Psychedelic-Assisted Therapy for Substance Use Disorders and Potential Mechanisms of Action

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Contents

Abstract Substance use disorders (SUD) represent a significant public health issue with a high need for novel and efficacious treatment options. In light of this high unmet need, recent results reporting beneficial outcomes of psychedelic-assisted therapy in SUD are particularly relevant. However, several questions remain with

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regard to this treatment approach. The clinical mechanisms of action of psychedelic substances in the treatment of SUD are not well understood. Closing this knowledge gap is critical to inform and optimize the psychotherapeutic embedding of the acute substance administration. In this chapter, we discuss potential mechanisms that have implications on psychotherapeutic approaches including induced neuroplasticity, alterations in brain network connectivity, reward and emotion processing, social connectedness, insight, and mystical experiences. Furthermore, we outline considerations and approaches that leverage these mechanisms in order to optimize the therapeutic embedding by maximizing synergy between substance effects and psychotherapy. Understanding the mechanisms of action, developing psychotherapeutic approaches accordingly, and evaluating their synergistic efficacy in scientific studies will be critical to advance the framework of psychedelic-assisted therapy for addiction, create evidence-based approaches, and achieve the best treatment outcome for patients with SUD.

Keywords Addiction · Hallucinogen · LSD · Mechanism of action · Psilocybin · Psychedelic · Psychedelic-assisted therapy · Substance use disorder · SUD

1 Introduction

Serotonergic psychedelic substances, also called hallucinogens, have been studied extensively in the 1950s and 1960s for the treatment of various psychiatric disorders (Vollenweider and Preller 2020). One major area of interest was the use of LSD in the treatment of substance use disorders (SUD) (Dyck 2006). While most of these early clinical studies do not comply with current scientific standards, a meta-analysis of six randomized trials testing LSD for alcohol dependence showed consistent treatment effects on drinking outcomes (Krebs and Johansen 2012). These early results remain of great interest given that alcohol addiction still accounts for a substantial proportion of global health burden and alcohol addicted patients lose more than 20 years in average life expectancy compared to the normal population (GBD 2018). Pharmacological treatment approaches for alcohol use disorder (AUD) have limited effectiveness with up to 50% relapse rates (Moos and Moos 2006). Currently, research on the therapeutic effects of psychedelics is gaining momentum again and various studies investigating the efficacy of psychedelics in the treatment of alcohol (NCT04620759, NCT04410913, NCT04141501), nicotine (NCT01943994), and cocaine addiction (NCT02037126) are ongoing. At this time, two modern clinical trials have been published, reporting beneficial long-term effects of psilocybin for nicotine and alcohol use disorder for up to 6 months (Bogenschutz et al. 2015; Johnson et al. 2017). Although these studies are small and lack appropriate control conditions, the results are promising. However, potential mechanisms of actions of psilocybin in patients with SUD have not been investigated.

Importantly, psychedelics are usually not administered without psychotherapeutic embedding. In the two published studies testing the effects of psychedelics in the treatment of SUD, one or two administrations of psilocybin were combined with various preparation and integration sessions based on cognitive-behavioral or motivational enhancement therapeutic approaches (Bogenschutz et al. 2015; Johnson et al. 2017). The use of psychedelics for treating psychiatric illnesses is therefore considered to be best described as pharmacologically-assisted psychotherapy (PAT) that leverages psychedelic-induced neurobiological and psychological effects (Vollenweider and Preller 2020). However, two major questions remain regarding this approach:

1. What is the clinically relevant mechanism of action of psychedelics in SUD? In other words, what are the psychedelic-induced neurobiological and psychological effects that can be leveraged in psychotherapy?
2. What is the best way to conduct psychedelic-assisted psychotherapy in SUD?

These two questions are not unrelated. As discussed in detail below, understanding the clinical mechanisms of action will help to inform, optimize, and advance currently implemented psychotherapeutic approaches in the context of psychedelic-assisted therapy. Testing these approaches empirically is essential to be able to provide evidence-based psychedelic-assisted therapy and maximize the clinical potential of psychedelic substances in the treatment of SUD.

In this chapter, we discuss potential clinically relevant mechanisms of action of psychedelics and highlight current knowledge gaps. We use the term "psychedelics" to refer to 5-HT_{2A} receptor agonists, i.e., "classic psychedelics" such as psilocybin, LSD, ayahuasca/DMT, and mescaline. If other substances are discussed, this is noted in the text. Please note that the effects discussed here do not represent an exhaustive list of potential mechanisms of action, but rather focus on insights derived from studies with psychedelics that may be relevant for the treatment of SUD. Furthermore, we discuss the implications these mechanistic hypotheses have for the content and conduction of accompanying psychotherapy. While some of these mechanisms and considerations may be applicable for the treatment of other disorders as well, this chapter focuses specifically on SUD.

2 Potential Mechanisms of Action of Psychedelic Substances in the Treatment of Substance Use Disorders

2.1 Induced Neuroplasticity

Maladaptive learning and memory processes are major characteristics of SUD (Hyman 2005). Alcohol and other drugs of abuse have been suggested to hijack synaptic plasticity systems and create persistent links between reinforcing aspects of the drug-induced experience and associated stimuli (Kauer and Malenka 2007).

These associations between cues and drug experiences can contribute to relapse even after prolonged periods of abstinence (Lüscher 2016). Furthermore, chronic exposure to alcohol has been shown to reduce neuroplasticity as evidenced by dysregulations in long-term potentiation/long-term depression and Brain-derived neurotrophic factor (BDNF) signaling (Lovinger and Abrahao 2018). These long-term plasticity impairments may underlie learning deficits and reductions in cognitive flexibility observed in alcohol addicted patients (Beylergil et al. 2017). These neuroadaptations pose a major challenge for psychotherapeutic treatments in AUD. Treatment success may be severely limited by reductions in neuroplasticity as these treatment approaches require the patient to learn new strategies and skills that help them to abstain from drinking alcohol.

Classical psychedelics may open a window of opportunity for "therapeutic learning" by inducing neuroplasticity that potentially underlies the long-lasting effects of a single administration and could potentially be leveraged in the therapeutic process. In vivo and in vitro studies in rodents revealed that psychedelics increase neuritogenesis, spinogenesis, and synaptogenesis as well as gene expression of BDNF and Immediate Early Genes associated with plasticity (Catlow et al. 2013; Ly et al. 2018; Nichols 2016; Shao et al. 2021; Zhang et al. 2013). These neuroplastic changes appear to be mediated through activation of the 5-HT_{2A} receptor, tyrosine receptor kinase B (TrkB), and mammalian target of rapamycin (mTOR) signaling pathways (Ly et al. 2018). Another recent study in pigs reports significantly higher Synaptic vesicle glycoprotein 2A density – a marker of presynaptic density – in the hippocampus and the prefrontal cortex 7 days after a single dose of psilocybin (Raval et al. 2021). Importantly, animal studies also provide evidence for psychedelic-induced functional neuroplastic changes as low doses of psilocybin lead to significantly faster extinction learning in a cued fear conditioning paradigm than saline in mice (Catlow et al. 2013). In a recent study, psilocybin evoked dendritic spinal density, widths of spinal heads, and spine protrusion lengths in the medial prefrontal cortex in mice (Shao et al. 2021). Furthermore, half of the newly formed spines remained stable until day 7 (Shao et al. 2021).

It still needs to be investigated if these neuroplastic effects observed in animals translate to humans. So far, only indirect evidence has been presented such as increased levels of medial prefrontal cortical glutamate during the acute experience (Mason et al. 2020) and post-acute reductions of glutamate + glutamine in the posterior cingulate cortex (Sampedro et al. 2017). If future studies find evidence that psychedelics increase neuroplasticity and facilitate (extinction) learning, this may have important implications for the therapeutic embedding of a psychedelic experience and may open up various opportunities to beneficially leverage the synergy between drug-induced effects and psychotherapy.

2.2 Alterations in Brain Networks Connectivity

Previous studies report widespread changes in the functional architecture of the brain in patients suffering from SUD as measured with connectivity metrics during resting

state. Specifically, reductions in functional connectivity of the precuneus, postcentral gyrus, insula, and visual cortex were reported in AUD (Vergara et al. 2017). Changes within the dorsal anterior cingulate cortex-striatum circuit have repeatedly been reported in nicotine dependence (Scarlata et al. 2021). Salience and default mode network dysregulation has been shown to predict treatment outcome in chronic cocaine users (Geng et al. 2017). Additionally, converging evidence points to changes between and within cortical midline structures as a common mechanism underlying various SUD such as alcohol, nicotine, cannabis, and heroin addiction (Ersche et al. 2020; Zhang and Volkow 2019).

Acutely, psychedelics have been shown to alter thalamo-cortical connectivity patterns (Mueller et al. 2017; Preller et al. 2018). Specifically, increased functional connectivity between the thalamus and sensory brain areas and increased effective connectivity from the thalamus to the posterior cingulate cortex have been reported (Preller et al. 2018, 2019). These changes, together with results obtained with neurophysiological measurements such as prepulse inhibition (Quednow et al. 2012; Riba et al. 2002; Schmid et al. 2015; Vollenweider et al. 2007), point to changes in thalamic gating of internal and external sensory and cognitive information. Additionally, increased synchronization of sensory brain areas (including the visual cortex, postcentral gyrus, and precuneus) together with a de-synchronization of associative brain regions under the acute influence of LSD and psilocybin suggests a disruption of cortical information processing and changes in information integration in the psychedelic state (Barrett et al. 2020; Preller et al. 2018; Preller et al. 2020). In line with this, Mason et al. (2021) reported increased ratings of creativity after psilocybin administration, which were predicted by acutely decreased resting-state functional MRI connectivity of the default mode network. These changes in information integration could enable patients to escape rigid thinking patterns and potentially help develop novel insights into problems during the therapeutic work after a psychedelic dose.

Unfortunately, little is known yet about long-lasting effects of psychedelics on brain connectivity. Two studies report psilocybin-induced changes in resting-state functional connectivity measured 1 week and 1 month after administration (Barrett et al. 2020; McCulloch et al. 2021). Furthermore, post-acute changes in default mode network connectivity were detectable 1 day after ayahuasca administration (Pasquini et al. 2020; Sampedro et al. 2017). Although only investigated in healthy participants so far, this result could implicate lasting functional re-organization effects that may normalize pathological connectivity patterns specifically with regard to connectivity with and between cortical midline structures in clinical populations.

2.3 Alterations in Emotion Processing

Patients with SUD show difficulties in regulating negative emotions and believe it to be less socially acceptable to express negative feelings, compared to healthy controls (Dingle et al. 2018). Suppression or avoidance of negative emotions is amplifying

negative mood (Bastian et al. 2012) which may in turn increase maladaptive drinking pattern to reduce negative emotional states. Several key motivation factors for substance misuse, such as escape or avoidance of negative affect (Baker et al. 2004), chronic irritability, emotional pain, dysphoria, or alexithymia (Koob and Le Moal 2005), point to the inability to regulate negative emotions as an important mechanistic candidate in the pathogenesis of SUD. An additional maladaptive strategy to deal with negative emotions is the engagement in rumination, which is the repetitive focusing on one's emotion and its underlying cause (Aldao et al. 2010). Rumination has been positively associated with psychopathology in anxiety disorders, depression, eating disorders, and SUD (Aldao et al. 2010). Additionally, patients with AUD show difficulties in decoding other people's emotions (Le Berre 2019).

Recent studies report that psilocybin and LSD acutely attenuate the recognition of negative facial expressions in healthy participants (Bershad et al. 2019; Dolder et al. 2016; Kometer et al. 2012). Furthermore, psilocybin and LSD reduced the neural response to negative stimuli in the amygdala (Kraehenmann et al. 2015; Mueller et al. 2017), an effect that was sustained for 1 week after administration (Barrett et al. 2020). However, one study reported increased amygdala reactivity in depressed patients the morning after psilocybin administration, suggesting increased emotional responsiveness in this patient group before therapeutic integration work had started (Roseman et al. 2018). Additionally, psilocybin has been shown to enhance autobiographical memory recall, which was associated with subjective well-being in healthy participants (Carhart-Harris et al. 2012).

Together, these results suggest a modulatory effect of psychedelics on emotion processing, in particular the perception of negative stimuli. The clinical importance of these effects is supported by Watts et al. (2017) who report beneficial changes in emotion processing characterized by reduced avoidance and concurrently increased acceptance of emotions in depressed patients after psilocybin-supported treatment. Increased acceptance may also decrease ruminative thoughts, as patients accept the current mood state instead of repetitively thinking about its underlying causes and consequences. Given the deficits in regulating negative emotions reported in SUD patients, psychedelics could have a positive effect on the maladaptive processes by reducing negative affect, enhancing the ability to regulate negative affect, and strengthening adaptive problem solving, which may in turn decrease substance use.

2.4 Alterations in Reward and Stress Processing

Reinforcing effects are key characteristics of psychoactive substances and motivate their use. Neurobiologically, these reinforcing effects depend on dopamine release in the ventral tegmental area (VTA) and subsequently in the Nucleus Accumbens (NAcc) (Wise 2008). Dopamine release from VTA to NAcc plays a central role in the reward circuit and motivational processes (Salamone and Correa 2012; Volkow et al. 2019). Reinforcing effects are also caused by environmental factors, as

substance craving and use is often triggered by sensitization, stress, priming dose, or drug-related cues (Belin et al. 2013; Jasinska et al. 2014). These triggers can drive drug users to compulsive drug taking (Volkow et al. 2011b). Repeated perturbation of reward systems leads to long-lasting decreases in dopamine D2 receptors and decreased dopamine cell activity (Volkow et al. 2003). Specifically, chronic drug use induces neuroadaptations in the dopamine striato-thalamo-cortical and limbic pathways (Volkow et al. 2019). Various brain imaging studies have shown that these neuroadaptations cause a long-lasting decrease in sensitivity to natural reinforcers, such as monetary reward and social interaction (e.g., Goldstein et al. 2007; Preller et al. 2014; Tobler et al. 2016). Furthermore, obsessive-compulsive thoughts related to cocaine use and lifetime cocaine consumption were associated with impaired reward sensitivity for natural reinforcers in cocaine users (Kirschner et al. 2018). Therefore, modifying maladaptive reward sensitivity and reinstating natural reward responsiveness is a promising therapeutic strategy in SUD.

An additional neurotransmitter influencing the cycle of addiction is serotonin. Serotonin is involved in the regulation of stress, anxiety, cognitive functions, social behavior, and reinforcement of properties of drugs (Belmer et al. 2016). Serotonin neurotransmission is reduced in patients with AUD after alcohol-withdrawal leading to increased stress-induced anxiety, which in turn reinforces craving and relapse (Belmer et al. 2016). Furthermore, frontolimbic 5-HT_{2A} receptor binding correlates with anxiety and difficulties in the regulation of stress (Frokjaer et al. 2008). Therefore, stimulation of serotonergic neurotransmission by the administration of psychedelics may decrease stress-induced anxiety, improve mood, and reduce attentional bias, and in turn decrease craving (Bogenschutz and Pommy 2012). This is in line with participants being treated with psilocybin for smoking cessation reporting reduced withdrawal symptoms and craving (Noorani et al. 2018).

2.5 Increased Social Connectedness

Potentially related to impaired responsiveness to natural rewards, patients with SUD show dysfunctional social cognition and interaction, subsequently leading to decreased social contact and support. This may result in increased social isolation (Quednow 2020; Tobler et al. 2016). For example, cocaine users showed decreased social interaction and brain activity in regions related to reward processing. This decreased brain activity was associated with a decreased social network size, suggesting that reduced social reward processing is leading to impairments of social behavior in real life (Preller et al. 2014). Similarly, patients with AUD showed reduced theory of mind skills (Le Berre 2019). Such difficulties may increase the probability of relapse and hinder treatment efficacy. Therefore, the training of social and emotional skills should be implemented in therapy of SUD.

Studies with healthy controls have shown that classic psychedelics acutely decrease feelings of social exclusion and increase emotional empathy, prosocial behavior, and the desire to be with other people (Dolder et al. 2016; Pokorny et al.

2017; Preller et al. 2016). Positive social effects and interpersonal closeness were increased up to 1 year after the psychedelic experience (Griffiths et al. 2008, 2018; Schmid and Liechti 2018). Furthermore, participants receiving psilocybin in the treatment of smoking cessation reported feelings of love and a sense of unity and interconnection with their environment, which they identified to be important factors for staying abstinent from smoking (Noorani et al. 2018). Additionally, participants engaged more in social activities after the therapy (Noorani et al. 2018). After the administration of a single dose of (±)3,4-methylendioxymethamphetamine (MDMA), the reopening of a critical period for social reward learning was shown in mice (Nardou et al. 2019). However, MDMA is not a classic psychedelic, but rather an "entactogen" and these effects may therefore not translate to classic psychedelics. Classic psychedelics may counteract social withdrawal associated with SUD by decreasing social anxiety and increasing emotional empathy, prosociality, and interpersonal closeness. Psychedelics may not only improve social ties within daily life, but also the patient-therapist relationship. This may suggest that a group setting for discussing the experience or including a person close to the patient into the preparation or follow-up therapy sessions may be beneficial.

2.6 Subjective Experiences and Personal Meaning of the Experiences

Self-awareness, interoception, and insight are related constructs that describe the ability to identify one's own behaviors, emotions, and mental states (David et al. 2012). Patients suffering from SUD often show difficulties in self-awareness, interoception, and insight (Goldstein et al. 2009). Specifically, patients with SUD fail to perceive the personal importance of stimuli or situations that have a meaning to the self. This leads to drug-biased attention, deviant processing of non-drug-related cues, and abnormalities in social cognition (Moeller and Goldstein 2014). A dysfunctional neural circuit involving the insula, anterior cingulate cortices, probably orbitofrontal cortex (Goldstein et al. 2009), and ventromedial prefrontal cortex (Moeller and Goldstein 2014) may underlie these difficulties. Consequently, patients with SUD show difficulties in recognizing and understanding their feelings, and gaining insight into potential dysfunctional behavior. Furthermore, impaired self-awareness is often associated with increased illness severity, poorer prognosis, and decreased insight into the severity of the disorder (David et al. 2012). Therefore, increasing self-awareness and improving insight into problematic behavior could represent a promising therapeutic approach.

Some studies propose that mystical experiences are essential to attribute personal meaning to the psychedelic-induced experience and a positive treatment outcome (e.g., Davis et al. 2020; Garcia-Romeu et al. 2019; Griffiths et al. 2016, 2018; Ross et al. 2016). Mystical experience refers to the first-person experience during a psychedelic session such as feeling of unity, blissful state, insightfulness, and feeling

of awe. In a study in nicotine addiction, mystical experiences were associated with smoking cessation at 6-month and 12-month follow-up (Garcia-Romeu et al. 2014; Johnson et al. 2017). Similarly, in patients with AUD, changes in drinking pattern were associated with mystical experiences, but also the general intensity of subjective effects as measured with the Altered State of Consciousness Scale (Bogenschutz et al. 2015). Why and how mystical experiences influence treatment outcomes is not well understood, but Bogenschutz and Pommy (2012) suggest that the high personal meaning of the experience is associated with increased self-efficacy to stay abstinent and decrease temptation to use the substance. In line with this, feeling of awe has been suggested as a driving mechanism in long-term effects of classic psychedelic-assisted therapy by influencing unitive experience and ego dissolution, which in turn affects ineffability, sacredness, positive mood, and insight (Hendricks 2018).

Additionally, insightfulness – partially overlapping with the concept of mystical experiences – is often an essential characteristic of the psychedelic experience (Bogenschutz et al. 2018; Noorani et al. 2018). Insight can refer to a patient's understanding of their disorder, problematic behavior, emotions, and feelings. Such insight has been suggested to lead to enhanced self-efficacy and motivation to change (Bogenschutz and Pommy 2012). A previous online survey showed that increased insight in a non-clinical setting correlates with decreased alcohol use (Garcia-Romeu et al. 2019) and may therefore represent an important mediator of treatment success in SUD.

Associated with increased insight, psychedelics may also (1) increase realization and understanding of negative consequences of problematic behavior patterns and substance use, which may lead to a heightened desire and motivation to change one's behavior, (2) alter the prospect of life, (3) influence one's conviction that change is possible, (4) reduce ambivalence, and (5) facilitate personality change (Bogenschutz and Pommy 2012). However, divergent results were reported for personality change after psychedelic admission. For example, psilocybin increased openness, but did not influence neuroticism, extraversion, agreeableness, or conscientiousness in healthy participants post-acutely (MacLean et al. 2011; Madsen et al. 2020). Similarly, patients with treatment resistant depression showed increased openness, but also increased extraversion and decreased neuroticism following psilocybin sessions (Erritzoe et al. 2018). On the other hand, LSD in healthy participants did not affect openness, but increased conscientiousness in one study (Schmid and Liechti 2018) but not another (Carhart-Harris et al. 2016).

Importantly, SUD patients also reported post-acute alterations of self-perception and more control over their own choices and behavior after a psychedelic experience within a clinical setting (Bogenschutz et al. 2018; Noorani et al. 2018). Together, these results suggest that the acute experience of altered self-perception facilitates treatment success in SUD and has a long-lasting impact on perception of self-efficacy.

Further research is needed to investigate how subjective experiences relate to positive treatment outcomes and whether specific subjective experiences are more beneficial than others to promote treatment success (Bogenschutz et al. 2015). Studies in patients with SUD have not yet investigated the potential relationship

between other subjective experiences and therapeutic outcome measures, such as visual/auditive alterations, anxiety, or alterations in cognition and control.

In contrast to results pointing to the importance of subjective effects for beneficial clinical effects, two studies in mice reported neuroplasticity was induced by psilocybin with ketanserin pretreatment (Shao et al. 2021) and tabernanthalog (Cameron et al. 2021), a non-hallucinogenic 5-HT_{2A} agonist, which also reduced alcohol-seeking. These results may challenge the idea that subjective effects are necessary for treatment success in AUD. However, these effects still need to be replicated in humans.

3 Therapeutic Implications

It is widely accepted that psychedelics should be administered in combination with psychotherapeutic treatment that includes preparation and integration sessions, and transfer to daily life. The psychotherapeutic embedding is considered vital to ensure safety and efficacy (e.g., Watts and Luoma 2020). However, it remains unknown which psychotherapeutic strategies are best suited to be combined with psychedelic interventions in the context of SUD. Here, we briefly describe some of the main psychotherapeutic interventions for SUD often applied in clinical settings, and discuss the potential benefits of their combination with psychedelics based on their mechanisms of action as outlined above.

Existing evidence-based psychotherapeutic interventions for SUD include mainly contingency management (CM), cognitive-behavioral therapy (CBT), and motivational interviewing (MI), or variants and combinations thereof. CM is a behavioral intervention in which non-drug taking behavior and other positive behavioral changes are "reinforced" or rewarded, therefore supporting a shift from substance-related to non-substance related behaviors based on principles of reward learning (Petry et al. 2001, 2013). It therefore seeks to reduce the imbalance in reward processing that is at the core of SUD. Although there is good evidence for the application of CM in general, one of the major challenges is to achieve sustained effects that have a positive impact on substance use that outlasts the reinforcement intervention (Prendergast et al. 2006). Here, we discuss how, e.g., neuroplasticity as induced by psychedelics might contribute to enhanced and more sustained effects of CM interventions (see Sects. 3.1, 3.2, and 3.3). Strengthening engagement in behaviors not related to substance use is also at the heart of other psychotherapies like MI. MI focuses on resolving ambivalence related to behavioral decisions between (continued) substance use and other activities, and enhancing motivational engagement in non-substance-related "rewarding" activities (Rollnick and Miller 1995). Accordingly, it has been suggested that MI remodels maladaptive reward learning associated with addiction-related behaviors and leads to changes within the corresponding brain circuitries (Feldstein Ewing et al. 2011). However, effect sizes for MI are rather low (Stein et al. 2009). We expect that fostering brain connectivity changes by psychedelics may enhance the therapeutic potential of MI interventions

(see Sect. 2.2). Moreover, as in MI it sometimes proves to be challenging for patients to develop new attractive goals in life that are unrelated to substance use, and, in addition, to generate creative novel ways to achieve them, psychedelics might support MI approaches by enabling "out-of-the-box-thinking" not restricted by rigid thinking patterns. In addition, increased insight into problematic behavior and changes in self-perception and self-efficacy that both have been related to the mystical experiences induced by psychedelics are considered key factors contributing to the clinical effects of MI. Therefore, we expect that MI based interventions and psychedelic therapy are ideally suited to complement each other.

For example, we are currently conducting a study investigating clinical and mechanistic effects of psilocybin in AUD (NCT04141501). Our accompanying psychotherapeutic interventions are based on the BRENDA-approach that is rooted in the principles of MI, which involves "(1) a biopsychosocial evaluation; (2) a report of findings from the evaluation given to the patient; (3) empathy; (4) addressing patient needs; (5) providing direct advice; and (6) assessing patient reaction to advice and adjusting the treatment plan as needed" (p.1, Starosta et al. 2006). The BRENDA psychosocial therapeutic approach has specifically been designed to be combined with pharmacological interventions in AUD (Starosta et al. 2006). It has successfully been implemented in various clinical trials testing the efficacy of pharmacotherapies in SUD (Monterosso et al. 2001; Pettinati et al. 2000). In our study, we extended the BRENDA-approach to include therapeutic elements specific for psychedelic-assisted therapy. After assessing the patients' medical history and their reasons for drinking alcohol in a first visit, patients are prepared for the substance session in a second visit. Patients' previous experiences with psychedelics, their expectations and concerns, handling of challenging situations and potential effects of psilocybin are discussed. Furthermore, patients define intentions for the substance session and goals for their future. On the day of psilocybin administration (visit 3), we instruct patients to focus on themselves, to immerse themselves in whatever may come up even if it may be challenging or unpleasant and to avoid judging the situation or the content. In a fourth visit, the patients revisit the substance session together with their therapist. This includes the discussion of challenging situations and emotions during the day. The interpretation and integration of the experience takes place in the fifth and sixth visits. Here, we discuss how potential insights can lead to beneficial changes in daily life.

We suggest that leveraging synergies between psychedelic-specific mechanisms of action and psychotherapeutic elements in future trials will contribute to optimizing the success of the treatment. Targeted approaches informed by the underlying mechanisms of action will need to be developed to achieve the goal of delivering the best psychedelic-assisted therapy possible. Based on the potential mechanisms of action in SUD outlined above, we are discussing potential therapeutic elements below (for an overview see Fig. 1) and suggest testing the efficacy of these targeted approaches in future studies.

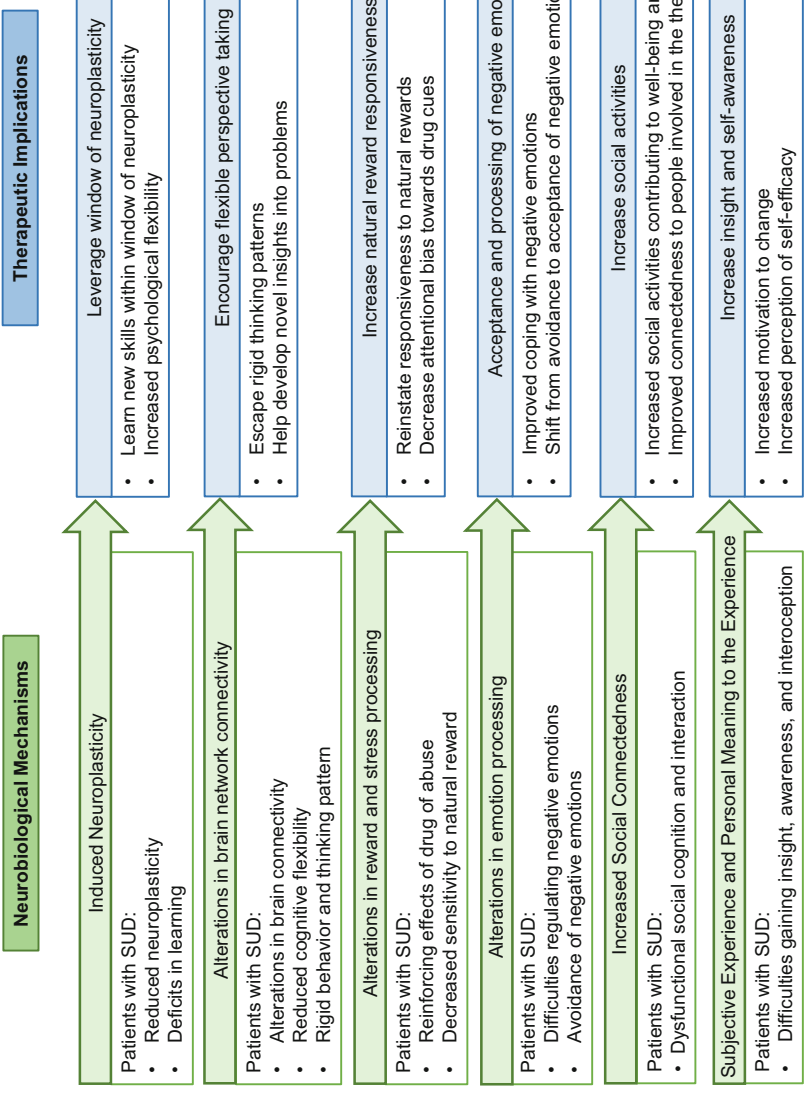

Fig. 1 Overview of neurobiological mechanisms and their therapeutic implications

3.1 Implications of Induced Neuroplasticity

As outlined in Sect. 2.1 psychedelics may open a neuroplastic window of opportunity during which learning (including extinction learning) is facilitated. Unfortunately, we currently do not know if these results translate to humans. Furthermore, we do not have a clear understanding of when and how long this neuroplastic effect can be leveraged. Nevertheless, as outlined above, patients suffering from SUD benefit from learning new behaviors that can replace drug use habits. This may help patients to stay abstinent and weaken the association between drug cues and craving. It is conceivable that psychedelic-induced neuroplasticity may greatly facilitate these processes.

For example, CM is mainly based on operant conditioning, a form of associative learning, where a voluntary behavior is modified or strengthened by reinforcement. Patients usually receive incentives to reinforce drug abstinence. While effect sizes for this intervention are large as long as the target behavior is reinforced, these effects are often not well sustained beyond the therapeutic intervention. Therefore, psychedelic-induced neuroplasticity may enhance and extend the learning effects associated with CM and other psychotherapeutic learning interventions.

Moreover, in synergy with psychedelic-induced plasticity, therapeutic approaches based on extinction learning (i.e., exposure to drug stimuli without providing the drug of abuse itself) may also prove to be more effective in SUD. Leveraging these approaches in combination with immersive technology such as Virtual Reality (e.g., Segawa et al. 2019) may further support the translation to real life as it allows to create realistic scenes (e.g., visiting a bar, seeing other people drink alcohol) that have been shown to trigger craving in AUD patients. Additionally, neurofeedback approaches are helpful tools to specifically train self-regulation of brain activity, and, in combination with psychedelics, could support patients in either learning to reduce their reactions to drug cues, or to enhance their sensitivity to non-drug related reinforcers in a very precise manner (Kirschner et al. 2018).

Increased psychological flexibility resulting from induced neuroplasticity may furthermore be beneficial in supporting creative problem solving specifically with regard to developing novel strategies to avoid relapse or deal with negative emotions. The therapist may encourage the patient to engage in "out-of-the-box" thinking to come up with alternative behaviors that support the patients in staying abstinent. It has to be noted though that LSD did not enhance cognitive flexibility acutely in one study (Pokorny et al. 2020). It is therefore important to consider the timing of these interventions.

While these approaches are likely to be effective after the acute effects have subsided, the finding of increased acute plasticity raises the question of how the acute experience shapes treatment outcomes. If induced neuroplasticity is already present while the patient experiences psychedelic effects, the quality and content of these experiences is likely to have a long-lasting impact. It may therefore be important to avoid deeply frightening experiences during the acute effects as this could potentially lead to enduring anxiety. Positive experiences, on the other hand,

may support treatment success. Therefore, a "framing" towards positive and non-drug-related experiences during preparation sessions might be beneficial for subsequent behavioral change. Moreover, the environment could be adapted to the specific needs of the patients, for example by using a group setting if reductions of social problems are a treatment goal.

3.2 Implications of Alterations in Brain Network Connectivity

Acute changes in brain connectivity reveal a pattern of increased connectivity between sensory and decreased connectivity between associative brain regions under the influence of LSD and psilocybin (Preller et al. 2018, 2020). These effects point to alterations in information integration and cognitive control that may allow patients to gain a new perspective on themselves and their lives by escaping rigid thinking patterns. Therapists could leverage this effect by specifically discussing novel perspectives with the patient and encouraging the patient to challenge old ideas and habits. Therefore, psychedelics appear ideally suited to support "change talk", i.e. self-expressed speech that argues for change, which is considered one of the key elements of MI.

It is currently unclear if these changes in brain connectivity – and associated with this, information processing – persist beyond the acute drug effects. It may therefore be critical to (re-)engage in these discussions as soon as possible after the peak effects have subsided. This challenges the idea of therapists not interfering with the acute experience and emphasizes directing the content of the experience towards specific, personalized topics that have ideally been discussed in the preparation sessions. Depending on the dose administered, this may not be possible while the patient is experiencing a strong altered state of consciousness, but may be feasible towards the end of the acute effects. Alternatively, lower doses may suffice to induce changes in connectivity between associative brain regions and, together with a targeted intervention that encourages a change of perspective, may promote beneficial clinical outcomes. Future studies investigating changes in brain connectivity induced by psychedelics at various doses and time points may help to uncover the optimal dose and time point for more targeted psychotherapeutic interventions under the influence of or in combination with psychedelics.

Additionally, the strength of psilocybin-induced changes in brain connectivity was predicted by baseline connectivity in healthy participants (Preller et al. 2020). It is therefore possible that the functional architecture of an individual's brain as measured with resting-state functional magnetic resonance imaging may represent a predictive biomarker for acute psychedelic effects and treatment success. Future studies need to explore if this measure can serve as a stratifying factor predicting who is likely/unlikely to benefit from psychedelic-assisted therapy.

3.3 *Implications of Alterations in Emotion, Stress, and Reward Processing*

During the acute and post-acute phase of psychedelic drug action, the neural response to negative stimuli is decreased. Therefore, psychedelics may provide the patient with the opportunity to face negative memories and emotions instead of suppressing or avoiding them. Dealing with the negative emotions possibly coming up during acute psychedelic experience is often more comfortable than pushing them away (Watts and Luoma 2020). Negative emotions may be less hurtful, thus accessible and possible to process (Kraehenmann et al. 2015; Mueller et al. 2017). With the increased processing of difficult situations, rumination may decrease concurrently. As the reduced neural response to negative stimuli is prolonged up to 1 week after psychedelic administration (Barrett et al. 2020), it may be beneficial to process negative life events within this timeframe. This way, psychedelic interventions may complement and enhance the effects of psychotherapeutic interventions like CBT or mindfulness-based relapse prevention that aim at developing skills to cope with heightened stress levels that are often associated with craving and drug use (Bowen et al. 2014). Mindfulness techniques used in relapse prevention are often used to increase tolerance of negative emotional and cognitive states, thereby decreasing the need to alleviate discomfort by engaging in substance use.

Furthermore, the stimulation of serotonin receptors by psychedelics may normalize serotonin neurotransmission and in turn decrease craving by increasing mood and reducing stress and attentional bias (Bogenschutz and Pommy 2012). With heightened mood and reduced attentional bias, drug cues may become less important and drug rewards less worth striving for. Therefore, integration sessions could focus on the normalization of natural rewards processing. To sustain decreased attentional bias, drug-cue reactivity combined with neurofeedback or virtual reality practice may support long-term changes and reinstate natural reward sensitivity.

However, as one study in depressed individuals showed that the neural response to negative emotions was increased the day after psilocybin administration before any integration therapy had taken place (Roseman et al. 2018), it is necessary that the process of negative emotion processing is carefully embedded in therapy and closely accompanied by a trained therapist. Especially shortly after the psychedelic experience, patients may be more vulnerable and may need more support from the therapists. Future research should investigate when best to discuss negative life events, whether patients need more support right after psychedelic administration, and what type of integration is necessary to achieve long-term improvements in emotion processing.

3.4 Implications of Social Connectedness

Increased emotional empathy induced by psilocybin may benefit the treatment of SUD by increasing social activity and decreasing social isolation. While SUD are often associated with severe social harms (Nutt et al. 2010; Volkow et al. 2011a) in combination with more general anhedonia (Garfield et al. 2014), patients with SUD receiving psychedelics may feel more connected with their environment and the people close to them especially during acute effects. This could not only improve the patient-therapist relationship but also make social interactions in general more meaningful and valuable. As long-term increases in prosocial behavior and interaction with the environment have been reported after exposure to a psychedelic, therapists should support patients in engaging in social activities that contribute to the patients' well-being. More specifically, psychedelics seem well suited to be combined with and enhance therapeutic benefits of approaches like behavioral activation treatment that aim at increasing social engagement of patients (Daughters et al. 2018). We also propose to evaluate carefully if group therapy sessions have an additional beneficial effect on therapeutic outcomes as interaction with other people is necessary to deepen social activities and social connectedness (Anderson et al. 2020; Kettner et al. 2021). Another approach could be to include family members or people close to the patients in the therapeutic process, which is already being done in MDMA-assisted treatment of PTSD-patients (e.g., Monson et al. 2020). However, therapists need to be aware that the experience of increased social connectedness induced by psychedelic substances requires them to be particularly mindful to keep their professional distance.

3.5 Implications of Subjective Experiences and Personal Meaning

The personal meaning of the experience seems to be essential for psychedelics to induce self-awareness, create insight, and increase interoception. Thus, it ought to be beneficial for patients to attribute personal meaning to the experience, gain insight and a better understanding of their disorder, increase self-awareness, and motivation. Furthermore, insight may give patients a new perspective on their dysfunctional behavior (i.e., avoidance, suppression, or rumination) and may lead to new ideas about the rationale for their addiction-related behaviors and potential possibility of change (i.e., acceptance). It has to be noted that excessive self-awareness has been associated with poor mental health as it can induce anxiety and rumination (Nezlek 2002). Psychedelic-induced self-awareness and facilitated insights might therefore need to be guided towards the development of new goals in life. This way, they could provide a rich source of ideas that can be further developed and applied in well-established semi-structured therapeutic approaches like MI. An increased range of possibilities and more flexible thinking together with altered self-perception may

lead to the perception of increased self-efficacy to change their (substance use) behavior. Although self-efficacy is a good predictor of treatment outcome in SUD, there is no clear consensus on how to therapeutically enhance the perception of self-efficacy in SUD patients. Psychedelics may provide an important contribution in this context. Therefore, it may be essential to focus on topics like personal meaning, insight, awareness, and self-efficacy during preparation, the acute psychedelic experience, and the following integration sessions. These processes could potentially be augmented by practicing mindfulness techniques (see also Sect. 3.3) before or after the psychedelic experience to re-induce some aspects of the experience. Additionally, Hendricks (2018) suggests increasing the feeling of awe during the acute experience via exposure to nature, art, and music. Furthermore, gained insight needs to be transferred and implemented into daily life in order to facilitate long-term changes.

One main mechanism of action of psychedelics is gaining insight. Therefore, it seems essential to outline dysfunctional behavior patterns and define goals for the future during the preparation phase and also encourage changing of behavior and thinking patterns during integration sessions. Furthermore, new habits need to be strengthened to support long-term change. Current clinical studies in humans suggest that the subjective experience is necessary to gain insight and support positive clinical outcomes (e.g., Bogenschutz et al. 2015; Garcia-Romeu et al. 2014). However, recent research in mice contradicts these findings (Cameron et al. 2021). Further research is needed to answer this question.

3.6 Implications for Dose-Finding and Dosing Regimen

It is currently unknown which dose or dosing regimen is leading to the most positive treatment outcomes. In in-vivo experiments in mice, significant faster extinction learning in a cued fear conditioning paradigm was observed with low doses of psilocybin compared to high doses (Catlow et al. 2013). This study furthermore showed a dose-dependent decrease in hippocampal neurogenesis; with a trend towards increased neurogenesis by low doses of psilocybin (Catlow et al. 2013). However, there are currently no studies investigating the effect of psychedelics on learning in humans. Translating these animal findings into human studies is necessary to understand the impact of different doses on potential clinical mechanisms of action.

While these results point to the beneficial effect of low doses, Kurland et al. (1967) and Chwelos et al. (1959) proposed the administration of relatively high doses of LSD in patients with AUD to elicit a "peak-psychedelic" or mystical experience of ego loss. Additionally, Bogenschutz et al. (2015) reported lower acute effects in patients with AUD (measured with mystical experience questionnaire (MEQ) and hallucinogen rating scale (HRS)) than in healthy volunteers and, therefore, suggest that these patients require higher doses to have a strong acute experience. Given the assumption that mystical experiences are essential for positive treatment outcomes (Bogenschutz et al. 2015; Garcia-Romeu et al. 2014), higher

doses of the psychedelic may be needed for clinical efficacy in this patient population. Yet, anecdotal reports also suggest a beneficial effect of very low, sub-threshold doses of psychedelics, so-called microdoses. Future research therefore needs to investigate whether microdoses of psychedelics (1) indeed have clinical efficacy and (2) if these effects are induced by a different mechanism of action as compared to those described in Sect. 2. Another question that has not been resolved yet is the most promising dosing regimen, i.e. is a single dose enough or are repeated doses necessary for a positive long-term treatment outcome? Our currently ongoing study will provide some answers to this question as it involves the administration of only a single dose and allows for results to be compared with previous studies using repeated dosing in patients with AUD and smoking cessation (Bogenschutz et al. 2015; Garcia-Romeu et al. 2014). Furthermore, it needs to be investigated if long-lasting results can be fostered by repeating the treatment cycle after some months.

4 Conclusion

In this chapter, we have outlined various potential mechanisms of action of psychedelics that could prove to have significant synergies with psychotherapeutic approaches. Today, most clinical trials that involve the administration of a psychedelic substance for the treatment of SUD include multiple sessions of preparation and integration based on anecdotal reports of therapists working with these substances – usually some form of talk therapy – combined with motivational enhancement approaches. However, given the momentum this research has gained including efforts to test psychedelic-assisted therapy in larger phase III trials in the future, it will be important to establish evidence-based psychotherapeutic interventions and optimize therapeutic approaches in order to achieve maximally beneficial treatment effects for patients. Understanding the clinical mechanisms of action of psychedelics will be critical to guide this optimization process as leveraging synergies between pharmacological mechanisms and non-pharmacological interventions represent a promising approach to achieve optimal treatment effects. In this chapter, we have outlined knowledge gaps, but also make concrete suggestions about possible psychotherapeutic interventions that seem well suited for a psychedelic-assisted therapy of SUD based on our current understanding of the neurobiology of these substances. We suggest exploring the benefits of fostering creative thinking styles, including family members or friends in the therapeutic process, and enable changes of perspectives and behaviors within an MI framework. We further propose to enhance learning strategies as conceptualized in CM or extinction learning approaches for SUD by psychedelic-induced neuroplasticity. Psychedelics have the potential to support behavioral therapies such as behavioral activation aiming at increasing social engagement. Additionally, we propose to leverage novel technologies, for example VR-based approaches and neurofeedback, to promote and sustain these effects. The efficacy of these combined approaches as well as optimal dose and timing needs to be investigated in future studies. Furthermore, the potential of personalizing these approaches as well as predictive markers for treatment success

need to be studied. If these knowledge gaps can be filled, psychedelic-assisted therapy has a great potential to become an efficacious, evidence-based, and modern treatment for patients suffering from SUD.

References

Aldao A, Nolen-Hoeksema S, Schweizer S (2010) Emotion-regulation strategies across psychopathology: a meta-analytic review. Clin Psychol Rev 30:217–237. https://doi.org/10.1016/j.cpr.2009.11.004

Anderson BT, Danforth A, Daroff R, Stauffer C, Ekman E, Agin-Liebes G, Trope A, Boden MT, Dilley J, Mitchell J, Woolley J (2020) Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: an open-label safety and feasibility pilot study. EClinicalMedicine 27:1–11. https://doi.org/10.1016/j.eclinm.2020.100538

Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC (2004) Addiction motivation reformulated: an affective processing model of negative reinforcement. Psychol Rev 111:33–51. https://doi.org/10.1037/0033-295X.111.1.33

Barrett FS, Doss MK, Sepeda ND, Pekar JJ, Griffiths RR (2020) Emotions and brain function are altered up to one month after a single high dose of psilocybin. Sci Rep 10:1–14. https://doi.org/10.1038/s41598-020-59282-y

Bastian B, Kuppens P, Hornsey MJ, Park J, Koval P, Uchida Y (2012) Feeling bad about being sad: the role of social expectancies in amplifying negative mood. Emotion 12:69–80. https://doi.org/10.1037/a0024755

Belin D, Belin-Rauscent A, Murray JE, Everitt BJ (2013) Addiction: failure of control over maladaptive incentive habits. Curr Opin Neurobiol 23:564–572. https://doi.org/10.1016/j.conb.2013.01.025

Belmer A, Patkar OL, Pitman KM, Bartlett SE (2016) Serotonergic neuroplasticity in alcohol addiction. Brain Plast 1:177–206. https://doi.org/10.3233/BPL-150022

Bershad AK, Schepers ST, Bremmer MP, Lee R, de Wit H (2019) Acute subjective and behavioral effects of microdoses of lysergic acid diethylamide in healthy human volunteers. Biol Psychiatry 86:792–800. https://doi.org/10.1016/j.biopsych.2019.05.019

Beylergil SB, Beck A, Deserno L, Lorenz RC, Rapp MA, Schlagenhauf F, Heinz A, Obermayer K (2017) Dorsolateral prefrontal cortex contributes to the impaired behavioral adaptation in alcohol dependence. Neuroimage Clin 15:80–94. https://doi.org/10.1016/j.nicl.2017.04.010

Bogenschutz MP, Pommy JM (2012) Therapeutic mechanisms of classic hallucinogens in the treatment of addictions: from indirect evidence to testable hypotheses. Drug Test Anal 4:543–555. https://doi.org/10.1002/dta.1376

Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PCR, Strassman RJ (2015) Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol (Oxf) 29:289–299. https://doi.org/10.1177/0269881114565144

Bogenschutz MP, Podrebarac SK, Duane JH, Amegadzie SS, Malone TC, Owens LT, Ross S, Mennenga SE (2018) Clinical interpretations of patient experience in a trial of psilocybin-assisted psychotherapy for alcohol use disorder. Front Pharmacol 9:1–10. https://doi.org/10.3389/fphar.2018.00100

Bowen S, Witkiewitz K, Clifasefi SL, Grow J, Chawla N, Hsu SH, Carroll HA, Harrop E, Collins SE, Lustyk MK, Larimer ME (2014) Relative efficacy of mindfulness-based relapse prevention, standard relapse prevention, and treatment as usual for substance use disorders: a randomized clinical trial. JAMA Psychiatry 71:547–556. https://doi.org/10.1001/jamapsychiatry.2013.4546

Cameron LP, Tombari RJ, Lu J, Pell AJ, Hurley ZQ, Ehinger Y, Vargas MV, McCarroll MN, Taylor JC, Myers-Turnbull D, Liu T, Yaghoobi B, Laskowski LJ, Anderson EI, Zhang G, Viswanathan J, Brown BM, Tjia M, Dunlap LE, Rabow ZT, Fiehn O, Wulff H, McCorvy JD,

Lein PJ, Kokel D, Ron D, Peters J, Zuo Y, Olson DE (2021) A non-hallucinogenic psychedelic analogue with therapeutic potential. Nature 589:474–479. https://doi.org/10.1038/s41586-020-3008-z

Carhart-Harris RL, Leech R, Williams TM, Erritzoe D, Abbasi N, Bargiotas T, Hobden P, Sharp DJ, Evans J, Feilding A, Wise RG, Nutt DJ (2012) Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. Br J Psychiatry 200:238–244. https://doi.org/10.1192/bjp.bp.111.103309

Carhart-Harris RL, Kaelen M, Bolstridge M, Williams TM, Williams LT, Underwood R, Feilding A, Nutt DJ (2016) The paradoxical psychological effects of lysergic acid diethylamide (LSD). Psychol Med 46:1379–1390. https://doi.org/10.1017/S0033291715002901

Catlow BJ, Song S, Paredes DA, Kirstein CL, Sanchez-Ramos J (2013) Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning. Exp Brain Res 228:481–491. https://doi.org/10.1007/s00221-013-3579-0

Chwelos N, Blewett DB, Smith CM, Hoffer A (1959) Use of d -lysergic acid diethylamide in the treatment of alcoholism. Q J Stud Alcohol 20:577–590. https://doi.org/10.15288/qjsa.1959.20.577

Daughters SB, Magidson JF, Anand D, Seitz-Brown CJ, Chen Y, Baker S (2018) The effect of a behavioral activation treatment for substance use on post-treatment abstinence: a randomized controlled trial. Addiction 113:535–544. https://doi.org/10.1111/add.14049

David AS, Bedford N, Wiffen B, Gilleen J (2012) Failures of metacognition and lack of insight in neuropsychiatric disorders. Philos Trans R Soc Lond Ser B Biol Sci 367:1379–1390. https://doi.org/10.1098/rstb.2012.0002

Davis AK, Barrett FS, Griffiths RR (2020) Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. J Contextual Behav Sci 15:39–45. https://doi.org/10.1016/j.jcbs.2019.11.004

Dingle GA, Da Neves DC, Alhadad SSJ, Hides L (2018) Individual and interpersonal emotion regulation among adults with substance use disorders and matched controls. Br J Clin Psychol 57:186–202. https://doi.org/10.1111/bjc.12168

Dolder PC, Schmid Y, Müller F, Borgwardt S, Liechti ME (2016) LSD acutely impairs fear recognition and enhances emotional empathy and sociality. Neuropsychopharmacology 41:2638–2646. https://doi.org/10.1038/npp.2016.82

Dyck E (2006) 'Hitting highs at rock bottom': LSD treatment for alcoholism, 1950–1970. Soc Hist Med 19:313–329. https://doi.org/10.1093/shm/hkl039

Erritzoe D, Roseman L, Nour MM, MacLean K, Kaelen M, Nutt DJ, Carhart-Harris RL (2018) Effects of psilocybin therapy on personality structure. Acta Psychiatr Scand 138:368–378. https://doi.org/10.1111/acps.12904

Ersche KD, Meng C, Ziauddeen H, Stochl J, Williams GB, Bullmore ET, Robbins TW (2020) Brain networks underlying vulnerability and resilience to drug addiction. Proc Natl Acad Sci U S A 117:15253–15261. https://doi.org/10.1073/pnas.2002509117

Feldstein Ewing SW, Filbey FM, Hendershot CS, McEachern AD, Hutchison KE (2011) Proposed model of the neurobiological mechanisms underlying psychosocial alcohol interventions: the example of motivational interviewing. J Stud Alcohol Drugs 72:903–916. https://doi.org/10.15288/jsad.2011.72.903

Frokjaer VG, Mortensen EL, Nielsen FA, Haugbol S, Pinborg LH, Adams KH, Svarer C, Hasselbalch SG, Holm S, Paulson OB, Knudsen GM (2008) Frontolimbic serotonin 2A receptor binding in healthy subjects is associated with personality risk factors for affective disorder. Biol Psychiatry 63:569–576. https://doi.org/10.1016/j.biopsych.2007.07.009

Garcia-Romeu A, Griffiths RR, Johnson MW (2014) Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 7:157–164. https://doi.org/10.2174/1874473708666150107121331

Garcia-Romeu A, Davis AK, Erowid F, Erowid E, Griffiths RR, Johnson MW (2019) Cessation and reduction in alcohol consumption and misuse after psychedelic use. J Psychopharmacol (Oxf) 33:1088–1101. https://doi.org/10.1177/0269881119845793

Garfield JBB, Lubman DI, Yücel M (2014) Anhedonia in substance use disorders: a systematic review of its nature, course and clinical correlates. Aust N Z J Psychiatry 48:36–51. https://doi.org/10.1177/0004867413508455

GBD 2017 Risk Factor Collaborators (2018) Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392:1923–1994. https://doi.org/10.1016/S0140-6736(18)32225-6

Geng X, Hu Y, Gu H, Salmeron BJ, Adinoff B, Stein EA, Yang Y (2017) Salience and default mode network dysregulation in chronic cocaine users predict treatment outcome. Brain 140:1513–1524. https://doi.org/10.1093/brain/awx036

Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND (2007) Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? Am J Psychiatry 164:43–51. https://doi.org/10.1176/ajp.2007.164.1.43

Goldstein RZ, Craig ADB, Bechara A, Garavan H, Childress AR, Paulus MP, Volkow ND (2009) The neurocircuitry of impaired insight in drug addiction. Trends Cogn Sci 13:372–380. https://doi.org/10.1016/j.tics.2009.06.004

Griffiths R, Richards W, Johnson M, McCann U, Jesse R (2008) Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol (Oxf) 22:621–632. https://doi.org/10.1177/0269881108094300

Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol (Oxf) 30:1181–1197. https://doi.org/10.1177/0269881116675513

Griffiths RR, Johnson MW, Richards WA, Richards BD, Jesse R, MacLean KA, Barrett FS, Cosimano MP, Klinedinst MA (2018) Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. J Psychopharmacol (Oxf) 32:49–69. https://doi.org/10.1177/0269881117731279

Hendricks PS (2018) Awe: a putative mechanism underlying the effects of classic psychedelic-assisted psychotherapy. Int Rev Psychiatry 30:331–342. https://doi.org/10.1080/09540261.2018.1474185

Hyman SE (2005) Addiction: a disease of learning and memory. Am J Psychiatry 162:1414–1422. https://doi.org/10.1176/appi.ajp.162.8.1414

Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y (2014) Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci Biobehav Rev 38:1–16. https://doi.org/10.1016/j.neubiorev.2013.10.013

Johnson MW, Garcia-Romeu A, Griffiths RR (2017) Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse 43:55–60. https://doi.org/10.3109/00952990.2016.1170135

Kauer JA, Malenka RC (2007) Synaptic plasticity and addiction. Nat Rev Neurosci 8:844–858. https://doi.org/10.1038/nrn2234

Kettner H, Rosas FE, Timmermann C, Kärtner L, Carhart-Harris RL, Roseman L (2021) Psychedelic communitas: intersubjective experience during psychedelic group sessions predicts enduring changes in psychological wellbeing and social connectedness. Front Pharmacol 12:1–20. https://doi.org/10.3389/fphar.2021.623985

Kirschner M, Sladky R, Haugg A, Stämpfli P, Jehli E, Hodel M, Engeli E, Hösli S, Baumgartner MR, Sulzer J, Huys QJM, Seifritz E, Quednow BB, Scharnowski F, Herdener M (2018) Self-regulation of the dopaminergic reward circuit in cocaine users with mental imagery and neurofeedback. EBioMedicine 37:489–498. https://doi.org/10.1016/j.ebiom.2018.10.052

Kometer M, Schmidt A, Bachmann R, Studerus E, Seifritz E, Vollenweider FX (2012) Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. Biol Psychiatry 72:898–906. https://doi.org/10.1016/j.biopsych.2012.04.005

Koob GF, Le Moal M (2005) Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci 8:1442–1444. https://doi.org/10.1038/nn1105-1442

Kraehenmann R, Preller KH, Scheidegger M, Pokorny T, Bosch OG, Seifritz E, Vollenweider FX (2015) Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. Biol Psychiatry 78:572–581. https://doi.org/10.1016/j.biopsych.2014.04.010

Krebs TS, Johansen P-Ø (2012) Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol (Oxf) 26:994–1002. https://doi.org/10.1177/0269881112439253

Kurland AA, Unger S, Shaffer JW, Savage C (1967) Psychedelic therapy utilizing LSD in the treatment of the alcoholic patient: a preliminary report. Am J Psychiatry 123:1202–1209. https://doi.org/10.1176/ajp.123.10.1202

Le Berre A-P (2019) Emotional processing and social cognition in alcohol use disorder. Neuropsychology 33:808–821. https://doi.org/10.1037/neu0000572

Lovinger DM, Abrahao KP (2018) Synaptic plasticity mechanisms common to learning and alcohol use disorder. Learn Mem 25:425–434. https://doi.org/10.1101/lm.046722.117

Lüscher C (2016) The emergence of a circuit model for addiction. Annu Rev Neurosci 39:257–276. https://doi.org/10.1146/annurev-neuro-070815-013920

Ly C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC, Burbach KF, Soltanzadeh Zarandi S, Sood A, Paddy MR, Duim WC, Dennis MY, McAllister AK, Ori-McKenney KM, Gray JA, Olson DE (2018) Psychedelics promote structural and functional neural plasticity. Cell Rep 23:3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022

MacLean KA, Johnson MW, Griffiths RR (2011) Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. J Psychopharmacol (Oxf) 25:1453–1461. https://doi.org/10.1177/0269881111420188

Madsen MK, Fisher PM, Stenbæk DS, Kristiansen S, Burmester D, Lehel S, Páleníček T, Kuchař M, Svarer C, Ozenne B, Knudsen GM (2020) A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-HT2A receptor binding. Eur Neuropsychopharmacol 33:71–80. https://doi.org/10.1016/j.euroneuro.2020.02.001

Mason NL, Kuypers KPC, Müller F, Reckweg J, Tse DHY, Toennes SW, Hutten NRPW, Jansen JFA, Stiers P, Feilding A, Ramaekers JG (2020) Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin. Neuropsychopharmacology 45:2003–2011. https://doi.org/10.1038/s41386-020-0718-8

Mason NL, Kuypers KPC, Reckweg JT, Müller F, Tse DHY, Da Rios B, Toennes SW, Stiers P, Feilding A, Ramaekers JG (2021) Spontaneous and deliberate creative cognition during and after psilocybin exposure. Transl Psychiatry 11:1–13. https://doi.org/10.1038/s41398-021-01335-5

McCulloch DE-W, Madsen MK, Stenbæk DS, Kristiansen S, Ozenne B, Jensen PS, Knudsen GM, Fisher PM (2021) Lasting effects of a single psilocybin dose on resting-state functional connectivity in healthy individuals. J Psychopharmacol (Oxf):1–11. https://doi.org/10.1177/02698811211026454

Moeller SJ, Goldstein RZ (2014) Impaired self-awareness in human addiction: deficient attribution of personal relevance. Trends Cogn Sci 18:635–641. https://doi.org/10.1016/j.tics.2014.09.003

Monson CM, Wagner AC, Mithoefer AT, Liebman RE, Feduccia AA, Jerome L, Yazar-Klosinski-B, Emerson A, Doblin R, Mithoefer MC (2020) MDMA-facilitated cognitive-behavioural conjoint therapy for posttraumatic stress disorder: an uncontrolled trial. Eur J Psychotraumatol 11:1–7. https://doi.org/10.1080/20008198.2020.1840123

Monterosso JR, Flannery BA, Pettinati HM, Oslin DW, Rukstalis M, O'Brien CP, Volpicelli JR (2001) Predicting treatment response to naltrexone: the influence of craving and family history. Am J Addict 10(3):258–268. https://doi.org/10.1080/105504901750532148

Moos RH, Moos BS (2006) Rates and predictors of relapse after natural and treated remission from alcohol use disorders. Addiction 101:212–222. https://doi.org/10.1111/j.1360-0443.2006.01310.x

Mueller F, Lenz C, Dolder PC, Harder S, Schmid Y, Lang UE, Liechti ME, Borgwardt S (2017) Acute effects of LSD on amygdala activity during processing of fearful stimuli in healthy subjects. Transl Psychiatry 7:1–5. https://doi.org/10.1038/tp.2017.54

Nardou R, Lewis EM, Rothhaas R, Xu R, Yang A, Boyden E, Dölen G (2019) Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature 569:116–120. https://doi.org/10.1038/s41586-019-1075-9

Nezlek JB (2002) Day-to-day relationships between self-awareness, daily events, and anxiety. J Pers 70:249–275. https://doi.org/10.1111/1467-6494.05005

Nichols DE (2016) Psychedelics. Pharmacol Rev 68:264–355. https://doi.org/10.1124/pr.115.011478

Noorani T, Garcia-Romeu A, Swift TC, Griffiths RR, Johnson MW (2018) Psychedelic therapy for smoking cessation: qualitative analysis of participant accounts. J Psychopharmacol (Oxf) 32:756–769. https://doi.org/10.1177/0269881118780612

Nutt DJ, King LA, Phillips LD (2010) Drug harms in the UK: a multicriteria decision analysis. Lancet 376:1558–1565. https://doi.org/10.1016/S0140-6736(10)61462-6

Pasquini L, Palhano-Fontes F, Araujo DB (2020) Subacute effects of the psychedelic ayahuasca on the salience and default mode networks. J Psychopharmacol (Oxf) 34:623–635. https://doi.org/10.1177/0269881120909409

Petry NM, Petrakis I, Trevisan L, Wiredu G, Boutros NN, Martin B, Kosten TR (2001) Contingency management interventions: from research to practice. Am J Psychiatry 158:694–702. https://doi.org/10.1176/appi.ajp.158.5.694

Petry NM, Alessi SM, Rash CJ (2013) A randomized study of contingency management in cocaine-dependent patients with severe and persistent mental health disorders. Drug Alcohol Depend 130:234–237. https://doi.org/10.1016/j.drugalcdep.2012.10.017

Pettinati HM, Volpicelli JR, Pierce JD, O'Brien CP (2000) Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. J Addict Dis 19(1):71–83. https://doi.org/10.1300/J069v19n01_06

Pokorny T, Preller KH, Kometer M, Dziobek I, Vollenweider FX (2017) Effect of psilocybin on empathy and moral decision-making. Int J Neuropsychopharmacol 20:747–757. https://doi.org/10.1093/ijnp/pyx047

Pokorny T, Duerler P, Seifritz E, Vollenweider FX, Preller KH (2020) LSD acutely impairs working memory, executive functions, and cognitive flexibility, but not risk-based decision-making. Psychol Med 50:2255–2264. https://doi.org/10.1017/S0033291719002393

Preller KH, Herdener M, Schilbach L, Stämpfli P, Hulka LM, Vonmoos M, Ingold N, Vogeley K, Tobler PN, Seifritz E, Quednow BB (2014) Functional changes of the reward system underlie blunted response to social gaze in cocaine users. Proc Natl Acad Sci U S A 111:2842–2847. https://doi.org/10.1073/pnas.1317090111

Preller KH, Pokorny T, Hock A, Kraehenmann R, Stämpfli P, Seifritz E, Scheidegger M, Vollenweider FX (2016) Effects of serotonin 2A/1A receptor stimulation on social exclusion processing. Proc Natl Acad Sci U S A 113:5119–5124. https://doi.org/10.1073/pnas.1524187113

Preller KH, Burt JB, Ji JL, Schleifer CH, Adkinson BD, Stämpfli P, Seifritz E, Repovs G, Krystal JH, Murray JD, Vollenweider FX, Anticevic A, Hunt LT, Behrens TE (2018) Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor. elife 27:451–457. https://doi.org/10.7554/eLife.35082

Preller KH, Razi A, Zeidman P, Stämpfli P, Friston KJ, Vollenweider FX (2019) Effective connectivity changes in LSD-induced altered states of consciousness in humans. Proc Natl Acad Sci 116:2743–2748

Preller KH, Duerler P, Burt JB, Ji JL, Adkinson B, Stämpfli P, Seifritz E, Repovs G, Krystal JH, Murray JD (2020) Psilocybin induces time-dependent changes in global functional connectivity: psi-induced changes in brain connectivity. Biol Psychiatry 88:197–207. https://doi.org/10.1016/j.biopsych.2019.12.027

Prendergast M, Podus D, Finney J, Greenwell L, Roll J (2006) Contingency management for treatment of substance use disorders: a meta-analysis. Addiction 101:1546–1560. https://doi.org/10.1111/j.1360-0443.2006.01581.x

Quednow BB (2020) Social cognition in addiction. In: Verdejo-Garcia A (ed) Cognition and addiction. Academic Press, pp 63–78

Quednow BB, Kometer M, Geyer MA, Vollenweider FX (2012) Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. Neuropsychopharmacology 37:630–640. https://doi.org/10.1038/npp.2011.228

Raval NR, Johansen A, Donovan LL, Ros NF, Ozenne B, Hansen HD, Knudsen GM (2021) A single dose of psilocybin increases synaptic density and decreases 5-HT2A receptor density in the pig brain. Int J Mol Sci 22:1–14. https://doi.org/10.3390/ijms22020835

Riba J, Rodríguez-Fornells A, Barbanoj MJ (2002) Effects of ayahuasca on sensory and sensorimotor gating in humans as measured by P50 suppression and prepulse inhibition of the startle reflex, respectively. Psychopharmacology 165:18–28. https://doi.org/10.1007/s00213-002-1237-5

Rollnick S, Miller WR (1995) What is motivational interviewing? Behav Cogn Psychoth 23:325–334

Roseman L, Demetriou L, Wall MB, Nutt DJ, Carhart-Harris RL (2018) Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology 142:263–269. https://doi.org/10.1016/j.neuropharm.2017.12.041

Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, Mennenga SE, Belser A, Kalliontzi K, Babb J, Su Z, Corby P, Schmidt BL (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol (Oxf) 30:1165–1180. https://doi.org/10.1177/0269881116675512

Salamone JD, Correa M (2012) The mysterious motivational functions of mesolimbic dopamine. Neuron 76:470–485. https://doi.org/10.1016/j.neuron.2012.10.021

Sampedro F, de La Fuente Revenga M, Valle M, Roberto N, Domínguez-Clavé E, Elices M, Luna LE, Crippa JAS, Hallak JEC, de Araujo DB, Friedlander P, Barker SA, Álvarez E, Soler J, Pascual JC, Feilding A, Riba J (2017) Assessing the psychedelic "after-glow" in Ayahuasca users: post-acute neurometabolic and functional connectivity changes are associated with enhanced mindfulness capacities. Int J Neuropsychopharmacol 20:698–711. https://doi.org/10.1093/ijnp/pyx036

Scarlata MJ, Keeley RJ, Stein EA (2021) Nicotine addiction: translational insights from circuit neuroscience. Pharmacol Biochem Behav 204:1–7. https://doi.org/10.1016/j.pbb.2021.173171

Schmid Y, Liechti ME (2018) Long-lasting subjective effects of LSD in normal subjects. Psychopharmacology 235:535–545. https://doi.org/10.1007/s00213-017-4733-3

Schmid Y, Enzler F, Gasser P, Grouzmann E, Preller KH, Vollenweider FX, Brenneisen R, Müller F, Borgwardt S, Liechti ME (2015) Acute effects of lysergic acid diethylamide in healthy subjects. Biol Psychiatry 78:544–553. https://doi.org/10.1016/j.biopsych.2014.11.015

Segawa T, Baudry T, Bourla A, Blanc J-V, Peretti C-S, Mouchabac S, Ferreri F (2019) Virtual reality (VR) in assessment and treatment of addictive disorders: a systematic review. Front Neurosci 13:1–14. https://doi.org/10.3389/fnins.2019.01409

Shao L-X, Liao C, Gregg I, Davoudian PA, Savalia NK, Delagarza K, Kwan AC (2021) Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. Neuron 109:2535–2544. https://doi.org/10.1016/j.neuron.2021.06.008

Starosta AN, Leeman RF, Volpicelli JR (2006) The BRENDA model: integrating psychosocial treatment and pharmacotherapy for the treatment of alcohol use disorders. J Psychiatr Pract 12 (2):80–89. https://doi.org/10.1097/00131746-200603000-00003

Stein MD, Herman DS, Anderson BJ (2009) A motivational intervention trial to reduce cocaine use. J Subst Abus Treat 36:118–125. https://doi.org/10.1016/j.jsat.2008.05.003

Tobler PN, Preller KH, Campbell-Meiklejohn DK, Kirschner M, Kraehenmann R, Stämpfli P, Herdener M, Seifritz E, Quednow BB (2016) Shared neural basis of social and non-social reward deficits in chronic cocaine users. Soc Cogn Affect Neurosci 11:1017–1025. https://doi.org/10.1093/scan/nsw030

Vergara VM, Liu J, Claus ED, Hutchison K, Calhoun V (2017) Alterations of resting state functional network connectivity in the brain of nicotine and alcohol users. NeuroImage 151: 45–54. https://doi.org/10.1016/j.neuroimage.2016.11.012

Volkow ND, Fowler JS, Wang G-J (2003) The addicted human brain: insights from imaging studies. J Clin Invest 111:1444–1451. https://doi.org/10.1172/JCI18533

Volkow ND, Baler RD, Goldstein RZ (2011a) Addiction: pulling at the neural threads of social behaviors. Neuron 69:599–602. https://doi.org/10.1016/j.neuron.2011.01.027

Volkow ND, Tomasi D, Wang G-J, Fowler JS, Telang F, Goldstein RZ, Alia-Klein N, Wong C (2011b) Reduced metabolism in brain "control networks" following cocaine-cues exposure in female cocaine abusers. PLoS One 6:1–7. https://doi.org/10.1371/journal.pone.0016573

Volkow ND, Michaelides M, Baler R (2019) The neuroscience of drug reward and addiction. Physiol Rev 99:2115–2140. https://doi.org/10.1152/physrev.00014.2018

Vollenweider FX, Preller KH (2020) Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. Nat Rev Neurosci 21:611–624. https://doi.org/10.1038/s41583-020-0367-2

Vollenweider FX, Csomor PA, Knappe B, Geyer MA, Quednow BB (2007) The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. Neuropsychopharmacology 32:1876–1887. https://doi.org/10.1038/sj.npp.1301324

Watts R, Luoma JB (2020) The use of the psychological flexibility model to support psychedelic assisted therapy. J Contextual Behav Sci 15:92–102. https://doi.org/10.1016/j.jcbs.2019.12.004

Watts R, Day C, Krzanowski J, Nutt D, Carhart-Harris R (2017) Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. J Humanist Psychol 57:520–564. https://doi.org/10.1177/0022167817709585

Wise RA (2008) Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox Res 14: 169–183. https://doi.org/10.1007/BF03033808

Zhang G, Ásgeirsdóttir HN, Cohen SJ, Munchow AH, Barrera MP, Stackman RW (2013) Stimulation of serotonin 2A receptors facilitates consolidation and extinction of fear memory in C57BL/6J mice. Neuropharmacology 64:403–413. https://doi.org/10.1016/j.neuropharm.2012.06.007

Zhang R, Volkow ND (2019) Brain default-mode network dysfunction in addiction. NeuroImage 200:313–331. https://doi.org/10.1016/j.neuroimage.2019.06.036