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FROM RECOVERY TO RELAPSE: HOW DOES BORDERLINE PERSONALITY DISORDER INFLUENCE OF METHAMPHETAMINE ADDICTION TREATMENT OUTCOMES? AN EXPLORATORY REVIEW

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Abstract

The dual-diagnosis group of Co-occurring Borderline Personality Disorder (BPD) and methamphetamine (MA) use disorder is a high-risk group with a uniquely high rate of relapse, great withdrawal syndrome, and low treatment outcomes. This is a synthesis of neurodevelopmental, structural, functional and neurochemical data used to explain the mechanism behind this increased vulnerability. BPD is characterized by a baseline emotional hyperreactivity, impulsivity and dysregulation of stress, which is worsened by neuroadaptations associated with MA such as dopaminergic surges, neuroinflammation and synaptic damage. The structural deficits, hippocampal and amygdala atrophy, CA1 dendritic retraction, combine with functional deficits in the prefrontal-limbic circuits and neurotransmitter system(s) dysregulation (monoamines, opioid/oxytocin) to result in a self-feeding loop of emotional dysregulation, withdrawal distress, and compulsive drug-seeking. Adversity in early life and epigenetic adaptations like hypermethylation of the NR3C1 contribute to increased vulnerability and poor adaptive coping. The review points to the fact that longitudinal tracking of BPD-MA comorbidity is still a research gap and restricts the knowledge regarding neuroadaptive changes and the processes of relapse over time. The use of pharmacological, psychotherapeutic, and neuromodulator interventions as integrative, neuroscience-based treatment methods is necessary to address the vulnerabilities in multiple levels, increase top-down regulation, and improve the results of recovery. The next research directions should be individualized, trauma-informed methods to reduce the rates of relapse and enhance resilience among this dual-diagnostic group.

INTRODUCTION

Addiction and BPD in Methamphetamine Use

According to the American Psychiatric Association (2022), addiction is a relapsing and chronic disorder distinguished by compulsive interpretation of drug-seeking regardless of the damaging effects. Methamphetamine (MA) is a strong psychostimulant that causes sharp increases in dopamine, serotonin and norepinephrine, which induces strong euphoria and reinforcement of motivated behavior (Chang et al., 2007; Koob

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and Volkow, 2010). The repeated exposure leads to such deep neuroadaptations as neuroinflammation, oxidative stress, and synaptic degeneration, which are most evident in the ventral tegmental area (VTA), hippocampus, striatum, and prefrontal cortex (Barral et al., 2017; Hu et al., 2019). Further deteriorating the executive control, metabolic changes occur in the orbitofrontal cortex (OFC), a part of the brain believed to be essential in risk-reward assessment and controlling compulsive behavior, which may continue long into the abstinence period, with only partial recovery being noted after several years of abstinence (Volkow et al., 2001). (see fig.3).

Moreover, the neuroinflammation induced by MA can persist already two years after discontinuation, which highlights persistent neurotoxicity of the drug (Khan et al., 2025). All these disruptions lead to impaired executive functioning, decreased reward sensitivity, and impaired cognitive control, and chronic use causes impairment in attention, working memory, and verbal learning (Chang et al., 2007; Prasad et al., 2023). Extended exposure to MA also robs dopamine stores and destroys dopaminergic and serotonergic endings.

The Borderline Personality Disorder (BPD) (also known as Emotionally Unstable Personality Disorder (EUPD)) is a complicated and multidimensional psychiatric disorder that normally appears in early adulthood and covers a population of 1-2 percent of the general population. It tends to manifest itself during adolescence and is defined in the DSM-5-TR (American Psychiatric Association, 2022), as widespread and unremitting disturbances in emotional stability, impulsivity, habitual self-harm, and a suicidal mortality rate of about 10%, 50 times more than that of the general population. BPD patients are more sensitive to stress, have disrupted impulse control, and dysregulated emotions - aspects that directly overlap with neural circuits impaired using methamphetamine (MA) (Silvers and Guassi Moreira, 2021; Wilson et al., 2021). Even though stimulants like MA have the potential to provide temporarily relieving affective impact in BPD, a priori orbitofrontal and wider front-limbic impairments aggravate impulsive conduct and maladaptive decision-making, which in turn strengthen the vicious dynamics of dysregulation and relapse (Silvers and Guassi Moreira, 2021; Wilson et al., 2021). The result of MA use is the aggravation of emotional instability, impulsivity, and interpersonal turmoil, which perpetuate the use of drugs due to affective reasons and further deteriorate the level of functional impairment (Barral et al., 2017). Relapse is one of the most significant clinical issues: about 61 per cent of MA consumers resume the use within the first year of treatment (Elhadi et al., 2023). However, little is known about relapse patterns among those with co-occurring BPD, even though the research has found that BPD is a good predictor of resistance to treatment, early relapse, and poor long-term outcomes in populations with SUD (Fenton et al., 2012; Fletcher and Reback, 2013).

Fluctuations between neurotoxic effects of MA and inherent emotional instability of the BPD result in high-risk clinical phenotype with rapid relapse, low distress tolerance and severe psychosocial deficiency (Bornovalova and Daughters, 2007; Friedel, 2004). The converging literature indicates that both conditions have dysfunctions in common, suggesting shared dysfunctions of neural systems that are involved in the regulation of emotion, reward processing, and stress responsivity, including prefrontal hypoactivity, hyperactivity of the amygdala, malfunctions of mesolimbic dopamine signaling, and increased susceptibility to stress-induced relapse (Silvers and Guassi Moreira, 2021; Wilson et al., 2021; Koob and Volkow, 2010).

Dual Diagnosis of Personality Disorders and Substance Use.

Dual diagnosis is a significant clinical problem, as it is a co-occurring personality disorder (PD) and substance use disorder (SUD), which occurs in 50-92% of patients with PDs (Zhang et al., 2018). Comorbidity PD is also a major complication of SUD progression: the affected individuals experience shorter abstinence duration and increased rates of treatment dropout (Parmar & Kaloiya, 2018) as well as The SUD alone is unlikely to result in the successful remission of the

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co-morbid PD, which underscores the importance of combined treatment choices.

The use of MA is especially an issue in BPD because of the overlaps in vulnerability to impulsivity, emotional dysregulation, and reward-based decision-making (Koob and Volkow, 2010; Barral et al., 2017), and substance use tends to serve as one of the maladaptive affect regulation strategies.

Neurobiology Characteristics of BPD and Correlation to Methamphetamine Addiction.

The condition is characterized by the deregulation of fronto-limbic circuitry most prominently, prefrontal hypoactivity, and amygdala hyperreactivity that affect emotion regulation, increases stress reactivity, and weakens cognitive control (Wilson et al., 2021; Silvers and Guassi Moreira, 2021). Such weaknesses heighten dependence on maladaptive coping mechanisms such as using drugs which further increases vulnerability to addictions to stimulants (Bornovalova & Daughters, 2007). MA exacerbates these deficits through the generation of surges of monoamine neurotransmitters and the development of neuroinflammation, oxidative stress, and synaptic degeneration in the VTA, hippocampus, striatum and prefrontal cortex (Barral et al., 2017; Hu et al., 2019). There is also a further decrease in executive function, attention, working memory, and verbal learning in chronic MA exposure, which undermines neural systems that are important in maintaining abstinence (Chang et al., 2007; Prasad et al., 2023).

New findings highlight a neurobiological overlapping dysfunction in both BPD and MA addiction such as prefrontal hypoactivity, amygdala hyperreactivity, dysregulated mesolimbic dopamine release, and increased stress-induced relapse vulnerability (Silvers and Guassi Moreira, 2021; Wilson et al., 2021; Koob and Volkow, 2010). These neural circuits become even more unstable by early trauma and developmental adversity, which is so prevalent in BPD, and which further supports the use of MA as a maladaptive emotion-regulation strategy (Leichsenring et al., 2024), which is a major contributor to a poor treatment outcome in the case of methamphetamine addiction.

METHODOLOGY

Study Design:

In this review, qualitative literature review was used to analyze the neurobiological and clinical nature of co-occurring borderline personality disorder (BPD) and Methamphetamine Addiction (MA). The combination of theory-oriented and integrative approach allowed the review to summarize convergent evidence in the areas of molecular neuroscience, neuropsychology, and epidemiology without losing sight of mechanisms that are pertinent to relapse risk in BPD-MA comorbidity.

Search Strategy:

The search through PubMed, APA PsycNet, ScienceDirect, and Google Scholar included English language research published to January 2025. The keywords were BPD, methamphetamine use disorder, dual diagnosis, and relapse and Boolean operators were applied to narrow down the search. Other records were located by manual searches, such as reference chaining and citation of the most significant articles (see Fig.1 below).

Inclusion Criteria:

- Peer-reviewed, English studies (1992–2025).
- Empirical data on BPD and/or methamphetamine use disorder.
- Data on treatment outcomes, relapse, or neuroimaging.

Exclusion Criteria:

- Non-English or outside the date range.
- Focused on disorders other than BPD.
- Lacked sufficient methodological rigor or clinical detail.
- case reports with fewer than five participants.

Data extraction and Synthesis:

Assessment of the Literature was conducted independently by the author. A **narrative and**

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descriptive synthesis approach was used**. Quantitative** data (e.g., relapse rates, neurobiological findings, and treatment outcomes) were summarized as reported in the reviewed literature. **Qualitative** data were analyzed thematically to highlight the common neurobiological vulnerabilities and psychosocial dynamics associated with dual diagnoses.

The following domains were considered in the evaluation: Adequacy of sample size and representativeness, clarity and consistency of diagnostic criteria (DSM-IV, DSM-5, ICD-10), reliability of outcome reporting (e.g., relapse rates, treatment response, neuroimaging findings), transparency of analytic strategy, and reporting confounders and other potential sources of bias.. Given the single-reviewer design, discrepancies were not applicable. No automation tools were employed.

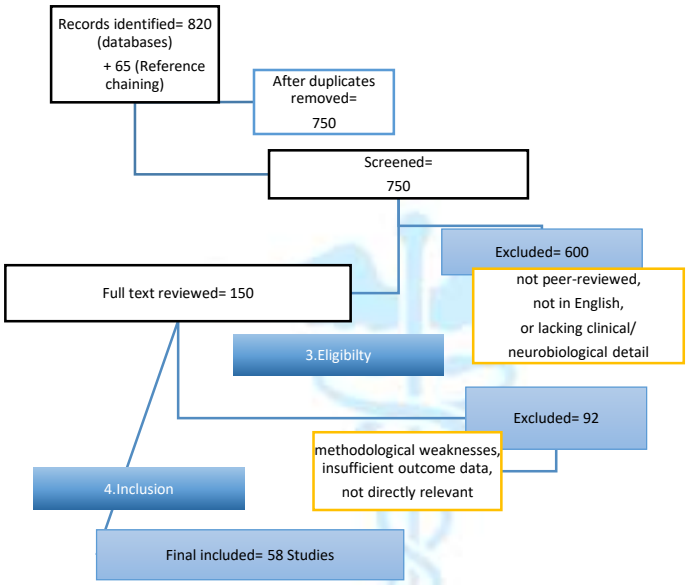

Figure 1 The process of identification, screening and selection is summarized in a PRISMA flow diagram.

NEUROBIOLOGY:

Short-Term Effects of Methamphetamine

Methamphetamine exerts its primary psychoactive effects by sharply increasing extracellular concentrations of monoamines—dopamine (DA), serotonin (5-HT), and norepinephrine (NE)—in brain regions critical to reward, motivation, and emotional regulation (Chang et al., 2007; Koob & Volkow, 2010). This surge activates the mesolimbic reward pathway, particularly dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), producing intense euphoria and reinforcing drug-seeking behavior (Hu et al., 2019; May et al., 2020).

The graphic illustration below depicts that it induces the highest amount and most sustained increase in dopamine in the Reward center in the brain, among the four drugs shown. (See Figure 2, Bottom-Right Panel) Methamphetamine Produces an enormous surge in dopamine—up to approximately **1,500**% above basal levels—within the first hour, followed by a rapid decline within three hours**,** its action are mediated by the mesolimbic pathway in brain. Unlike cocaine, which has a short plasma half-life of approximately 90 minutes, methamphetamine remains active for up to 12 hours, resulting in prolonged stimulation and heightened abuse potential (Rusyniak, 2011).

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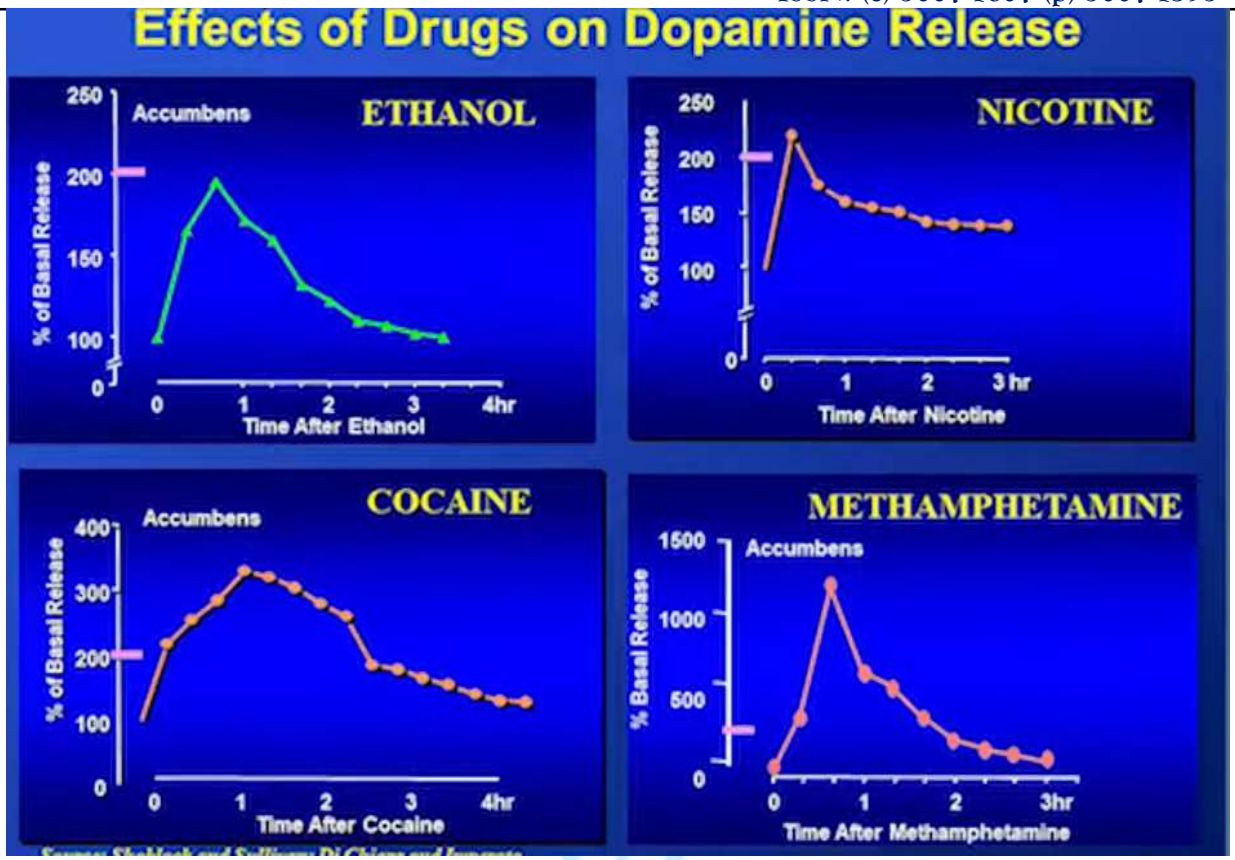

Figure 2 Neuropharmacology of Methamphetamine, and Effects of drugs on the brain's reward center -Nucleus Accumbens (NAc)

Pharmacologically, the pharmacological profile of methamphetamine resembles the pharmacological profile of acute stress response. It causes tachycardia, hypertension, vasoconstriction, bronchodilation, and hyperglycemia- changes associated with an increase in catecholaminergic activity (Rusyniak, 2011). It is a powerful CNS-stimulant which causes one to be more alert, cheerier, more confident, and temporarily less anxious or less fatigued-effects that might seem at first glance to be adaptive particularly in people with a predisposed affective dysregulation or cognitive impairments (Rusyniak, 2011).

From Reward to Habit: Neurocircuitry of Compulsive Drug Use

First, there is a mesolimbic reward pathway through which the acute reinforcing effects of drug use are mediated. The ventral tegmental area (VTA) dopaminergic neurons release abundant dopamine into the nucleus accumbens (NAc), which is the brain central reward center, in the ventral striatum, to bring about euphoria and promote reward learning (Chang et al., 2007). The D1 receptor-expressing medium spiny neurons (MSNs) of the NAc activate this feedback to the midbrain structures and enhance the association of drug-associated cues with a reward.

With repeated exposure, dopaminergic projections progressively extend from the **Ventral Striatum or NAc shell** to the **core** and then to the **dorsal striatum**, reinforcing stimulus–response associations and driving the transition from goal-directed to habitual drug-seeking behavior (Barral et al., 2017). This progression follows a **spiraling connectivity pattern** striatum, moving from **ventral to dorsal domains**.

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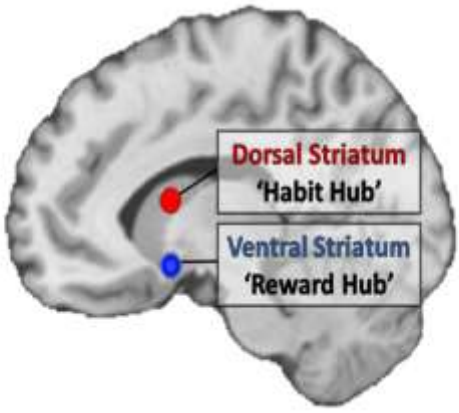

Figure 3 The pathway from impulsive to compulsive drug-use is marked from ventral to dorsal striatum, as shown in the illustration above.

Chronic hyperactivation of this system also leads to **reduced dopamine receptor availability, blunted responsiveness to natural rewards**, and **narrowed behavioral flexibility** (Koob & Volkow, 2010; Ferrer-Ferrer et al., 2023). Prolonged methamphetamine exposure depletes dopamine reserves and damages dopamine and serotonergic terminals. PET studies show that methamphetamine use reduces striatal dopamine D2 receptor availability, dopamine transporter (DAT), serotonin transporter (SERT, also known as 5-HTT or SLC6A4), and vesicular monoamine transporter 2 (VMAT2), leading to persistent cognitive and motor deficits (Chang et al., 2007; Volkow et al., 1997).

Within this circuit:

- the **medial prefrontal cortex (mPFC)** regulates early inhibitory control and adaptive decision-making
- the **orbitofrontal cortex (OFC)** governs later, compulsive phases via projections to the **substantia nigra pars compacta (SNc)** (Elhadi et al., 2023)
- . Dysregulation of these cortical regions, particularly OFC hypoactivity and disrupted glutamatergic signaling, exacerbates **cue-induced craving** and strengthens automated drug-seeking behaviors (Liu et al., 2024)

Ultimately, chronic engagement of dorsal striatal pathways, compounded by diminished prefrontal regulation, produces the hallmark features of addiction (see Figure 3). **compulsive drug use, reduced sensitivity to consequences, and persistent relapse vulnerability** (Koob & Volkow, 2010; Barral et al., 2017; Ferrer-Ferrer et al., 2023).

Neural Landscape in Borderline Personality Disorder.

The interplay of interpersonal hypersensitivity, early-life environmental adversity, epigenetic modulations, and genetic vulnerability also leads to the development of the neurodevelopmental phenotype of emotional dysregulation, impulsivity, and interpersonal hypersensitivity in Borderline Personality Disorder (BPD). Heritable causes are factors that play approximately 42 percent of the responsibility of BPD, and they affect primarily serotonergic and dopaminergic as well as stress-response mechanisms, rendering individuals vulnerable to emotional hyperactivity and impulsive behaviors (Wilson et al., 2021). Gene-environment interactions including the MAOA-L allele, childhood maltreatment, and SERT (5-HTTLPR-S) non-DRD2/DRD4 polymorphism are once more conducive to the impulsivity and affective lability and the polymorphism of SERT (5-HTTLPR-S) and DRD2/DRD4 is again supportive of the reward-seeking behavior and interpersonal hypersensitivity (Frazzetto et al., 2007; Trull et al., 200 The epigenetic alterations, including NR3C1

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hypermethylation that disrupts the negative feedback of the HPA-axis, and heightens CRH-mediated hyperarousal, are triggered by early misfortunes, including emotional negligence, inconsistent care giving, and prenatal stress (Martin-Blanco et al., 2015; Winsper et al., 2017). These molecular and epigenetic abnormalities are centered on fronto-limbic networks: affective instability, identity confusion, hyper-responsiveness to social data, and ineffective formation of stress responses is premised on reduced functioning of the dorsolateral and medial prefrontal cortices, increased functioning of the amygdala and impaired hippocampal plasticity (Neu and Robinson, 2003; Farrell and Shaw, 2012; Soloff et al., 2008). Oxytocinergic and m-opioid dysfunction is also another factor that further depletes social-affective buffering and hedonic control and alexithymia is a manifestation of ineffective interoception and emotion recognition that makes them vulnerable to maladaptive coping and substance use (Wilson et al., 2021; Stanley and Siever, 2010; Miller et al., 2020).

This molecular architecture is backed by both anatomical and neurocircuitry evidence that demonstrates an overlap of structural and functional damage in the fronto-limbic and corticolimbic and reward circuits. The affective regulation and executive control are lost by volumetric losses of hippocampus (16-21%), amygdala (~8%), impaired frontal gray matter, and hyperactive reactions of amygdala to social and affective stimuli, which supports the increases of interpersonal sensitivity (see Table 1) (Lis et al., 2007; Johnson et al., 2003; Leichsenring et al., 2011; Begemann et al., 2023).

The deficits in the orbitofrontal cortex (OFC) risk/reward evaluation result in the facilitation of impulsive decision-making, and inefficient drug-seeking, and the hypoactivity of the anterior cingulate cortex (ACC) results in the restriction of adaptive reactions to stress and negative effect linked to withdrawal (Ochsner et al., 2004; Zanarini et al., 1998; Gowin et al., 2014). Hippocampal atrophy impairs contextual learning, memory consolidation, stress recovery, and is worsened by the effects of impaired synaptic plasticity and neurotrophic loss (BDNF-mediated) including effects of Val66Met polymorphism (Soloff et al., 2008; Perroud et al., 2013; Champagne et al., 2008).

Borderline Relapse Connection and Addiction levels.

Binge/ Intoxication Phase- Dopaminergic Amplification, Reward Systems and BPD Pre-disposition.

The elevated rapid rise of extracellular dopamine (DA) in nucleus accumbens (NAc), ventral tegmental area (VTA), caudate and dorsal striatum, reward valuation, learning reinforcement and habit formation are all involved in causing the binge/intoxication stage (Koob and Volkow, 2010). MA simultaneously increases synaptic norepinephrine (NE) and serotonin (5-HT), which only increase further arousal, hedonic tone and emotional disinhibition. These acute neurochemical developments produce the euphoria, increased self-confidence and amplification of senses that are a characteristic of intoxication by the stimulants.

These dopaminergic releases are very strong systems of negative-reinforcement to individuals with borderline personality disorder (BPD). The high in the dopaminergic is not proportionately rewarded, the high is a state of chronic affective dysregulation, interpersonal hypersensitivity and state of emotional pain as a base (Friedel, 2004; Stanley and Siever, 2010). The hyperirritability with being rejected and dysphoria, in turn, makes MA a potent means of affective evasion: the drug lights up a short-term blockage of chronic emptiness, anger, and fear of rejection, thereby supporting compulsory drug intake both hedonic and anti-dysphoric.

The neuroimaging operations of BPD show that the dorsal striatum and the posterior insula are over-activated toward interpersonal stress and anger provocation, and they depict augmented interoceptive and habit responses (Martin-Blanco et al., 2015; Krause-Utz et al., 2014). These circuits overlap directly with dopaminergic locations of action of MA. A neuroadaptive stressor of stimulant addiction is an early neuroadaptive stressor, a structurally and functionally sensitised

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dorsal striatum, accelerates the transition to goal-oriented to habitual use. The hyperreactivity of posterior insula of the magnified interoceptive distress enhances the rewarding value of the emotional numbing brought about by MA. These pre-existing BPD weaknesses coupled with those that happen at an accelerated rate contribute to cue encoding of the drug related cues and increased incentive salience leading to compulsive stimulant use. The genetic specificity of BPD is based on the alternative of the dopaminergic (DRD2, DRD4) and serotonergic (5-HTTLPR) signaling as well as variations of the MAOA that enhance impulsiveness and reward-seeking in the stress (Friedel, 2004; Frazzetto et al., 2007; Wilson et al., 2021). These genetic factors maximize reactivity of MA in striatum and predisposes an individual to react in short term compared to a long term effect- establishing a neurobiological foundation that is very susceptible to stimulant addiction.

Withdrawal/Negative Affect Stage: Stress Dysregulation, Neurotoxicity, and Convergent Fronto-limbic Impairments.

The withdrawal/ negative effect stage is the most sensitive and critical period of BPD patients. The impact of MA is gone and the dopamine and serotonin level returns to a lower level and it is substituted by the development of dysphoria, irritation and anhedonia states caused by the rise in dynorphin activity in the NAc (Koob and Le Moal, 2008). Simultaneously, MA withdrawal slows down the metabolic activity and functional activity in an anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and insula (Chang et al., 2007). These domains are already compromised in the case of BPD, conflict monitoring, distress tolerance and emotional labeling.

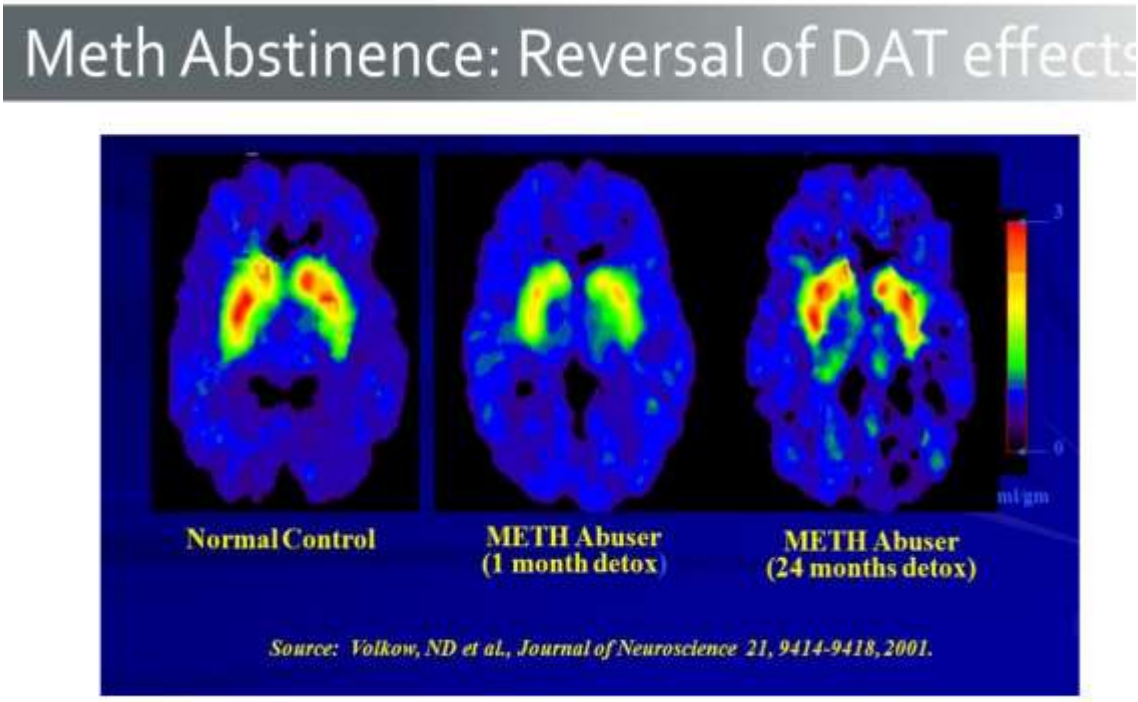

Figure 4 PET Scan shows partial recovery of Dopamine Transporter (DAT)and their density in the OFC (Orbitofrontal cortex) after prolonged abstinence (approximately 15months).

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MANO neurotoxicity elevates these impairments, such as a decrease in the density of dopamine transporter (DAT), destruction of serotonergic terminals, mitochondrion dysfunction, glutamate dysregulation, and inflammation in the brain (Ahmad, 2013; Nestler, 2018). PET studies have

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shown that there has been a decline in the striatal dopamine D2 receptor and dopamine transporter (DAT) density inclination that contributes to the long-term malfunction of executive functioning, working memory, episodic recall, and anhedonia (Volkow et al., 1997; Chang et al., 2007). Figure 4 indicates that the density in DAT in the OFC partly goes back to normal following approximately 24 months of abstinence (Volkow et al., 2001).

It also triggers the hypothalamic-pituitary-adrenal (HPA) axis during the withdrawal stage that increases the activity of corticotropin-releasing hormone (CRH) and the stress sensitivity. Epigenetic alterations common to BPD, such as the NR3C1 hypermethylations due to an early-life adversity event, the downregulation of glucocorticoid receptor, and the inability of negative feedback to be regulated, resulting in dysregulated HPA axis in the long-term (Martin-Blanco et al., 2015; Winsper et al., 2017). Thus, BPD individuals have been programmed in genetic and epigenetic terms to over-express the same stress-response processes that are triggered by MA withdrawal.

BPD is anatomically connected to a reduced hippocampal size, smaller amygdala size and the prefrontal cortex atrophy (Lis et al., 2007; Begemann et al., 2023). MA produces the identical consequences of neurotoxicity: hippocampal atrophy, oxidative stress, and glutamate-mediated excitotoxicity (Ahmad, 2013). The ongoing degeneration of hippocampus and amygdala disrupts the contextual fear control, memory consolidation and emotional processing-enhancing threat overgeneralization and growing distress associated with withdrawal.

The ACC and the OFC are also hypoactive in both disorders as far as functions are concerned. This withdrawal interferes with executive control of negative affect and it cannot reassess indications of craving. The emotional lability and impulsive behavioral responses in BPD are found on the same deficiency, which creates a synergistic and self-reinforcing malfunctioning. The result is a withdrawn state, that is, one that is highly dysphoric, highly irritable, and low, higher-order regulatory resources-things, which can readily lead to a relapse.

Neurobiological, genetic, and emotional vulnerability is combined at this stage: low serotonergic tone increases anger and rejection sensitivity, impaired oxytocinergic and m-opioid signals weaken social soothing and hedonic stability (Stanley and Siever, 2010; Wilson et al., 2021), and the inability to correctly recognize the state of internal withdrawal occurs due to Alexithymia (Miller et al., 2020). The resulting increment of withdrawal profile with emotional havoc, low distress tolerance and desperate attempts to flee intolerable internal conditions-transforms MA relapse into a given conclusion.

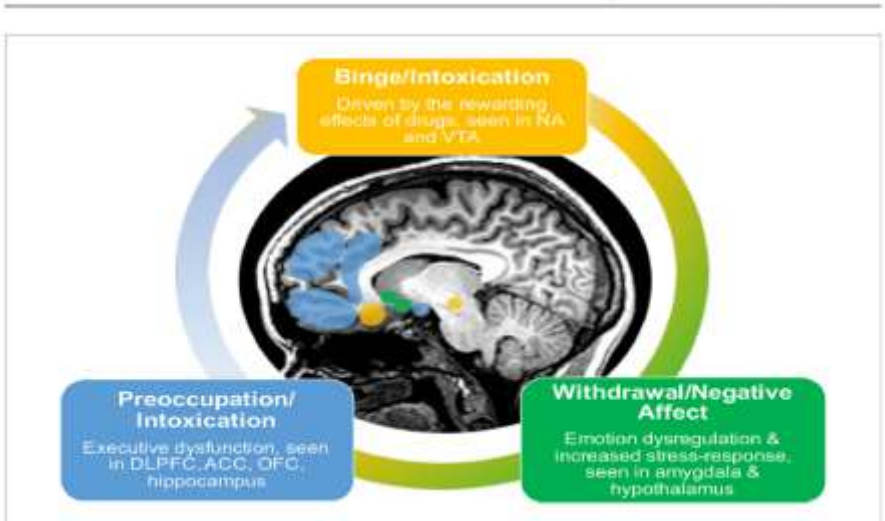

Figure 5 The role of negative reinforcement in methamphetamine addiction.
SOURCE: May et al.,2020.

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Preoccupation/Anticipation Stage: Craving Dynamics, Executive Breakdown, and Salience Network Destabilization

Preoccupation/anticipation phase involves the re-occurrence of the craving, intrusive rumination, sensitivity to cues and compulsive urge-relevant behaviors. The phase is a chronic malfunction of the circuits of salience detection, value appraisal, future-focused decision-making the OFC, ventromedial prefrontal cortex (vmPFC), amygdala, hippocampus, and insula in stimulant addiction (Koob and Volkow, 2016; Chang et al., 2007).

Hypoactivity of the OFC and the vmPFC of the users of MA impairs the determination of the long-term outcomes and suppression of well-developed drug-seeking behavior. The process of structural recovery is gradual: The PET results show that a partial restoration of the density of DAT does not happen until 12-20 months later, when the reward systems are still hypersensitive to cues and biased to instant relief (Chang et al., 2007). (see fig4).

Parallel deficits in BPD are caused by developmental trauma, insecure attachment and chronic hyperarousal. OfC dysfunction reduces the risk-reward assessment, whilst the count of dorsal ACC, and the dorsal ACC and the vmPFC leads to resolve conflicts on emotions and maintenance of the goals (Ochsner et al., 2004; Leichsenring et al., 2011). These places are also critical in overcoming the desire to want things. Their poor functioning in BPD means that the drug cues become significantly more escapable as compared to long-term treatment goals. The hyperreactive amygdala also over-enhances the craving, by enhancing emotional memory of the drug cues, and amplifying affective responses during interpersonal stress of BPD (Soloff et al., 2008). There is a loss in contextual modulation of cues due to the hippocampal atrophy coupled with the aggravation of neurotoxic effects of MAs resulting in stimuli pertaining to the pre-drug use being excessively salient and hard-to-disassociate (Teicher et al., 2016).

One of the networks that integrate interoceptive state and motivational requirements is salience network (insula + dorsal ACC). In both forms of addiction BPD and MA, this network is dysfunctional: hyperactivation of insula increases the severity of body distress and hypoactivity dorsal ACC suppresses the calibration of responses (Martin-Blanco et al., 2015; Okita et al., 2016). This is an imbalance and it develops a cue induced craving and compulsive rumination of drug taking. Notably, rumination and emotion suppressive coping by patients with BPD activate the default mode network (DMN) to the degradation of the executive control. This biased DMN control heightens the force of intrusive craving-filled thoughts and reduces sensitivity to the cognitive-behavioral solutions (Ochsner and Gross, 2014). The result is a vicious cycle of **craving → emotional overload → impaired regulation → relapse**.

Neurodevelopmental vulnerabilities—including defective dorsolateral prefrontal cortex (dlPFC) maturation, disrupted temporo-parietal junction (TPJ) functioning, and impaired hippocampal plasticity—further diminish self-representation, impulse control, and contextual decision-making (De Kloet & Joëls, 2023; Svrakic & Zorumski, n.d.). Because these circuits support the capacity to hold long-term goals in mind, their dysfunction predisposes individuals to relapse during high-risk emotional states. The dynorphin–κ-opioid system plays an additional role in the preoccupation stage. Elevated dynorphin during and after withdrawal induces dysphoria and anhedonia, amplifying core BPD symptoms such as emptiness and emotional pain. This neurochemical environment increases motivational pressure to seek MA as a means of restoring hedonic balance (Koob & Volkow, 2016; Stanley & Siever, 2010).

Table 1 Detailed Comparison of Brain Regions with overlapping Abnormalities in BPD and Methamphetamine Addiction(MA).

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Dorsolateral Prefrontal Cortex (Dlpfc)	Markedly reduced activity and lower **N-acetylaspartate (NAA)** concentrations (indicative of compromised neuronal integrity) leading to impaired executive function and emotion regulation (Tebartz van Elst et al., 2001; Johnson et al., 2003).	Chronic methamphetamine use further diminishes dlPFC function, contributing to deficits in executive control and decision-making during withdrawal and recovery (Chang et al., 2007).	✓
Ventromedial Prefrontal Cortex (vmPFC)	Hypoactivity in the vmPFC impairs the integration of emotional and social information, reducing "top–down" regulatory control (Johnson et al., 2003; Leichsenring et al., 2011).	Methamphetamine-induced neuroadaptations further disrupt vmPFC regulation, exacerbating poor decision-making and emotion dysregulation (Chang et al., 2007).	✓
Orbitofrontal Cortex (OFC)	Underactivity in the OFC contributes to impaired risk-reward evaluation and poor decision-making (Leichsenring et al., 2011).	Neurotoxic effects from methamphetamine compromise OFC function, further affecting risk assessment and impulse control (Chang et al., 2007).	✓
Anterior Cingulate Cortex (ACC)	Reduced ACC activation impairs conflict monitoring and the regulation of negative emotions, affecting self-soothing capacities (Leichsenring et al., 2011; Stevens et al., 2011).	Altered ACC metabolism and blood flow have been observed during withdrawal, indicating disrupted cognitive control and emotional regulation (Stevens et al., 2011).	✓
Amygdala	Hyperactivity in the amygdala, with reports of approximately an **8%** reduction in volume, underlies intense emotional reactivity and impulsivity (Johnson et al., 2003; Leichsenring et al., 2011).	Methamphetamine use heightens amygdala responsiveness, contributing to persistent negative affect and stress reactivity, though specific volume reductions are less consistently reported.	✓
Hippocampus	Significant reduction in hippocampal volume (approximately **16–21%**) compromises memory and stress regulation, affecting synaptic plasticity (Lis et al., 2007; Champagne et al., 2008).	Neurotoxic effects of methamphetamine further impair hippocampal plasticity and function, worsening memory deficits and stress responsiveness during withdrawal (Chang et al., 2007).	✓
Insula	Altered insular activation is associated with heightened sensitivity to interpersonal cues and contributes to overall emotional dysregulation (Ochsner et al., 2004).	Abnormal insular processing is linked to disrupted risk evaluation and increased vulnerability to relapse in methamphetamine users (Gowin et al., 2014; Huang et al., 2022).	✓

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Parietal Cortex	Abnormal activation patterns in the parietal cortex may impair the integration of sensory information, contributing to emotional and cognitive deficits (Ochsner et al., 2004).	Some studies report altered parietal cortex function in methamphetamine addiction, although quantification is less robust; these alterations may affect attentional processing during recovery (Huang et al., 2022).	✓
Dorsal Striatum	While not a primary focus in BPD, dopaminergic dysregulation may indirectly affect dorsal striatal function, influencing habit formation and impulse control (Friedel, 2004).	The dorsal striatum is heavily involved in the transition to compulsive drug-seeking behavior, with methamphetamine-induced changes contributing to persistent habits (Wickens & Kotter, 1995; Calabresi et al., 1997).	✓
Nucleus Accumbens (NAc)	Although less directly studied in BPD, disruptions in reward processing implicate abnormal NAc function in the context of impulsivity and affect dysregulation (Gunderson & Lyons-Ruth, 2008).	Critical for reward and reinforcement, the NAc undergoes significant neuroadaptive changes due to methamphetamine use, altering its response to natural rewards and contributing to compulsive drug-seeking (Friedel, 2004).	✓

Structural Vulnerabilities

- Reduced hippocampal volume (16–21%) and amygdala volume (~8%) in BPD relative to healthy controls (Johnson et al., 2003; Lis et al., 2007).
- CA1 dendritic deficits impair synaptic plasticity and long-term potentiation (Ahmad, 2013; De Kloet & Joels, 2023).
- Orbitofrontal cortex (OFC) abnormalities impact valuation, inhibitory control, and reward processing (Chang et al., 2007; Koob & Volkow, 2010).

Functional Dysregulation

- Anterior cingulate cortex (ACC) hypoactivity compromises conflict monitoring and error detection (Ochsner et al., 2004; Zanarini et al., 1998).
- Insula dysfunction disrupts interoceptive awareness (Huang et al., 2022).
- Dorsolateral prefrontal cortex (DLPFC) imbalances top-reduce control and decision-making (Svrakic & Zorumski, n.d.).

Neurotransmitter Dysregulation

- Dopamine depletion and receptor downregulation exacerbate reward-seeking behaviors (Koob & Volkow, 2016; Nestler, 2018).
- Mu-opioid receptor (MOR) / kappa-opioid receptor (KOR) imbalance heightens dysphoria and withdrawal intensity (Gowin et al., 2014).
- Hyperactive HPA axis and dysregulated corticotropin-releasing factor (CRF) increase stress reactivity (Leichsenring et al., 2011).
- Oxytocin and endogenous opioid deficits reduce natural soothing and emotion regulation (Okita et al., 2016).

Behavioral and Clinical Findings

- Elevated sensitivity to emotional and social stressors (Champagne et al., 2008; Martín-Blanco et al., 2015).
- Impaired recognition and processing of internal states (alexithymia) promote affect-driven relapse (Huang et al., 2022).
- Intensified withdrawal dysphoria and compulsive, emotion-driven drug-seeking behavior (Elhadi et al., 2023; Fenton et al., 2012).

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Epidemiological Burden, Prevalence, and Clinical Relevance of BPD and Methamphetamine Use

Co-occurring Borderline Personality Disorder (BPD) and methamphetamine (MA) use disorder represents a high-risk, complex dual-diagnosis population with significant clinical and public health implications. Epidemiological studies indicate that approximately 80% of individuals with BPD develop a substance use disorder, with a particular predilection for stimulants and sedatives rather than alcohol (Friedel, 2004; Trull et al., 2018; Barral et al., 2017). The prevalence of BPD is significantly greater among MA users than among other disorders; 35.5% of participants with methamphetamine-induced psychosis have BPD, and 6.6% have antisocial personality disorder (Eslami-Shahrbabaki et al., 2015). In line with the borderline traits, there is an additional influence of personality types typified by high novelty-seeking and harm avoidance, which predisposes people to the MA initiation and compulsive use (Ma et al., 2020).

BPD-MA comorbidity is clinically linked with a disproportionately poor outcome. Patients have a higher level of emotional dysregulation, impulsiveness, and interpersonal instability, which deter abstinence, raise treatment dropout risk, and worsen the relapse risk (Bornovalova and Daughters, 2007; Fenton et al., 2012). In contrast to the use of substances in antisocial personality disorder, which is mainly externally affected, BPD-related MA use mostly acts as an emotion-regulation mechanism, which helps to alleviate internal distress (Philips et al., 2012; Morken et al., 2017). This negative-reinforcement cycle is maladaptive and leads to long lasting dependence especially when there is interpersonal or emotional pressure. The complex interaction of neurobiological risk factors, and coping behavioral deficits makes BPD-MA dual diagnosis a high-risk clinical paradigm that needs combined, neuroscience-based interventions. Investigating the specific mechanistic associations between personality characteristics, stress response, and the course of relapses, however, cannot be included in the scope of this review and is already a research gap that requires critical attention in the future.

DISCUSSION

The neurobiological basis of Borderline Personality Disorder (BPD) and methamphetamine (MA) addiction have a common basis in their facilitation of emotional ineptitude, impulsive reward seeking and relapse in stress management responses. This comorbidity is not an additive risk condition, rather, it is a convergent and mutually reinforcing neurodevelopmental and neurocircuitry pathology, which entails damage to fronto-limbic regulation, stress-axis destabilization, monoaminergic volatility, and neuroplastic resilience. The present synthesis combines molecular, neurodevelopmental and systems-wide evidence that indicates why individuals with BPD experience disproportionately high levels of relapse after being exposed to MA.

Genetic, Epigenetic, and Monoaminergic Vulnerabilities Intensifying Reward and Stress Reactivity

It is a trait of a biologic pattern of an unfortunate serotonergic and dopaminergic activity to have the item of hereditary factors (approximately 42 percent of the BPD liability) (Wilson et al., 2021). SERT (5-HTTLPR-S) polymorphisms lower the functioning of the transporter and enhance the reaction of the amygdala to stress or interpersonal danger or desertion-associated indicators, one of the important instigators of MA craving and relapse. Parallel DRD2/DRD4 changes increase reward sensitivity and impulsivity (Trull et al., 2000; Friedel, 2004), which exposes one to outbursts of dopaminergic MA.

The MAOA-L childhood maltreatment interaction has been a disorder-specific monoaminergic sensitisation model. The researchers (Frazzetto et al., 2007) established the fact that inmates of the MAOA-L genotype who suffer BPD and those who suffer the ASPD but experienced early adversity have substantial quantities of impulsiveness. This is an inactive genotype that promotes serotonin, dopamine and norepinephrine synaptic turnover to bring about an affectively volatile, stress-sensitive phenotype 4 directly boosted by the pharmacodynamics of MA. This intersection is among the reasons of the

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outbreak of the controlled to compulsive use of MA in BPD patients.

NR3C1 hypermethylation, present in BPD groups (Martin-Blanco et al., 2015) blocks glucocorticoid receptor, glucocorticoids negative feeding, maintains cortisol, which enhances the craving, increases amygdala responses and deviant PFC-mediated suppression. Adversity in early-life also changes CRH/CRHR2 signalling and this augments the prolonged hyperarousal of the amygdala, precisely the circuitry that contributes to negative reinforcement, withdrawal distress and relapse during MA withdrawal (Schmahl et al., 2003). The monoaminergic and stress-axis vulnerability leads to a pre-disposition towards emotional instability which is enhanced by the pharmacodynamic pattern of MA excessive dopamine, serotonin depletion and noradrenergic stimulation leading to the amplified reward-driven behavior, lack of impulse control and relapses due to stress.

Neurodevelopmental and Synaptic Plasticity Deficits: Structural Vulnerability Exacerbated by MA

Times of childhood maltreatment produce long-term alterations in the hippocampal CA1 dendrites and synaptic plasticity, neurotrophic signaling. Champagne et al. (2008) could demonstrate that low maternal licking/grooming leads to decreased length of dendrites, the density of the spine and the impairment of the long-term potentiation (LTP) of the CA1 which is mediated by the epigenetic repression of hippocampal glucocorticoid receptors. The adaptive emotional learning, contextual memory and stress regulation are compromised by these changes.

This vulnerability is compounded by the exposure of MA which activates neurotrypsin, a protease required to remodel the synaptic structure; hyper neurotrypsin leads to poor synaptic architecture, poor learning and impaired LTP (Elhadi et al., 2023). Neurotrypsin-dysregulation caused by MA-stimulation increases the frequency of dendritic spine degeneration, inhibits plasticity in CA1, and reduces neurocognitive flexibility in pre-existing brain damage that impairs the capacities of relapse prevention directly. The low BDNF levels also lead to a further decrease in synapse repair ability, recovery of emotions and learning through extinction, which characterize BPD, especially in Val66Met carriers (Soloff et al., 2008; Perroud et al., 2013). A complex of compromised hippocampal plasticity, reduced BDNF signaling and neurotoxicity by MA also creates neurobiological environment of low stress resilience and absence of learning of adverse consequences, both of which are genetic factors of relapse.

In Figure 6, CA1 dendritic length. They show the Representative Golgi-stained CA1 of adult rats brought up by low-licking/grooming (LG), and high-LG mothers, respectively. The dendrites complexity variation is presented by the apical dendrites (blue) and basal dendrites (green). LoLG offspring have dendritic complexity that is lower than that of high-LG offspring resulting in a comparison of the influence that maternal care differences have on hippocampal plasticity (Champagne et al., 2008).

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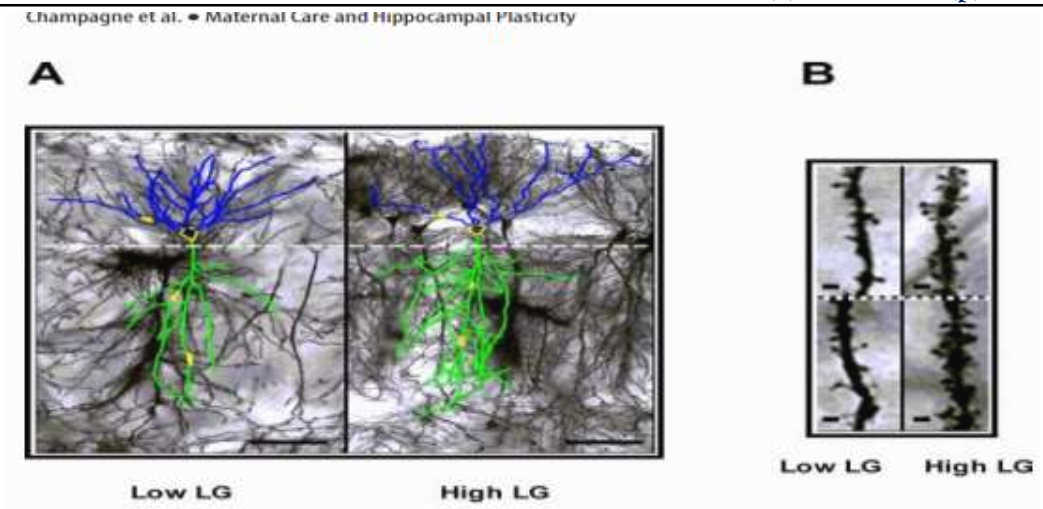

Figure 2. Quantitative morphological analysis of dendritic length. ***A***, Representative photographs of Golgi-stained CA1 pyramidal neurons accompanied by typical drawing taken from adult rats that received low (left) versus high (right) amounts of LG in infancy. Apical dendrites on top (blue) and basal dendrites at the bottom (green) are delineated by a dotted line. Yellow marks represent typical locations where spine density was assessed. Drawings are based on three-dimensional stacks of Golgi-stained cells allowing accurate distinction between the cell of interest and neighboring cells. Note that the length of dendritic trees (both basal and apical dendrites) is significantly shorter in low LG ($n = 6$) compared with high LG ($n = 7$) offspring. Magnification, 40×. Scale bars, 200 μm. ***B***, Representative photographs depicting spine density for low (left) and high (right) LG offspring. Basal dendrites at the top and apical dendrites at the bottom are delineated by a dotted line. Note that spine density is lower in offspring of low LG ($n = 6$) compared with high LG ($n = 7$) mothers. Magnification, 630×. Scale bars, 2.5 μm. From each cell, two 20 μm segments from the apical dendrite and one 20 μm segment from basal dendrite were analyzed (see yellow marks for typical locations in ***A***).

Figure 6 Quantitative Morphological Analysis of CA1 Dendritic Length.

Fronto-Limbic Disintegration: Impaired Top-Down Control and Heightened Bottom-Up Threat Processing

The structural and functional imaging continuously demonstrates that BPD is associated with a decrease in hippocampal volume (16-21) and amygdala volume (~8), a decrease in frontal gray matter and impaired PFC- amygdala connectivity (Lis et al., 2007; Johnson et al., 2003; Begemann et al., 2023). These alterations resemble the MA-induced neurotoxicity which entails the loss of dopaminergic terminal, glial inflammation and worsen of metabolic functions in PFC, striatum and limbic regions (Chang et al., 2007). The combination of all these deficiencies inhibits the top-down inhibitory response and exaggerates the bottom-up threat and reward impulses, which offers a neural condition that supports the development of compulsive and affect-based relapse.

Cerebral Cortex: The lateral prefrontal cortex is a subdivision of the prefrontal cortex situated on the right hemisphere of the brain. <|human|>Lateral Prefrontal Cortex (LPC)Cerebral cortex: This is a division located on the right brain in the prefrontal cortex.

DLPFC plays an important role in memory, cognitive flexibility and inhibitory control. This is related to impulsive decision making and lack of ability to control emotional reactions in BPD because the hypoactivation of this region disrupts the executive functioning. The DLPFC integrity is also disrupted by MA, which reduces cognitive control over the drug-seeking behavior and makes the habitual process of relapse more addictive with the help of the stimuli (Goldstein and Volkow 2012).

Orbitofrontal Cortex (OFC)

The valuation of rewards, risk measurement and integrating outcomes are under the control of the

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OFC. The BPD dysfunction symptoms may be viewed as impulsiveness, unhealthy rewards seeking, and failure to learn due to the negative consequences (Ochsner et al., 2004; Zanarini et al., 1998). MA elevates the dopaminergic tone of mesolimbic reward systems and does not involve the regulation of the OFC. This difference in the reward enhances the salience of drug cues relative to natural reward, which facilitates compulsive drug seeking and distorts of the long-term outcomes (Koob and Volkow, 2016; Nestler, 2018). The consequences of the deficits as the symptoms of abstinence are the biases in attention to MA signals, lack of motivation to recover, and the devaluation of the other rewards.

Anterior Cingulate Cortex (ACC)

The ACC balances the conflict monitoring, error tracking and integration of mental and emotional information. BPD hypoactivity decreases the capacity of managing competing emotional urges, and it eliminates maladaptive behaviors (Gowin et al., 2014; Leichsenring et al., 2011; Zanarini et al., 1998). ACC functioning suffers even more when MA dependence is released that would worsen distress tolerance, augment vivo to negative affectiveness and deprive oneself of self-monitoring (Goldstein and Volkow, 2012). The withdrawal process is hypoactivated by ACC resulting in extreme reactions to internal stimuli and insufficient impulse regulation that creates relapse vulnerability

Insular and Salience Network Disturbances.

The insula is an interoceptual, affective and salience processing unit. Emotional circumstances that BPD patients undergo lead to hyperactivity of insula to negative affect and threat cues and the patients become more sensitive to negative effects and threats (Koob and Volkow, 2010). During MA addiction, the use of an insular performance may be flattened with the completion of a cognitive control task and reduces the perception of inner physiological activity and risk evaluation (Paulus et al., 2005; Okita et al., 2016). This leaves the salience network of the dual-diagnosis individuals unstable: the hyper-reactive emotional responses are combined with the inability to react to the inner indicators of relapse, which facilitates quick, emotionally-driven relapse.

Thalamus and Extended Amygdala.

The negative feedback that increases thalamus and extends amygdala activity (especially when participants are in interpersonal stress) is the target of negative feedback that triggers the negative reinforcement loop that causes MA relapse. CRF-dependent prolonged amygdala processes away the fear-linked aversion and withdrawal distress towards amplifying the demand and destructive consumption (Koob and Volkow, 2010). These circuits are greatly responsive to hyper-reactivity to social threat that is BPD-related, converging at a point of convergence in relapse due to stress.

Convergent Mechanism of Alexithymia as the Root of Relapse and Emotional Dysregulation.

The inability to identify and elaborate inner sensation of emotions- Alexithymia- is typical of BPD and directly correlated with the ongoing MA use (Huang et al., 2022; De Berardis et al., 2020). The weakness of the alexithymic attributes to the trauma histories, maternal rejection, and insecure attachment worsens the negative effect, prolongs emotional responses and inhibits expressive adaptation.

At the neurobiological level, alexithymia implies:

Downregulation of bilateral ventrolateral PFC of inhibitory control and response monitoring (Goldstein and Volkow, 2012).

Discontinuous connectivity between frontal and insular areas, that influences emotional awareness and interoceptive accuracy.

Impaired dopaminergic communication or missing expected interaction among alexithymia and D2 receptor concentration in MA consumers (Okita et al., 2016).

A high probability of relapse is also a consequence of alexithymia that presents with confusion of emotional distress, physiological states, and emotion regulation as well as intensification of cues triggered craving. Dual-diagnosis groups have a higher effect of neurochemical malregulation caused by MA, leading to a relapse-sensitive phenotype because of the effect of Alexithymia.

Opioid-Dopamine Interactions: Dysphoria, the degree of withdrawal and Compulsive Relapse.

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The underlying factors in chronic dysphoria, emotional numbing, and hedonic incapacity are endogenous opioid dysregulation, including the loss of mu-opioid receptor (MOR) tone and the increased activity of kappa-opioid receptor (KOR) (Stanley and Siever, 2010). The disruption of oxytocin pathway also decreases social reward, affectionate security and affective regulation.

MA has a short-term effect of enhancing opioid and dopaminergic stimulations leading to euphoria. The withdrawal is, however, characterized by:

Steep dopamine depletion

Reduced MOR signaling

Greater dysphoria was KOR-mediated.

These changes increase affective instability, increase withdrawal distress and increase compulsive drug-seeking. Franto-limbic impairments and alexithymia in combination with uncontrolled opioid-dopamine systems present a powerful neurobiological relapse-fertilizing mechanism in BPD and MA-addicted patients.

This neurochemical disorder massively enhances emotional suffering, numbness and distress-states, which are already present in the patients with BPD. Consequently, withdrawal in BPD-MA patients is not only unpleasant but neurobiologically devastating and it generates a rapid reversion to via the negative reinforcement of the drug use as the means of restoring hedonic balance (Friedel, 2004; Koob and Volkow, 2016; Morken et al., 2017).

Integrated Mechanistic Pathway: The Uniqueness of Relapse Risk in BPD-MA.

The combination of neurobiological, developmental, and neurochemical results will allow the creation of one framework to describe the elevated relapse rates of the patients with a comorbid BPD and methamphetamine (MA) use disorder. A predisposition to emotional vulnerability, reward responsiveness, and stress responsiveness is a genetic and epigenetic vulnerability that comprises SERT-S, DRD2/DRD4, MAOA-L polymorphisms, and NR3C1 hypermethylation (Frazzetto et al., 2007; Martin-Blanco et al., 2015; Wilson et al., 2021). This predisposition is enhanced by early-life stress that destroys the hippocampal CA1 dendritic architecture, reduces synaptic plasticity and BDNF expression that subsequently reduces stress resiliency and adaptive learning during emotional processing (Champagne et al., 2008; Soloff et al., 2008).

The interference with the structural and functional networks such as the hippocampus, amygdala, DLPFC, OFC, ACC, insula and thalamus disrupt the top-down cognitive control and increases the bottom-up threat/interoceptive system, which results in an excessive emotional lability and impulsiveness. The negative effect of withdrawal, and oxytocinergic CRF signaling are also caused by mal-adaptive HPA axis signaling and oxytocinergic and endogenous opioid deficiency, respectively, which makes them unable to control their emotions naturally, requiring MA to affect their effect. The complex of these effects is explained by the fact that Alexithymia does not allow adaptive emotional processing and even encourages compulsive substance use, which is emotionally-driven (Okita et al., 2016; Huang et al., 2022).

MA pharmacodynamics particularly exploits these vulnerabilities to cause dopaminergic hyperstimulation, serotonergic depletion, neuroinflammation and degradation of synapses by neurotrypsin. Each episode of relapse adds up to the system and amplifies the dysfunction of the circuits, reduces the stress resistance, and further impairs prefrontal-limbic control. The result is a neurobiological phenotype of high relapse potential, which is qualitatively and quantitatively worse than either of the conditions alone. The cellular and molecular mechanisms underlying this convergence i.e. MA-stimulated microglial-response or epigenetic-regulation of synaptic proteins are beyond the scope of this review, which has emerged as a major research gap in future studies.

This integrative access point presents why the conventional addiction interventions are no longer sufficient to BPD-MA comorbidity and presents a mechanistic account of neuroscience-based multimodal treatment interventions, which must respond to the prior-existing vulnerability as

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well as to the neuroadaptations itself following MA.

CONCLUSION

The population of patients with co-occurring Borderline Personality Disorder (BPD) and methamphetamine (MA) use disorder is a vulnerable and more susceptible group with considerably higher rates of relapse, greater withdrawal symptoms, and poorer prognosis than the groups with a MA use disorder only (Fenton et al., 2012; Elhadi et al., 2023). This comorbidity is an action of a synergistic overlap of neurodevelopmental, structural, functional and neurochemical frailty reinforced by adolescent-life misery and inappropriate coping interventions. These factors play more than a summative role in enhancing chronicity and the severity of the addiction to constitute a highly relapse prone clinical path, which is more qualitatively and quantitatively poor than either disorder.

The basis of baseline vulnerability in BPD has been identified as emotional hyperreactivity, impulsiveness, and inability to effectively manage stresses, which MA pharmacodynamics takes advantage of in a relatively short period. It preexists a disproportion in reward value, inhibitory control, surveillance of conflict, and interoceptive processing that preconditions a predisposition to compulsive drug-seeking, exaggerated craving and negative engagement in therapeutic interventions. The developmental and epigenetic factors that contribute to the further formation of lifelong stress responsiveness and emotional control patterns include early trauma and hypermethylation of NR3C1. Neuroadaptive responses, elevated levels of dopamine, neuroinflammation and synaptic damage are initiated by exposure to MA, exacerbating underlying impairments in a vicious cycle of emotional dysregulation, withdrawal distress, and relapse. The precise molecular mechanism of MA-induced neurotoxicity and epigenetic modifications in BPD are outside the scope of this review, which forms a significant gap in the research that needs to be addressed by additional research. Covering this gap would help to clarify the mechanisms of treatment resistance and to obtain valuable information in the time and pattern of planned interventions.

This evidence underscores that integrative strategies of treatment, which are based on neuroscience, are highly required to overcome the process of neuroadaptability and the psychosocial susceptibilities of BPD and methamphetamine co-occurrence. One of the promising interventions is a mix of pharmacological and psychotherapeutic interventions. Pharmacological treatments with selective serotonin reuptake inhibitors (SSRI) may be effective in the treatment of mood swings and impulsive violence, and new vaccines targeting Toll-Like Receptor 4 (TLR-4) may be useful in the reduction of neuroinflammation and neurotoxicity, however, further investigations are required to assess their efficacy and safety in humans. Anti-inflammatory medications, NSAIDs, and antioxidants like N-acetyl-L-cysteine (NAC), and active immunopharmacological treatments would be beneficial to reduce neurotoxic effects, as well as to reduce the risk of it. The Mentalization-Based Treatment (MBT) and the Dynamic Deconstructive Psychotherapy (DDP) have proven to be effective psychotherapeutic interventions that may be implemented in the treatment of emotional dysregulation and improvement of interpersonal functioning. Examples of neuromodulatory methods which can be used to potentially restore interruptions caused by prefrontal-limbic connections and enhance top-down regulatory capacity are: Deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS).

Future research is also more likely to focus on longitudinal studies to evaluate the effects of childhood traumas and early-life adversity on outcomes of dual-diagnosis and track neuroadaptive changes over time. There is a necessity of individualized, comprehensive treatment approaches, based on both neurobiological and psychosocial susceptibility, that will address both the encouragement of resilience and reduction in relapse rate, as well as the long-term outcome of recovery. Irrespective of the limitations of the current literature, including the absence of the research specifically focused on the issue of BPD-MA comorbidity and self-

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reported information, this review can provide useful critical evidence to professionals, investigators, and policymakers. The further evolution of the neuroscience-based, person-centered interventions will be important in enhancing the engagement of the treatment and avoiding the relapse, and the prognosis of the patients who encounter the twin crises of BPD and methamphetamine addiction

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APPENDIX A

Boolean Search Strings

PubMed Search

"Borderline Personality Disorder"[MeSH] OR "Emotionally Unstable Personality Disorder" OR "BPD")
AND
("Methamphetamine"[MeSH] OR "Methamphetamine Addiction" OR "MA" OR "Stimulant Use Disorder")
AND
("Relapse" OR "Recurrence" OR "Treatment Outcome" OR "Recovery")
AND
("Neuroimaging" OR "Prefrontal Cortex" OR "Amygdala" OR "Neurocircuitry" OR "Emotion Regulation")

Google Scholar (Simplified Keyword Strategy)

"Borderline Personality Disorder" AND "Methamphetamine" AND "Relapse"
AND ("Prefrontal Cortex" OR "Amygdala" OR "Emotion Regulation")