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MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?

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ABSTRACT

MDMA-assisted psychotherapy for treatment of PTSD has recently progressed to Phase 3 clinical trials and received Breakthrough Therapy designation by the FDA. MDMA used as an adjunct during psychotherapy sessions has demonstrated effectiveness and acceptable safety in reducing PTSD symptoms in Phase 2 trials, with durable remission of PTSD diagnosis in 68% of participants. The underlying psychological and neurological mechanisms for the robust effects in mitigating PTSD are being investigated in animal models and in studies of healthy volunteers. This review explores the potential role of memory reconsolidation and fear extinction during MDMA-assisted psychotherapy. MDMA enhances release of monoamines (serotonin, norepinephrine, dopamine), hormones (oxytocin, cortisol), and other downstream signaling molecules (BDNF) to dynamically modulate emotional memory circuits. By reducing activation in brain regions implicated in the expression of fear- and anxiety-related behaviors, namely the amygdala and insula, and increasing connectivity between the amygdala and hippocampus, MDMA may allow for reprocessing of traumatic memories and emotional engagement with therapeutic processes. Based on the pharmacology of MDMA and the available translational literature of memory reconsolidation, fear learning, and PTSD, this review suggests a neurobiological rationale to explain, at least in part, the large effect sizes demonstrated for MDMA in treating PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) may develop after exposure to a single traumatic event or from repeated stressful experiences, such as childhood abuse, and often causes long-lasting and debilitating symptoms that can significantly impact a person's daily functioning. In patients with PTSD, adaptations in normal brain function have been observed that underlie alterations in emotional processing and regulation, cognition, and many aspects of behavior, though clinical symptoms and changes in brain activity are not homogenous across patients. Exposure-based therapies used to treat PTSD rely on imaginal visualization of the traumatic events and exposure to trauma-related cues that trigger fear responses; the goal being to extinguish conditioned fear to cues associated with trauma. Some patients experience a reduction in PTSD symptoms after therapy, however 40–60% of patients do not respond adequately (Bradley et al., 2005; Brady et al., 2000; Davidson et al., 2001). Emotional detachment, fragmentation of the trauma memories or an inability to complete the sessions due to inability to tolerate re-experiencing emotional content of the traumatic memory could all contribute to non-response and high treatment dropout rates (Goetter et al., 2015; Mott et al., 2014). The search for pharmacological agents to augment exposure therapies and other psychotherapies for PTSD to improve outcomes and reduce dropout rates has been underway for many years. Studies in animals have shown potential for drugs, in particular D-cycloserine, to enhance fear extinction and memory reconsolidation of conditioned cues (Fitzgerald et al., 2014).

MDMA is a psychoactive substance that promotes release of serotonin, (nor)epinephrine, and dopamine by reversing membrane-bound transporter proteins and inhibiting reuptake in the mesolimbocortical circuitry (Feduccia and Duvauchelle, 2008; Nash and Brodkin, 1991) and by stimulating neurohormonal signaling of oxytocin, cortisol, prolactin, and vasopressin (de la Torre et al., 2000; Dumont et al., 2009; Emanuele et al., 2006; Nash Jr et al., 1988). The dynamic interaction of these neurotransmitters and hormones give rise to an array of subjective effects that reportedly enhance aspects of therapy, such as increasing introspection and maintaining the therapeutic alliance (Mithoefer, 2013). MDMA-assisted psychotherapy is effective in reducing PTSD symptoms after only 2–3 administrations of MDMA in conjunction with several nondrug therapy sessions (Mithoefer et al., 2011; Oehen et al., 2013), with long-lasting PTSD remission (Mithoefer et al.,

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Table 1
MDMA enhances molecules involved in memory, learning, and fear extinction.

MDMA-mediated molecules	Memory, learning, and fear extinction mechanisms	References
Serotonin	• Induce affective states to alter fear memories with safety information • Increases DA release • Increases oxytocin release • Modulates MDMA-enhanced fear expression	(Hogberg et al., 2011; Koch and Galloway, 1997; Thompson et al., 2007)
Dopamine	• Increases attention • Induces prediction error • Destabilization of memory traces • Positive behavioral reinforcement	(Asan, 1997; Esber et al., 2012; Merlo et al., 2015; Schultz et al., 1997)
(Nor)epinephrine	• Increases emotional arousal • Enhances learning and memory • Enhances extinction learning • Modulator of cortisol effects	(Berlau and McGaugh, 2006; Liang et al., 1986; McGaugh, 2000; Mueller et al., 2008; Roozendaal and McGaugh, 1996; Roozendaal et al., 2006a; Roozendaal et al., 2006b)
Acetylcholine	• Promotes synaptic plasticity • Increases glutamate release (nAChR)	(Acquas et al., 2001; Fisher and Dani, 2000; Garcia-Rates et al., 2010; Gray et al., 1996; Nair and Gudelsky, 2006; Radcliffe and Dani, 1998)
Glutamate	• Promotes synaptic plasticity	(Abad et al., 2014)
BDNF	• Enhances learning and memory • Modulates synaptic plasticity	(Abad et al., 2014; Bramham and Messaoudi, 2005; Edut et al., 2014; Edut et al., 2011; Young et al., 2015)
Oxytocin	• Mediates socially reinforced learning • Suppresses amygdala activity	(Eckstein et al., 2015; Ferrier et al., 1980; Guastella et al., 2008; Heinrichs et al., 2004; Hurlemann et al., 2010; Rimmele et al., 2009; Savaskan et al., 2008)
Cortisol	• Increases emotional arousal • Modulates learning and memory	(de Quervain et al., 2011; Hamacher-Dang et al., 2013; Izquierdo et al., 2006; Meir Drexler and Wolf, 2017; Soravia et al., 2006)

2013). Six Phase 2 studies (n = 103) showed promising safety and efficacy outcomes, with 52.7% of participants in active dose (MDMA 75–125 mg) group not meeting PTSD criteria on CAPS-4 at the primary endpoint compared to 22.6% in the control group (MDMA 0–40 mg; Feduccia et al., 2018). After comparing results to the two approved PTSD medications, paroxetine and sertraline, U.S. FDA designated MDMA-assisted psychotherapy as a Breakthrough Therapy and approved large-scale Phase 3 trials set to start in the spring of 2018.

The therapeutic methods used in these Phase 2 trials were adapted from research with psychedelics before these drugs were placed on the Schedule 1 drug list, and described in 'A Manual for MDMA-assisted Psychotherapy in the Treatment of PTSD' (Mithoefer, 2017). The first MDMA session is proceed by three preparatory 90-min nondrug sessions to establish rapport and a trusting therapeutic relationship between the participant and therapists. During 8-hour MDMA-assisted sessions at monthly intervals, the approach is largely non-directive with a male/female co-therapist team creating a setting of safety and support. The participant alternates periods of internal reflection while wearing eyeshades and listening to music with periods of talking with the therapists about thoughts, emotions and memories that arise. Therapists give support and encouragement for participants to reflect on and discuss whatever is unfolding, including traumatic memories as well as other psychologically relevant material, and will offer redirection as a choice if the participant appears unable to move forward in the process. This approach is based on observations that the pharmacological effects of MDMA in this setting facilitate a variety of therapeutic experiences. These typically include reprocessing of traumatic memories with clearer recall and increased equanimity without emotional numbing or dissociation. Study participants with PTSD also often have valuable insights about other aspects of their lives, and these insights appear to play a role in their overall recovery from PTSD. The manualized therapy allows flexibility for the elements of other psychotherapies that frequently arise spontaneously rather than at the direction of the therapists. These include imaginal exposure, cognitive restructuring, psychodynamic insights, increased somatic awareness, as well as elements of other modalities, such as Internal Family Systems therapy, Hakomi, and mindfulness practices. After each MDMA session, participants have three 90-min integrative sessions, one the morning after MDMA and two during the month following, to further process and integrate the experiences catalyzed by MDMA.

Long-term durability of PTSD symptom reduction has been reported on average of 3.5 years after termination from an MDMA-assisted psychotherapy trial (Mithoefer et al., 2013), indicative of enduring outcomes after treatment with MDMA has ended. Based on clinical observations and qualitative review of video recorded sessions, it appears the therapeutic mechanisms are complex and may vary from individual to individual. Several theoretical explanations have been posed to explain the treatment effects. This review attempts to expand the understanding of the mechanism of action of MDMA to treat PTSD, taking into account memory reconsolidation theory, fear extinction models, and the known pharmacology of MDMA. Ongoing research in both nonclinical and clinical protocols aimed at characterizing the physiological and psychological mechanisms responsible for the large effects may lead to investigations of MDMA in conjunction with other therapeutic modalities as well as optimizing outcomes with current approaches.

2. Memory reconsolidation and fear extinction

Clinical observations and subjective reports of the prosocial effects of MDMA strongly suggest that the enhanced therapeutic relationship during MDMA-assisted psychotherapy is an important mediator for positive outcomes; however, because MDMA potentiates the release of monoamines, and psychotherapy relies on processing of traumatic memories, it is possible that MDMA could also reduce PTSD symptoms through altered memory reconsolidation or facilitated fear extinction learning and retention (Table 1). Based on the activated neural substrates and by definition, memory reconsolidation and fear extinction are two distinct processes (Monfils et al., 2009) and MDMA-assisted psychotherapy may theoretically target both processes. The term, memory reconsolidation, describes a type of neuroplasticity that involves the process of an established memory being reactivated, destabilized, and then modified or updated with additional information. When a memory is recalled, for a limited period of time, it may enter a labile state that can be modified and reconsolidated through a protein synthesis dependent-process. A prediction error or mismatch of the memory trace to present moment happenings may be a particularly strong signal to induce a malleable state of the engram (Nader et al., 2000; Sevenster et al., 2013). Hypothetically, when trauma memories are retrieved while under the influence of MDMA during therapy, a strong prediction error is generated by the unique internal state of MDMA-stimulated elevation of neurochemicals/hormones and the supportive therapeutic setting. This mismatch of experience, i.e. recall of memory with strong fear/anxiety vs. recall with additional emotions

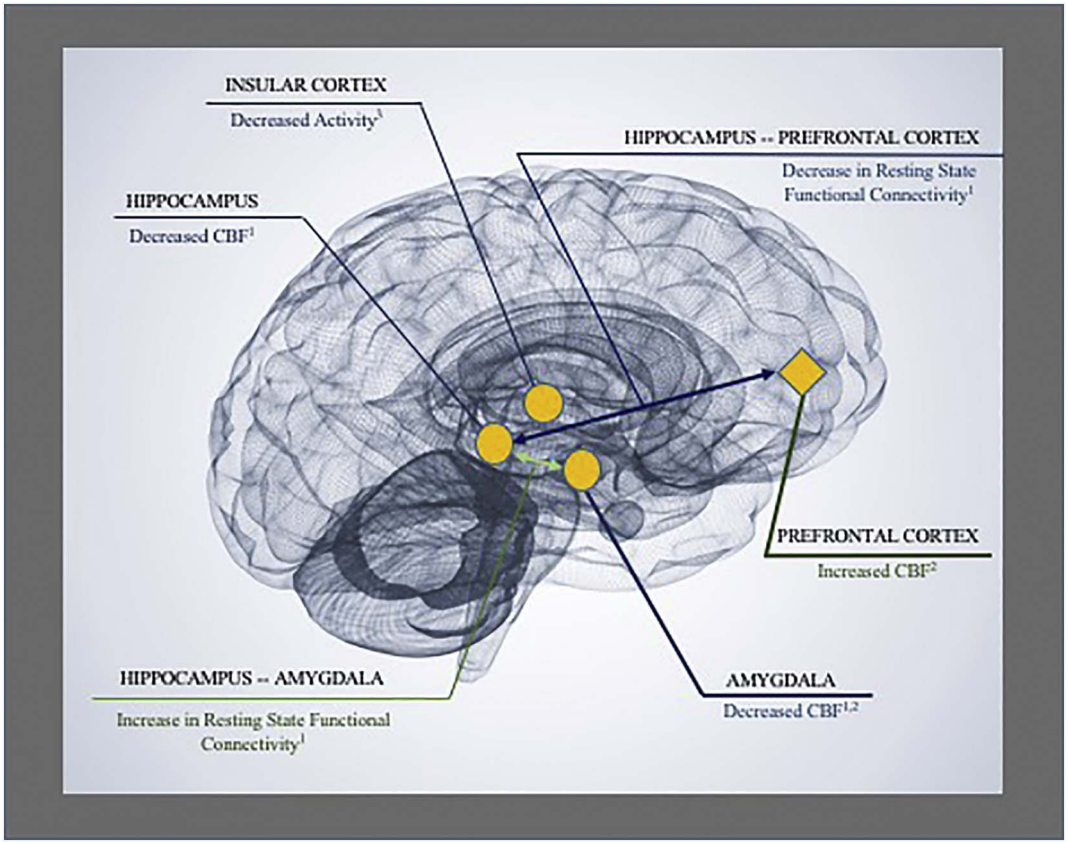

Fig. 1. MDMA modulates brain regions involved in Learning, Memory, Emotion, and Attention. In neuroimaging studies of healthy individuals, MDMA reduced cerebral blood flow (CBF) to amygdala (Carhart-Harris et al., 2015)[1] (Gamma et al., 2000)[2] and hippocampus (Carhart-Harris et al., 2015)[1]; decreased resting state connectivity between the medial prefrontal cortex (mPFC) and hippocampus (Carhart-Harris et al., 2015)[1]; decreased activity in the insular cortex (Walpola et al., 2017)[3;] and increased CBF in the ventromedial prefrontal cortex (Gamma et al., 2000)[2].

such as love or empathy, would allow for an update of information through molecular mechanisms. MDMA increases release of dopamine (DA) in the striatum and midbrain DA positively correlates with prediction error (Schultz et al., 1997); hence, MDMA-stimulated DA efflux may amplify and drive a prediction error related to the traumatic memory. Furthermore, DA signaling via VTA projections to the amygdala is specifically associated with destabilization of a memory (Asan, 1997; Esber et al., 2012; Merlo et al., 2015), but is not involved in modification or restabilization of the trace (Reichelt et al., 2013). Once a memory becomes destabilized and labile during a therapy session, MDMA may influence activity in neurocircuitry necessary for learning and memory. Through enhanced serotonin release, MDMA can induce positive affective states and prosocial effects (Liechti and Vollenweider, 2001) that signal a safe and supportive setting. Prior reconsolidation research during affective psychotherapy suggests feelings of safety is necessary for traumatic memories to be amended with less fear (Hogberg et al., 2011). In healthy individuals (Fig. 1), MDMA increased the resting state functional connectivity between the hippocampus and amygdala (Carhart-Harris et al., 2015), limbic regions responsible for emotional memory processing and previously shown to have decreased coupling in patients with PTSD (Sripada et al., 2012). The enhanced cross talk between these two regions could be the neural correlate for the reorganization of emotional information contained within memories of the trauma; however, imaging studies of MDMA in a PTSD population have yet to be published and are needed to determine if the same response is observed during recall of traumatic memories. Presumably, the memory trace is updated with new information based on the present perspective of the individual to diminish negative salience that triggers symptoms of PTSD during normal daily life. Participant subjective reports support this idea of a reconstruction of the trauma memory from a juxtaposition of the past memory with a modifiable trace during the MDMA therapy session. For example, a participant from a MAPS-sponsored MDMA-assisted psychotherapy clinical trial described this by saying,

> "One thing the MDMA facilitates is thinking about traumatic experiences in a neutral, safe manner. I could objectively think about them and talk about them. Then, it seems those memories are put back in their place in the brain in a different configuration — a configuration that does not cause as many problems, such as bad dreams, intrusive thoughts all the time or having horrible insomnia. This has continued to this day, a year and a half after the last MDMA session."
>
> Huston, 2015.

Studies in healthy individuals have demonstrated that MDMA mediates emotional memory processing. MDMA reduced left amygdala response to angry facial expressions (Bedi et al., 2009) and caused unpleasant memories to be rated as less negative, visualized as less activation of the left anterior temporal lobe and greater activation of the superior frontal gyrus/dorsal medial prefrontal cortex (Carhart-Harris et al., 2014). Administration of MDMA (1 mg/kg) during the encoding or retrieval phase of a memory task did not impact overall memory accuracy. However, during encoding MDMA attenuated recollection of positive or negative details, but not neutral stimuli, indicative of alterations in emotional memory representations (Doss et al., 2018). In context of PTSD treatment, the authors posit that reducing details of emotional events may be advantageous to re-encode trauma memories with novel emotional associations. Diminishing positive details appears counterproductive, but in people with PTSD recall of trauma-related events is generally always associated with negative

valence. The following quote from a participant with PTSD in a MDMA trial illustrates that aversive memories are recalled with prominent negative details but while on MDMA a positive emotion to be felt in the present allowing for a novel perspective to emerge.

> "The first place I saw was this maze. I went in. There was so much trauma. I had never remembered these terrible, terrible things. And before MDMA, I really did think it was my fault. I felt it in my bones that something was so wrong with me, that I deserved those things. Being on MDMA was the first time I ever felt compassion for myself. I realized that I was a child when it happened. I had no choice."
>
> Brenda, 2015.

In addition to modifying the encoding of emotional memory or blocking reconsolidation fear stimuli associated with trauma memories, during therapy MDMA may be acting through another mechanism to extinguish fear associated with memories. Classical conditioning models describe that an unconditioned stimulus, e.g. a traumatic event with associated fear response, may develop into expression of fear to cues (conditioned stimuli) associated with the traumatic event, resulting in fear reactions (conditioned responses). The process of learning through repeated exposure to the conditioned stimuli without encountering the unconditioned stimuli is known as extinction and leads to reduction in the fear response while leaving the original fear memory intact (Ponnusamy et al., 2016). PTSD occurs in some individuals after one or repeated experiences that are frightening or extremely aversive, resulting in the development of physiological conditioned fear responses that can induce stress and avoidance of cues related to the traumatic event and exaggerated startle, that continue after the immediate threat is no longer present and often progressively worsen over time. Exposure therapies used to treat PTSD aim to extinguish fear by presenting fear-triggering cues in imaginal narratives and reality-based situations while the person is in a safe setting.

Rodent fear extinction paradigms are a translational model for exposure-based approaches used in humans. Two recent fear extinction studies in mice have tested MDMA to understand if the drug affects extinction learning. MDMA (7.8 mg/kg, i.p.) administered to fear conditioned mice 30 min before extinction training enhanced long-lasting extinction of conditioned freezing and reduced the fear response when subsequently re-exposed to conditioned stimuli (Young et al., 2015). A follow-up study by the same group showed that MDMA (7.8 mg/kg, i.p.) administered to mice reduced fear-potentiated startle during the extinction test (Young et al., 2017). A MAPS-sponsored study in healthy humans is currently underway to assess whether administration of MDMA prior to extinction of conditioned fear will reduce startle responses during extinction recall (NCT03181763), as suggested by the rodent experiments. If MDMA proves to facilitate extinction, future Phase 2 clinical trials will investigate whether MDMA adjunctive to exposure-therapies, such as prolonged exposure, could improve outcomes for treating PTSD.

While the manualized therapeutic approach currently employed in Phase 2/3 trials doesn't follow traditional exposure therapy methods, clinical observations and participant reports show that MDMA allows for vivid recall and a self-directed re-exposure to events. During MDMA sessions, some participants verbally describe past experiences, often incorporating metaphors and imaginal imagery, while others will later report to therapists that they returned to the place and time of traumatic events while listening to music with eye shades on. A veteran undergoing MDMA-assisted psychotherapy told therapists,

> "The medicine just brought me a folder. I'm sitting at this big desk in a comfortable chair and the medicine goes and then rematerializes in physical form bringing me the next thing - this is a folder with my service record. It says I need to review it and talk to you about it from the beginning so it can be properly filed."
>
> Mithoefer, 2013.

Encountering the past while on MDMA in a safe and supportive setting may extinguish the fear associated with traumatic events through the same processes of exposure-based therapies, but in a more rapid and effective way due to the physiological effects of MDMA.

To date, no studies have administered MDMA to people with PTSD while undergoing brain imaging; however, neuroimaging findings of MDMA in healthy subjects have demonstrated that MDMA acts in key neural pathways for memory and emotional processing. MDMA administration to healthy volunteers reduced cerebral blood flow to amygdala, the core node driving fear, and simultaneously decreased coupling between the medial prefrontal cortex (mPFC) and hippocampus (Carhart-Harris et al., 2015). Anxiety modulated by the 5-HT1A receptor is associated with increased connectivity between mPFC and hippocampus (Adhikari et al., 2010); therefore, MDMA is likely reducing fear in people with PTSD to allow for expanded access to and reprocessing of traumatic memories by reducing hyperactivity of the amygdala and inhibiting top-down overmodulation of the mPFC on emotional processing of limbic regions (Sierra and Berrios, 1998). In support of this hypothesis, diminished PFC inputs to amygdala in humans was shown to be important when extinction of a conditioned stimuli temporally coincided with threat memory reconsolidation (Schiller et al., 2013). In contrast, optogenetic activation of the infralimbic (IL) subregion of the mPFC during extinction training reduced fear expression in rats and increased extinction of auditory fear memory the next day (Do-Monte et al., 2015). The analogous region of IL in humans, the ventromedial prefrontal cortex (vmPFC), was activated during the retention phase of extinction learning, suggesting that subregions of the PFC may be differentially activated during extinction training and retention/recall of extinction (Milad et al., 2007; Phelps et al., 2004). Functional magnetic resonance imaging (fMRI) of healthy individuals during recall of negative memories after MDMA (100 mg) ingestion found reduced activation in the left anterior temporal cortex or temporal pole, suggestive of attenuation of negative emotional impact of painful memories (Carhart-Harris et al., 2014). Furthermore, attenuation of insular cortex activity during MDMA (100 mg) administration (Walpola et al., 2017) possibly counters heightened activation of this region observed in anxiety disorders (Etkin and Wager, 2007). Participants with PTSD in MDMA therapy trials have noted that MDMA reduces fear to allow for the therapeutic process to unfold, which was captured in these veterans' quotes,

> "It gives you euphoria and love. You can go into the darkness and not be afraid," he said, "referring to addressing the trauma of war."
>
> James, 2016.

> "It allowed me to see my trauma without fear or hesitation and finally process things and move forwar."
>
> Hardin, 2016.

A PET imaging study in healthy volunteers administered MDMA (1.7 mg/kg) also observed a decrease in left amygdalar cerebral blood flow (CBF), but contrary to the fMRI study, described increased CBF in the ventromedial prefrontal cortex (Gamma et al., 2000). The discrepancy in findings may be due to the different imaging techniques and tasks employed during each of the respective studies, but it does raise the question of whether MDMA differentially effects neural activity in dissociative subtypes of PTSD. A dissociative subtype of PTSD is characterized by detachment and emotional numbing and is visualized in the brain as hyperactivity of the corticolimbic activity, while the other more common non-dissociative subtype presents symptoms of hyperarousal and re-experiencing, an emotional dysregulation theoretically mediated by hypoactivity of the prefrontal cortex on limbic regions (Lanius et al., 2010). The therapeutic techniques used during MDMA-assisted psychotherapy, analogous to tasks in imaging studies, could drive brain activation in different regions. Clearly more research is needed to understand the effects of MDMA on brain circuitry in both subtypes of PTSD and during various elements of psychotherapy, such as revisiting of traumatic memories with emotional engagement

(imaginal exposure), arriving at new insights and points of view (cognitive restructuring), or feeling understood and connected to others (secure attachment).

2.1. Synaptic plasticity – BDNF and excitatory neurotransmitters (acetylcholine and glutamate)

Synaptic plasticity is the underlying molecular basis of learning and memory, which occurs by strengthening or weakening of synaptic connections mediated by functional alterations of membrane-bound receptors and through intracellular second messengers. Brain-derived neurotropic factor (BDNF) is the most abundant neurotrophin in the brain, implicated through actions of TrkB receptor intracellular signaling cascades as a modulator in a vast myriad of functions, notably synaptic plasticity and memory processes (Bramham and Messaoudi, 2005). BDNF signaling dysregulation is associated with mood disorders and cognitive impairment (Karege et al., 2005; Licinio and Wong, 2002; Shimizu et al., 2003), with lower levels of BDNF occurring after acute and chronic stress and prominently reduced in postmortem brains of depressed patients (Chen et al., 2001; Dwivedi et al., 2003). Antidepressant treatment increases BDNF through a serotonergic and/or noradrenergic mechanism (Ivy et al., 2003; Martinowich and Lu, 2008; Vaidya et al., 1997). Given MDMA's strong propensity to release 5-HT and NE, BDNF involvement in MDMA-driven memory reconsolidation and fear extinction is plausible and has been demonstrated in rodents. After extinction training with MDMA, expression of the early-response gene Fos and Bdnf in the amygdala of mice was increased; however, MDMA without training failed to show these effects. Direct infusion of MDMA (1 μg) into the basolateral amygdala (BLA) also enhanced extinction training which was blocked by disrupting of BDNF signaling in this region, suggesting that MDMA augments fear extinction learning in the amygdala through a BDNF-dependent mechanism (Young et al., 2015). Blocking the 5-HT transporter (5-HTT) with citalopram reduced MDMA enhancement of fear extinction which the authors note may be due to indirect inhibitory effects on 5-HT_{2A} (Young et al., 2017). If MDMA does in fact boost BDNF during psychotherapy, as suggested by the rodent studies, then fear extinction learning and new perspectives gained around traumatic memories may be acquired more readily by MDMA activation of BDNF signaling cascades that induce long-term potentiation and retention into long-term memory stores. Interestingly, a mouse model of minimal traumatic brain injury found that pretreatment of MDMA (10 mg/kg) increased BDNF levels in the striatum and cortex and protected against injury-induced cognitive deficits through a dopamine-dependent mechanism (Edut et al., 2014; Edut et al., 2011). Future nonclinical research should further elucidate the role of MDMA-stimulated elevation of BDNF in various paradigms with doses corresponding to those used in human Phase 2 clinical trials (approximately 1–3 mg/kg), and should attempt to replicate the findings in rat models since known differences exists in MDMA's effects between mice and rats. Many published reports of nonclinical data are limited in translation to MDMA-assisted psychotherapy because of binge administration paradigms and extremely large doses given to rodents inaccurately derived from interspecies scaling (Baumann et al., 2009; Green et al., 2009; Green et al., 2012).

In rats, high doses of MDMA (20 mg/kg, s.c. repeated for 4 days), although not in range with human therapeutic doses (approximately 1–3 mg/kg), improved spatial learning and reference memory processes in the Morris water maze compared to saline treated animals. An increase in glutamate and BDNF expression accompanied by an enhancement of spine densities in the CA1 region of the hippocampus was reported for the MDMA trained group. In behavioral tests, the MDMA exposed rats exhibited more rapid adaptability to a novel environment and reduced anxiety-like behavior by exploring the central area more frequently than controls. This could partially explain the potentiated learning effects (Abad et al., 2014). In humans with PTSD, avoidance of situations or memories that trigger fear, often including new places and encountering unknown persons, is a common coping strategy that becomes maladaptive for treatments that require exposure for recovery. MDMA-assisted psychotherapy has been shown to produce persisting personality change in the traits openness and neuroticism, increased openness, but not reduced neuroticism, mediated the relationship between PTSD symptom reduction and MDMA (Wagner et al., 2017). The authors speculate that the epigenetic modifications may be responsible for the personality shifts after profound experiences during MDMA sessions since DNA methylation of the BDNF promoter region is associated with risk for psychopathology. An alternative hypothesis is a modification of synaptic transmission, through learning-related changes, that preferentially permits neural patterns that favor ways of thinking and patterns of being congruent with traits of openness. LSD has also been shown to increase the trait openness two weeks following administration, which correlated with brain entropy measured during the acute exposure, providing evidence that alterations of brain dynamics may underlie lasting personality changes (Lebedev et al., 2016).

MDMA may play a role in facilitating synaptic plasticity in the hippocampus and amygdala through cholinergic signaling. Nicotinic receptor (nAChRs) agonists enhance learning and memory by increasing intracellular Ca^{2+} concentrations through voltage-dependent calcium channels thereby regulating neuronal excitability and neurotransmission essential for long-term potentiation (Albuquerque et al., 1995). Synaptic transmission in these regions is modulated by nAChRs localized on pyramidal cells (somatodendritic α7), GABAergic interneurons (α7, α4β2*, and α3β4, *denotes possible other subunits), and glutamatergic neurons (α7). MDMA has affinity for α7 and α4β nicotinic receptors at low micromolar concentrations and also directly stimulates release of ACh in the hippocampus and PFC (Acquas et al., 2001; Fisher and Dani, 2000; Garcia-Rates et al., 2010; Nair and Gudelsky, 2006). Activation of presynaptic α7 receptors can enhance release of glutamate release onto pyramidal neurons (Gray et al., 1996; Radcliffe and Dani, 1998) and reduce inhibition of GABAergic interneurons to disinhibit pyramidal neurons, both ultimately facilitating long-term potentiation in the amygdala and hippocampus (Feduccia et al., 2012).

Taken together, evidence from rodent studies demonstrates that MDMA modulates BDNF activity and excitatory neurotransmission in brain regions important for learning and memory processes. More research is needed to understand if these signaling pathways are targeted in humans in a similar manner during MDMA-assisted psychotherapy. Given the high response rate, long-lasting remission of PTSD, and persistent changes in personality, it seems plausible that mechanisms of learning, to some extent, underlie the treatment effects.

2.2. Modulators of memory reconsolidation and fear extinction: cortisol, (nor)epinephrine, glucocorticoids (GCs)

Emotional arousal is deemed important to the success of various psychotherapeutic approaches (Lane et al., 2015), that is, overcoming avoidance behavior of fear-inducing memories is beneficial for engaging in emotional processing that promotes positive outcomes for PTSD treatment. Glucocorticoid receptors are densely localized in the hippocampus and amygdala (Jafari et al., 2012; Johnson et al., 2005), and glucocorticoid hormones (cortisol in humans, corticosterone in rodents) are potent modulators of memory, especially those encoding fear (Meir Drexler and Wolf, 2017). Cortisol and stress can enhance exposure-based therapies (de Quervain et al., 2011; Soravia et al., 2006) and extinction training (Hamacher-Dang et al., 2013), possibly through a mechanism that disrupts retrieval and salience of the trauma memory (de Quervain and Margraf, 2008). MDMA increases release of cortisol (peak difference in plasma cortisol concentrations for placebo vs. 125 mg MDMA was 23 μg/dl) (Mas et al., 1999) and acts as a sympathomimetic, increasing blood pressure and heart rate in a dose-dependent manner (Lester et al., 2000). During psychotherapy, MDMA-stimulated enhancement of cortisol may increase extinction learning by

allowing for emotional engagement without interference of avoidance mechanisms commonly applied by individuals with PTSD undergoing exposure therapy (Jaycox et al., 1998).

On the other hand, high levels of stress prior to training can impair extinction in rodents (Izquierdo et al., 2006) and chronic stress through activation of the sympathetic nervous system intrinsic of PTSD is thought to be one reason why fear around a traumatic event is not extinguished (Milad et al., 2008). A common reaction to MDMA is transient increases in anxiety and stress (Mithoefer et al., 2011), especially when confronting emotionally difficult material or when the initial drug effects are being experienced. During non-drug preparatory sessions, the co-therapy team teach participants stress inoculation and anxiety management techniques, such as diaphragmatic breathing, that are later drawn upon if anxiety escalates during MDMA sessions. With support of two therapists and other pharmacological effects of MDMA (serotonin and oxytocin), participants are able are to continue the therapeutic process in these aroused states without either being overwhelmed by or avoiding emotions arising from revisiting traumatic memories.

> "Under the influence of MDMA, I was able to talk about and work through these things without having that physiological reaction," he said. "It kind of rewires the brain back to baseline before the PTSD."
>
> Tatera, 2016.

In addition to cortisol effects, noradrenergic signaling can enhance fear extinction learning (Berlau and McGaugh, 2006; Mueller et al., 2008). Findings are mixed for the direction of effects (enhancement or inhibition) of GCs on memory reconsolidation, suggesting other factors are at play – for example, degree of cortisol elevations, emotional arousal, and phase of memory being studied. Norepinephrine is a known modulator of GCs in the amygdala. Rodent studies showed activation of noradrenergic signaling in the amygdala by arousal is crucial for corticosteroid facilitation of memory formation (Roozendaal et al., 2006a; Roozendaal et al., 2006b). MDMA increases release of epinephrine and cortisol, as can traumatic memory reactivation, which could boost acquisition of new memories or facilitate memory reconsolidation through synergistic stimulatory effects on the amygdala during MDMA-assisted psychotherapy. The significance of the experience would be encoded with greater strength as seen with activation of these systems through stress or exogenous agonists to adrenergic and glucocorticoid receptors (Gold and Van Buskirk, 1975; Lupien and McEwen, 1997; Sandi and Rose, 1994).

After MDMA therapy, a participant with PTSD stated,

> "I felt as if I was literally reprogramming my brain and confronting all of the fixed thought patterns and belief structures that were keeping the PTSD in place, that were making me relive the past over and over again. I was able to file those memories in the past."
>
> Hope, 2015.

The basal lateral amygdala (BLA) is important for modulating memory processes of the hippocampus (McGaugh, 2004). Disruption of BLA signaling through B-adrenergic receptor antagonists or lesion blocks the memory enhancing effects of GCs administered directly into the hippocampus or systemically (Liang et al., 1986; McGaugh, 2000; Roozendaal and McGaugh, 1996). Propranolol, a B-adrenergic receptor antagonist, and mifepristone, glucocorticoid antagonist, have been investigated as pharmacological adjuncts to therapy for PTSD treatment because administration to rodents modulates fear extinction (Fitzgerald et al., 2014; Pitman et al., 2011), presumably by blocking the memory enhancing effects of GC and B-adrenergic stimulation that could make fear memories resistant to extinction. However, clinical trials have not been able to show consistent effects in humans for PTSD symptom reduction (Wood et al., 2015).

2.3. Oxytocin

The neuropeptide oxytocin modulates key neural substrates, namely the amygdala and PFC, implicated in PTSD, learning and memory, and fear extinction. MDMA-stimulated 5-HT efflux or direct affinity to 5-HT receptors enhances oxytocin release, which contributes to the prosocial effects of MDMA (Thompson et al., 2007). Oxytocin decreases amygdala activity (Eckstein et al., 2015), a possible mechanism for attenuated amygdala activation after MDMA (Carhart-Harris et al., 2015; Gamma et al., 2000), and reduces anxiety and neural threat processing (Kirsch et al., 2005). Depending on whether or not learning is accompanied with social reinforcement (Hurlemann et al., 2010), oxytocin can potentiate (Guastella et al., 2008; Rimmele et al., 2009; Savaskan et al., 2008) or decrease (Ferrier et al., 1980; Heinrichs et al., 2004) memory and learning in humans. In the context of psychotherapy, MDMA is delivered with support from a co-therapy team which may permit oxytocin signaling to preferentially enhance memory reconsolidation during recall of traumatic memories. During an MDMA session, a participant with PTSD described,

> "You are sitting on a couch, and there are two people in the room with you. They are the two people you have been meeting with, and that you fully trust to guide you along on this journey of self-discovery."
>
> Withem, 2016.

3. Conclusion

In summary, this review has provided evidence that the beneficial synergistic effects of MDMA with psychotherapy are attributed, at least in part, to the complex neuropharmacological profile of this entactogen creating a neural setting primed to facilitate new learning and extinguish fear related to traumatic memories. With actions on numerous neurotransmitter and neural pathways, MDMA can theoretically manipulate modulators of emotional learning and memory during psychotherapy in key brain regions, including the amygdala, hippocampus, and prefrontal cortex. Activation of mesocorticolimbic dopaminergic and noradrenergic systems by MDMA can significantly contribute to processes of attention and memory. Future studies using clinically relevant doses can further elucidate the role of MDMA in emotional memory processing, and delineate specific mechanisms of MDMA-assisted psychotherapy for reducing symptoms of PTSD.

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