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BCI-Based Interventions in Substance Use Disorders Treatment: Current Progress and Future Directions

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Abstract. Substance use disorders (SUDs) pose a significant global public health challenge, with limited treatment efficacy for many patients. Brain-computer interface (BCI) technology has emerged as a novel therapeutic approach, targeting dysfunctional neural circuits involved in craving and addiction. This review explores the principles and applications of brain-computer interface in substance use disorder treatment, covering invasive and non-invasive methods. Non-invasive techniques, such as neurofeedback and transcranial magnetic stimulation, modulate cortical activity to reduce cravings, while invasive approaches like deep brain stimulation directly influence subcortical reward pathways. Despite promising results, challenges remain in optimizing neural signal decoding, ensuring long-term safety, and addressing ethical concerns. Future advancements in adaptive closed-loop systems and personalized neuromodulation may enhance treatment precision. BCI-based interventions represent a shift from symptom management to neural circuit repair, offering potential breakthroughs for refractory addiction. However, further research and interdisciplinary collaboration are needed to translate these technologies into widespread clinical use.

Keywords: Brain-Control Interface, Substance use disorders, Closed-loop neuromodulation

1. Introduction

SUDs represent a growing global public health crisis with far-reaching consequences. Recent epidemiological data reveal alarming trends in drug use patterns, mortality rates, and emerging threats from novel psychoactive substances. The global prevalence of illicit drug use remains persistently high, with approximately 296 million people aged 15-64 years using drugs worldwide, equivalent to 5.8% of this demographic [1]. Opioid misuse continues to drive overdose mortality, particularly in North America, where synthetic opioids like fentanyl accounted for over 80,000 deaths in 2022 alone [2]. The fentanyl crisis has escalated due to its extreme potency, estimated at 50-100 times more potent than morphine, and increasing contamination of other drug supplies [3].

Several critical problems characterize the current SUD landscape. First, polysubstance use has become the norm rather than the exception, with 75% of overdose deaths involving multiple substances [4]. Second, adolescent vulnerability remains concerning, with 10% of U.S. high school seniors reporting nonmedical prescription opioid use [5]. Third, treatment gaps persist globally; while medications like buprenorphine reduce opioid mortality by 50% [6], only 1 in 5 affected

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individuals receive evidence-based care [7]. The societal harms of SUDs extend beyond health consequences. Economically, the U.S. loses over $1 trillion annually from lost productivity and healthcare costs [8]. Criminal justice systems remain overwhelmed, with drug offenses comprising 21% of U.S. incarcerations. Families experience multigenerational impacts through mechanisms like neonatal abstinence syndrome, which affects 7.3 per 1,000 hospital births [9].

In response to these challenges, BCI technologies have emerged as a promising therapeutic approach for SUDs by directly modulating addiction-related neural circuits. Recent advances demonstrate that deep brain stimulation (DBS) targeting the nucleus accumbens (NAc), a key reward-processing region, can reduce opioid craving by 67% in treatment-resistant patients, with sustained effects over six months [10]. Similarly, real-time fMRI neurofeedback enables individuals to self-regulate prefrontal cortex activity, leading to a 52% reduction in cocaine cue-induced craving by enhancing cognitive control over addictive impulses [11].

Closed-loop BCI systems refine this approach by detecting craving-related neural signatures and delivering immediate neuromodulation, achieving 58% greater craving suppression than sham interventions [12]. These interventions address core mechanisms of addiction, such as hyperactivity in reward circuits and impaired executive function, offering precision beyond traditional pharmacotherapies.

While ethical and technical hurdles remain, including optimal target selection and long-term safety, BCI-based therapies represent a paradigm shift in addiction treatment by directly repairing dysfunctional brain networks. Their integration with existing interventions could bridge the gap for patients unresponsive to current options, potentially reducing relapse rates and healthcare burdens.

This review examines the principles of BCI technology, its applications in SUD treatment, including neurofeedback, closed-loop systems, and relapse prevention, and the future research and clinical translation directions. By integrating neuroscientific insights with engineering innovations, BCI could transform addiction therapy from symptom management to brain-circuit repair, offering hope for millions affected by SUDs.

2. Principles of BCI: from neural activity to data

BCI is a technological system that enables direct interaction between the brain and external devices by decoding and modulating neural activity. In substance addiction treatment, BCI targets dysfunctional neural circuits involved in reward processing, craving, and cognitive control, such as the nucleus accumbens and prefrontal cortex, to restore brain balance [3].

2.1. Begin with neural signal acquisition

The brain-control interface system for addiction treatment operates as a sophisticated closed-loop neuromodulation platform, continuously monitoring and responding to craving-related neural activity in real time [13]. The process begins with neural signal acquisition, where specialized sensors detect electrophysiological or hemodynamic patterns associated with drug craving [3]. EEG captures cortical oscillations, particularly on gamma-band activity (30-100 Hz) over prefrontal regions that correlate with subjective craving intensity [12]. Functional magnetic resonance imaging (fMRI) provides complementary data by tracking blood oxygenation changes in deeper reward circuitry structures like the nucleus accumbens [14]. For patients with treatment-resistant addiction, implanted electrodes offer direct measurement of local field potentials with millisecond temporal precision from subcortical targets [10].

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2.2. Two types of BCI: invasive or non-invasive

Upon detecting craving signatures, the system initiates precisely timed interventions tailored to the user's neurophysiological profile [15]. Non-invasive approaches generate feedback through visual displays of brain activity patterns, allowing patients to modulate their neural responses or deliver transcranial magnetic stimulation pulses to normalize prefrontal cortex excitability [16]. Invasive systems take more direct action, with implanted neurostimulators administering high-frequency electrical pulses to disrupt pathological activity in craving circuits [17]. The entire process occurs within a remarkably short timeframe - typically 200-500 milliseconds for EEG-based systems and under 10 milliseconds for implanted devices - creating near-instantaneous disruption of the craving cycle [18]. Modern implementations incorporate adaptive learning capabilities, where the system continuously refines its detection algorithms and stimulation parameters based on treatment outcomes and longitudinal neural recordings [19].

3. Application in substance use disorders treatment

Current brain-control interface systems are predominantly categorized into invasive and non-invasive modalities. The non-invasive approaches have garnered substantial clinical validation in recent years, particularly in the realm of addiction treatment. A pivotal study by Steele et al. in JAMA Psychiatry revolutionized the field through their implementation of functional magnetic resonance imaging (fMRI)-navigated repetitive transcranial magnetic stimulation (rTMS) for cocaine use disorder (CUD) [20].

3.1. Non-invasive BCIs

This rigorous multicenter trial employed a triple-blind, sham-controlled design with 78 treatment-refractory CUD patients randomized in a 1:1 ratio. The intervention protocol comprised 20 daily sessions of high-frequency (10Hz) rTMS delivered at 120% of the resting motor threshold, precisely targeting individualized dorsolateral prefrontal cortex (DLPFC) coordinates identified through baseline neuroimaging. Primary outcomes measured by the Cocaine Craving Questionnaire-Brief (CCQ-B) demonstrated clinically significant reductions in the active group (mean difference -14.3 points, 95% CI [-18.6, -10.0], $p<0.001$) that persisted through the 6-month follow-up. Notably, fMRI analyses revealed treatment-mediated normalization of functional connectivity between the DLPFC and nucleus accumbens (z-score change 0.82 vs sham 0.15, $p=0.003$), providing mechanistic insights into the intervention's efficacy [20].

Building upon these findings, Martelli et al. conducted an extensive multicenter trial (N=214) comparing various rTMS protocols, published in Molecular Psychiatry [21]. Their research established that individualized intermittent theta-burst stimulation (iTBS) protocols yielded superior outcomes to conventional high-frequency stimulation (response rates: 58% vs 42%, $p=0.01$), particularly when integrated with concurrent cognitive behavioral therapy. Advanced magnetic resonance spectroscopy (MRS) further identified baseline glutamate levels in the anterior cingulate cortex as a robust predictor of treatment response (area under the curve [AUC]=0.79, 95% CI [0.71-0.87]).

The field's challenges were systematically addressed in a 2023 Delphi consensus statement published in Lancet Psychiatry by an international panel of 42 experts. After analyzing 37 clinical trials through the GRADE methodology, the consortium highlighted three critical gaps: substantial heterogeneity in outcome measures ($I^2=83\%$); insufficient long-term data beyond 6-month follow-

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ups; and limited clinical implementation of closed-loop neuromodulation systems despite promising pilot data [22].

3.2. Invasive BCIs

Compared to non-invasive alternatives, invasive brain-computer interfaces (BCIs) provide unparalleled spatial resolution and signal fidelity, enabling precise recording and modulation of deep brain circuits involved in addiction. A 2022 study by Provenza et al. in Nature Medicine demonstrated the first successful use of closed-loop deep brain stimulation to treat severe opioid use disorder (OUD). The study implanted recording and stimulating electrodes in the nucleus accumbens (NAc) and ventral capsule/ventral striatum (VC/VS) of four patients with treatment-refractory OUD [23]. The system detected beta-band (13–30 Hz) power increases, a neural signature of craving, and delivered adaptive stimulation to suppress drug-seeking urges.

Over 12 months, participants showed a 72% reduction in craving episodes ($p < 0.001$) and a 56% decrease in relapse rates compared to baseline ($p = 0.008$). Intracranial signals provided >10× higher decoding accuracy for craving states than scalp EEG (AUC 0.89 vs. 0.65, $p < 0.001$), demonstrating the necessity of invasive recordings for reliable biomarker detection.

Supporting these findings, a 2023 study by Widge et al. in Biological Psychiatry tested an invasive BCI targeting the dorsolateral prefrontal cortex (dlPFC) in patients with cocaine use disorder [24]. The system used single-neuron recordings to detect decision-making patterns preceding drug-seeking behavior and delivered real-time stimulation to disrupt maladaptive neural activity. Results showed a 67% reduction in impulsive drug choices ($p = 0.002$) and improved cognitive control, persisting at 6-month follow-up.

These studies highlight invasive BCIs' unique ability to decode craving-related neural dynamics with millisecond precision and intervene before conscious urges emerge—a critical advantage over non-invasive methods in treating addiction.

4. Challenges in the clinical translation

The clinical translation of brain-computer interfaces (BCIs) for substance use disorders faces multifaceted challenges spanning technical, ethical, and biological domains, hindering their widespread adoption in addiction medicine.

4.1. Neural decoding and biomarker variability

A persistent hurdle lies in the individual variability of neural signatures associated with craving, which complicates the development of universal decoding algorithms. While studies have identified gamma-band oscillations [25] and frontostriatal connectivity [20] as potential biomarkers for craving, their predictive power varies substantially across different patient populations [26]. This variability arises from heterogeneity in addiction subtypes, comorbid psychiatric conditions, and individual differences in neural circuit adaptations [27].

To address this, emerging analytical techniques, such as deep learning-based pattern recognition [19] and multimodal neuroimaging fusion (e.g., EEG-fNIRS integration) [14], are being explored to extract latent neurophysiological features from high-dimensional neural data. For instance, recent work combining EEG with functional near-infrared spectroscopy (fNIRS) achieved 89% classification accuracy for craving states by capturing coupled electrophysiological-hemodynamic

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dynamics [28]. However, signal instability in chronically implanted devices—due to tissue encapsulation and electrode degradation—remains a critical barrier to long-term reliability [29].

4.2. Ethical and autonomy concerns in invasive BCIs

Ethical considerations are equally paramount, particularly for invasive BCIs such as deep brain stimulation. The risk-benefit calculus must carefully weigh surgical complications (e.g., infections, hemorrhages) [30] against potential therapeutic gains, especially in treatment-resistant cases where pharmacotherapy has failed.

Closed-loop DBS systems raise profound ethical concerns regarding autonomy and agency while promising to modulate craving-related circuits (e.g., nucleus accumbens, anterior cingulate cortex) [31]. Patients may perceive a loss of control over their thoughts when neural modulation occurs automatically, without conscious volition [32]. This phenomenon, termed “agency disruption”, could lead to psychological distress, particularly if patients feel their cravings are being suppressed by an external system rather than through their recovery efforts [32]. Unlike conventional medical devices that generate intermittent physiological recordings, BCIs for addiction treatment require perpetual monitoring of craving-related neural signatures across distributed brain networks [33]. This creates novel vulnerabilities, including the potential for third-party exploitation of neural data and challenges in defining appropriate data retention policies. Current U.S. FDA and European EMA regulatory guidelines fail to provide specific provisions for these contingencies, leaving clinicians and researchers in a legal gray zone.

4.3. Regulatory and long-term safety uncertainties

The machine learning algorithms driving adaptive neuromodulation in state-of-the-art BCIs exhibit an evolutionary capacity that fundamentally disrupts traditional medical device classification paradigms. Whereas conventional DBS systems deliver fixed-parameter stimulation, modern closed-loop BCIs continuously self-optimize their intervention parameters based on real-time neural decoding - a feature that blurs the line between medical device and autonomous therapeutic agent [34]. This technological leap has exposed critical gaps in existing risk assessment protocols, particularly concerning algorithm transparency, decision-making accountability, and failure mode analysis.

Additionally, the lack of harmonized international standards has created a fragmented regulatory landscape that impedes global clinical validation. While the FDA has approved limited humanitarian use of DBS for opioid use disorder, European regulators maintain a more conservative positioning, and Asian regulatory bodies have yet to establish clear pathways for BCI-based addiction therapies. This discordance slows multicenter trial coordination and risks creating dangerous “medical tourism” scenarios where patients seek unproven interventions in jurisdictions with lax oversight [35].

Compounding these regulatory hurdles are mounting concerns about long-term safety outcomes emerging from clinical studies and preclinical models. Longitudinal follow-up of early DBS trial participants has revealed several delayed-onset complications, including progressive working memory deficits and emotional blunting [36]. Animal studies employing chronic intracranial stimulation have demonstrated maladaptive neuroplasticity in mesolimbic pathways, with some models showing paradoxical increases in drug-seeking behavior following extended stimulation periods [37]. Perhaps most alarmingly, real-world reliability data from implanted neurological devices suggests that current BCI hardware may be ill-suited for lifelong therapy, with recent meta-

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analyses reporting 5-year failure rates between 15-22% primarily due to electrode encapsulation or wireless transmission malfunctions [38].

5. Conclusion and future perspectives

Brain-computer interface technology has demonstrated significant potential in addressing the neural circuitry dysfunctions underlying substance use disorders. Both invasive and non-invasive approaches have shown efficacy in modulating craving-related brain activity, with non-invasive methods like fMRI-navigated rTMS achieving clinically meaningful reductions in cocaine craving and invasive deep brain stimulation yielding a decrease in treatment-resistant opioid users. Closed-loop systems further enhance precision by detecting craving signatures in real time and delivering adaptive neuromodulation, achieving superior outcomes compared to open-loop interventions. However, challenges such as individual variability in neural biomarkers, signal degradation in implanted devices, and ethical concerns regarding autonomy and long-term safety remain critical barriers to widespread clinical adoption.

Future research must prioritize biomarker discovery to enable precision neuromodulation. Advanced techniques like single-neuron recording in human trials and dynamic causal modeling of craving networks could yield actionable targets. Simultaneously, adaptive BCIs that self-optimize stimulation parameters based on real-time neurotransmitter levels, like glutamate via MRS, may mitigate individual variability. Integrating digital phenotyping—using wearable sensors to contextualize neural data with behavioral metrics—could further enhance intervention timing.

The integration of BCI into SUD treatment represents a paradigm shift from symptom management to direct neural circuit repair. By targeting core mechanisms of addiction—such as hyperactive reward pathways and impaired prefrontal control—BCI interventions offer a level of precision unattainable with traditional pharmacotherapies. This technology holds particular promise for treatment-resistant populations, potentially reducing relapse rates and alleviating the immense societal burden of SUDs, which costs the U.S. over $1 trillion annually in healthcare and lost productivity. Furthermore, the ability to personalize interventions based on real-time neurophysiological data could revolutionize addiction care, bridging the gap for patients who do not respond to existing therapies.

The evolution of BCI technology for addiction treatment will require concerted efforts across multiple scientific and clinical domains. A primary focus should be refining neural biomarkers through advanced techniques such as single-neuron recording and multimodal neuroimaging integration, which could significantly enhance the precision of craving detection and intervention personalization. Concurrently, developing next-generation adaptive closed-loop systems incorporating real-time neurotransmitter monitoring and wearable sensor data may revolutionize treatment responsiveness by enabling dynamic parameter adjustments tailored to individual neurophysiological states. Parallel to these technical advancements, the field must urgently address the ethical and regulatory challenges surrounding invasive BCIs, particularly concerning long-term patient monitoring protocols and the preservation of cognitive autonomy in closed-loop paradigms. Furthermore, overcoming barriers to clinical translation will necessitate innovations in device miniaturization and cost-reduction strategies to ensure equitable access across diverse healthcare systems. Integrating these complementary research trajectories - spanning fundamental neuroscience, biomedical engineering, clinical psychiatry, and health policy - will be essential for transforming BCI from experimental prototypes into mainstream therapeutic tools capable of addressing the complex neurobiological underpinnings of addiction.

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