants in chronic stress models: molecular and cellular mechanisms. Chronic Stress 1:1–16
36. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. 2002 Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci 22:6810–8 [PubMed: 12151561]
37. Bennur S, Shankaranarayana Rao BS, Pawlak R, Strickland S, McEwen BS, Chattarji S. 2007 Stress-induced spine loss in the medial amygdala is mediated by tissue-plasminogen activator. Neuroscience 144:8–16 [PubMed: 17049177]
38. Lakshminarasimhan H, Chattarji S. 2012 Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. PLoS One 7:e30481 [PubMed: 22272355]
39. Mitra R, Jadhav S, McEwen BS, Vyas A, Chattarji S. 2005 Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc Natl Acad Sci U S A 102:9371–6 [PubMed: 15967994]
40. Mitra R, Sapolsky RM. 2008 Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy. Proc Natl Acad Sci U S A 105:5573–8 [PubMed: 18391224]
41. Conrad CD, LeDoux JE, Magarinos AM, McEwen BS. 1999 Repeated restraint stress facilitates fear conditioning independently of causing hippocampal CA3 dendritic atrophy. Behav Neurosci 113:902–13 [PubMed: 10571474]

42. Radley JJ, Rocher AB, Janssen WG, Hof PR, McEwen BS, Morrison JH. 2005 Reversibility of apical dendritic retraction in the rat medial prefrontal cortex following repeated stress. Exp Neurol 196:199–203 [PubMed: 16095592]
43. Vyas A, Pillai AG, Chattarji S. 2004 Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. Neuroscience 128:667–73 [PubMed: 15464275]
44. Christoffel DJ, Golden SA, Heshmati M, Graham A, Birnbaum S, et al. 2012 Effects of inhibitor of kappaB kinase activity in the nucleus accumbens on emotional behavior. Neuropsychopharmacology 37:2615–23 [PubMed: 22781845]
45. Muhammad A, Carroll C, Kolb B. 2012 Stress during development alters dendritic morphology in the nucleus accumbens and prefrontal cortex. Neuroscience 216:103–9 [PubMed: 22542675]
46. Warren BL, Sial OK, Alcantara LF, Greenwood MA, Brewer JS, et al. 2014 Altered gene expression and spine density in nucleus accumbens of adolescent and adult male mice exposed to emotional and physical stress. Dev Neurosci 36:250–60 [PubMed: 24943326]
47. Christoffel DJ, Golden SA, Dumitriu D, Robison AJ, Janssen WG, et al. 2011 IkappaB kinase regulates social defeat stress-induced synaptic and behavioral plasticity. J Neurosci 31:314–21 [PubMed: 21209217]
48. Campioni MR, Xu M, McGehee DS. 2009 Stress-induced changes in nucleus accumbens glutamate synaptic plasticity. J Neurophysiol 101:3192–8 [PubMed: 19357347]
49. Coplan JD, Lu D, El Sehamy AM, Tang C, Jackowski AP, et al. 2018 Early Life Stress Associated with Increased Striatal N-acetylaspartate (NAA): Cerebrospinal Fluid (CSF) Corticotropin-Releasing Factor (CRF) Concentrations, Hippocampal Volume, Body Mass and Behavioral Correlates. Chronic Stress 2:In Press
50. Chaudhury D, Walsh JJ, Friedman AK, Juarez B, Ku SM, et al. 2013 Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature 493:532–6 [PubMed: 23235832]
51. Walsh JJ, Friedman AK, Sun H, Heller EA, Ku SM, et al. 2014 Stress and CRF gate neural activation of BDNF in the mesolimbic reward pathway. Nat Neurosci 17:27–9 [PubMed: 24270188]
52. Wook Koo J, Labonte B, Engmann O, Calipari ES, Juarez B, et al. 2016 Essential Role of Mesolimbic Brain-Derived Neurotrophic Factor in Chronic Social Stress-Induced Depressive Behaviors. Biol Psychiatry 80:469–78 [PubMed: 26858215]
53. Krishnan V, Nestler EJ. 2008 The molecular neurobiology of depression. Nature 455:894–902 [PubMed: 18923511]
54. Melo A, Kokras N, Dalla C, Ferreira C, Ventura-Silva AP, et al. 2015 The positive effect on ketamine as a priming adjuvant in antidepressant treatment. Translational psychiatry 5:e573 [PubMed: 26080090]
55. Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, et al. 1995 MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. Am J Psychiatry 152:973–81 [PubMed: 7793467]
56. Yehuda R, Golier JA, Tischler L, Harvey PD, Newmark R, et al. 2007 Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: relation to risk and resilience factors. J Psychiatr Res 41:435–45 [PubMed: 16445942]
57. Kuo JR, Kaloupek DG, Woodward SH. 2012 Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study. Arch Gen Psychiatry 69:1080–6 [PubMed: 23026958]
58. Morey RA, Gold AL, LaBar KS, Beall SK, Brown VM, et al. 2012 Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Arch Gen Psychiatry 69:1169–78 [PubMed: 23117638]
59. Abdallah CG, Jackowski A, Salas R, Gupta S, Sato JR, et al. 2017 The Nucleus Accumbens and Ketamine Treatment in Major Depressive Disorder. Neuropsychopharmacology 42:1739–46 [PubMed: 28272497]

60. Abdallah CG, Coplan JD, Jackowski A, Sato JR, Mao X, et al. 2013 A pilot study of hippocampal volume and N-acetylaspartate (NAA) as response biomarkers in riluzole-treated patients with GAD. Eur Neuropsychopharmacol 23:276–84 [PubMed: 22739126]
61. Abdallah CG, Jackowski A, Sato JR, Mao X, Kang G, et al. 2015 Prefrontal cortical GABA abnormalities are associated with reduced hippocampal volume in major depressive disorder. Eur Neuropsychopharmacol 25:1082–90 [PubMed: 25983019]
62. Valenti O, Gill KM, Grace AA. 2012 Different stressors produce excitation or inhibition of mesolimbic dopamine neuron activity: response alteration by stress pre-exposure. Eur J Neurosci 35:1312–21 [PubMed: 22512259]
63. Holly EN, Miczek KA. 2016 Ventral tegmental area dopamine revisited: effects of acute and repeated stress. Psychopharmacology (Berl) 233:163–86 [PubMed: 26676983]
64. Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai HC, et al. 2013 Dopamine neurons modulate neural encoding and expression of depression-related behaviour. Nature 493:537–41 [PubMed: 23235822]
65. Krishnan V, Han MH, Graham DL, Berton O, Renthal W, et al. 2007 Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131:391–404 [PubMed: 17956738]
66. Flandreau EI, Toth M. 2017 Animal Models of PTSD: A Critical Review. Current topics in behavioral neurosciences
67. Goswami S, Rodriguez-Sierra O, Cascardi M, Pare D. 2013 Animal models of post-traumatic stress disorder: face validity. Front Neurosci 7:89 [PubMed: 23754973]
68. Izquierdo A, Wellman CL, Holmes A. 2006 Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice. J Neurosci 26:5733–8 [PubMed: 16723530]
69. Shalev AY, Freedman S, Peri T, Brandes D, Sahar T, et al. 1998 Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry 155:630–7 [PubMed: 9585714]
70. Abdallah CG, Wrocklage KM, Averill CL, Akiki T, Schweinsburg B, et al. 2017 Anterior hippocampal dysconnectivity in posttraumatic stress disorder: a dimensional and multimodal approach. Translational psychiatry 7:e1045 [PubMed: 28244983]
71. Akiki TJ, Averill CL, Wrocklage KM, Schweinsburg B, Scott JC, et al. 2017 The Association of PTSD Symptom Severity with Localized Hippocampus and Amygdala Abnormalities. Chronic Stress 1:2470547017724069
72. Averill CL, Satodiya RM, Scott JC, Wrocklage KM, Schweinsburg B, et al. 2017 Posttraumatic Stress Disorder and Depression Symptom Severities Are Differentially Associated With Hippocampal Subfield Volume Loss in Combat Veterans. Chronic Stress 1:2470547017744538
73. Averill LA, Abdallah CG, Pietrzak RH, Averill CL, Southwick SM, et al. 2017 Combat Exposure Severity is Associated with Reduced Cortical Thickness in Combat Veterans: A Preliminary Report. Chronic Stress 1:2470547017724714
74. Pietrzak RH, Averill LA, Abdallah CG, Neumeister A, Krystal JH, et al. 2015 Amygdala-hippocampal volume and the phenotypic heterogeneity of posttraumatic stress disorder: a cross-sectional study. JAMA psychiatry 72:396–8 [PubMed: 25692480]
75. Wrocklage KM, Averill LA, Cobb Scott J, Averill CL, Schweinsburg B, et al. 2017 Cortical thickness reduction in combat exposed U.S. veterans with and without PTSD. Eur Neuropsychopharmacol 27:515–25 [PubMed: 28279623]
76. Southwick SM, Krystal JH, Bremner JD, Morgan CA, 3rd, Nicolaou AL, et al. 1997 Noradrenergic and serotonergic function in posttraumatic stress disorder. Arch Gen Psychiatry 54:749–58 [PubMed: 9283511]
77. Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, et al. 1993 Abnormal noradrenergic function in posttraumatic stress disorder. Arch Gen Psychiatry 50:266–74 [PubMed: 8466387]
78. Abdallah CG, Averill LA, Krystal JH, Southwick SM, Arnsten AF. 2016 Glutamate and norepinephrine interaction: Relevance to higher cognitive operations and psychopathology. Behav Brain Sci 39:e201 [PubMed: 28347382]

79. Arnsten AF. 2015 Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci 18:1376–85 [PubMed: 26404712]
80. Logue MW, van Rooij SJH, Dennis EL, Davis SL, Hayes JP, et al. 2018 Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. Biol Psychiatry 83:244–53 [PubMed: 29217296]
81. Schmaal L, Veltman DJ, van Erp TG, Samann PG, Frodl T, et al. 2016 Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. Mol Psychiatry 21:806–12 [PubMed: 26122586]
82. O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. 2015 A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res 232:1–33 [PubMed: 25735885]
83. Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, et al. 2011 Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Archives of General Psychiatry 68:675–90 [PubMed: 21727252]
84. Kwon JS, Shin YW, Kim CW, Kim YI, Youn T, et al. 2003 Similarity and disparity of obsessive-compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus-amygdala complex. J Neurol Neurosurg Psychiatry 74:962–4 [PubMed: 12810792]
85. Anticevic A, Brumbaugh MS, Winkler AM, Lombardo LE, Barrett J, et al. 2013 Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history. Biol Psychiatry 73:565–73 [PubMed: 22980587]
86. Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, et al. 2014 Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. Biol Psychiatry 75:595–605 [PubMed: 24314349]
87. Haukvik UK, Westlye LT, Morch-Johnsen L, Jorgensen KN, Lange EH, et al. 2015 In vivo hippocampal subfield volumes in schizophrenia and bipolar disorder. Biol Psychiatry 77:581–8 [PubMed: 25127742]
88. Syed SA, Nemeroff CB. 2017 Early Life Stress, Mood, and Anxiety Disorders. Chronic Stress 1:2470547017694461
89. Matosin N, Cruceanu C, Binder EB. 2017 Preclinical and Clinical Evidence of DNA Methylation Changes in Response to Trauma and Chronic Stress. Chronic Stress 1:2470547017710764
90. Sheth C, McGlade E, Yurgelun-Todd D. 2017 Chronic Stress in Adolescents and Its Neurobiological and Psychopathological Consequences: An RDoC Perspective. Chronic Stress 1:2470547017715645
91. Adams TG, Kelmendi B, Brake CA, Gruner P, Badour CL, Pittenger C. 2018 The Role of Stress in the Pathogenesis and Maintenance of Obsessive-Compulsive Disorder. Chronic Stress 2:2470547018758043
92. Goddard AW. 2017 The Neurobiology of Panic: A Chronic Stress Disorder. Chronic Stress 1:2470547017736038
93. Zanos P, Thompson SM, Duman RS, Zarate CA, Jr., Gould TD. 2018 Convergent Mechanisms Underlying Rapid Antidepressant Action. CNS Drugs 32:197–227 [PubMed: 29516301]
94. Abdallah CG, Salas R, Jackowski A, Baldwin P, Sato JR, Mathew SJ. 2015 Hippocampal volume and the rapid antidepressant effect of ketamine. J Psychopharmacol 29:591–5 [PubMed: 25122038]
95. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, et al. 2012 Biological studies of post-traumatic stress disorder. Nat Rev Neurosci 13:769–87 [PubMed: 23047775]
96. Admon R, Lubin G, Stern O, Rosenberg K, Sela L, et al. 2009 Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. Proc Natl Acad Sci U S A 106:14120–5 [PubMed: 19666562]
97. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, et al. 2002 Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5:1242–7 [PubMed: 12379862]

98. Schwabe L, Dalm S, Schachinger H, Oitzl MS. 2008 Chronic stress modulates the use of spatial and stimulus-response learning strategies in mice and man. Neurobiol Learn Mem 90:495–503 [PubMed: 18707011]

99. Schwabe L, Joels M, Roozendaal B, Wolf OT, Oitzl MS. 2012 Stress effects on memory: an update and integration. Neurosci Biobehav Rev 36:1740–9 [PubMed: 21771612]

100. de Quervain D, Schwabe L, Roozendaal B. 2017 Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nat Rev Neurosci 18:7–19 [PubMed: 27881856]

101. Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. 2016 Aberrant Resting-State Brain Activity in Posttraumatic Stress Disorder: A Meta-Analysis and Systematic Review. Depress Anxiety 33:592–605 [PubMed: 26918313]

102. Menon V 2011 Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15:483–506 [PubMed: 21908230]

103. Akiki TJ, Averill CL, Abdallah CG. 2017 A Network-Based Neurobiological Model of PTSD: Evidence From Structural and Functional Neuroimaging Studies. Curr Psychiatry Rep 19:81 [PubMed: 28924828]

104. Akiki TJ, Abdallah CG. 2018 Determining the Hierarchical Architecture of the Human Brain Using Subject-Level Clustering of Functional Networks. bioRxiv

105. Buckner RL, Andrews-Hanna JR, Schacter DL. 2008 The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1–38 [PubMed: 18400922]

106. Akiki TJ, Averill CL, Wrocklage KM, Scott JC, Averill LA, et al. 2018 Default mode network abnormalities in posttraumatic stress disorder: A novel network-restricted topology approach. Neuroimage 176:489–98 [PubMed: 29730491]

107. Sripada RK, King AP, Welsh RC, Garfinkel SN, Wang X, et al. 2012 Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. Psychosom Med 74:904–11 [PubMed: 23115342]

108. King AP, Block SR, Sripada RK, Rauch S, Giardino N, et al. 2016 Altered Default Mode Network (Dmn) Resting State Functional Connectivity Following a Mindfulness-Based Exposure Therapy for Posttraumatic Stress Disorder (Ptsd) in Combat Veterans of Afghanistan and Iraq. Depress Anxiety 33:289–99 [PubMed: 27038410]

109. Cisler JM, Scott Steele J, Smitherman S, Lenow JK, Kilts CD. 2013 Neural processing correlates of assaultive violence exposure and PTSD symptoms during implicit threat processing: a network-level analysis among adolescent girls. Psychiatry Res 214:238–46 [PubMed: 23969000]

110. Goulden N, Khusnulina A, Davis NJ, Bracewell RM, Bokde AL, et al. 2014 The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. Neuroimage 99:180–90 [PubMed: 24862074]

111. Brown VM, LaBar KS, Haswell CC, Gold AL, Mid-Atlantic MW, et al. 2014 Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. Neuropsychopharmacology 39:351–9 [PubMed: 23929546]

112. Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, et al. 2013 DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry 170:59–70 [PubMed: 23111466]

113. Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, et al. 2011 Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA 306:493–502 [PubMed: 21813427]

114. Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, et al. 2018 Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans. N Engl J Med 378:507–17 [PubMed: 29414272]

115. Forbes D, Creamer M, Bisson JI, Cohen JA, Crow BE, et al. 2010 A guide to guidelines for the treatment of PTSD and related conditions. J Trauma Stress 23:537–52 [PubMed: 20839310]

116. Delgado PL, Miller HL, Salomon RM, Licinio J, Krystal JH, et al. 1999 Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. Biol Psychiatry 46:212–20 [PubMed: 10418696]

117. Coplan JD, Gopinath S, Abdallah CG, Berry BR. 2014 A neurobiological hypothesis of treatment-resistant depression - mechanisms for selective serotonin reuptake inhibitor non-efficacy. Frontiers in behavioral neuroscience 8:189 [PubMed: 24904340]
118. Duman RS, Heninger GR, Nestler EJ. 1997 A molecular and cellular theory of depression. Arch Gen Psychiatry 54:597–606 [PubMed: 9236543]
119. Friedman MJ, Bernardy NC. 2016 Considering future pharmacotherapy for PTSD. Neurosci Lett
120. Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, et al. 2017 Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychol Med:1–10
121. Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. 2013 Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. J Clin Psychiatry 74:e541–50 [PubMed: 23842024]
122. Bernardy NC, Friedman MJ. 2017 Pharmacological management of posttraumatic stress disorder. Curr Opin Psychol 14:116–21 [PubMed: 28813308]
123. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, et al. 2000 Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–4 [PubMed: 10686270]
124. Abdallah CG, Averill LA, Krystal JH. 2015 Ketamine as a promising prototype for a new generation of rapid-acting antidepressants. Ann N Y Acad Sci 1344:66–77 [PubMed: 25727103]
125. McGirr A, Berlim MT, Bond DJ, Fleck MP, Yatham LN, Lam RW. 2015 A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 45:693–704 [PubMed: 25010396]
126. Abdallah CG, De Feyter HM, Averill LA, Jiang L, Averill CL, et al. 2018 The effects of ketamine on prefrontal glutamate neurotransmission in healthy and depressed subjects. Neuropsychopharmacology
127. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, et al. 2011 Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol Psychiatry 69:754–61 [PubMed: 21292242]
128. Abdallah CG, Averill CL, Salas R, Averill LA, Baldwin PR, et al. 2017 Prefrontal Connectivity and Glutamate Transmission: Relevance to Depression Pathophysiology and Ketamine Treatment. Biol Psychiatry Cogn Neurosci Neuroimaging 2:566–74 [PubMed: 29034354]
129. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, et al. 2017 Ketamine Treatment and Global Brain Connectivity in Major Depression. Neuropsychopharmacology 42:1210–9 [PubMed: 27604566]
130. Glue P, Medlicott NJ, Harland S, Neehoff S, Anderson-Fahey B, et al. 2017 Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. J Psychopharmacol 31:1302–5 [PubMed: 28441895]
131. Ivan Ezquerra-Romano I, Lawn W, Krupitsky E, Morgan CJA. 2018 Ketamine for the treatment of addiction: Evidence and potential mechanisms. Neuropharmacology
132. Rodriguez CI, Kegeles LS, Levinson A, Feng T, Marcus SM, et al. 2013 Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology 38:2475–83 [PubMed: 23783065]
133. Taylor JH, Landeros-Weisenberger A, Coughlin C, Mulqueen J, Johnson JA, et al. 2018 Ketamine for Social Anxiety Disorder: A Randomized, Placebo-Controlled Crossover Trial. Neuropsychopharmacology 43:325–33 [PubMed: 28849779]
134. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, et al. 2018 The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis. Am J Psychiatry 175:150–8 [PubMed: 28969441]
135. Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, et al. 2018 Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. Am J Psychiatry 175:327–35 [PubMed: 29202655]
136. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, et al. 2014 Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA psychiatry 71:681–8 [PubMed: 24740528]

137. Hartberg J, Garrett-Walcott S, De Gioannis A. 2018 Impact of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: a retrospective study. Psychopharmacology (Berl) 235:393–8 [PubMed: 29151192]

138. Guina J, Rossetter SR, De RB, Nahhas RW, Welton RS. 2015 Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. J Psychiatr Pract 21:281–303 [PubMed: 26164054]

139. Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL, Jr., Mason JW 1990 Low urinary cortisol excretion in patients with posttraumatic stress disorder. J Nerv Ment Dis 178:366–9 [PubMed: 2348190]

140. Howlett JR, Stein MB. 2016 Prevention of Trauma and Stressor-Related Disorders: A Review. Neuropsychopharmacology 41:357–69 [PubMed: 26315508]

141. Sippel LM, Allington CE, Pietrzak RH, Harpaz-Rotem I, Mayes LC, Olff M. 2017 Oxytocin and Stress-related Disorders: Neurobiological Mechanisms and Treatment Opportunities. Chronic Stress 1:2470547016687996

142. Walker DL, Ressler KJ, Lu KT, Davis M. 2002 Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci 22:2343–51 [PubMed: 11896173]

143. Litz BT, Salters-Pedneault K, Steenkamp MM, Hermos JA, Bryant RA, et al. 2012 A randomized placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder. J Psychiatr Res 46:1184–90 [PubMed: 22694905]

144. Brunet A, Saumier D, Liu A, Streiner DL, Tremblay J, Pitman RK. 2018 Reduction of PTSD Symptoms With Pre-Reactivation Propranolol Therapy: A Randomized Controlled Trial. Am J Psychiatry:appiajp201717050481

145. Kelmendi B, Adams TG, Yarnell S, Southwick S, Abdallah CG, Krystal JH. 2016 PTSD: from neurobiology to pharmacological treatments. Eur J Psychotraumatol 7:31858 [PubMed: 27837583]

146. Amoroso T, Workman M. 2016 Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy. J Psychopharmacol 30:595–600 [PubMed: 27118529]

147. Davidson J, Baldwin D, Stein DJ, Kuper E, Benattia I, et al. 2006 Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. Arch Gen Psychiatry 63:1158–65 [PubMed: 17015818]

148. Villarreal G, Hamner MB, Canive JM, Robert S, Calais LA, et al. 2016 Efficacy of Quetiapine Monotherapy in Posttraumatic Stress Disorder: A Randomized, Placebo-Controlled Trial. Am J Psychiatry 173:1205–12 [PubMed: 27418378]

149. Khachatryan D, Groll D, Booij L, Sepehry AA, Schutz CG. 2016 Prazosin for treating sleep disturbances in adults with posttraumatic stress disorder: a systematic review and meta-analysis of randomized controlled trials. Gen Hosp Psychiatry 39:46–52 [PubMed: 26644317]

150. Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, et al. 2013 A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry 170:1003–10 [PubMed: 23846759]

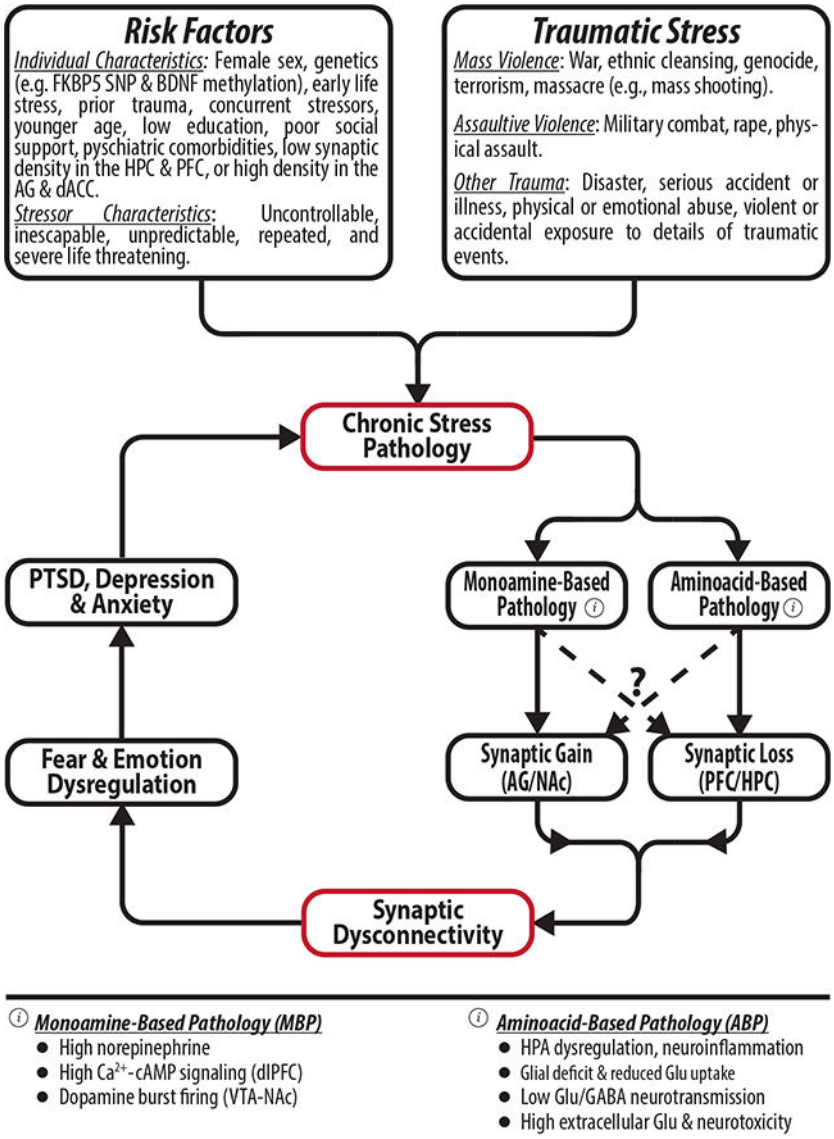

Figure 1. The "vicious cycle" of chronic stress pathology: A synaptic model of posttraumatic stress disorder (PTSD).

It is believed that traumatic stress interacts with predisposing factors to precipitate chronic stress pathology, consistent with localized synaptic loss and/or gain, leading to behavioral disruptions, which further exacerbate the chronic stress pathology. Abbreviations: FKBP5 = FK506-binding protein 5; SNP = single nucleotide polymorphism; BDNF = brain derived neurotrophic factor; HPC = hippocampus; PFC = prefrontal cortex; AG = amygdala; dACC = dorsal anterior cingulate; NAc = nucleus accumbens; dlPFC = dorsolateral PFC; VTA = ventral tegmental area; HPA = hypothalamic-pituitary axis; Glu = glutamate; The figure was adapted with permission from the Emerge Research Program (emerge.care).

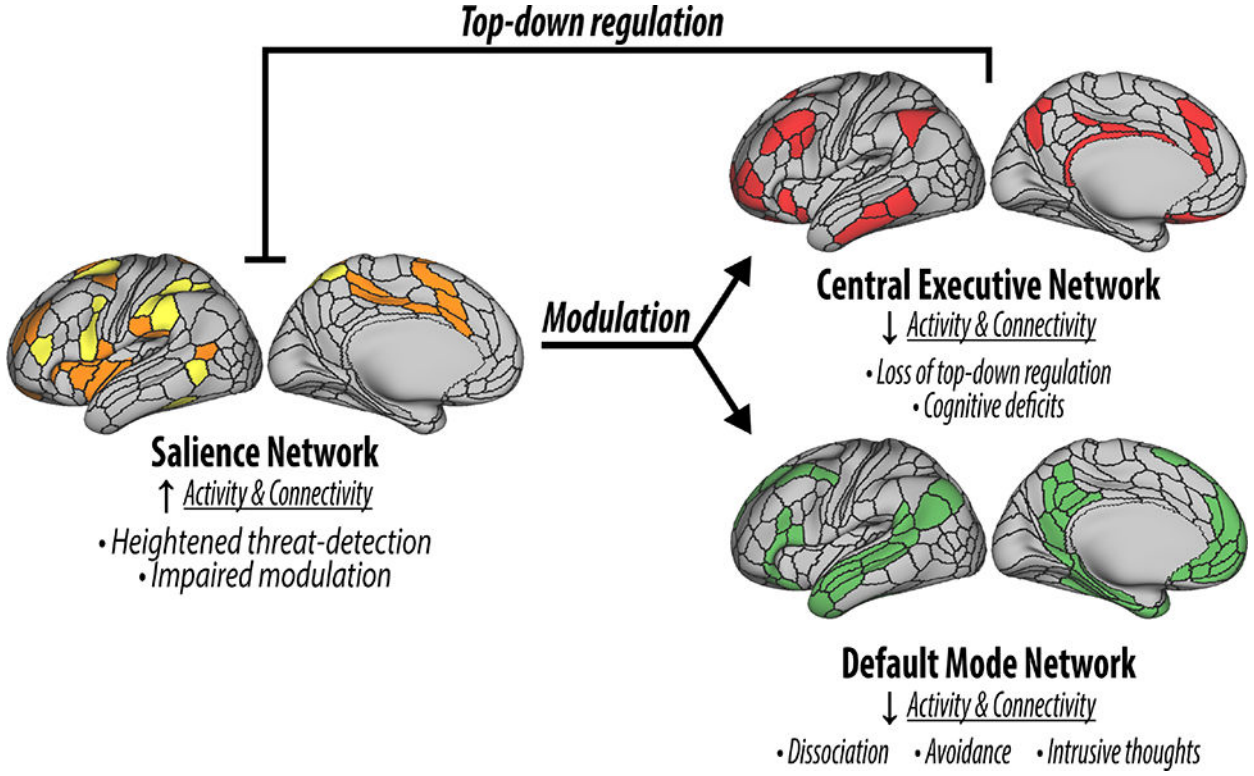

Figure 2. A network-based model of posttraumatic stress disorder (PTSD).

The figure depicts the cortical representations of the salience network (SN; orange and yellow), central executive network (CEN; red), and default mode network (DMN; green). PTSD has been associated with hyperactive SN leading to heightened threat-detection and impaired modulation of the CEN and DMN. In turn, CEN and DMN deficits are associated with disruption in top-control, as well as several PTSD related symptomatology. The figure was adapted with permission from the Emerge Research Program (emerge.care).

Table 1.

Drugs commonly used to treat PTSD.

List of commonly used pharmacological agents in the treatment of PTSD, their putative mechanism of action, and their clinical therapeutic aims. * indicates FDA approval for PTSD.

Medication class	Commonly used agents	Putative mechanism	Therapeutic aim
Antidepressants (slow-acting)	Paroxetine*; Sertraline*; fluoxetine	Serotonin reuptake inhibition	Overall symptoms (115; 120; 121)
	Venlafaxine	Serotonin-norepinephrine reuptake inhibition	Overall symptoms (115; 120; 121); possibly less effective for hyperarousal symptoms (147)
	Mirtazapine	Serotonin 5-HT_2 and 5- HT_3 and adrenoreceptor α_2 antagonism	Overall symptoms (115; 120)
	Desipramine	Norepinephrine reuptake inhibition	Overall symptoms (115; 120)
	Phenelzine	Monoamine oxidase inhibition	Overall symptoms (115; 120)
Antipsychotics (second-generation)	Risperidone; quetiapine	Dopamine D_2 and serotonin 5-HT_2 antagonism	Primarily used for sleep symptoms with questionable evidence of efficacy (113); may possibly improve other symptoms (121; 148)
Anxiolytics or sedative-hypnotics	Prazosin	α_1-adrenoreceptor antagonism	Primarily used for sleep symptoms with inconsistent evidence of efficacy (114; 149); may possibly improve other symptoms (150)
	Alprazolam; clonazepam	$GABA_A$ receptor agonism	No evidence of efficacy; possible worsening of symptoms (138)