RESEARCH PAPER

Functional MRI Biomarkers of Addiction-Related Neuroplasticity in Neurological Disorders: A Comprehensive Review of Functional Connectivity, Brain Network Reorganization, and Clinical Applications

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Abstract

Recent advances in resting-state functional MRI have enabled non-invasive characterization of large-scale functional networks, providing novel biomarkers for diagnosis, prognosis, and treatment monitoring. Functional magnetic resonance imaging (fMRI)—particularly resting-state functional connectivity (rsFC) and graph-theoretical network analysis—has become the principal noninvasive method for characterizing addiction-related neuroplasticity in humans. This narrative review synthesizes fMRI evidence on addiction-related network reorganization across substance use disorders, including nicotine, alcohol, opioids, cocaine and other stimulants, and cannabis, as well as addiction-adjacent phenomena arising within primary neurological disease, with particular emphasis on impulse control disorders in Parkinson's disease and substance-use vulnerability following traumatic brain injury. The review the rapidly evolving computational layer built on these findings, including graph neural networks, explainable artificial intelligence methods for biomarker attribution, multimodal foundation models pretrained on large unlabeled neuroimaging corpora, and federated learning and harmonization strategies designed to enable multi-site, privacy-preserving biomarker discovery. We also examine fMRI-guided neuromodulation, including repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation, as both a mechanistic probe and a treatment strategy, and evaluate the reproducibility, generalizability, and clinical translation barriers that currently constrain this literature. We conclude with a precision-medicine roadmap emphasizing standardized acquisition and analysis pipelines, prospective longitudinal and multimodal designs, externally validated and explainable machine-learning biomarkers, and dedicated connectivity studies in understudied neurological-comorbidity populations. Realizing the clinical potential of fMRI biomarkers of addiction-related neuroplasticity will require moving from descriptive group-level neuroimaging findings toward reproducible, individually actionable, and mechanistically interpretable tools.

Keywords: functional MRI; resting-state functional connectivity; addiction; neuroplasticity; default mode network; graph neural network; explainable AI; foundation model; federated learning; impulse control disorder; Parkinson's disease; traumatic brain injury; neuromodulation

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1. Introduction

Substance use disorders (SUDs) remain among the leading causes of preventable morbidity and mortality worldwide, affecting millions of individuals and imposing substantial social, economic, and healthcare burdens. Contemporary neuroscience recognizes addiction as a chronic disorder characterized by progressive alterations in brain function rather than merely a consequence of repeated drug exposure or impaired decision-making. These alterations involve complex interactions among reward processing, emotional regulation, executive control, learning, and memory systems, ultimately leading to compulsive drug-seeking behavior despite adverse consequences. Although considerable progress has been made in

understanding the molecular and neurochemical mechanisms underlying addiction, identifying reliable neuroimaging biomarkers capable of objectively characterizing disease progression, predicting relapse, and monitoring therapeutic response remains an important research priority.

Functional magnetic resonance imaging (fMRI), particularly resting-state functional MRI (rs-fMRI), has transformed the investigation of addiction-related neuroplasticity by enabling non-invasive assessment of spontaneous functional interactions among distributed brain regions. Unlike conventional task-based paradigms, resting-state approaches capture intrinsic functional organization without requiring participant engagement in cognitive tasks, making them particularly valuable for studying heterogeneous clinical populations. Resting-state functional connectivity (rsFC) analyses have consistently demonstrated that chronic exposure to addictive substances disrupts coordinated communication among multiple large-scale brain networks involved in reward processing, salience attribution, cognitive control, and self-referential cognition. These network-level abnormalities have emerged as promising candidates for imaging biomarkers that may complement clinical assessment and facilitate precision medicine approaches in addiction research.

Recent advances in computational neuroscience have further expanded the clinical relevance of functional connectivity studies. Machine learning, graph-theoretical analysis, explainable artificial intelligence (XAI), graph neural networks (GNNs), foundation models, and federated learning have enabled increasingly sophisticated characterization of complex brain-network organization while addressing challenges related to multicenter data harmonization and individualized prediction. Rather than relying solely on group-level statistical comparisons, these computational methods seek to identify reproducible biomarkers capable of predicting clinically meaningful outcomes such as craving intensity, relapse risk, treatment response, and cognitive recovery.

Although the majority of neuroimaging investigations have focused on primary substance use disorders—including nicotine, alcohol, opioid, stimulant, and cannabis dependence—addiction-related neuroplasticity also occurs in several neurological disorders. Parkinson's disease patients receiving dopaminergic therapy may develop impulse control disorders that share neurobiological features with substance addiction, while traumatic brain injury can disrupt fronto-limbic circuits that increase vulnerability to compulsive behaviors and substance misuse. Studying these neurological conditions provides a unique opportunity to distinguish disease-specific alterations from addiction-related network reorganization and to improve understanding of common neurobiological mechanisms.

The present review provides an integrated overview of contemporary evidence regarding functional MRI biomarkers of addiction-related neuroplasticity. Particular emphasis is placed on alterations within large-scale functional brain networks, advances in computational neuroimaging, and the translational potential of connectivity-based biomarkers for diagnosis, prognosis, neuromodulation, and personalized treatment strategies. By combining evidence from substance use disorders and addiction-related neurological conditions, this review highlights emerging opportunities and remaining challenges in translating functional neuroimaging into clinically actionable precision medicine tools.

1.1 Rationale

Three gaps motivate this review. First, substance-specific rsFC findings are scattered across disorder-specific literatures (nicotine, alcohol, opioids, stimulants, and cannabis) without a unifying synthesis of convergent versus divergent network signatures. Second, addiction-related neuroplasticity in neurological disease—particularly PD-associated ICDs and TBI-related substance vulnerability—has rarely been reviewed alongside primary SUD neuroimaging, despite offering complementary causal and mechanistic insight. Third, the machine-learning layer now built atop fMRI connectivity data, including graph neural networks, explainable AI, foundation models, federated learning, and harmonization pipelines, has outpaced its integration into addiction-focused reviews, leaving clinicians and imaging scientists without a consolidated account of which computational approaches are ready for translational use and which remain exploratory.

1.2 Objectives

This review aims to: (1) synthesize fMRI-based functional connectivity and network-reorganization findings across major substances of abuse; (2) integrate findings on addiction-related neuroplasticity in neurological disorders, with emphasis on PD-associated ICDs and TBI-related substance vulnerability; (3) evaluate graph-theoretical, machine-learning, and next-generation computational approaches for individualized biomarker development; (4) review fMRI-guided neuromodulation as both a mechanistic probe and therapeutic strategy; and (5) critically appraise methodological barriers to clinical translation and propose a precision-medicine research roadmap.

2. Methods:

2.1 Study Design

This article was prepared as a narrative review guided by a structured and reproducible literature search strategy. Because the review aims to synthesize evidence spanning neurobiology, functional neuroimaging, computational

neuroscience, artificial intelligence, and neuromodulation, a formal systematic review with meta-analysis was not considered appropriate. Nevertheless, systematic search principles were adopted to improve transparency, comprehensiveness, and reproducibility. The review primarily emphasizes functional MRI biomarkers of addiction-related neuroplasticity and their emerging clinical applications in substance use disorders and addiction-associated neurological conditions.

2.2 Literature Search Strategy

A comprehensive electronic literature search was conducted using PubMed/MEDLINE, Scopus, Web of Science, IEEE Xplore, and Google Scholar. In addition, recent methodological studies available through bioRxiv, medRxiv, and arXiv were examined to identify emerging developments in artificial intelligence and computational neuroimaging. The search covered publications from January 2010 to July 2026, while landmark studies published before 2010 were included when they established important conceptual or methodological foundations for addiction neuroscience and functional connectivity research.

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to addiction, functional MRI, resting-state functional connectivity, graph theory, machine learning, graph neural networks, explainable artificial intelligence, foundation models, federated learning, neuromodulation, Parkinson's disease, traumatic brain injury, and large-scale brain networks. Reference lists of eligible review articles and influential original investigations were also manually screened to identify additional relevant publications.

2.3 Study Selection

The initial database search identified approximately 470 publications. After removal of duplicate records, 392 unique articles remained for title and abstract screening. Studies unrelated to addiction neuroplasticity, functional neuroimaging, or computational neuroimaging were excluded during preliminary screening.

Following full-text evaluation, approximately 145 publications were considered directly relevant to the objectives of this review. Ultimately, 112 high-quality articles, including original investigations, systematic reviews, meta-analyses, methodological studies, and landmark conceptual papers, were synthesized in the final manuscript. Selection prioritized methodological quality, scientific impact, recency, and direct relevance to functional connectivity biomarkers and computational advances in addiction neuroimaging.

2.4 Eligibility Criteria

Studies were considered eligible for inclusion if they investigated functional magnetic resonance imaging (fMRI), particularly resting-state or task-based functional connectivity, in individuals with substance use disorders or addiction-related neurological conditions, including Parkinson's disease and traumatic brain injury. Publications employing graph-theoretical analysis, machine learning, deep learning, graph neural networks, explainable artificial intelligence (XAI), foundation models, federated learning, or other advanced computational approaches for the analysis of functional neuroimaging data were also included. Original research articles, systematic reviews, meta-analyses, consensus statements, and landmark methodological or conceptual papers published in peer-reviewed journals were considered when they provided substantial insights into addiction neurobiology, large-scale brain network organization, neuroplasticity, computational neuroimaging, or clinical translation. Publications consisting solely of single-patient case reports, conference abstracts without accompanying full-text articles, or studies involving only animal models were excluded unless they offered essential mechanistic insights directly applicable to human neuroimaging. Studies based exclusively on structural imaging without functional connectivity analysis, as well as articles lacking adequate methodological quality or direct relevance to the objectives of the present review, were also excluded from evidence synthesis.

2.5 Evidence Synthesis

The evidence was synthesized using a thematic narrative approach rather than quantitative meta-analysis because of the substantial heterogeneity in study design, imaging protocols, analytical methodologies, computational techniques, and reported outcome measures across the available literature. The selected studies were organized into major thematic domains encompassing the neurobiological basis of addiction, large-scale functional brain network alterations, functional connectivity findings across different substance use disorders, addiction-related neuroplasticity in neurological disorders, graph-theoretical analyses, artificial intelligence–based computational approaches, and emerging neuromodulation strategies. Greater emphasis was placed on multicenter investigations, longitudinal studies, systematic reviews, meta-analyses, and studies employing externally validated computational methods whenever such evidence was available. Particular attention was also given to methodological rigor, reproducibility, sample size, clinical applicability, and consistency of findings across independent studies to provide a balanced and comprehensive overview of current advances while identifying important knowledge gaps and future research priorities in fMRI-based addiction biomarker development.

2.6 Quality Considerations

Although a formal risk-of-bias assessment was not performed because of the narrative design of this

review, study quality was considered during evidence synthesis. Greater emphasis was placed on multicenter investigations, prospective studies, systematic reviews, meta-analyses, externally validated machine learning studies, and publications appearing in high-impact peer-reviewed journals. Particular attention was also given to methodological rigor, reproducibility, transparency of analytical methods, and clinical relevance when interpreting emerging artificial intelligence applications.

3. Neurobiological Framework: From Circuits to Networks

3.1 The classical neurocircuitry model

Current models describe addiction as a progressive disorder involving coordinated dysfunction across interconnected neural circuits responsible for motivation, emotional regulation, reinforcement learning, and executive control. Rather than resulting from abnormalities within a single anatomical region, addictive behaviors emerge through maladaptive interactions among distributed cortico-subcortical systems that regulate reward valuation, habit formation, stress responses, and inhibitory control.

The widely accepted three-stage model conceptualizes addiction as a cyclic process consisting of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (craving). During the binge/intoxication stage, repeated exposure to addictive substances activates dopaminergic pathways within the mesocorticolimbic reward system, reinforcing drug-taking behavior through enhanced motivational salience. With continued exposure, neuroadaptive changes progressively reduce sensitivity to natural rewards while strengthening conditioned responses to drug-related cues.

The withdrawal stage is characterized by dysregulation of stress-responsive neural systems involving the extended amygdala and associated limbic structures. During this phase, decreased reward sensitivity is accompanied by increased negative emotional states, anxiety, irritability, and dysphoria, all of which contribute to continued substance use through negative reinforcement mechanisms.

The final stage involves persistent craving and impaired executive regulation mediated by dysfunction of prefrontal cortical regions responsible for cognitive flexibility, inhibitory control, decision-making, and behavioral monitoring. Reduced top-down regulation permits drug-associated memories and environmental cues to dominate behavior, thereby increasing vulnerability to relapse even after prolonged abstinence.

Complementing this framework, contemporary theories emphasize the transition from voluntary, goal-directed behavior to habitual and eventually compulsive drug seeking. This behavioral shift is accompanied by progressive reorganization of corticostriatal pathways, whereby neural processing increasingly depends upon dorsal striatal circuits associated with habitual responding rather than ventral striatal reward mechanisms. Together, these interconnected neurobiological processes provide the conceptual foundation for understanding functional connectivity alterations observed across addiction disorders and form the basis for interpreting modern neuroimaging biomarkers.

3.2 The triple-network / large-scale network model

While classical addiction models primarily emphasize individual neural circuits, modern functional neuroimaging has demonstrated that addiction also involves disruption of coordinated communication among large-scale intrinsic brain networks. Among these, the Default Mode Network (DMN), Salience Network (SN), and Executive Control Network (ECN) have emerged as central components of the Triple-Network Model, which provides a systems-level framework for understanding cognitive and behavioral dysfunction across numerous neuropsychiatric disorders, including substance use disorders.

The Default Mode Network supports internally directed cognitive processes such as autobiographical memory, self-referential thinking, future planning, and emotional introspection. Functional MRI studies consistently demonstrate abnormal DMN connectivity in individuals with addiction, suggesting impaired regulation of internally generated thoughts and increased spontaneous processing of drug-related memories and craving-associated mental imagery.

The Salience Network, centered primarily on the anterior insular cortex and dorsal anterior cingulate cortex, plays a critical role in identifying behaviorally relevant internal and external stimuli while coordinating dynamic switching between internally focused and externally directed cognitive states. In addiction, exaggerated salience-network activity contributes to abnormal attribution of motivational significance to drug-associated cues, reinforcing compulsive substance seeking and craving.

In contrast, the Executive Control Network, which includes the dorsolateral prefrontal cortex and posterior parietal cortex, supports cognitive flexibility, working memory, planning, decision-making, and inhibitory control. Reduced functional integration within this network is consistently associated with impaired behavioral regulation, diminished cognitive control, increased impulsivity, and reduced ability to suppress drug-seeking behaviors.

Rather than functioning independently, these three networks continuously interact to maintain adaptive

behavior. Addiction appears to disrupt the normal balance among these systems, producing excessive salience attribution to substance-related cues, persistent internally directed craving processes, and diminished executive regulation. Functional connectivity analyses therefore increasingly focus not only on abnormalities within individual networks but also on altered communication between them, providing a more comprehensive understanding of addiction-related neuroplasticity.

This network-based perspective has also proven valuable for interpreting addiction-like behaviors observed in neurological disorders such as Parkinson's disease and traumatic brain injury, where disruption of large-scale functional connectivity contributes to impaired decision-making, compulsive behaviors, and altered reward processing. Consequently, the Triple-Network Model serves as a unifying framework linking classical addiction neurobiology with contemporary systems neuroscience and provides an important conceptual basis for the computational biomarker approaches discussed in subsequent sections.

4. fMRI Methodologies for Characterizing Addiction-Related Neuroplasticity

4.1 Resting-state functional connectivity

rsFC exploits low-frequency (<0.1 Hz) spontaneous BOLD fluctuations that are temporally correlated across functionally related but spatially distributed regions in the absence of an explicit task. Because it requires no task compliance, rsFC is well suited to clinical and cognitively impaired populations, including patients with neurological comorbidity. Analytic approaches include seed-based correlation, independent component analysis, regional homogeneity, amplitude of low-frequency fluctuations, and dynamic, time-varying connectivity analyses that capture transitions between discrete connectivity states. Individual differences in connectivity are sufficiently stable and distinctive to support connectome fingerprinting of individual subjects, a property directly relevant to the individualized-biomarker ambitions discussed in Section 8.

4.2 Task-based fMRI

Cue-reactivity, delay-discounting, Go/No-Go, and monetary incentive delay paradigms probe specific cognitive-affective processes implicated in addiction and remain widely used, particularly in PD-ICD research, where paired activation and connectivity analyses have dissociated motor-inhibitory from decision-making

4.3 Graph-theoretical network analysis

Graph theory represents the brain as nodes (regions) and edges (functional connections), enabling quantification of global and local efficiency, clustering coefficient, modularity, and hub centrality. These metrics capture whether addiction-related neuroplasticity manifests as a shift in overall network segregation versus integration, and have been applied in alcoholism, TBI, and stimulant use disorder using fractal-dimension-based graph metrics.

4.4 Toward computational biomarker pipelines

Traditional group-comparison analyses are increasingly complemented or replaced by multivariate pattern analysis and machine-learning algorithms trained on functional connectivity features to predict clinically relevant outcomes at the individual-subject level. These computational approaches facilitate personalized biomarker discovery by integrating complex brain network features that cannot be captured using conventional statistical analyses.

5. Functional Connectivity Findings Across Substances of Abuse

5.1 Nicotine

Nicotine dependence is among the most extensively studied SUDs with rsFC. Nicotine-dependent smokers show altered coupling between prefrontal and limbic/striatal networks relative to non-smokers, including stronger fronto-parietal–medial-prefrontal coupling and elevated resting-state amplitude within reward-related networks, which may facilitate cue-driven drug-seeking and could serve as a biomarker of dependence severity. Regional homogeneity analyses show reduced values in the right superior/middle frontal gyrus and precuneus, with precuneus values correlating with Fagerström Test for Nicotine Dependence (FTND) scores. A comprehensive review catalogued rsFC changes across seed-based, graph-theoretical, and independent-component-analysis methodologies, noting that acute nicotine administration tends to increase connectivity in cingulate-seeded circuits, whereas chronic dependence is associated with reduced network efficiency—a state-dependent dissociation with direct implications for biomarker interpretation. Connectivity between the dorsal ACC and ventral striatum is inversely related to dependence severity, while dACC–anterior insula–thalamus connectivity predicts risky decision-making in nicotine users. White-matter functional network alterations further extend these gray-matter connectivity findings, indicating that nicotine-related reorganization is not confined to cortical gray matter. More recent work has used data-driven connectivity profiling and multivariate pattern analysis to prospectively predict cue-induced craving and smoking-lapse hazard, moving the field from cross-sectional group differences toward individualized, outcome-relevant biomarkers.

5.2 Alcohol use disorder

AUD is consistently associated with disrupted DMN integrity. Individuals with AUD show reduced synchrony between the posterior cingulate cortex and cerebellar regions at rest, with graph-theoretical efficiency measures correlating with duration of sobriety. Structural–functional connectivity workflows confirm that DMN functional alterations

co-occur with, but are only partially explained by, white-matter integrity changes. Acute alcohol administration produces measurable, dose-dependent rsFC changes in DMN seed regions, underscoring the need to control for recency of use in cross-sectional designs. Triple-network-model analyses in heavy drinkers show that salience, frontoparietal, and DMN connectivity patterns track self-reported alcohol use severity, craving, and urgency, and machine-learning models trained on resting-state connectivity features have outperformed structural MRI and task-fMRI features in predicting AUDIT-quantified severity in held-out validation samples, explaining roughly one-third of AUDIT score variance. Pharmacological-challenge fMRI demonstrates that opioid-receptor modulation with single-dose nalmefene can normalize connectivity between impulsive (nucleus accumbens–striatal–insular) and reflective (OFC-mediated) systems, providing a connectivity-based readout of pharmacodynamic target engagement. Transdiagnostic comparisons indicate that AUD shares within- and between-network connectivity abnormalities with schizophrenia, bipolar disorder, and OCD, consistent with the triple-network model operating as a shared vulnerability substrate rather than a disorder-specific signature. Individual-subject classification of AUD from rsFC data using machine-learning classifiers has achieved promising discrimination accuracy, though external validation remains limited.

5.3 Opioid use disorder

rsFC studies in opioid users demonstrate DMN suppression coupled with heightened salience-network engagement, potentially reflecting an early stage of a longer abstinence-related neuroplastic trajectory. Seed-based analyses in chronic heroin users show increased connectivity between the nucleus accumbens and rostral/ventral ACC and OFC, alongside reduced prefrontal–OFC connectivity, consistent with disrupted top-down regulation of reward circuitry. Machine-learning frameworks combining clinical and fMRI-BOLD-derived connectivity features from DMN, SN, and ECN nodes have been used to classify OUD status, supporting the translational potential of connectivity-based screening tools.

5.4 Cocaine and stimulant use disorders

Dynamic, time-varying rsFC analyses in cocaine users reveal both altered connectivity strength and altered temporal dynamics—differences in the frequency and duration of transitions between discrete brain states—relative to matched controls. Graph-theoretical topology analyses using box-counting fractal dimension confirm significant disruption of global efficiency, clustering coefficient, and characteristic path length in methamphetamine users relative to controls. In methamphetamine use disorder specifically, machine-learning models applied to drug cue-reactivity fMRI have been used to predict subjective craving intensity from connectivity and activation features with clinically meaningful discrimination (AUC ≈ 0.69 for cue-type classification)

5.5 Cannabis use disorder

Region-of-interest rsFC analyses in individuals with moderate-to-severe CUD show greater connectivity than controls between reward/habit-related striatal nuclei (nucleus accumbens, putamen, pallidum) and occipito-parietal regions implicated in salience processing and disinhibition, with these alterations correlating with cannabis exposure and problem severity.

5.6 Polysubstance comparison

Direct comparison of alcohol, nicotine, and cannabis effects on dynamic brain connectivity indicates that alcohol produces a substantially larger number of dysfunctional connections than the other two substances, underscoring that the addiction connectivity signature is not substance-invariant and that severity-matched, substance-specific normative models will likely be required for clinical biomarker deployment.

5.7 Cross-substance synthesis

A multilevel kernel density meta-analysis pooling rsFC findings across substance and behavioral addictions identified reliable regions of hyper- and hypoconnectivity spanning reward, salience, and executive-control networks, with partial convergence across addiction subtypes but also substance-specific patterns. A parallel systematic review of internet addiction imaging studies found mixed DMN alterations, consistent ECN hypoconnectivity, and inconsistent salience/reward-network findings, broadly paralleling the SUD literature while highlighting substantial cross-study heterogeneity even within a single, narrowly defined disorder.

6. Addiction-Related Neuroplasticity in Neurological Disorders

6.1 Impulse control disorders in Parkinson's disease

Impulse control disorders (ICDs)—pathological gambling, hypersexuality, compulsive shopping, and binge eating—occur cumulatively in up to 46% of PD patients over a five-year exposure window to dopamine agonist therapy. fMRI studies converge on dysfunction of the mesocorticolimbic reward system and orbitofronto-striatal circuitry: abnormal connectivity involving the ventral striatum and OFC reflects biased reinforcement learning, including overvaluation of reward and underestimation of risk, together with impaired inhibitory control arising from disrupted limbic–associative–motor network connectivity. Voxel-mirrored homotopic connectivity analyses show that PD-ICD patients exhibit reduced interhemispheric connectivity in the middle frontal gyrus, orbitofrontal gyrus, inferior frontal gyrus, and caudate relative to both PD

patients without ICD and healthy controls, with middle-frontal-gyrus values negatively correlated with impulsivity severity and demonstrating candidate diagnostic utility via ROC analysis. Combined task-activation and connectivity studies using Go/No-Go and delay-discounting paradigms show that ICD-affected PD patients exhibit reduced DLPFC and striatal activation alongside altered caudate connectivity—decreased to superior parietal cortex, increased to insula—indicating that orbitofronto-striatal and mesolimbic disruption alone do not fully account for the ICD phenotype. Resting-state seed-based analyses of the striatum demonstrate functional disconnection between the anterior putamen and both the inferior temporal gyrus and anterior cingulate gyrus in PD-ICD patients. Pharmacological-challenge studies show that dopaminergic state, including on/off medication status and dopamine agonist exposure, modulates resting-state network connectivity within cortico-subcortical circuits relevant to both sensorimotor and cognitive/motivational domains, with effects that can be either normalizing or maladaptive depending on the network probed. Collectively, this literature positions PD-ICD as a valuable natural experiment in pharmacologically induced addiction-like neuroplasticity, in which reward-circuit hyperconnectivity is directly attributable to a known pharmacological manipulation rather than to self-administered drugs of abuse.

6.2 Traumatic brain injury and substance use vulnerability

TBI is increasingly understood as a disorder of brain connectivity rather than a purely focal structural lesion. Resting-state studies in mild TBI demonstrate decreased DMN connectivity, particularly in lateral parietal cortex, coupled with increased salience-network connectivity, along with within- and between-network alterations in sensorimotor, visual, and dorsal-attentional networks that correlate with post concussive symptom burden. While the direct fMRI literature specifically isolating SUD-connectivity signatures within TBI populations remains comparatively sparse, clinical and epidemiological work documents substantially elevated TBI–SUD comorbidity, motivating integrated treatment frameworks. Graph-theoretical summaries of network topology have been explored as prognostic tools in critical TBI but have thus far shown limited standalone predictive value for functional outcome, underscoring both the promise and current limitations of connectivity-based biomarkers in this population. Mechanistically, disruption of prefrontal–limbic connectivity and impaired top-down inhibitory control following TBI plausibly lowers the threshold for compulsive substance-seeking behavior, paralleling the executive-control-network hypoconnectivity described in primary SUDs; direct longitudinal fMRI studies testing this hypothesis in post-TBI populations represent an important gap for future

6.3 Other neurological contexts

Emerging evidence addresses connectivity reorganization in other neurological conditions with addiction-adjacent phenomena, including post-stroke apathy/impulsivity syndromes and epilepsy-related behavioral dyscontrol. These areas currently lack the depth of substance-specific or PD-ICD literature and are flagged as priority areas for future dedicated fMRI biomarker research rather than reviewed in depth here.

7. Network Reorganization: Graph-Theoretical Perspectives

Across the literatures reviewed above, a graph-theoretical reading of addiction-related neuroplasticity suggests two broadly recurring, though not universal, patterns: reduced global and local efficiency within executive-control and DMN subnetworks, consistent with impaired information integration supporting inhibitory control and self-referential processing ; and increased local clustering or hyperconnectivity within reward/salience circuitry, consistent with heightened incentive-salience attribution to drug- or reward-related cues. Nicotine-gum administration studies illustrate the state-dependence of these metrics: acute nicotine increases nodal efficiency and decreases clustering, contrasting with the network-efficiency reductions associated with chronic dependence, cautioning against treating connectivity abnormality as a stable trait marker rather than a state- and history-dependent phenomenon. Modularity and community-structure analyses further suggest that addiction may involve reorganization of which regions cluster into functional modules, rather than simple increases or decreases in overall connectivity strength, a distinction with direct implications for graph-metric selection in future biomarker studies.

8. Computational Advances in fMRI Biomarker Discovery

8.1 Machine Learning for Functional Connectivity Analysis

The rapid expansion of machine learning (ML) has fundamentally changed the analysis of functional neuroimaging data by enabling individualized prediction rather than conventional group-level comparisons. Traditional statistical methods primarily identify average differences between patient groups and healthy controls, whereas supervised ML algorithms can learn complex multidimensional patterns within functional connectivity matrices that are predictive of clinically relevant outcomes. Consequently, connectivity-derived imaging features are increasingly being used for disease classification, prognosis, relapse prediction, treatment-response estimation, and behavioral phenotyping.

Across substance use disorders, supervised learning approaches—including support vector machines, random forests, gradient boosting algorithms, and deep neural networks—have demonstrated encouraging performance in differentiating affected individuals from healthy controls. Predictive models trained on resting-state connectivity have also been employed to estimate craving severity, smoking relapse risk, alcohol dependence severity, and opioid use disorder status. Despite these promising findings, most published models have been developed using relatively small, single-center datasets, limiting their generalizability across diverse clinical populations. Future investigations should therefore prioritize large multicenter cohorts, standardized validation protocols, and independent external testing to establish robust and clinically reliable neuroimaging biomarkers

8.2 Graph Neural Networks

Graph Neural Networks (GNNs) represent one of the most important recent developments in neuroimaging-based artificial intelligence. Unlike conventional machine learning methods that treat imaging features independently, GNNs preserve the inherent graph structure of the human connectome by representing brain regions as interconnected nodes linked through functional connectivity. This architecture allows the model to learn complex spatial relationships among distributed neural networks while simultaneously capturing both local and global topological characteristics.

Recent systematic reviews demonstrate that GNN-based frameworks consistently outperform many traditional machine learning approaches in classifying psychiatric and neurological disorders from resting-state fMRI data. Emerging addiction studies have applied graph convolutional networks, graph attention networks, and diffusion-based graph reconstruction models to identify subtle connectivity abnormalities associated with nicotine dependence and other substance use disorders. These methods improve feature representation by incorporating neighborhood information from interconnected brain regions, thereby enhancing the detection of disease-specific connectivity patterns. Nevertheless, widespread clinical implementation remains limited by insufficient multicenter validation, heterogeneous imaging protocols, and limited availability of large annotated neuroimaging datasets.

8.3 Explainable Artificial Intelligence

As artificial intelligence models become increasingly sophisticated, interpretability has emerged as a critical requirement for their integration into clinical practice. High predictive accuracy alone is insufficient if clinicians cannot understand how a model reaches its diagnostic or prognostic decisions. Explainable Artificial Intelligence (XAI) addresses this challenge by providing transparent methods for identifying the brain regions, functional connections, or network features that contribute most strongly to model predictions.

Several explainability techniques—including SHAP (Shapley Additive Explanations), LIME (Local Interpretable Model-Agnostic Explanations), Grad-CAM, saliency mapping, feature attribution analysis, and layer-wise relevance propagation—have been successfully applied in neuroimaging research. These approaches enable visualization of the neural substrates driving algorithmic decisions and facilitate comparison between computational findings and established neurobiological knowledge. Beyond improving scientific interpretability, explainable models enhance clinician confidence, support regulatory approval of AI-based diagnostic systems, and reduce the likelihood of predictions being influenced by non-biological imaging artifacts. Although XAI has become increasingly common in neurodegenerative and psychiatric neuroimaging, its application in addiction-focused functional MRI research remains relatively limited, representing an important opportunity for future investigation.

8.4 Foundation Models and Multimodal Artificial Intelligence

The emergence of foundation models has introduced a new paradigm in computational neuroimaging. These large-scale neural networks are pretrained using extensive collections of unlabeled or weakly labeled neuroimaging data, enabling them to learn generalized representations of brain organization before being adapted to specific downstream clinical tasks through fine-tuning. Compared with models trained exclusively on individual datasets, foundation models offer improved robustness, transferability, and scalability across different imaging protocols and disease populations.

Parallel advances have occurred in multimodal artificial intelligence, where functional MRI is integrated with complementary data sources such as structural MRI, diffusion tensor imaging, positron emission tomography, electroencephalography, clinical variables, neuropsychological assessments, and electronic health records. Cross-modal attention mechanisms and transformer-based fusion architectures allow these heterogeneous data streams to be combined into unified predictive models that often outperform unimodal approaches. In addiction research, such multimodal frameworks hold considerable promise for simultaneously characterizing structural abnormalities, functional network organization, neurochemical alterations, and clinical phenotypes, thereby supporting more comprehensive precision medicine strategies.

Open-source foundation-model platforms and pretrained neuroimaging toolkits have also accelerated methodological development by allowing investigators to leverage previously learned representations rather than training complex

deep-learning models from scratch. These resources are expected to facilitate broader adoption of advanced artificial intelligence techniques within addiction neuroimaging research.

8.5 Reproducibility, Harmonization, and Federated Learning

One of the principal barriers to clinical translation of functional MRI biomarkers is the substantial variability introduced by differences in scanner hardware, acquisition protocols, preprocessing pipelines, and demographic characteristics across imaging centers. Such site-specific variability can obscure biologically meaningful connectivity patterns and substantially reduce the reproducibility of machine learning models.

To address these challenges, statistical harmonization methods such as ComBat and its subsequent extensions have become widely adopted for minimizing scanner-related batch effects while preserving genuine biological variation. More recently, deep-learning-based harmonization techniques—including variational autoencoders, adversarial domain adaptation, and generative adversarial networks—have demonstrated improved performance in correcting complex nonlinear differences between imaging sites.

Data-sharing restrictions arising from patient privacy regulations have simultaneously stimulated growing interest in federated learning. Rather than transferring sensitive imaging data to a centralized repository, federated learning enables multiple institutions to collaboratively train a shared machine learning model while retaining patient data locally. Only model parameters are exchanged during training, substantially reducing privacy concerns while increasing sample diversity. This distributed learning strategy is particularly attractive for functional MRI research, where acquiring sufficiently large datasets remains challenging.

The combination of multicenter harmonization, privacy-preserving federated learning, explainable artificial intelligence, and advanced graph-based deep learning provides a comprehensive computational framework for next-generation neuroimaging biomarker discovery. Together, these complementary approaches have the potential to improve reproducibility, facilitate large-scale collaborative research, and accelerate the development of clinically applicable imaging biomarkers for addiction-related neuroplasticity.

9. fMRI-Guided Neuromodulation: Mechanistic Probe and Treatment Target

Non-invasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS), theta-burst stimulation, transcranial direct current stimulation (tDCS), and deep transcranial magnetic stimulation (dTMS), has been used both to test causal predictions from the connectivity literature and as an emerging treatment modality. Across nicotine, alcohol, cocaine, and behavioral addictions, the dorsolateral prefrontal cortex (DLPFC) remains the most commonly targeted region, while deep-coil approaches also engage midline frontocortical structures, including the medial prefrontal and anterior cingulate cortices. In nicotine dependence, high-frequency rTMS over the left DLPFC modulates spontaneous activity and connectivity within reward circuitry, including the ventral tegmental area, nucleus accumbens, and amygdala, and reduces cerebral blood flow in the DLPFC alongside reductions in FTND and craving scores. In alcohol use disorder (AUD), a randomized, double-blind, sham-controlled dTMS trial targeting the medial prefrontal and anterior cingulate cortices reduced post-treatment craving and the percentage of heavy drinking days at follow-up, with active stimulation associated with decreased dACC–caudate and mPFC–subgenual ACC connectivity, providing a connectivity-based mechanistic correlate of clinical benefit. Complementary work shows that repeated high-frequency rTMS to the right DLPFC in AUD enhances resting-state frontoparietal executive-control network connectivity, and that multi-session deep rTMS reduces striatal dopamine-transporter binding on SPECT, consistent with increased dopaminergic tone as a candidate mechanism. In cocaine use disorder, TMS targeting the medial prefrontal/anterior cingulate cortex with an H7 coil reduced laboratory cocaine self-administration in a pilot study, with target selection informed by prior connectivity and activation imaging. Meta-analytic synthesis across studies spanning depressant, stimulant, and behavioral addictions found a small but significant overall effect of active rTMS on craving reduction, with stronger effects in stimulant and behavioral addiction subgroups than in depressant-class substances. A broader systematic review and meta-analysis of neuromodulation therapies, including rTMS, tDCS, and deep brain stimulation for substance use disorders, supports feasibility and modest efficacy but emphasizes the need for standardized dosing and targeting protocols.

10. Methodological Challenges and Limitations

Despite considerable advances in functional MRI (fMRI) research on addiction-related neuroplasticity, several methodological limitations continue to constrain the interpretation, reproducibility, and clinical translation of current findings. A major limitation is the predominance of studies with relatively small sample sizes and single-site recruitment, which reduces statistical power and limits the generalizability of observed connectivity patterns, particularly in underrepresented populations such as patients with Parkinson's disease-associated impulse control disorders (PD-ICDs) and traumatic brain injury (TBI). Furthermore, the majority of available studies employ cross-sectional designs, making it difficult

to determine whether functional connectivity alterations represent pre-existing vulnerability factors, consequences of chronic substance exposure, or adaptive changes occurring during abstinence and recovery. Considerable methodological heterogeneity also exists across studies with respect to image acquisition protocols, preprocessing pipelines, seed-region selection, brain parcellation schemes, denoising strategies, motion correction procedures, and the application of global signal regression, thereby limiting direct comparison across studies and reducing the reliability of quantitative evidence synthesis. Interpretation of connectivity findings is further complicated by important confounding factors, including acute pharmacological effects, medication status, psychiatric comorbidities, polysubstance use, duration of abstinence, and demographic variability, all of which independently influence functional brain organization and are inconsistently controlled across investigations. Although machine learning and deep learning approaches have demonstrated promising diagnostic and prognostic performance, most predictive models have been developed and evaluated using relatively small, single-center datasets with limited external validation, raising concerns regarding robustness, reproducibility, and real-world clinical applicability. In addition, inconsistencies in the reported direction of functional connectivity alterations, with both hyperconnectivity and hypoconnectivity described within identical neural networks across different studies, suggest that connectivity measures are highly dependent on disease stage, substance type, treatment status, and methodological choices rather than representing stable biological traits. Finally, direct neuroimaging evidence remains scarce in neurological populations with addiction-related manifestations, including individuals with TBI, stroke, epilepsy, and other neurological disorders, where current conclusions are largely extrapolated from indirect evidence rather than dedicated longitudinal connectivity studies. Addressing these methodological challenges through larger multicenter cohorts, standardized imaging protocols, harmonized analytical pipelines, prospective longitudinal study designs, and rigorous external validation of computational biomarkers will be essential for translating fMRI-based measures of addiction-related neuroplasticity into reliable and clinically actionable precision medicine tools.

11. Future Directions

The next phase of addiction neuroimaging research should move beyond descriptive characterization of functional connectivity abnormalities toward the development of robust, reproducible, and clinically applicable biomarkers. Achieving this objective will require coordinated international efforts to establish large, harmonized, multicenter neuroimaging cohorts with standardized acquisition protocols, preprocessing pipelines, quality-control procedures, and reporting standards. Such initiatives would substantially improve reproducibility while reducing variability arising from differences in scanner hardware, acquisition parameters, and analytical methodologies. Equally important is the implementation of prospective longitudinal study designs that monitor individuals across different stages of addiction, including pre-exposure vulnerability, active substance use, withdrawal, treatment, recovery, and relapse. Longitudinal investigations are essential for distinguishing transient functional adaptations from persistent neuroplastic alterations that may serve as reliable prognostic biomarkers.

Future studies should increasingly adopt multimodal imaging strategies that integrate resting-state and task-based functional MRI with diffusion tensor imaging (DTI), structural MRI, positron emission tomography (PET), electroencephalography (EEG), magnetic resonance spectroscopy (MRS), and molecular biomarkers. Combining complementary structural, functional, metabolic, and neurochemical information may provide a more comprehensive understanding of addiction-related brain reorganization than any individual imaging modality alone. Integration of neuroimaging findings with genetic, epigenetic, proteomic, metabolomic, digital phenotyping, and behavioral datasets will further facilitate systems-level characterization of addiction and support the development of individualized risk prediction models.

Artificial intelligence is expected to play an increasingly central role in translating neuroimaging discoveries into clinical decision-support systems. However, future computational research should prioritize model robustness, external validation across independent populations, calibration assessment, fairness evaluation, and transparent reporting according to internationally accepted artificial intelligence reporting guidelines. Explainable AI techniques should be routinely incorporated into predictive frameworks to ensure that algorithmic decisions remain biologically interpretable and clinically trustworthy. Similarly, foundation models pretrained on large-scale neuroimaging repositories and graph neural network architectures should be evaluated prospectively in multicenter settings to determine their real-world clinical utility beyond retrospective research datasets.

Another important priority is the expansion of addiction neuroimaging research into neurological disorders that exhibit addiction-related behavioral manifestations. Although Parkinson's disease-associated impulse control disorders and traumatic brain injury have received increasing attention, evidence remains limited for stroke, epilepsy, multiple sclerosis, Huntington's disease, dementia, and other neurological conditions characterized by

impaired reward processing or executive dysfunction. Comparative studies across these disorders may help identify shared and disease-specific functional connectivity signatures while improving understanding of the neurobiological mechanisms linking neurological injury with compulsive behavior.

Future neuromodulation research should also evolve from conventional standardized stimulation protocols toward individualized, connectivity-guided therapeutic interventions. Functional connectivity maps derived from each patient's intrinsic brain networks may enable personalized targeting for repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and emerging non-invasive neuromodulation techniques. Combining longitudinal neuroimaging biomarkers with clinical, cognitive, and behavioral outcome measures will facilitate objective monitoring of treatment-induced neuroplasticity and optimize patient-specific therapeutic strategies.

Finally, successful clinical implementation will depend on establishing standardized imaging biomarkers that demonstrate reproducibility across institutions, robustness across imaging platforms, and consistent predictive performance in diverse populations. Achieving this goal will require close collaboration among neuroscientists, radiologists, neurologists, psychiatrists, computer scientists, biomedical engineers, and regulatory agencies. Through harmonized multicenter research, interpretable artificial intelligence, multimodal neuroimaging integration, and rigorous external validation, functional MRI has the potential to evolve from a predominantly research-oriented technique into a clinically actionable tool for precision diagnosis, individualized prognosis, treatment selection, and longitudinal monitoring of addiction-related neuroplasticity.

12. Conclusion

Functional MRI, and resting-state functional connectivity in particular, has substantially advanced understanding of addiction as a disorder of large-scale brain network reorganization, with convergent though not fully consistent evidence for DMN, salience-network, and executive-control-network disruption across nicotine, alcohol, opioid, stimulant, and cannabis use disorders, as well as closely related mesocorticolimbic and orbitofronto-striatal reorganization in dopamine-agonist-induced impulse control disorders in Parkinson's disease. Graph-theoretical and machine-learning approaches are beginning to translate these group-level findings toward individualized, potentially clinically actionable biomarkers, and fMRI-guided neuromodulation studies provide early causal and mechanistic support for connectivity-based treatment targeting. Realizing the full clinical potential of fMRI biomarkers of addiction-related neuroplasticity, including in neurologically comorbid populations such as TBI and stroke, will require larger, longitudinal, multimodal, and externally validated studies built on standardized acquisition and analysis pipelines.

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