Substance Abuse and Rehabilitation

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Updated Perspectives on the Neurobiology of Substance Use Disorders Using Neuroimaging

Kevin S Murnane[1], Amber N Edinoff[2], Elyse M Cornett[3], Alan D Kaye[3]

[1]Department of Pharmacology, Toxicology and Neuroscience, Louisiana State University Health Sciences Center at Shreveport, Shreveport, LA, USA; [2]Department of Psychiatry, Harvard Medical School, Boston, MA, USA; [3]Department of Anesthesiology, Louisiana State University Health Sciences Center at Shreveport, Shreveport, LA, USA

Correspondence: Kevin S Murnane, Louisiana State University Health Sciences Center at Shreveport, 1501 Kings Highway, Shreveport, LA, 71103, USA, Email kevin.murnane@lsuhs.edu

Abstract: Substance use problems impair social functioning, academic achievement, and employability. Psychological, biological, social, and environmental factors can contribute to substance use disorders. In recent years, neuroimaging breakthroughs have helped elucidate the mechanisms of substance misuse and its effects on the brain. Functional magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) are all examples. Neuroimaging studies suggest substance misuse affects executive function, reward, memory, and stress systems. Recent neuroimaging research attempts have provided clinicians with improved tools to diagnose patients who misuse substances, comprehend the complicated neuroanatomy and neurobiology involved, and devise individually tailored and monitorable treatment regimens for individuals with substance use disorders. This review describes the most recent developments in drug misuse neuroimaging, including the neurobiology of substance use disorders, neuroimaging, and substance use disorders, established neuroimaging techniques, recent developments with established neuroimaging techniques and substance use disorders, and emerging clinical neuroimaging technology.

Keywords: MRI, neurobiology, substance misuse, addiction, neuroimaging, AI, PET, fMRI, SPECT

Introduction

Substance use disorders have far-reaching consequences, leading to social, intellectual, and occupational impairments arising from the excessive consumption of substances such as nicotine, alcohol, and various drugs. These substances encompass both legal and illegal substances, including cannabis, sedatives, hypnotics, anxiolytics, inhalants, opioids, hallucinogens, and stimulants.[1,2] Substance use disorders include misuse, intoxication, physical or psychological dependency, withdrawal, and craving.[3]

The classification of substances of misuse is based on their effects on the central nervous system (CNS). These effects can range from heightened energy and euphoria with stimulants like methamphetamine and cocaine to profound sedation caused by depressants such as alcohol, heroin, and fentanyl.[4] Positive reinforcement occurs in the early stages of substance use disorders, where users experience well-being or euphoria. However, as physiological and psychological dependence progresses, the focus transitions to relief of dysphoria and withdrawal symptoms, eventually leading to preoccupation, anticipation, and craving.[5]

The development of substance use disorders is influenced by multiple factors, such as psychological, biological, sociocultural, and environmental elements. Co-occurring mental conditions, such as attention deficit hyperactivity disorder (ADHD) and bipolar affective disorders, increase the risk of developing substance use disorders into adulthood compared to the general population. Heightened stress levels have also been associated with negative mental and behavioral health outcomes, such as self-harming thoughts and substance misuse.[6,7] Genetic predisposition and environmental factors play significant roles in developing substance use disorders. Individual genetic differences can affect the stress response and predispose certain individuals to substance use disorders.[6,8]

Received: 5 October 2022
Accepted: 27 June 2023
Published: 10 August 2023

Neuroimaging has emerged as a powerful tool in substance misuse research, offering valuable insights into the effects of substance misuse on the brain. Techniques such as single-photon emission computed tomography, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy have advanced our understanding of the neurological impacts of illicit substances. Neuroimaging studies have revealed the involvement of brain regions and circuitry related to executive function, reward, memory, and stress systems involved in substance misuse.[6] These findings are based on imaging studies of the drug users' brains following prolonged substance use.[9] Primates exposed to drugs over an extended period have also demonstrated distinct alterations in neural circuitry, providing controlled conditions for studying drug use from initial exposure.[10–12] The prefrontal cortex (PFC), basal ganglia, and extended amygdala are particularly implicated in substance misuse and associated behaviors.[13]

Neuroimaging techniques offer insights into the brain's anatomical components and physiological processes, including neurotransmitter activity and blood flow. The ultimate goal of neuroimaging research is to equip clinicians with the necessary tools for accurate diagnosis, enhance understanding of the intricate neuroanatomy and neurobiology involved in substance misuse, gain insight into the behaviors of individuals who misuse substances, and develop tailored treatment regimens that can be closely monitored for patients who misuse substances. This review explores the latest advancements in neuroimaging research on substance misuse, covering topics such as the neurobiology of substance use disorders, the role of neuroimaging in understanding substance misuse, and contemporary clinical issues in the field.

Neurobiology of Substance Use Disorders

The disease model of substance addiction[14,15] is a widely accepted theory that views substance misuse as a chronic brain disorder characterized by significant alterations in brain structure and function. It recognizes substance misuse as a complex condition influenced by genetic and environmental factors, leading to dysregulation within the brain's reward and motivation pathways. This model emphasizes the chronic nature of substance misuse and highlights that it is not simply a result of moral failings or lack of willpower. Instead, it acknowledges that substance misuse involves an interplay of biological, psychological, and social factors that lead to long-lasting alterations in brain structure and function because of substance misuse.

Drugs of misuse raise dopamine (DA) levels in mesolimbic regions, which is essential for their reinforcing effects.[16,17] Drugs of misuse produce their reinforcing and addictive effects by directly activating supraphysiological DA action and by indirectly modulating other neurotransmitters (glutamate, aminobutyric acid (GABA), opioids, acetylcholine, cannabinoids, and serotonin) in the brain's reward circuit.[13] We discuss this in more detail below.

Neuroimaging studies have provided evidence of specific changes in brain regions such as the prefrontal cortex (PFC), nucleus accumbens (NAc), amygdala, and hippocampus, which are involved in decision-making, impulse control, reward processing, and memory.[5,11,18,19] These alterations contribute to the characteristic behaviors observed in individuals who misuse substances. Genetic factors also play a significant role in substance misuse vulnerability, as individuals may inherit genetic variations that influence their susceptibility to substance misuse behaviors.[20] These genetic factors can modulate an individual's response to drugs and their propensity to develop substance misuse.

Furthermore, substance misuse involves the dysregulation of the brain's reward and motivation pathways. Specifically, the mesolimbic dopamine system, which includes the ventral tegmental area (VTA) and NAc, is involved in releasing and modulating dopamine, a neurotransmitter associated with pleasure and reinforcement.[11] With substance misuse, this system becomes dysregulated, resulting in an enhanced response to drugs and decreased sensitivity to natural rewards.

Impaired inhibitory control and executive functions mediated by the PFC are also implicated in substance misuse. These impairments contribute to the difficulties individuals who misuse substances face in resisting drug-seeking behaviors and making adaptive decisions.

Additionally, the discontinuation of substance misuse leads to the emergence of withdrawal symptoms and craving, reinforcing the cycle of substance misuse.

Specifically, substance misuse can be categorized into three stages that recur in a cycle: binge/intoxication, withdrawal, and preoccupation/anticipation or craving, though there are differences in opinion among experts.[13,21] Each of these stages has distinct and measurable changes that occur. Nearly all drugs of misuse specifically target the brain's

reward system, which primarily comprises the mesolimbic dopamine pathways but extends to serotonergic, opioid, endocannabinoid, glutamatergic, and other systems. For example, PET studies show that alcohol ingested at intoxicating doses causes a fast release of dopamine and opioid peptides into the ventral striatum, which bind to low-affinity dopamine D1 receptors.[22] This fast release of dopamine and subsequent binding of D1 receptors is associated with a "high" feeling, creating the rewarding effect of drugs of misuse.

In contrast, high-affinity dopamine D2 receptor activation does not create drug reward.[23] The VTA, located in the midbrain, begins the mesolimbic dopamine pathway, directly or indirectly stimulated by various addictive substances. Dopaminergic neurons in the VTA project to the NAc, dorsal striatum, prefrontal cortex, extended amygdala, and the limbic system. In the absence of drugs of misuse, the NAc is essential for motivation, reward, and reinforcement learning. The prefrontal cortex regulates impulses, emotions, executive function, planning, and cognitive behavior. The limbic system controls motivation, drive, emotion, learning, and memory and comprises part of the VTA, NAc, amygdala, hippocampus, and cingulate gyrus. These brain areas are intricately connected through balanced circuits that exhibit proper stimulatory and inhibitory control. Drugs of misuse are believed to hijack these circuits and cause changes that lead to dysregulation of these circuits and impaired functioning of reward, motivation, stress reactivity, and emotional regulation.

The initial stage of binge/intoxication involves increases in dopamine, opioid peptides, serotonin, gamma-aminobutyric acid, and acetylcholine occurring in pathways involving the VTA and NAc.[13] This activation is triggered and sustained by signal transduction mechanisms and changes in gene transcription. For example, drugs of misuse can upregulate cAMP, protein kinase A (PKA), and PKA-dependent phosphorylation in the NAc.[24] The withdrawal/negative affect stage involves increases in corticotropin-releasing factor, dynorphin, norepinephrine, orexin, and substance P, and concurrent decreases in dopamine, serotonin, opioid peptide receptors, neuropeptide Y, nociception, endocannabinoids, and oxytocin occurring in pathways involving the VTA, central nucleus of the amygdala, the bed nucleus stria terminalis, the NAc shell, and the habenula. These changes in neurocircuitry induced by withdrawal from drugs of misuse can lead to states of stress involving irritability, emotional dysregulation, pain, malaise, dysphoria, and loss of motivation for otherwise natural rewards.[25,26] These changes can be surmised as "within-system neuroadaptations", where the primary neuronal response to a drug, which is for the neuronal circuit to neutralize the drug effects and return homeostasis to the neuronal circuit, persists after the effect of the drug is no longer present, thereby inducing a withdrawal state.[27] Specifically, decreased dopamine and serotonin transmission in the NAc are seen in animals and humans during amphetamine withdrawal.[28] Finally, the preoccupation/anticipation stage involves increases in dopamine, glutamate, orexin, serotonin, and corticotropin-releasing factor occurring in pathways involving the PFC, hippocampus, basolateral amygdala, the bed nucleus striatus terminalis, and the insula. In humans, cue-induced drug craving is mediated by drug-associated cues such as paraphernalia, which activate the PFC.[29] Cocaine craving specifically increases dopamine in the striatum, amygdala, and PFC, increasing opioid peptides in the anterior cingulate and frontal cortex.[30]

Neuroimaging and Substance Use Disorders

The study of the human brain has made unprecedented strides in the past two decades. The advent of structural and functional brain imaging techniques, which have revolutionized cognitive and behavioral neuroscience by providing a window into the brain activity underlying complex human behaviors, may be the most thrilling development. These technological advances have also facilitated the rapid translation of neuroscientific findings into more targeted clinical treatments.

Established Neuroimaging Techniques

Nuclear Medicine Imaging

PET

PET imaging allows for examining neurotransmitter systems implicated in behavioral reinforcement, such as dopamine, unveiling alterations in receptor availability, transporters, and release dynamics among individuals with substance use

disorders.[31] These findings significantly contribute to our understanding of the dysregulation within the brain's reward circuitry associated with addiction.[13]

Furthermore, PET studies have provided critical insights into the functional and metabolic consequences of chronic substance misuse. By measuring parameters like cerebral blood flow, glucose metabolism, and oxygen utilization, PET has revealed reduced regional brain metabolism in individuals with prolonged alcohol or cocaine use, shedding light on the detrimental effects of these substances on brain activity.[32]

PET imaging has also been instrumental in investigating the neuroadaptive changes occurring during withdrawal and abstinence from substances.[9] PET studies have demonstrated the brain's capacity for neuroplasticity in response to substance misuse by examining alterations in receptor binding and neuroinflammation. These findings have important implications for understanding withdrawal symptoms, cravings, and potential relapse.

Moreover, PET has proven invaluable in evaluating the effectiveness of pharmacological interventions and treatment strategies for substance use disorders.[33] By assessing changes in neuroreceptor binding and neurotransmitter release following treatment, PET offers objective measures of treatment response and aids in identifying personalized treatment approaches.

SPECT

Single Photon Emission Computed Tomography (SPECT) imaging utilizes radiotracers that emit gamma rays, measuring regional cerebral blood flow and metabolic activity, thereby enabling the visualization and quantification of brain function. SPECT imaging involves the injection of radiotracers, such as technetium-99m or iodine-123, which emit gamma rays that can be detected by a gamma camera surrounding the patient's head. By rotating the camera and acquiring multiple images from various angles, SPECT allows for reconstructing a 3D representation of regional cerebral blood flow.

SPECT has significantly contributed to our understanding of the neurochemical changes associated with substance misuse. Studies utilizing SPECT imaging have revealed receptor binding and availability alterations in individuals with substance use disorders.[34] For instance, SPECT studies have shown changes in dopamine D2 receptor availability in the striatum of individuals with cocaine addiction, indicating dysregulation within the brain's reward circuitry.[35] Similarly, alterations in serotonin receptor availability have been observed in individuals with alcohol dependence, highlighting the involvement of the serotonergic system in addiction.[36]

Furthermore, SPECT has shed light on the impact of chronic substance misuse on brain function. By comparing individuals with addiction to healthy controls, SPECT studies have demonstrated altered regional cerebral blood flow patterns in areas associated with reward processing, decision-making, and impulse control.[37] These findings provide insights into the functional consequences of addiction and the neural circuits involved in addictive behaviors.

SPECT neuroimaging has also been instrumental in evaluating treatment interventions for substance use disorders. By monitoring changes in cerebral blood flow or receptor binding following treatment, SPECT can assess treatment response and optimize therapeutic approaches. For example, SPECT studies have shown changes in cerebral blood flow in response to medications used to treat opioid addiction, providing objective measures of treatment efficacy.

Magnetic Resonance Imaging (MRI)

Structural MRI

Structural MRI utilizes a strong magnetic field and radiofrequency pulses to generate high-resolution brain images. It provides information about different brain regions' size, shape, and composition. By analyzing structural MRI scans, researchers and clinicians can study the brain's macrostructure, including gray matter, white matter, and cerebrospinal fluid.

One of the key advantages of structural MRI is its noninvasive nature, as it does not involve exposure to ionizing radiation. This makes it safe for repeated imaging and suitable for many individuals, including children and pregnant women. Additionally, structural MRI is highly versatile and can investigate various neurological diseases.

Structural MRI plays a crucial role in clinical practice by aiding in the diagnosis, treatment planning, and monitoring of patients with brain disorders. It allows for identifying abnormalities, such as tumors, vascular malformations, or

structural changes associated with degenerative diseases. It can also be used to assess the effects of interventions or track disease progression over time. For example, one study found that individuals with a history of multiple substance misuse have smaller frontal lobes than matched controls.[38] This has been confirmed in several other imaging studies.[39,40]

fMRI

fMRI relies on the same principles as structural MRI but focuses on the temporal changes in brain activity rather than the anatomical structures. By detecting changes in blood flow and oxygenation, fMRI can provide insights into which brain areas are activated during specific tasks or in response to certain stimuli. fMRI is noninvasive, allowing for repeated measurements and the study of various populations, including healthy individuals and patients with neurological or psychiatric disorders. fMRI has many applications, including investigating sensory perception, attention, memory, language processing, emotion regulation, and decision-making.

fMRI studies have demonstrated that cocaine-related cues have a neurological basis in cocaine-addicted individuals.[41] Studies also show that cognitive impairments in stimulant misusers are linked to drug-related brain alterations, eg, reduced activation in the PFC and anterior cingulate, which are responsible for behavioral and cognitive control.[42,43]

While fMRI has numerous strengths, it does have limitations. There are other neuroimaging technique that have better spatial resolution or that have been temporal resolution. Additionally, fMRI measures neural activity indirectly through hemodynamic responses, which can introduce some limitations in interpretation.

Blood Oxygen Level-Dependent Functional MRI (BOLD fMRI)

The BOLD fMRI technique takes advantage of the fact that neural activity is coupled with changes in regional cerebral blood flow. When a specific brain region becomes active, there is an increase in blood flow and oxygen delivery to that area. BOLD fMRI detects these changes in blood oxygenation levels by measuring the magnetic properties of deoxygenated and oxygenated blood.

By analyzing the BOLD signal, researchers can identify brain regions that exhibit increased or decreased activity during different cognitive processes or in response to stimuli. BOLD fMRI has been instrumental in mapping brain networks involved in sensory perception, attention, memory, language processing, and emotional regulation. For example, a study investigating students at risk for alcohol misuse showed neuronal reactivity to alcohol cues in the right insula, left anterior cingulate, left caudate, and left prefrontal cortex, consistent with their greater use of alcohol, suggesting insula activation to appetitive cues may be an early marker for risk of alcohol misuse.[44]

However, it is important to note that BOLD fMRI measures neural activity indirectly and relies on complex mathematical models for data analysis. The technique also has limitations in terms of spatial and temporal resolution. Nonetheless, BOLD fMRI remains a valuable tool in neuroscience, providing crucial insights into brain function, advancing our understanding of neurological and psychiatric disorders, and guiding future research and clinical interventions. An excellent review of BOLD fMRI and substance misuse can be found here.[45]

MR Spectroscopy (MRS)

MRS measures the radiofrequency signals emitted by different molecules in the brain, allowing researchers to analyze the concentrations of specific compounds, such as neurotransmitters, amino acids, energy metabolites, and markers of cellular integrity. By assessing these metabolites, MRS provides insights into brain function's biochemical and metabolic aspects.

One of the key advantages of MRS is its ability to provide quantitative measurements of metabolite concentrations, offering valuable information about the metabolic state of brain tissue. It can be used to investigate conditions such as brain tumors, neurodegenerative disorders, epilepsy, and psychiatric illnesses, providing valuable insights into the underlying pathophysiology and monitoring treatment response.

MRS is particularly useful in studying disorders with prominent neurochemical alterations, such as substance misuse. One study showed that methamphetamine misusers have reduced NAA concentrations in the basal ganglia and frontal cortex white matter compared to non-users.[46] This is also consistent with individuals who misuse cocaine.[47] A recent review can be found here.[48]

Despite its strengths, MRS has some limitations. It has lower spatial resolution than structural MRI and is often limited to specific brain regions of interest rather than whole-brain coverage. Additionally, interpreting MRS data requires expertise in spectroscopic analysis, and the acquisition and analysis can be time-consuming.

Electrophysiological Imaging Techniques

EEG

Electroencephalography (EEG) measures the electrical potentials generated by the brain's neurons by placing electrodes on the scalp. EEG provides temporal information about brain activity, allowing for the analysis of rapid changes in neural dynamics.

One of the key advantages of EEG is its high temporal resolution, which allows researchers to capture millisecond-level changes in brain activity. This makes it particularly useful for studying processes such as perception, attention, memory, and cognition that occur in real time. EEG can also assess abnormalities in brain rhythms and patterns, aiding in diagnosing and monitoring substance misuse. For example, cocaine misuse significantly modifies EEG activity markers; elevated beta, delta, and alpha frequencies.[49,50]

In addition to its standalone use, EEG can be combined with other neuroimaging techniques, such as fMRI or PET, to provide complementary information about brain function and substance misuse. This integration provides a more comprehensive understanding of brain activity and connectivity.[51]

Despite its strengths, EEG has some limitations. It has a relatively low spatial resolution, as the electrical signals are measured from the scalp surface. Additionally, interpreting EEG data can be challenging due to the complex nature of the signals and the need for specialized analysis techniques.

Magnetoencephalography (MEG)

MEG uses an array of highly sensitive sensors to measure the tiny magnetic fields produced by electrical currents in the brain. MEG captures millisecond-level changes in neural activity, making it ideal for investigating rapid brain processes such as sensory perception, motor control, language processing, and cognitive functions. By analyzing the magnetic fields, MEG allows researchers to map brain activity with excellent temporal precision and identify specific brain regions involved in various tasks or conditions. Particularly, MEG is well-suited to directly reflect the momentary neural activity fluctuations that characterize the main cognitive and reward processes associated with addiction.[52]

MEG also offers complementary information to other neuroimaging techniques like fMRI and EEG. While fMRI provides high spatial resolution but limited temporal resolution, and EEG provides high temporal resolution but limited spatial resolution, MEG combines the advantages of both techniques, providing a more comprehensive understanding of brain activity.[53]

Despite its strengths, MEG has some limitations. The cost of MEG systems and the need for specialized facilities and expertise can limit their accessibility. MEG signals are sensitive to environmental noise, requiring careful shielding and noise reduction measures during data acquisition. Additionally, MEG is limited in its ability to accurately localize deep brain structures due to the low magnetic field strength of the signals they produce.

Recent Developments with Established Neuroimaging Techniques

A 2023 narrative review on the molecular imaging studies of alcohol use disorder reported that several PET studies investigating alcohol-toxicity-induced neuroinflammation, which is detectable with PET ligands for the microglial marker translocator protein (TSPO), demonstrate reversible increases in TSPO binding in Alcohol Use Disorder (AUD), and preclinical evidence suggests that opioid antagonists can mitigate these inflammatory reactions. Numerous PET/SPECT studies demonstrate changes in dopaminergic markers, which are generally consistent with dopamine synthesis impairment and release among AUD patients, as seen in several other addictions; this may reflect the combination of an underlying deficiency in reward mechanisms that predisposes to AUD and acquired changes in dopamine signaling. Studies with opioid receptor ligands imply a specific upregulation of the mu-opioid receptor subtype in AUD, but little evidence exists for altered serotonin markers. Charting the landscape of molecular imaging in AUD is

complicated by the substantial heterogeneity of drinking patterns, gender differences, and variable contributions of genetics and preexisting vulnerability characteristics.[54]

A 2022 study investigating brain glucose metabolism patterns associated with morphine consumption in rats found significant brain metabolic differences between Lewis and Fisher rat strains in the cortex, hypothalamus, brainstem, and cerebellum. Different brain metabolic patterns observed via PET imaging after morphine self-administration suggests differences in potential predisposition to morphine misuse between individuals.[55]

One group of researchers performed a data-driven study in 2022 to evaluate the predictive efficacy of resting-state functional magnetic resonance imaging (rs-fMRI) during early abstinence from alcohol dependency.[56] They reported that alcohol dependency was related to deficits in regional homogeneity of the left postcentral gyrus, low-frequency fluctuations of the right fusiform gyrus, and frontal cortex between the right fusiform gyrus and the right middle cingulum. In addition, they reported that the functional connectivity between the left precentral region and the left cerebellum was reduced in the relapse group, suggesting that a reduction in the connection between the frontal lobe and the cerebellum may play a role in the pathogenesis of alcohol dependence relapse and may serve as a biomarker to predict relapse.[56]

A separate 2022 study investigated fluorodeoxyglucose positron emission tomography scans in patients with alcohol use disorder.[57] Diminished fluorodeoxyglucose (FDG) uptake was observed in patients with alcohol use disorder (AUD). And in addition to widespread metabolic abnormalities, AUD was also associated with decreased metabolic rates in frontal executive areas, which is consistent with diminished impulse control. Increases in metabolic rates were pronounced in the striatum and cingulate areas, consistent with a suppressed reward system.[57]

Another study of 162 people assessed risk- and resilience-related alterations in corticostriatal functional circuits in stimulant drug users with and without addiction, siblings of people with substance use disorders, and control volunteers. The risk of addiction, whether owing to family predisposition or drug use, was linked to hypoconnectivity in orbitofrontal and ventromedial prefrontal cortical-striatal networks. Resilience against a substance use disorder diagnosis was related to hyperconnectivity in two networks: 1) the lateral prefrontal cortex and medial caudate nucleus and 2) the supplementary motor area, superior medial frontal cortex, and putamen. These findings suggest a predisposing susceptibility to addiction, connected to defective goal-directed activities and opposing resilience mechanisms involved in behavioral control, which may guide innovative therapeutic and preventive approaches.[58] Similarly, a resting-state fMRI in primates with a very long history of taking cocaine revealed disrupted connectivity between the prefrontal cortex and striatum, which was associated with loss of control over cocaine-taking behavior,[59] which was assessed using specialized equipment to allow the primates to be scanned in the absence of anesthesia.[60] This phenotype could potentially be reversed by antagonism of serotonin receptors,[61] which is consistent with receptor regulation induced by psychedelic drugs that promote resilience.[62]

A 2019 literature review investigating the effects of substance misuse on white matter reported that diffusion tensor imaging (DTI), an MRI technique that measures white matter in vivo, can be used to infer levels of white matter microstructure fractional atrophy (FA).[63] FA is a composite measure of the extent to which water diffusion is constrained in a particular direction (axons and their associated myelinated sheaths restrict water diffusion in the axis parallel to the main direction of axons), and a lower FA number is correlated with a lower or "worse" white matter coherence. The study summarized cross-sectional research studies and longitudinal studies. Overall, the cross-sectional studies suggest that alcohol, cocaine, and opiate use are associated with lower FA in the corpus callosum. Within this group, alcohol and opiate use had a higher effect than controls. Cannabis and nicotine showed mixed results in both direction and effect size. The longitudinal studies suggest for alcohol, age-related decline of FA in white matter; for cannabis, heavy use is associated with a significant decline in white matter FA; for cocaine, that exposed adolescents have lower FA in cingulum and superior longitudinal fasciculus and a separate study showed that higher FA was associated with abstinence from cocaine.[64] Both opiates and nicotine are lacking in longitudinal studies. A 2020 systemic review and meta-analysis investigating gray and white matter morphology in substance use disorders used coordinate-based anatomic likelihood estimation (ALE) to pool the effects of substance use disorders compared to brain region volume. The data suggest that the gray matter (putamen, thalamus, insula, and anterior cingulate gyrus) and white matter (corpus callosum, thalamus, and corticospinal tract) show converging and diverging effects depending on the severity and type of misused substance,

suggesting there are substance misuse-associated changes in white and gray matter.[65] A 2021 systemic review and meta-analysis investigated volumetric whole-brain voxel-based morphometry in substance use disorder patients' gray and white matter. Substance use disorders disrupt the normal function of the limbic loop of the basal ganglia, and the severity of the substance use disorder is associated with neuroplastic adaptations in cortical and subcortical regions. Furthermore, they report consistent volumetric alterations in white matter in the insula, putamen, thalamus, and anterior cingulate cortex in gray matter and internal capsule and thalamic radiations in white matter, suggesting neuroadaptations to the entire limbic loop of the basal ganglia with substance use disorders. Finally, they found that substance use disorders were associated with a lower thalamic gray and white matter with alcohol, cocaine, nicotine, methamphetamine, opioids, and cannabis, and the severity of the reduced structural and functional activity of the thalamus is correlated with the severity of substance use disorder.[65]

A 2020 meta-analysis of 64 neuroimaging studies indicated that drug-related cues activate occipital cortices and anterior cingulate cortex in legal and illicit drug consumers, consistent with their perceptual salience of drug stimuli.

Additionally, they found a more frequent activation of the subcortical reward pathway (the VTA, NAc, the amygdala) in illicit drug users. These findings are consistent with animal and human research showing that abnormal activity of the mesocorticolimbic dopamine pathway may be responsible for this phenomenon; the VTA, the NAc, and the amygdala are essential structures for cue-elicited reward-seeking behaviors.

Unexpectedly, two additional brain regions outside the mesocorticolimbic system, the inferior temporal cortex, and the precuneus, were more frequently activated in those addicted to illicit drugs. Only the medial dorsal anterior cingulate cortex (dACC) was more commonly engaged in legal substance misusers.

Overall, these findings suggest some initial practical considerations: drug-cue brain reactivity, an index of craving intensity, and, possibly, the risk of relapse into addiction is influenced by the potential harm of a given substance and the internal and contextual determinants. As treatment-seeking patients are characterized by the activation of specific brain reactions to drug cues depending on the substance, rehabilitation, particularly when cue-extinction strategies are employed, may therefore benefit from individualized interventions that consider the influence of environmental and internal contingencies when subjects are likely to be exposed to drug cues.[66]

Emerging Clinical Neuroimaging Technology

Although these imaging techniques listed below represent the latest advancements in the field, there is currently limited published research on their application in individuals with substance misuse. Nevertheless, their inclusion is noteworthy due to their potential for advancing our understanding of substance misuse at a molecular level and uncovering detailed insights. Further investigation and studies utilizing these cutting-edge technologies are warranted to explore their potential implications in the field of substance misuse and to elucidate more comprehensive molecular findings. By shedding light on the intricate neurobiology underlying substance misuse, these emerging technologies can contribute significantly to our knowledge and potentially pave the way for innovative approaches to preventing, diagnosing, and treating substance use disorders. Therefore, despite the limited evidence available to date, the mention of these new imaging technologies is essential, as it highlights their potential significance in shaping future research and clinical practices in substance misuse.

3D Amplified MRI (3D aMRI)

Amplified MRI (aMRI) was recently introduced as a new brain motion detection and visualization method that considerably amplifies brain tissue response to blood pulsation and CSF movement. The aMRI technique makes it possible to observe the biomechanical response of the brain in minute detail due to the high spatial and temporal resolution underpinning the raw data acquisition and the contrast between brain tissue and CSF.[67,68] A phase-based motion magnification algorithm is the foundation of aMRI, which produces an amplified "movie" of brain motion using 2D multi-slice cardiac gated (MRI) data. Amplified flow imaging (aFlow) in aMRI has demonstrated promise for displaying cerebrovascular motion. When applied to 3D PC-MRA, aFlow can capture the traits of transient events occurring in brain tissue (ie, blood flow contact with artery walls).

MAGNETOM Terra.X and MAGNETOM Cima.X: MRI Scanners

The Magnetom Terra.X is a MR imaging system with a field strength of 7T. The higher signal strength at 7T allows for extremely high-resolution imaging, particularly in the head region. This is particularly advantageous in diseases where detecting small lesions plays a crucial role in treatment decisions.

The Magnetom Terra.X incorporates innovative hardware and software known as "Ultra IQ technology".[69] This technology significantly enhances the capabilities of the 7T system. MR imaging at such high field strengths can sometimes result in decreased image quality, especially in the lower part of the head. However, with the Magnetom Terra.X, potentially relevant findings are visible even at the periphery of the image, overcoming the limitations typically associated with lower image quality in these regions.

Furthermore, the increased field strength of 7T allows for better visualization of substances beyond water in the body, such as sodium. This extends the scope of MR imaging beyond mere anatomical representation and enables the visualization of metabolic processes within the body.

Regarding research applications, both the Magnetom Terra.X and Magnetom Terra offer notable advancements. The Open Recon platform enables the execution of reconstruction algorithms directly on the scanner, facilitating the translation of research developments into clinical practice. Additionally, these scanners incorporate assistance systems that assist with scan preparation and operation, ensuring user-friendly operation and seamless integration into existing scanner fleets with minimal training requirements.[70]

The 3T Magnetom Cima.X, featuring Siemens Healthineers' most powerful gradient allows for visualization of microstructures that are typically challenging to visualize with conventional MR imaging. This capability may aid in deciphering the mechanisms underlying neurological diseases and provide novel biomarkers for therapeutic responses. Furthermore, the improved visualization of microstructures may facilitate earlier initiation of treatment, thereby potentially improving patient outcomes.[70]

Siemens also has the MAGNETOM Viato.Mobile, a mobile MRI scanner installed in a trailer to offer more flexibility in employing MRI imaging. The MRI can be easily transported between locations or stay fixed. Importantly, the trailer comes to the patient, which offers MRI imaging to many more patient populations in need. The imaging can be done remotely via the Internet or 4G connection, which allows for remote setup and fewer onsite personnel.[71]

Finally, another novel technology from Siemens is NAEOTOM Alpha, the world's first photon-counting computed tomography (CT) system. NAEOTOM Alpha provides high-resolution images with minimal radiation dose, spectral information in each scan, and enhanced contrast with reduced noise.[72]

Direct Imaging of Neuronal Activity (DIANA)

Direct imaging of neuronal activity (DIANA) uses existing MRI technology to take quickfire, partial images. It combines those images to create a high-resolution picture of which areas of the brain are active and when. This would be the first technique that allows noninvasive measures of neuronal activity with high spatial and temporal resolution. This system was first successfully tested in anesthetized mice,[73] and was recently tested in humans, although the study did not observe a clear DIANA signal in human subjects.[74] More testing in humans is currently underway.

Artificial Intelligence (AI)

Clinical neuroscience has recently shifted toward "multivariate" techniques that aim to categorize disease characteristics based on the multivariate pattern of input brain imaging data or "features". Artificial intelligence (AI) has demonstrated significant promise, especially in neuroimaging.[75] These techniques are under the broad genre of supervised "machine learning" (ML) techniques used in biomedical research since they frequently require some level of model training. AI refers to computer systems designed to conduct tasks requiring human intelligence. Machine learning (ML), a branch of AI, is the discipline where computers learn from data without being explicitly programmed. It is the subset of artificial intelligence responsible for its ability to match or even surpass humans in certain tasks. Machine learning can then be sub-classified into supervised and unsupervised learning, where unsupervised learning is training machines to utilize data that are neither classified nor labeled.[76] With the growing need for data processing and image interpretation, the potential

to augment and assist physicians with artificial intelligence could improve the quality of patient care. AI can forecast patient wait times and may enable more effective patient scheduling. AI can also shorten imaging times and save time during repeat magnetic resonance neuroimaging. With little to no reduction in sensitivity for spotting lesions, AI can read CT, MRI, and PET images.[77] AI has been used to successfully predict current clinical status and persistent behavior in individuals who misuse prescription opioids.[78] AI has also successfully classified cocaine-dependent individuals compared to non-dependent individuals.[79] However, current AI-based neuroimaging analyses are inconsistent. For example, a 2023 systematic review investigating the evaluation risk in neuroimaging-based AI models for psychiatric disease diagnosis found that of the 517 studies reviewed, 461 had a high risk of bias based on the prediction model risk of bias assessment tool (PROBAST), and none of the AI models were deemed acceptable for use in clinical practice. These data suggest that AI models need to be refined before use in clinical practice.[80] Overall, the success of AI use in clinical practice relies upon training machine learning with large datasets, which is where research efforts are currently focused.[81] There is reason to believe that with careful assessment, and risk of bias safeguards in place, AI will be a useful tool in clinical practice.[76]

Conclusion

Human brain research has made extraordinary strides, yielding unprecedented progress. Notably, advanced structural and functional brain imaging techniques have profoundly transformed the landscape of cognitive and behavioral neuroscience. By unveiling the intricate brain activity that underlies complex human behaviors, these technological breakthroughs have emerged as the most captivating development in the field.

These sophisticated imaging modalities have propelled our understanding and facilitated the rapid translation of neuroscientific discoveries into targeted clinical interventions. Well-established neuroimaging methodologies, such as PET, SPECT, MRI, fMRI, MEG, and EEG, have made substantial contributions to unraveling the intricacies of substance misuse and its associated underlying mechanisms.

However, the field is poised for even greater advancements with the emergence of novel neuroimaging techniques. Three-dimensional arterial spin labeling magnetic resonance imaging (3D aMRI), enhanced MRI scanners with heightened field strength, diffusion imaging with apparent diffusion coefficient mapping (DIANA), and the integration of artificial intelligence (AI) methodologies are anticipated to provide unprecedented insights into the mechanisms underlying substance misuse. Rigorous investigation and research employing these cutting-edge technologies are imperative to explore their potential implications in the realm of substance misuse and to elucidate comprehensive molecular findings.

By shedding light on the intricate neurobiology that underlies substance misuse, these emerging neuroimaging technologies hold tremendous promise in expanding our knowledge base and, potentially, revolutionizing the landscape of prevention, diagnosis, and treatment of substance use disorders. Their integration into clinical practice and research endeavors has the potential to drive innovative approaches that address the complexities of substance misuse from a holistic perspective.

In conclusion, the study of the human brain has witnessed remarkable advancements over the past two decades, fueled by the introduction of advanced structural and functional brain imaging techniques. With well-established neuroimaging methodologies and the emergence of cutting-edge technologies, our understanding of substance misuse and its molecular underpinnings has substantially deepened. By leveraging and further exploring these advancements, we can pave the way for groundbreaking strategies in combating substance use disorders, thereby addressing a significant societal challenge with enhanced precision and efficacy.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Eastlack SC, Cornett EM, Kaye AD. Kratom-pharmacology, clinical implications, and outlook: a comprehensive review. *Pain Ther*. 2020;9(1):55–69. doi:10.1007/s40122-020-00151-x
2. Urits I, Charipova K, Gress K, et al. Adverse effects of recreational and medical cannabis. *Psychopharmacol Bull*. 2021;51(1):94–109.

3. Hayes A, Herlinger K, Paterson L, Lingford-Hughes A. The neurobiology of substance use and addiction: evidence from neuroimaging and relevance to treatment. *B J Psych Adv*. 2020;26(6):367–378. doi:10.1192/bja.2020.68
4. Edinoff AN, Kaufman SE, Green KM, et al. Methamphetamine use: a narrative review of adverse effects and related toxicities. *Health Psychol Res*. 2022;10(3):38161. doi:10.52965/001c.38161
5. Ceceli AO, Bradberry CW, Goldstein RZ. The neurobiology of drug addiction: cross-species insights into the dysfunction and recovery of the prefrontal cortex. *Neuropsychopharmacology*. 2022;47(1):276–291. doi:10.1038/s41386-021-01153-9
6. Sagrera CE, Alderman L, Goeders NE, Murnane KS. Elucidating the role of trauma and significant life stress in the disease of addiction may provide new targets for medication development. *CNS Neurol Disord Drug Targets*. 2022. doi:10.2174/1871527321666220511145230
7. McPherson P, Alderman LL, Temple J, et al. Teen Advisory Council Survey's factors associated with self-harming thoughts. *Front Psychiatry*. 2022;13:851477. doi:10.3389/fpsyt.2022.851477
8. Volkow ND, Boyle M. Neuroscience of addiction: relevance to prevention and treatment. *Am J Psychiatry*. 2018;175(8):729–740. doi:10.1176/appi.ajp.2018.17101174
9. Fowler JS, Volkow ND, Kassed CA, Chang L. Imaging the addicted human brain. *Sci Pract Perspect*. 2007;3(2):4–16. doi:10.1151/spp07324
10. Henry PK, Murnane KS, Votaw JR, Howell LL. Acute brain metabolic effects of cocaine in rhesus monkeys with a history of cocaine use. *Brain Imaging Behav*. 2010;4(3–4):212–219. doi:10.1007/s11682-010-9100-5
11. Howell LL, Murnane KS. Nonhuman primate neuroimaging and the neurobiology of psychostimulant addiction. *Ann N Y Acad Sci*. 2008;1141(1):176–194. doi:10.1196/annals.1441.023
12. Murnane KS. The renaissance in psychedelic research: what do preclinical models have to offer. *Prog Brain Res*. 2018;242:25–67. doi:10.1016/bs.pbr.2018.08.003
13. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760–773. doi:10.1016/S2215-0366(16)00104-8
14. Heilig M, MacKillop J, Martinez D, Rehm J, Leggio L, Vanderschuren LJMJ. Addiction as a brain disease revised: why it still matters, and the need for consilience. *Neuropsychopharmacology*. 2021;46(10):1715–1723. doi:10.1038/s41386-020-00950-y
15. Volkow ND, Koob GF, McLellan AT, Longo DL. Neurobiologic advances from the brain disease model of addiction. *N Engl J Med*. 2016;374(4):363–371. doi:10.1056/NEJMra1511480
16. Koob GF, Caine B, Markou A, Pulvirenti L, Weiss F. Role for the mesocortical dopamine system in the motivating effects of cocaine. *NIDA Res Monogr*. 1994;145:1–18.
17. Di Chiara G. A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. *J Psychopharmacol Oxf Engl*. 1998;12(1):54–67. doi:10.1177/026988119801200108
18. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: beyond dopamine reward circuitry. *Proc Natl Acad Sci U S A*. 2011;108(37):15037–15042. doi:10.1073/pnas.1010654108
19. Murnane KS, Howell LL. Neuroimaging and drug taking in primates. *Psychopharmacology*. 2011;216(2):153–171. doi:10.1007/s00213-011-2222-7
20. Volkow ND, Muenke M. The genetics of addiction. *Hum Genet*. 2012;131(6):773–777. doi:10.1007/s00439-012-1173-3
21. Tiffany ST, Carter BL, Singleton EG. Challenges in the manipulation, assessment and interpretation of craving relevant variables. *Addict Abingdon Engl*. 2000;95(Suppl 2):S177–S187. doi:10.1080/09652140050111753
22. Mitchell JM, O'Neil JP, Janabi M, Marks SM, Jagust WJ, Fields HL. Alcohol consumption induces endogenous opioid release in the human orbitofrontal cortex and nucleus accumbens. *Sci Transl Med*. 2012;4(116):116ra6. doi:10.1126/scitranslmed.3002902
23. Caine SB, Negus SS, Mello NK, et al. Role of dopamine D2-like receptors in cocaine self-administration: studies with D2 receptor mutant mice and novel D2 receptor antagonists. *J Neurosci*. 2002;22(7):2977–2988. doi:10.1523/JNEUROSCI.22-07-02977.2002
24. Self DW, Genova LM, Hope BT, Barnhart WJ, Spencer JJ, Nestler EJ. Involvement of cAMP-dependent protein kinase in the nucleus accumbens in cocaine self-administration and relapse of cocaine-seeking behavior. *J Neurosci*. 1998;18(5):1848–1859. doi:10.1523/JNEUROSCI.18-05-01848.1998
25. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the "dark side" of drug addiction. *Nat Neurosci*. 2005;8(11):1442–1444. doi:10.1038/nn1105-1442
26. Garavan H, Pankiewicz J, Bloom A, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry*. 2000;157(11):1789–1798. doi:10.1176/appi.ajp.157.11.1789
27. Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. *Science*. 1988;242(4879):715–723. doi:10.1126/science.2903550
28. Volkow ND, Wang GJ, Fowler JS, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature*. 1997;386(6627):830–833. doi:10.1038/386830a0
29. Risinger RC, Salmeron BJ, Ross TJ, et al. Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. *NeuroImage*. 2005;26(4):1097–1108. doi:10.1016/j.neuroimage.2005.03.030
30. Milella MS, Fotros A, Gravel P, et al. Cocaine cue–induced dopamine release in the human prefrontal cortex. *J Psychiatry Neurosci*. 2016;41(5):322–330. doi:10.1503/jpn.150207
31. Fowler JS, Volkow ND. PET imaging studies in drug abuse. *J Toxicol Clin Toxicol*. 1998;36(3):163–174. doi:10.3109/15563659809028936
32. Volkow ND, Hitzemann R, Wang GJ, et al. Long-term frontal brain metabolic changes in cocaine abusers. *Synap N Y N*. 1992;11(3):184–190. doi:10.1002/syn.890110303
33. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. *J Clin Invest*. 2003;111(10):1444–1451. doi:10.1172/JCI18533
34. Amen DG, Willeumier K, Johnson R. The clinical utility of brain SPECT imaging in process addictions. *J Psychoactive Drugs*. 2012;44(1):18–26. doi:10.1080/02791072.2012.660101
35. Malison RT, Best SE, van Dyck CH, et al. Elevated striatal dopamine transporters during acute cocaine abstinence as measured by [123I] beta-CIT SPECT. *Am J Psychiatry*. 1998;155(6):832–834. doi:10.1176/ajp.155.6.832
36. Volkow ND, Fowler JS, Wang GJ. Positron emission tomography and single-photon emission computed tomography in substance abuse research. *Semin Nucl Med*. 2003;33(2):114–128. doi:10.1053/snuc.2003.127300
37. Murray DE, Durazzo TC, Schmidt TP, et al. Regional cerebral blood flow in opiate dependence relates to substance use and neuropsychological performance. *Addict Biol*. 2018;23(2):781–795. doi:10.1111/adb.12523

38. Liu X, Matochik JA, Cadet JL, London ED. Smaller volume of prefrontal lobe in polysubstance abusers: a magnetic resonance imaging study. *Neuropsychopharmacol*. 1998;18(4):243–252. doi:10.1016/S0893-133X(97)00143-7
39. Thompson PM, Hayashi KM, Simon SL, et al. Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neurosci*. 2004;24(26):6028–6036. doi:10.1523/JNEUROSCI.0713-04.2004
40. Volkow ND, Fowler JS, Wolf AP, et al. Changes in brain glucose metabolism in cocaine dependence and withdrawal. *Am J Psychiatry*. 1991;148(5):621–626.
41. Wexler BE, Gottschalk CH, Fulbright RK, et al. Functional magnetic resonance imaging of cocaine craving. *Am J Psychiatry*. 2001;158(1):86–95. doi:10.1176/appi.ajp.158.1.86
42. Paulus MP, Hozack NE, Zauscher BE, et al. Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacol*. 2002;26(1):53–63. doi:10.1016/S0893-133X(01)00334-7
43. Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci*. 2003;23(21):7839–7843. doi:10.1523/JNEUROSCI.23-21-07839.2003
44. Ray S, Hanson C, Hanson SJ, Bates ME. fMRI BOLD response in high-risk college students (part 1): during exposure to alcohol, marijuana, polydrug and emotional picture cues. *Alcohol Alcohol Oxf Oxfs*. 2010;45(5):437–443. doi:10.1093/alcalc/agq042
45. Martz ME, Hart T, Heitzeg MM, Peltier SJ. Neuromodulation of brain activation associated with addiction: a review of real-time fMRI neurofeedback studies. *NeuroImage Clin*. 2020;27:102350. doi:10.1016/j.nicl.2020.102350
46. Ernst T, Chang L, Leonido-Yee M, Speck O. Evidence for long-term neurotoxicity associated with methamphetamine abuse: a 1H MRS study. *Neurology*. 2000;54(6):1344–1349. doi:10.1212/WNL.54.6.1344
47. Chang L, Ernst T, Strickland T, Mehringer CM. Gender effects on persistent cerebral metabolite changes in the frontal lobes of abstinent cocaine users. *Am J Psychiatry*. 1999;156(5):716–722. doi:10.1176/ajp.156.5.716
48. Kohut SJ, Kaufman MJ. Magnetic resonance spectroscopy studies of substance use disorders: current landscape and potential future directions. *Pharmacol Biochem Behav*. 2021;200:173090. doi:10.1016/j.pbb.2020.173090
49. Alper KR, Chabot RJ, Kim AH, Prichep LS, John ER. Quantitative EEG correlates of crack cocaine dependence. *Psychiatry Res*. 1990;35(2):95–105. doi:10.1016/0925-4927(90)90013-V
50. Costa L, Bauer L. Quantitative electroencephalographic differences associated with alcohol, cocaine, heroin and dual-substance dependence. *Drug Alcohol Depend*. 1997;46(1–2):87–93. doi:10.1016/S0376-8716(97)00058-6
51. Sokhadze TM, Cannon RL, Trudeau DL. EEG biofeedback as a treatment for substance use disorders: review, rating of efficacy, and recommendations for further research. *Appl Psychophysiol Biofeedback*. 2008;33(1):1–28. doi:10.1007/s10484-007-9047-5
52. Stewart JL, May AC. Electrophysiology for addiction medicine: from methodology to conceptualization of reward deficits. *Prog Brain Res*. 2016;224:67–84.
53. Houston RJ, Schlienz NJ. Event-related potentials as biomarkers of behavior change mechanisms in substance use disorder treatment. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(1):30–40. doi:10.1016/j.bpsc.2017.09.006
54. Bach P, de Timary P, Gründer G, Cumming P. Molecular imaging studies of alcohol use disorder. *Curr Top Behav Neurosci*. 2023;2023:1–31.
55. Soto-Montenegro ML, García-Vázquez V, Lamanna-Rama N, López-Montoya G, Desco M, Ambrosio E. Neuroimaging reveals distinct brain glucose metabolism patterns associated with morphine consumption in Lewis and Fischer 344 rat strains. *Sci Rep*. 2022;12(1):4643. doi:10.1038/s41598-022-08698-9
56. Deng R, Yang X, Meng Y-J, et al. Data-driven study on resting-state functional magnetic resonance imaging during early abstinence of alcohol dependence in male patients and its predictive value for relapse. *BMC Psychiatry*. 2022;22(1):143. doi:10.1186/s12888-022-03782-w
57. Bralet MC, Mitelman SA, Goodman CR, Lincoln S, Hazlett EA, Buchsbaum MS. Fluorodeoxyglucose positron emission tomography scans in patients with alcohol use disorder. *Alcohol Clin Exp Res*. 2022;46(6):994–1010. doi:10.1111/acer.14845
58. Ersche KD, Meng C, Ziauddeen H, et al. Brain networks underlying vulnerability and resilience to drug addiction. *Proc Natl Acad Sci*. 2020;117(26):15253–15261. doi:10.1073/pnas.2002509117
59. Murnane KS, Gopinath KS, Maltbie E, Daunais JB, Telesford QK, Howell LL. Functional connectivity in frontal-striatal brain networks and cocaine self-administration in female rhesus monkeys. *Psychopharmacology*. 2015;232(4):745–754. doi:10.1007/s00213-014-3709-9
60. Murnane KS, Howell LL. Development of an apparatus and methodology for conducting functional magnetic resonance imaging (fMRI) with pharmacological stimuli in conscious rhesus monkeys. *J Neurosci Methods*. 2010;191(1):11–20. doi:10.1016/j.jneumeth.2010.06.001
61. Murnane KS, Winschel J, Schmidt KT, et al. Serotonin 2A receptors differentially contribute to abuse-related effects of cocaine and cocaine-induced nigrostriatal and mesolimbic dopamine overflow in nonhuman primates. *J Neurosci*. 2013;33(33):13367–13374. doi:10.1523/JNEUROSCI.1437-13.2013
62. Murnane KS. Serotonin 2A receptors are a stress response system: implications for post-traumatic stress disorder. *Behav Pharmacol*. 2019;30(2 and 3–Spec Issue):151–162. doi:10.1097/FBP.0000000000000459
63. Hampton WH, Hanik IM, Olson IR. Substance abuse and white matter: findings, limitations, and future of diffusion tensor imaging research. *Drug Alcohol Depend*. 2019;197:288–298. doi:10.1016/j.drugalcdep.2019.02.005
64. Bell RP, Foxe JJ, Nierenberg J, Hoptman MJ, Garavan H. Assessing white matter integrity as a function of abstinence duration in former cocaine-dependent individuals. *Drug Alcohol Depend*. 2011;114(2–3):159–168. doi:10.1016/j.drugalcdep.2010.10.001
65. Pando-Naude V, Toxto S, Fernandez-Lozano S, Parsons CE, Alcauter S, Garza-Villarreal EA. Gray and white matter morphology in substance use disorders: a neuroimaging systematic review and meta-analysis. *Transl Psychiatry*. 2021;11(1):1–18. doi:10.1038/s41398-020-01128-2
66. Devoto F, Zapparoli L, Spinelli G, Scotti G, Paulesu E. How the harm of drugs and their availability affect brain reactions to drug cues: a meta-analysis of 64 neuroimaging activation studies. *Transl Psychiatry*. 2020;10(1):1–11. doi:10.1038/s41398-020-01115-7
67. Terem I, Dang L, Champagne A, et al. 3D amplified MRI (aMRI). *Magn Reson Med*. 2021;86(3):1674–1686. doi:10.1002/mrm.28797
68. Terem I, Ni WW, Goubran M, et al. Revealing sub-voxel motions of brain tissue using phase-based amplified MRI (aMRI). *Magn Reson Med*. 2018;80(6):2549–2559. doi:10.1002/mrm.27236
69. Siemens healthineers USA [Internet]; 2023. Available from: https://www.siemens-healthineers.com/en-us. Accessed June 27, 2023.
70. Two new high-end MRI scanners for clinical and scientific use presented [Internet]; 2023. Available from: https://healthcare-in-europe.com/en/news/siemens-high-end-mri-scanners-clinical-scientific-use.html. Accessed June 27, 2023.

71. Siemens healthineers introduces new mobile magnetic resonance imaging scanner Magnetom Viato.Mobile [Internet]; 2023. Available from: https://www.siemens-healthineers.com/press/releases/magnetom-viato-mobile. Accessed June 27, 2023.
72. Photon counting CT [Internet]; 2023. Available from: https://www.siemens-healthineers.com/en-us/computed-tomography/technologies-and-innovations/photon-counting-ct. Accessed June 27, 2023.
73. Toi PT, Jang HJ, Min K, et al. In vivo direct imaging of neuronal activity at high temporospatial resolution. *Science*. 2022;378(6616):160–168. doi:10.1126/science.abh4340
74. Hodono S, Rideaux R, van Kerkoerle T, Cloos MA. Initial experiences with direct imaging of neuronal activity (DIANA) in humans [Internet]. arXiv; 2023. Available from: http://arxiv.org/abs/2303.00161. Accessed June 27, 2023.
75. Boyle AJ, Gaudet VC, Black SE, Vasdev N, Rosa-Neto P, Zukotynski KA. Artificial intelligence for molecular neuroimaging. *Ann Transl Med*. 2021;9(9):822. doi:10.21037/atm-20-6220
76. Yang L, Du Y, Yang W, Liu J. Machine learning with neuroimaging biomarkers: application in the diagnosis and prediction of drug addiction. *Addict Biol*. 2023;28(2):e13267. doi:10.1111/adb.13267
77. Monsour R, Dutta M, Mohamed AZ, Borkowski A, Viswanadhan NA. Neuroimaging in the era of artificial intelligence: current applications. *Fed Pract*. 2022;39(Suppl 1):S14–S20. doi:10.12788/fp.0231
78. Mill RD, Winfield EC, Cole MW, Ray S. Structural MRI and functional connectivity features predict current clinical status and persistence behavior in prescription opioid users. *NeuroImage Clin*. 2021;30:102663. doi:10.1016/j.nicl.2021.102663
79. Mete M, Sakoglu U, Spence JS, Devous MD, Harris TS, Adinoff B. Successful classification of cocaine dependence using brain imaging: a generalizable machine learning approach. *BMC Bioinform*. 2016;17(Suppl 13):357. doi:10.1186/s12859-016-1218-z
80. Chen Z, Liu X, Yang Q, et al. Evaluation of risk of bias in neuroimaging-based artificial intelligence models for psychiatric diagnosis. *JAMA Netw Open*. 2023;6(3):e231671. doi:10.1001/jamanetworkopen.2023.1671
81. Gowin JL, Ernst M, Ball T, et al. Using neuroimaging to predict relapse in stimulant dependence: a comparison of linear and machine learning models. *NeuroImage Clin*. 2019;11(21):101676. doi:10.1016/j.nicl.2019.101676