Neuroimaging Biomarkers in Addiction

Hamed Ekhtiari, M.D., Ph.D., Arshiya Sangchooli, M.D., Owen Carmichael, Ph.D., F. Gerard Moeller, M.D., Patricio O'Donnell, M.D., Ph.D., Maria Oquendo, M.D., Ph.D., Martin P. Paulus, M.D., Diego A. Pizzagalli, Ph.D., Tatiana Ramey, M.D., Ph.D., Joseph Schacht, Ph.D., Mehran Zare-Bidoky M.D., Anna Rose Childress, Ph.D., Kathleen Brady, M.D., Ph.D.

Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA (Ekhtiari); Laureate Institute for Brain Research (LIBR), Tulsa, OK, USA (Ekhtiari, Paulus); School of Psychological Sciences, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia (Sangchooli); Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA (Carmichael); Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA (Oquendo, Childress); Institute for Drug and Alcohol Studies, Virginia Commonwealth University, Richmond, VA, USA (Moeller); Translational Medicine, Sage Therapeutics, Cambridge, MA, USA and McLean Hospital, Department of Psychiatry, Harvard Medical School, Belmont, MA, USA (O'Donnell); Division of Depression and Anxiety, McLean Hospital, Belmont, MA, USA (Pizzaggali); National Institute on Drug Abuse, Bethesda, MD, USA (Ramey); Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO, USA (Schacht); Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, Tehran, Iran (Zare-Bidoky); Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA (Brady)

Send correspondence to dr. Ekhtiari (ekhti001@umn.edu)

ABSTRACT

As a neurobiological process, addiction involves pathological patterns of engagement with substances and a range of behaviors with a chronic and relapsing course. Neuroimaging technologies assess brain activity, structure, physiology, and metabolism at scales ranging from neurotransmitter receptors to large-scale brain networks, providing unique windows into the core neural processes implicated in substance use disorders. Identified aberrations in the neural substrates of reward and salience processing, response inhibition, interoception, and executive functions with neuroimaging can inform the development of pharmacological, neuromodulatory, and psychotherapeutic interventions to modulate the disordered neurobiology. Based on our systematic search, 409 protocols registered on ClinicalTrials.gov include the use of one or more neuroimaging paradigms as an outcome measure in addiction, with the majority (N=268) employing functional magnetic resonance imaging (fMRI), followed by positron emission tomography (PET) (N=71), electroencephalography (EEG) (N=50), structural magnetic resonance imaging (MRI) (N=35) and magnetic resonance spectroscopy (MRS) (N=35). Furthermore, in a PubMed systematic review, we identified 61 meta-analyses including 30 fMRI, 22 structural MRI, 8 EEG, 7 PET, and 3 MRS meta-analyses suggesting potential biomarkers in addictions. These studies can facilitate the development of a range of biomarkers that may prove useful in the arsenal of addiction treatments in the coming years. There is

evidence that these markers of large-scale brain structure and activity may indicate vulnerability or separate disease subtypes, predict response to treatment, or provide objective measures of treatment response or recovery. Neuroimaging biomarkers can also suggest novel targets for interventions. Closed or open loop interventions can integrate these biomarkers with neuromodulation in real-time or offline to personalize stimulation parameters and deliver the precise intervention. This review provides an overview of neuroimaging modalities in addiction, potential neuroimaging biomarkers, and their physiologic and clinical relevance. Future directions and challenges in bringing these putative biomarkers from the bench to the bedside are also discussed.

INTRODUCTION

Substance use disorders (SUDs), including alcohol, cause significant and increasing mortality and morbidity worldwide [1,2]. In the United States alone, yearly costs of medical care, lost productivity and law enforcement associated with SUDs exceed an estimated $700 billion [3]. As the designation suggests, SUDs have conventionally been viewed as disorders of "substance use" [4]; but increasing evidence suggests that this harmful substance use is both driven by and contributes to pervasive brain alterations which underlie profound cognitive and behavioral manifestations broader than substance use [5]. Since early pneumoencephalography studies revealed general brain atrophy in chronic alcohol users [6], decades of neuroimaging research have increasingly caused a shift towards a "brain disease" model of SUDs [7–9]. Under this neuroimaging-informed model, genetic, developmental, social, and biological influences converge on combinations of core neurocognitive aberrations: the mesocorticolimbic reward network is sensitized by drugs of abuse, leading to excessive attribution of salience to drug-associated stimuli; anti-reward and stress systems across the basal ganglia and the extended amygdala become over-reactive, contributing to withdrawal symptoms and negative-affective states which can motivate substance use; and executive control networks centered around prefrontal regions are disrupted, with the degradation of top-down frontal control leading to disinhibited substance use [7–11].

Considering the evidence for neural aberrations in SUDs that can be objectively assessed using neuroimaging technologies, there is growing interest in using neuroimaging to inform clinical care and intervention development for SUDs [12,13]. Objective measures of SUDs are currently limited to measures of psychoactive substances or their metabolites in biological samples (National Institutes of Health, 2020a) or reflect toxic effects of use [14]. These measures of substance use are not informed by the neurocognitive processes which underlie addiction, and thus have limited use in distinguishing at-risk individuals, offering prognostic insight, or informing interventions [8]. In this context, neuroimaging technologies provide objective measures which could be used as novel "biomarkers" for SUDs, enabling the translation of neuroscientific insights to the bedside [15]. This echoes broader trends in precision psychiatry and efforts to develop and utilize so-called "biomarkers" in psychiatric practice and research more extensively [16,17]. Neuroimaging biomarkers, which can indicate specific aberrations of brain structure and function in SUDs, bring a three-fold advantage: first, they provide a direct window into proximal potential neurobiological mechanisms of disease and recovery in individuals with SUDs; second, they suggest novel treatment targets and provide neurophysiological evidence of effectiveness to facilitate intervention development; and third, mechanistically-grounded markers could be used directly for clinical purposes: to distinguish different sub-populations of substance-using individuals and inform personalized interventions and ongoing monitoring tailored for patients with specific brain abnormalities [18–22].

It is important to note that the "brain disease" model is not the only account of addiction etiology. For example, alternative explanations posit that addiction is a disease of choice and may be caused by a lack of alternative reinforcers [23], some contest whether addiction is a "disease" [24], and others simply argue that neurobiological explanations cannot be privileged over others [25]. Moreover, the "brain disease" model has faced criticism on

scientific, philosophical, and political grounds [26–28]; and while it is generally agreed that alcohol and substance use disorders involve brain changes [22,29], some have argued that the current body of neurobiological evidence may not be sufficient to conclude that neurobiological dysfunctions are specific and primary causes of addiction broadly [30]. However, while we would argue that the addiction neuroimaging literature to date both aligns with a "brain disease" model of addiction and supports the development of neuroimaging biomarkers, adherence to the former is not strictly necessary for the latter: According to the FDA-NIH Biomarker Working Group, a biomarker is simply "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions" [31]. Regardless of whether addictive disorders are primarily caused or sustained by neurological dysfunction, neuroimaging biomarkers of aberrant brain structure or function associated with specific mechanisms of addiction and recovery could illuminate neural pathology, facilitate intervention development, and guide clinical care. A pertinent example is hypertension: the fact that the disease can be caused in large part by social and environmental factors does not diminish the importance of blood pressure as a biomarker to diagnose and monitor hypertension and develop interventions [32,33].

To lay the conceptual framework for a discussion of potential neuroimaging biomarkers in SUDs, we will provide an overview of the current status of neuroimaging paradigms in translational addiction neuroscience, informed by a systematic review of neuroimaging outcome measures in 409 protocols registered on ClinicalTrials.gov between its inception and November 17, 2021. Together, the 409 protocols have utilized 479 imaging modalities, and 688 neuroimaging outcome measures and provide a broad estimate of the clinically-relevant uses of neuroimaging in addiction neuroscience. We supplement this discussion with another systematic review of 61 meta-analyses between inception and November 10, 2023 of neuroimaging biomarkers in SUDs, and highlight biomarkers that have replicated in meta-analyses across multiple contexts and diagnoses. We then discuss different neuroimaging biomarkers which may be developed for SUDs based on taxonomy developed by the FDA-NIH Biomarker Working Group [34] and highlight challenges and future directions to provide clinicians and researchers with an understanding of opportunities and challenges in neuroimaging biomarker research.

RESULTS

The present manuscript is informed by two systematic reviews. The first covered SUD clinical research protocols which include neuroimaging outcome measures, obtained by querying the ClinicalTrials.gov repository between inception and November 17, 2021 (Supplementary Figure 1a). This systematic review yielded a final result of 409 protocols. The second systematic review was conducted on PubMed, focusing on meta-analyses of neuroimaging studies of SUDs and finding 61 meta-analyses from which 83 meta-analytic findings were extracted (Supplementary Figure 1b). In this paper, while we seek to structure the discussion around replicated findings that have held across SUDs, some findings pertain only to specific SUDs, in which cases the particular SUD is highlighted. It should also be noted that the neuroimaging measures and findings in included protocols and meta-analyses do not constitute validated biomarkers: Any objective

measure needs to undergo an extensive validation process to qualify as an actual biomarker of disease or recovery, which is not the case for any of the measures we discuss. Essential validation steps are discussed in the future directions. The systematic reviews serve to highlight replicated neuroimaging findings in SUDs and demonstrate the different exploratory purposes for which neuroimaging modalities are already used in clinical research. These purposes or "contexts of use" are grouped under corresponding categories of biomarkers to outline what measures might come to serve as actual neuroimaging biomarkers of SUDs, and motivate a discussion of challenges which need to be surmounted in the process.

NEUROIMAGING MODALITIES IN ADDICTION MEDICINE

Interest in clinical uses of neuroimaging paradigms for virtually all SUDs has increased over time, with 87.3% of the protocols in our systematic review starting in 2010 or later. This is particularly the case with alcohol (N=139) and nicotine use disorders, but a growing number of protocols are using neuroimaging as an outcome measure for cocaine (N=44), cannabis (N=36), and opioid use disorder (N=31) (Figure 1a and Supplementray Figure 2). The growing interest in using neuroimaging paradigms has also been reflected in the conducted meta-analyses (Note that three of the studies are mega-analyses rather than meta-analyses, though we use the term meta-analysis to refer to these for simplicity). with all of them conducted after 2011 and more than half of them (N=31 out of 61) in the last 3 years. Most of the meta-analyses were conducted on multi substances (N=28) followed by analyzing studies focusing solely on alcohol (N=13) (Supplementary Figure 3). With some exceptions, neuroimaging paradigms in addiction neuroscience can be broadly categorized into "structural" imaging techniques which probe brain structure statically, "functional" paradigms which evaluate changes in a signal associated with brain function during the scan, and "molecular" paradigms which assess the static or changing distribution of important molecules/metabolites within the brain. These various paradigms are converging on a multi-scale perspective into brain changes in SUDs and may be used to develop clinically-relevant biomarkers [35,36].

Brain Structure: Gray and White Matter

While a few studies have utilized CT scans to interrogate brain structure alterations in SUDs [37], arguably the most popular structural neuroimaging paradigm in addiction neuroscience is structural magnetic resonance imaging (sMRI), used by 35 protocols in our trials database as the only neuroimaging paradigm and by 27 protocols in conjunction with another paradigm (Figure 1b). Among the meta-analytic findings reviewed, 22 out of 83 were aberrations observed with structural MRI. Using MRI, algorithms such as voxel-based morphometry can isolate and quantify gray matter [38], and meta-analyses of these and similar techniques have revealed wide-spread losses of gray matter across cortical and subcortical regions across a number of different SUDs [39-44], though there is some evidence that these may recover with abstinence [45]. "Mega-analyses" of MRI data collected from thousands of individuals with a variety of SUD types have also revealed an overall loss of gray matter, particularly in the insula and prefrontal and parietal cortices,

and suggest that use severity may be correlated with lower amygdala and nucleus accumbens volume, particularly in alcohol use disorder [46]. Simultaneously, studies of white matter structure with diffusion-weighted imaging have broadly revealed white matter degeneration in commissural tracts, the internal capsule, and corpus callosum across several SUDs [39,47–49]. Observed structural changes in the gray and white matter might explain both deficits in higher-order cognitive processes and bottom-up processes in SUDs, with striking alterations in both frontal, parietal, and insular cortical regions involved in interoception, attention, and executive control and in the amygdala and nucleus accumbens which subtend bottom-up reward and affective processing [46,50].
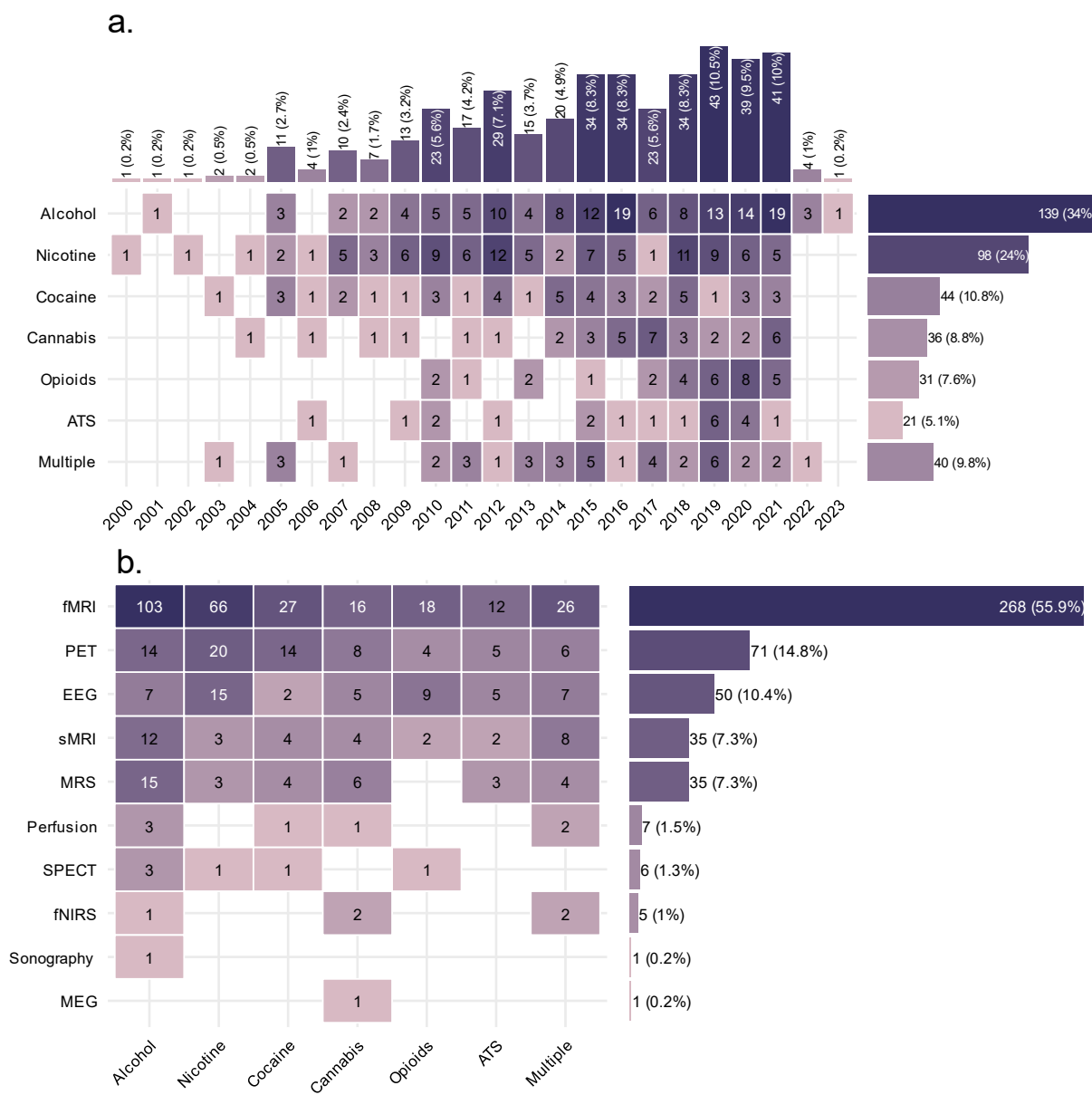
Figure 1: Distribution of the neuroimaging protocols based on year and substance.
a. Number of protocols starting for each substance each year (n= 409). Years are obtained from the ClinicalTrials.gov database indicating actual or planned start years. b. Number of neuroimaging modalities used in each protocol for each substance. Numbers on this figure sum to 479 for 409 protocols, since 70 protocols used multiple imaging modalities. ATS: Amphetamine-type Stimulants; sMRI: structural MRI, including whole-brain T1 imaging, gray matter volumetry, or diffusion tensor imaging; Perfusion: brain perfusion imaging, including arterial spin labeling, cerebral blood flow imaging, and magnetic resonance angiography; MRS: magnetic resonance-spectroscopy. Data were collected from ClinicalTrials.gov on November 17, 2021.

Brain Function: Hemodynamics and Electrophysiology

While structural neuroimaging paradigms are useful, the brain is engaged in constant activity during task performance and even idleness or sleep [51] and alterations in these rich neural dynamics underlie the cognitive-behavioral profiles typical of SUDs [52]. This necessitates the use of "functional" neuroimaging paradigms that can measure brain activity either during the performance of various tasks ("task-based" imaging, 342 out of 688 instances in protocol database and 30 out of 83 in our meta-analysis database) or during rest ("resting-state" imaging, 217 instances in our protocol database and 4 in our meta-analysis database) [53]. For example, "cue-reactivity paradigms" involve the presentation of stimuli associated with substances, such as pictures, scents or tastes, to assess neural reactivity and sensitization to these cues [54], and are used by 130 protocols in our protocol database (and 10 meta-analytic findings in SUDs). Other tasks can be used to probe other aspects of reward processing (42 instances across protocols, 6 meta-analytic findings), response inhibition (36 instances across protocols, 3 meta-analytic findings) and decision making (22 instances across protocols, 1 meta-analytic finding), all processes whose neural circuitry is impacted in SUDs [11,55] (Figure 2 and 3).
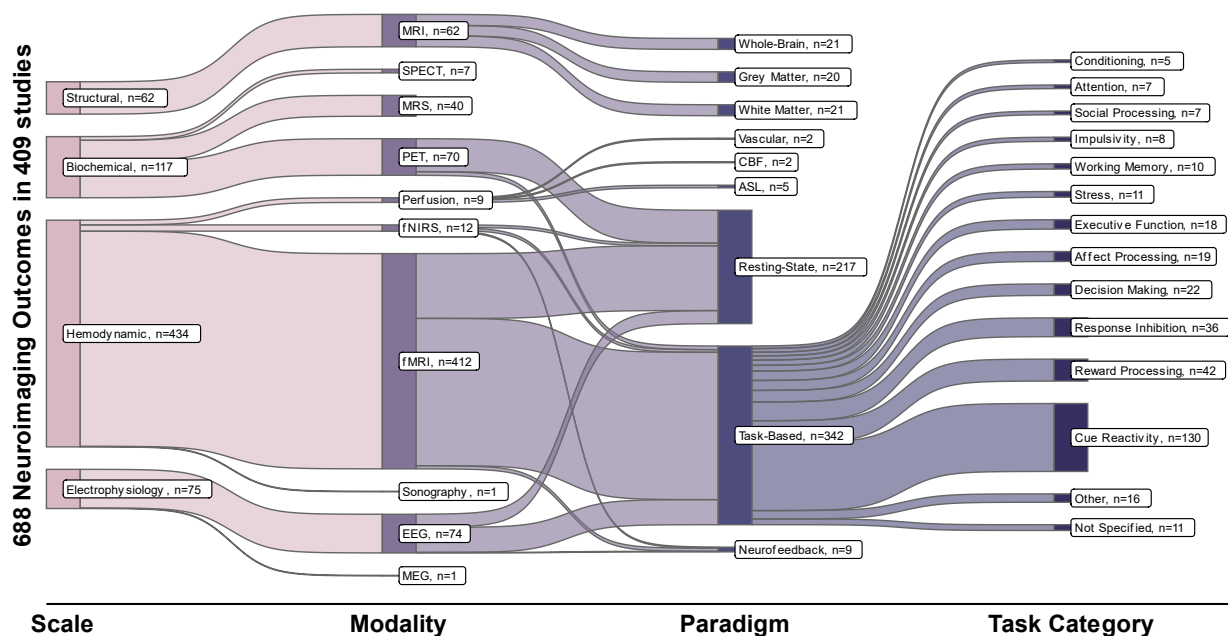
Figure 2: Multi-level characteristics of 688 neuroimaging outcome measures in 409 registered protocols. *These levels include the scales at which neuroimaging modalities have probed the nervous system (structural, biochemical, hemodynamic or electrophysiology), the neuroimaging modality, different paradigms in each modality, and the types of tasks used in task-based functional neuroimaging paradigms. All "structural" paradigms in our database were variants of MRI; "biochemical" paradigms include SPECT, MRS, and PET; "hemodynamic" paradigms include fMRI, fNIRS, less common perfusion imaging modalities, and ultrasound; and EEG and MEG constitute "electrophysiological" imaging paradigms. These modalities have been used for static structural scans of brain gray or white matter and vasculature, resting-state functional scans, or task-related functional scans with various tasks. Note that many protocols have utilized more than one neuroimaging outcome measure and the total number of outcome measures is 688, more than the number of protocols (n=409). Data is collected from ClinicalTrials.gov on November 17, 2021.* EEG: electroencephalography; *fMRI:functional* magnetic resonance imaging; fNIRS: Functional near-infrared spectroscopy; MEG: magnetoencephalography; *MRI:* magnetic resonance imaging; *MRS: magnetic resonance-spectroscopy; PET:* positron emission tomography; *SPECT: Single-photon emission computed tomography;*
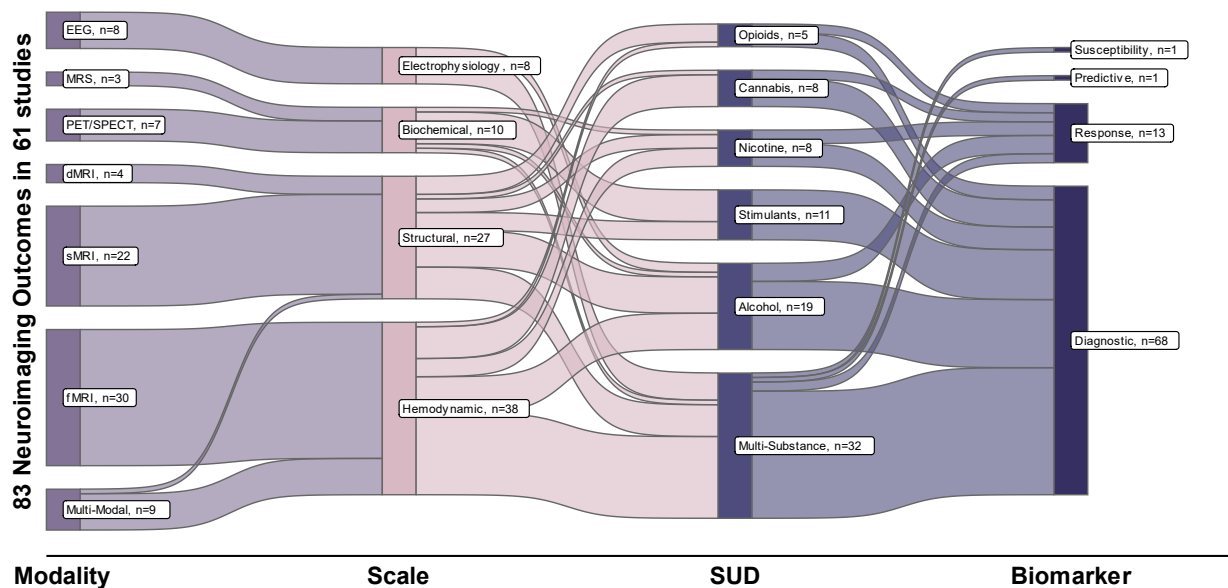
Figure 3: Multi-level characteristics of 83 neuroimaging outcome measures in 61 meta-analyses. *These levels include the scales at which neuroimaging modalities have probed the nervous system (structural, biochemical, hemodynamic or electrophysiology), the neuroimaging modality, different paradigms in each modality, and the types of tasks used in task-based functional neuroimaging paradigms. All "structural" paradigms in our database were variants of MRI; "biochemical" paradigms include SPECT, MRS, and PET; "hemodynamic" paradigms include fMRI, fNIRS, less common perfusion imaging modalities, and ultrasound; and EEG and MEG constitute "electrophysiological" imaging paradigms. These modalities have been used for assessment of people with different kinds of SUDs. These assessment can be categorized into different biomarker categories. Note that some meta-analyses have utilized more than one neuroimaging outcome measure and the total number of outcome measures is 83, more than the number of total meta-analyses (n=61). Further, 3 of the 83 findings are from mega-analyses rather than meta-analyses, though we use the term meta-analysis to refer to these for simplicity.* dMRI: diffusion magnetic resonance imaging ; EEG: electroencephalography; *fMRI: functional* magnetic resonance imaging; fNIRS: Functional near-infrared spectroscopy; MEG: magnetoencephalography; *MRI:* magnetic resonance imaging; *MRS: magnetic resonance-spectroscopy; PET:* positron emission tomography; *sMRI: structural* magnetic resonance imaging; *SPECT: Single-photon emission computed tomography; SUD: Substance user disorder*

The first major group of functional neuroimaging outcomes (433 instances across protocols and 30 findings across meta-analyses) is "hemodynamic" techniques that include blood oxygenation level-dependent (BOLD) and arterial spin labeling (ASL) functional MRI, functional near-infrared spectroscopy, and cerebral perfusion imaging methods [56–59]. fMRI is the most commonly used neuroimaging paradigm in addiction neuroscience, with 412 instances of fMRI as an outcome measure in our database out of the 688 neuroimaging outcome measures used in the 409 protocols (Figure 1b, Figure 2).

Further, 39 meta-analytic findings across neuroimaging SUD studies are from meta-analyses which include fMRI studies, alone (30 findings) or in combination with other modalities (Figure 3). There is extensive task-based fMRI evidence of disruption during reward-processing [60], and drug cue exposure results in a cascading hyperactivation of limbic circuits which subtend valuation and salience processing and disruption of prefrontal control, which can end in drug use [55,61]. On the other hand, resting-state fMRI studies have revealed that SUDs are associated with weaker connections in the executive control network and stronger couplings within and between salience, reward, and "default mode" networks, suggesting that this might account for impaired response inhibition and the abnormal salience of drugs [11,62]. Other hemodynamic paradigms have converged on similar findings, with aberrant function and perfusion in the middle frontal and orbitofrontal cortices, among others, observed in SUDs [57,63]

The second group of functional imaging modalities focuses on the brain's electrophysiological properties: electroencephalography (EEG) and magnetoencephalography (MEG) record, respectively, the electrical and magnetic fields generated during brain activity using extra-cranial probes to infer the underlying brain activity [64,65]. Owing to its low cost and portability, EEG is the more common paradigm with 74 instances in our protocol database (and 8 findings in our meta-analysis database) compared to a single protocol with MEG. Event-related potentials elicited during task performance are usually split into components associated with underlying cognitive processes. For example, There is evidence that the P300 component of ERPs elicited by drug cues may be associated with reward valuation and the late positive potential with drug use motivation in individuals with SUDs, while the error-related negativity and feedback-related negativity components are associated with cognitive control and self-regulation [66,67]. Another approach is to decompose the recorded EEG or MEG signal into specific "bands" with different frequencies, which has revealed decreases in EEG beta band power in opioid and alcohol use disorders [68]. As with fMRI and fNIRS, EEG recordings also revealed network-level changes in individuals with SUDs: Examples include disruptions in the communication of the parietal lobe with other brain regions [69] and reductions in global integration and locally specialized connectivity [70].

Brain Biochemistry: Molecular Systems

On a molecular level, positron emission tomography (PET) and single photon-emission computed tomography (SPECT) use radiotracers with specific patterns of distribution across the tissue. Psychiatric SPECT and PET imaging increasingly use complex ligands known to preferentially bind to molecules of interest to probe both the density and binding potential of a certain neurotransmitter system across the brain, and dynamic changes in neurotransmission induced by a pharmacological agent or during cognitive and behavioral tasks [71]. Magnetic resonance spectroscopy (MRS) is a different approach to investigating molecular concentrations across the brain, using magnetic resonance rather than ionizing radiation to assess relative levels of different metabolites, such as choline and N-acetylaspartate, and neurotransmitters, such as glutamate, GABA, and glutamine [72].

All three modalities are used in our protocol database as outcome measures, with 70 instances of PET, 7 instances of SPECT, and 40 instances of MRS (Figure 2), and 16 meta-analytic PET/SPECT findings (7 findings from meta-analyses of studies using only PET/SPECT, 9 in combination with fMRI studies). PET and SPECT studies have demonstrated that dopamine transporter and D2 dopamine receptor availability are consistently downregulated in SUDs, especially D2 receptors in the striatum whose downregulation is associated with compulsive drug use [73]. This has been extensively corroborated in stimulant use disorders, with several recent meta-analyses [74,75]. These observations and further aberrations in dopamine synthesis and release are consistent with dysfunctional dopaminergic neuroadaptations in the reward network and accompany changes in other neurotransmitter systems implicated in the neuro-cognitive abnormalities observed in SUDs, such as serotonergic disruptions potentially related to affective deregulation and opioidergic down-regulation which may explain tolerance and dependence [76–78]. At the same time, meta-analyses of MRS studies have revealed decreased N-acetylaspartate levels across frontal and cingulate regions, suggesting decreased neuronal and axonal viability [79,80]; and others have reported aberrations in glutamate and GABA levels in the prefrontal cortex and basal ganglia which correlate with disease severity and cognitive function across SUDS [81,82]. These findings suggest that neurotransmitter abnormalities may account for some neuro-cognitive abnormalities in attention and executive function observed in SUDs.

NEUROIMAGING BIOMARKERS IN ADDICTION

Given the observation of brain abnormalities across different domains in SUDs, there are ongoing efforts to utilize these brain aberrations as biomarkers for specific contexts of use. The neuroimaging technologies discussed above have distinct advantages and disadvantages, and thus each may be better suited for use in certain contexts and/or for different SUDs. The systematic review of the registered protocols discussed above expectedly identified mostly neuroimaging biomarkers used to measure the effect of an intervention in a trial. However, neuroimaging biomarkers could go beyond treatment response assessment. The FDA-NIH Biomarker Working Group has formally defined distinct biomarker types which correspond to different stages of addiction, recovery, and clinical intervention [34]: In the context of SUDs, "susceptibility" biomarkers indicate the risk that individuals develop a SUD and "diagnostic" biomarkers can distinguish individuals with SUDs from recreational users or between clinically relevant subtypes of SUDs. For individuals with an established SUD diagnosis, "prognostic" biomarkers can predict the future progression of patients towards relapse versus remission and "monitoring" biomarkers can be measured over time to assess changes.

When developing or implementing a clinical intervention for SUDs, "predictive" biomarkers can predict the clinical impact of an intervention, and "safety" biomarkers can be measured to assess the safety of an intervention or novel substance; while "response" biomarkers reflect an individual's response to an intervention and, under certain conditions, can be used as "surrogate endpoints": biomarkers which can demonstrate the likely clinical effectiveness of an intervention before actual clinical outcomes develop [83,84]. A schematic of the different stages of SUDs and intervention is presented in Figure 4. It is important to note that a single neuroimaging measure may conceivably serve multiple

biomarker roles in different contexts: as an example, higher baseline ventral striatal fMRI drug cue-reactivity can distinguish relapsing individuals with stimulant use disorder from non-relapsing individuals 3 months after the scan (prognosis) [85] and predict the clinical response of individuals with alcohol use disorder to naltrexone (prediction) [86]. At the same time, striatal cue-reactivity in individuals with alcohol use disorder can be reduced through treatment (response) [87]. Such converging evidence can support the clinical validity of a biomarker.
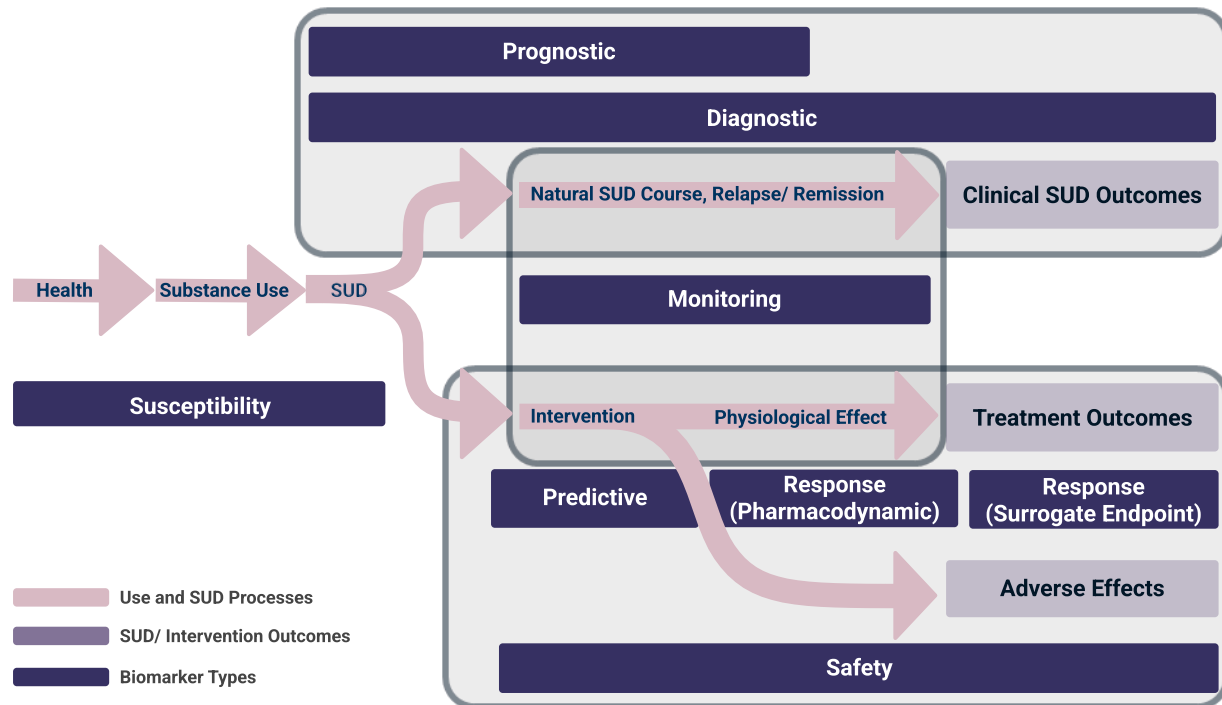

Figure 4: Schematic representation of stages in substance use and SUDs and their therapeutic interventions and corresponding biomarker types. Susceptibility biomarkers can predict transition to substance use or disorder, prognostic biomarkers can predict the future progression of the disorder, diagnostic biomarkers can distinguish clinically-relevant populations, monitoring biomarkers facilitate ongoing information about the course of the disorder with or without intervention, predictive biomarkers can predict treatment response, response biomarkers can reflect the physiological impact of an intervention and potentially be used as surrogate endpoints in lieu of clinical outcomes, and safety biomarkers can help assess the potential hazards of various substances used in clinical or non-clinical settings.

Based on an assessment of the structure of the reviewed protocols, the 409 protocols have collectively used 510 neuroimaging measures as putative SUD biomarkers. These 510 putative neuroimaging-based biomarkers are broken down based on biomarker type, substances, and neuroimaging modalities in Figure 5. Based on the systematic review of meta-analyses, several of these markers have also been suggested across several SUDs or contexts of use in meta-analyses of neuroimaging studies. Such suggested findings were observed in 55 meta-analyses in our database and are summarized in Table 1. The following sections review these biomarker types in greater detail.

Table 1: Meta-analytic neuroimaging markers that have been suggested across SUDs or contexts of use. Note that this table includes only findings supported by more than one meta-analyses across SUDs or contexts of use, and thus only 55 out of the 61 meta-analyses in the full database are included COU: Context of Use dMRI: diffusion magnetic resonance imaging ; EEG: electroencephalography; *fMRI: functional* magnetic resonance imaging; fNIRS: Functional near-infrared spectroscopy; MEG: magnetoencephalography; *MRI:* magnetic resonance imaging; *MRS: magnetic resonance-spectroscopy; PET:* positron emission tomography; *sMRI: structural* magnetic resonance imaging; SPECT: Single-photon emission computed tomography; SUD: Substance user disorder

Modality	Number of Meta-Analyses	SUD	COU	Observations	References
Gray and White Matter					
dMRI (last study White Matter VBM)	6	Alcohol, Stimulants, Opioids	Diagnostic, Response	Macro- and microstructural evidence of white matter degeneration across the corpus callosum, internal capsule, and frontal and limbic projections. Evidence of white matter recovery with abstinence at least in alcohol use diroder	39,47–49,221,222
sMRI	18	Alcohol, Nicotine, Stimulants, Opioids, Cannabis	Diagnostic, Response	Reduction in cortical thickness and gray matter volume across superior temporal, inferior parietal, precentral, insular, frontal, cingulate, hippocampal and parahippocampal cortices and the striatum and thalamus. Further, at least in the case of nicotine, agnoists impact some of the brain areas where reductions in gray matter volume are prominent.	39–45,132,133,194,212,223–229
Neurotransmitter Systems and Metabolites					
PET/SPECT	2	Stimulants	Diagnostic	Overall downregulation of striatal dopaminergic signaling, including decreases in dopamine release, reduced dopamine transporter density and availability, and reduced dopamine receptor density, availability and binding potential.	74,75
MRS	2	Alcohol, stimulants	Diagnostic	Lower N-acetylaspartate levels across frontal and cingulate regions suggesting decreased neuronal and axonal viability, lower cortical and higher subcortical creatine levels.	79,80
Electrophysiological Activity					

EEG (Response Inhibition)	3	Alcohol, General (Opioids, Stimulants, Nicotine, Cannabis)	Diagnostic, Response	SUDs are associated with the attenuation of error-related negativity and EEG components such as N200. Alcohol administration leads to acute reduction of ERN.	198,206,230
EEG (Cue-Reactivity)	2	General (stimulants, opioids, alcohol, nicotine)	Diagnostic, Response	SUDs are associated with the enhancement of the salience-related P300 potential in response to drug-related cues, which also shows signs of time-dependent recovery with abstinence.	197,198
EEG (Attention and Surprise)	2	General (alcohol, opioids, nicotine, stimulants, others)	Diagnostic, , Susceptibility	Reduced P300 amplitude in response to tasks which involve attention and surprise (such as the oddball paradigm) is associated with SUDs, and may susceptibility to SUDs.	204,231
Hemodynamic Activity					
fMRI/PET (Cue-Reactivity)	11	Alcohol, Nicotine, Stimulants, Opioids, Cannabis, General	Diagnostic, Susceptibility, Response	SUDs is associated with higher fMRI drug cue reactivity (FDCR) across mesocorticolimbic and nigrostriatal regions, the precuneus, cingulate and insula, various frontal and temporal regions, sensory cortices, and the cerebellum. FDCR may indicate susceptibility as well, particularly striatal FDCR in adolescents. Abstinence may lead to short-term hyperactivations in some of the regions, but in the long term treatment can normalize FDCR across regions, particularly striatum, insula, and prefrontal regions.	96,135,137,195,199,200,232–236
fMRI (Reward Processing)	4	Alcohol, General (alcohol, nicotine, stimulants, cannabis)	Diagnostic	Both anticipation and receipt of reward and loss are associated with pervasive hypo-and hyper-activations across striatal, prefrontal, orbitofrontal, sensory, insular and temporal cortices.	60,136,138,237
fMRI (Response Inhibition)	3	Alcohol, General (stimulant, alcohol, nicotine, opioid)	Diagnostic,	In SUDs compared to HCs, response inhibition is associated with lower activations across cingulate, frontal, inferior parietal, insular and temporal cortices.	207–209
fMRI (Rest)	2	General (stimulants, heroin, alcohol, cannabis, nicotine)	Diagnostic	Aberrant resting-state functional connectivity patterns across limbic, salience, frontoparietal and default-mode networks.	238,239

Neuroimaging Biomarkers for Assessment

The most straightforward application of neuroimaging biomarkers for SUDs would be for assessment purposes, since any structural, functional, or biochemical brain differences between individuals with and without SUDs could, hypothetically, be used to at least support the existence of disease. Accordingly. we identified 110 putative assessment neuroimaging markers in our systematic review of clinical research protocols and 69 across meta-analyses of neuroimaging studies in SUDs. However, mere diagnosis may not be the best use of neuroimaging biomarkers. Currently, diagnoses rely ultimately on relatively inexpensive clinical interviews, but these diagnostic criteria lead to heterogeneous patient populations, and moreover diagnoses rely ultimately on relatively inexpensive clinical interviews and the added benefit of biomarkers is unclear [88]. More promising may be the use of neuroimaging biomarkers for clinically-relevant subtyping, prognosis, and patient monitoring.

Biomarkers for diagnosis, subtyping, and susceptibility assessment:

Conceivably useful assessment neuroimaging biomarkers for SUDs fall into a few contexts of use. One would be "**diagnostic**" biomarkers which differentiate healthy and disordered substance use rather than individuals with SUD and non-drug users, given that distinguishing dependent and recreational use purely on the basis of self-report and drug use quantity is difficult [89]. We identified 88 instances of potential diagnostic biomarkers across protocols (Figure 5) and 68 across meta-analyses (Figure 3) in our systematic review databases. Several neuroimaging biomarkers may help distinguish dependent and non-dependent users. For example, dependent compared to light alcohol use may be associated with greater alcohol-cue-induced BOLD signal in the dorsal striatum but lower signal in the ventral striatum [90] and dependent cannabis users have lower OFC volume compared to recreational users [91]. Such diagnostic biomarkers may be especially relevant in the staging of SUDs, given the recently proposed category of "pre-addiction" [92]. Another use of diagnostic biomarkers could be to distinguish SUD patients with the same diagnosis, but different underlying neuro-cognitive pathology. For example, heavy alcohol drinkers who drink primarily for "relief" from negative affect have greater alcohol-cue-induced BOLD signal in the dorsal striatum as compared to "reward" drinkers [93].

Another useful class of assessment biomarkers would be markers of "**susceptibility**", biomarkers which predict the development of SUD in at-risk individuals in the absence of diagnosable disease. Only two of the registered protocols and one meta-analysis had putative susceptibility biomarkers, which require studying healthy participants for the development of SUDs. Much of the previous SUD-susceptibility neuroimaging research has been conducted in adolescents, who are particularly at risk of initiating substance use and transitioning to SUDs due to reward deficits associated with the striatal dopaminergic reorganization and the faster development of limbic emotion and reward systems compared to the prefrontal control circuitry [94]. Consistent with this theory, task-related fMRI investigations have shown that dorsal striatal hyper-activation during reward tasks

may be a marker of substance use vulnerability and is linked with co-existing externalizing psychopathology, and stronger responses of the reward-related nucleus accumbens and orbitofrontal regions to alcohol cues can distinguish individuals who transition to heavy drinking [95,96]. Moreover, response inhibition fMRI studies have shown that blunted frontoparietal activity during inhibition and hyperactivation during inhibition failures predict the initiation of substance use [97]. Structural MRI studies have converged on similar findings: Both lower volumes and lower white matter integrity in fronto-limbic regions involved in reward processing and decision-making may be markers of susceptibility to substance use initiation and the development of SUDs [98].
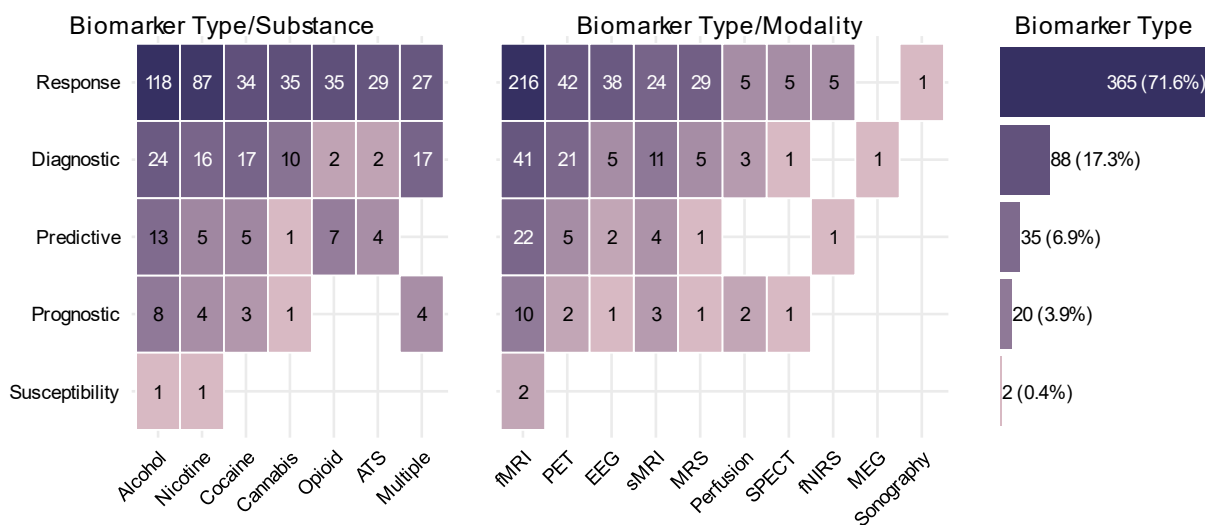

Figure 5: Putative neuroimaging biomarkers reported in registered protocols in various substance use disorders (SUDs) and neuroimaging modalities. *Biomarker types are divided between the substance of interest and neuroimaging modalities used in the protocol (510 biomarkers across 409 protocols). The horizontally aligned bars represent the total number of each biomarker type. Note that some of the protocols include more than one biomarker type. Some protocols did not report enough details for neuroimaging modalities in a way that fit any biomarker's definition. Data is collected from ClinicalTrials.gov on November 17, 2021.*

Biomarkers for prognosis and monitoring:

With the rising number and larger sample sizes of studies with prospective and longitudinal designs, it has become possible to investigate relationships between neuroimaging parameters and subsequent clinical trajectories, enabling the development of "**prognostic**" biomarkers, with 20 examples in our systematic review of study protocols. An important clinical use of these biomarkers would be to predict relapse in

abstinent individuals more accurately than is possible using self-report or behavioral task performance alone. Task-based fMRI studies have shown that individuals who require high neural activation for response inhibition are more prone to relapse, even with normative behavioral task performance [97], and baseline nucleus accumbens drug cue-reactivity may predict relapse with an accuracy outperforming conventional measures [85]. Resting-state fMRI has further demonstrated that the weaker inter-regional synchrony in the executive control network may account for poorer response inhibition and can predict relapse [99].

Neuroimaging biomarkers that are measured over time can also be used as "**monitoring**" biomarkers, offering insights into the development and abatement of neuro-cognitive pathology to complement the clinical picture. These biomarkers are difficult to develop since they require repeated neuroimaging measurements and a model of their correspondence with clinical states and clinically-relevant phenotypes over time. None of the protocols or meta-analyses in our databases had the requisite structure to contribute to the development of potential monitoring biomarkers. Nevertheless, much of the research on using neuroimaging outcomes for putative monitoring markers has focused on neurological recovery during abstinence: longitudinal studies have shown that both gray and white matter degeneration in the frontal cortices of individuals with SUD can recover after abstinence [100,101], and in PET and SPECT studies striatal dopamine transporters downregulated in methamphetamine use disorder can recover during abstinence [102,103]. A striking finding is the observation that individuals with SUD experience an "incubation" and accumulation of drug craving following abstinence which may predispose them to relapse. Another study has revealed that this "craving incubation" is reflected in the amplitude of the late positive potential, a marker of attention bias to drug cues which follows an expected parabolic trajectory during abstinence and a feature that would be missed by relying purely on self-report measures [67].

Biomarkers for Intervention

Perhaps even more important than diagnostic, prognostic or susceptibility assessment of SUDs would be the use of neuroimaging biomarkers in interventional contexts; for example, to develop or implement interventions, objectively assess their neurophysiological impact in clinical trials or psychiatric practice or predict their outcomes and therefore serve to guide intervention selection. Furthermore, neuroimaging biomarkers of cognitive processes such as cue-induced craving and reward processing can directly become targets for intervention. According to our systematic review of ClinicalTrials.gov protocols, several multi-scale brain aberrations identified in observational studies of SUDs are under investigation as putative interventional biomarkers. Some of these are illustrated in Figure 6. Protocols with potential interventional biomarkers constitute a majority of the protocol database and contain 400 putative biomarkers. this is unsurprising since we reviewed ClinicalTrials.gov protocols, which mostly consist of interventional studies. Across meta-analyses however, there were only 14 examples of findings relevant to interventional contexts of use.
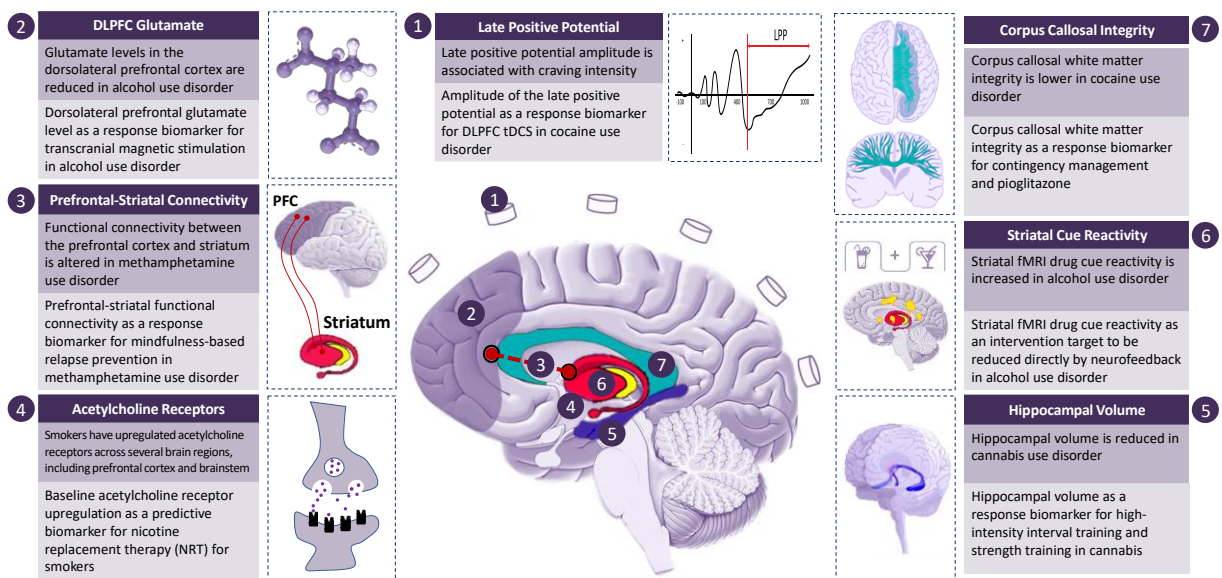
Figure 6: Multi-scale brain aberrations as putative neuroimaging biomarkers in trials for substance use disorders (SUDs). *Seven examples of brain aberrations identified in SUDs (yellow boxes) that have been investigated as putative "response" or "predictive" biomarkers or intervention targets in protocols registered in ClinicalTrials.gov (light blue boxes). The relevant literature is referenced in supplementary table 2. FC: Functional Connectivity; FDCR: fMRI Drug Cue Reactivity; PFC: Prefrontal Cortex. tDCS: Transcranial Direct Current Stimulation.*

Biomarkers of intervention response and safety:

The effectiveness of interventions for SUDs is generally assessed by measuring their impact on drug use, which provides little information about neuro-cognitive recovery [8]. A paradigmatic group of interventional biomarkers is "**response**" biomarkers. In early phases of intervention development, "**pharmacodynamic**" response biomarkers can indicate the presence of a treatment effect on neuroimaging biomarkers of recognized importance in SUDs and provide some estimate of the intensity and location of this effect. In our systematic reviews, 365 neuroimaging outcomes were used as putative response/pharmacodynamic biomarkers across protocols and 13 neuroimaging response markers were discovered across meta-analyses. Response biomarkers can be used to screen candidate therapeutics and prioritize those with plausible effectiveness, as in the "Fast-Fail" initiative of the National Institute of Mental Health[104]. In this context, research could be focused on therapies that engage brain substrates of SUDs. For example, pharmaco-fMRI studies have shown that baclofen can dampen increased drug cue-reactivity [105,106], and PET imaging can directly measure the dose-dependent impact of various therapies on neurotransmitter systems [107].

A narrower and more impactful subclass of "**response**" biomarkers are "**surrogate endpoints**". These neuroimaging measures would not only correlate with the clinical

effect of a therapy but causally lie along the physiological route between an intervention and its clinical effect in SUDs. A paradigmatic example of a surrogate endpoint in medicine is blood pressure, widely accepted as an outcome measure in clinical trials since it is known that anti-hypertensive medications offer clinical benefit through lowering high blood pressure, even though blood pressure in itself is not a clinical endpoint [108]. Rigorous clinical trials might be able to establish that the impact of therapies such as dlPFC stimulation on craving is mediated through the modulation of cue-related neural activation and connectivity, leading to the development of surrogate endpoints [63].

Biomarkers assessed over time can be used as "**monitoring**" biomarkers in the context of interventions as well, establishing links between a neuroimaging biomarker and clinical response. For example, multiple imaging rounds in a trial of naltrexone for alcohol use disorder showed that naltrexone lowers ventral striatal fMRI drug cue-reactivity from baseline and greater reduction is associated with a larger clinical response [109], and event-related potentials recorded with EEG or MEG can be assessed during and after treatment to demonstrate the normalization of ERP components associated with attention bias or error-processing [66].

While we classified markers which show the neural impact of novel compounds as "response" biomarkers since their protocols did not explicitly use them to indicate the safety of interventions, neuroimaging biomarkers could also be used to gauge the **safety** and toxicity of various compounds of interest in addiction medicine. One example would be the use of neuroimaging to inform ongoing discussions on the safety of electronic cigarette products, where fMRI has been used to demonstrate that e-cigarette smoking may immediately induce activation across sensorimotor areas [110] and sweet-tasting products may synergize with nicotine content to increase the influence of e-cigarettes on nucleus accumbens reactivity [111]. Another pertinent use-case is assessing the abuse potential of analgesic medications. Many such therapeutics, and in particular opioid medications, may lead to addictive substance use in some individuals, and neuroimaging biomarkers of safety may serve as early warning signs both during drug development and treatment [112]. Neuroimaging safety biomarkers may also be useful to assess the brain impact of alcohol and opioid medications in individuals with genetic susceptibility to addiction, such as those with certain variants of dopamine and opioid receptor genes [113,114].

Biomarkers for treatment targeting and implementation:

Data on the effectiveness of current interventions for SUDs remains inconsistent, necessitating the development of more consistently efficacious interventions and subtyping individuals with SUDs to develop personalized treatment protocols/plans [115]. Beyond providing information about the neural impact of treatment, neuroimaging biomarkers could enable individually targeted SUD treatment by reflecting a patient's baseline or dynamically changing neural state. An example of this is targeting brain stimulation at important hubs of aberrant networks in each patient since electric and magnetic neuromodulation have connectivity-dependent effects (Siddiqi et al., 2019;

Weigand et al., 2018) and it has been proposed that both structural and functional MRI can be used to optimally target the stimulation the inhibitory frontoparietal network in patients with SUD [116]. The importance of targeting specific networks for intervention is further supported by recent observational evidence that brain lesions which affect areas functionally connected to cingulate, prefrontal, insular, and temporal regions can consistently induce remission in individuals with SUD [117]. In addition to using baseline neuroimaging, more sophisticated technologies are paving the way for concurrent neuromodulation and brain imaging. These include TMS or tDCS with simultaneous EEG, MEG, fNIRS, or fMRI [118–122]. These methods provide immediate readouts of the effects of neuromodulation on network activity and can be used to develop "closed-loop" stimulation systems where neuromodulation is dynamically adjusted for optimal impact [123]. Lastly, EEG and fMRI biomarkers that are correlated with undesirable SUD-related symptoms such as craving have been successfully used in neurofeedback training, where patients with tobacco or alcohol use disorder learned to attenuate these signals based on dynamic feedback [124,125].

Biomarkers to predict treatment effect:

The final potential use case of biomarkers in an interventional context would be to **predict** the impact of therapies. We identified 35 neuroimaging outcome measures in our systematic review of protocols that serve as putative predictive biomarkers, though only one relevant marker was identified in the systematic review of meta-analyses. As the variability in the effectiveness of interventions for SUDs may be, in part, due to distinct baseline neurocognitive states, neuroimaging biomarkers could help the selection of interventions most likely to ameliorate the underlying pathology in each patient [20,126]. For example, among individuals with AUD, a reduction of fMRI drug cue-reactivity in both the left putamen and the right ventral striatum can predict the effectiveness of naltrexone [109,127]; for individuals with cocaine use disorder, greater persistence of the cue-triggered brain response across the cue task predicts poor drug use outcome [128]. Machine-learning algorithms using task-related and resting-state fMRI data have been able to predict treatment response and completion in individuals with stimulant and heroin use disorders [129,130]. Structural connectivity biomarkers may also have predictive value: reduced structural connectivity between the right anterior insula and nucleus accumbens at baseline can predict relapse to stimulant use up to six months after residential treatment [131].

Arguably, a robust neuroimaging biomarker of SUDs would be valid in several different contexts of use. Further, if the biomarker reflects physiological changes which are broadly important in the etiogenesis of SUDs and in recovery, such physiological changes would likely be detectable with different neuroimaging modalities and in different substance use disorders. Several neuroimaging markers with converging supporting evidence across meta-analyses have been discussed in Table 1, but a particularly promising set of examples are those which reflect the structure, function and connections of the striatum. Textbox 1 is dedicated to a discussion of findings of striatal involvement across SUDs,

evidence supporting the use of striatal markers across neuroimaging modalities and contexts of use.

Textbox 1: Striatal neuroimaging biomarkers in SUDs. *A discussion of the potential of neuroimaging markers of striatal function and structure across different contexts of use in SUDs and important next steps.*

There is overwhelming evidence that the striatum is involved in the pathogenesis of SUDs. Meta-analyses have shown striatal atrophy across substance use disorders [132,133], impaired dopamine neurotransmission [74,75], and striatal dysfunction across substances and task paradigms, particularly in reward-related tasks and those which induce craving [60,134–138]. Based on these observations and studies in animal models, major neuroscientific theories of addiction feature striatal dysfunction as a central cause of the aberrant reward processing, impulsivity, and incentive sensitization which drive SUDs [7,139].

This body of literature, paired with relevant findings across contexts of use, provides an extensive foundation to support the clinical validation of neuroimaging biomarkers of striatal structure and function. As an example, striatal fMRI drug cue reactivity might indicate individual susceptibility to alcohol use disorder [140], diagnostically [93] and prognostically [85] demarcate clinically relevant subtypes of disease, predict treatment response [86], and reflect treatment response [141] *or monitor it across time* [109]. An important next step would be investigating analyaitcal properties of striatal neuroimaging biomarkers, data on which is sparse. There is evidence supporting the longitudinal stability of striatal fMRI drug cue reactivity [142,143]. There is also evidence for reasonable test-retest reliability of striatal PET imaging [144,145] and morphometry and cortico-straiatal integrity measures [146] in non-SUD samples; but these should be further replicated across larger samples with different SUDs.

Further, there is little formal guidance and consensus on best methodological practices for striatal neuroimaging, which may differ from those for cortical neuroimaging. For example, a 32-channel receiving coil may be more sensitive to cortical signals than an 8-channel coil but less sensitive to subcortical activations [147], and fMRI with higher field strengths seems to be more crucial for imaging the striatum than the cortex [148]. Any striatal neuroimaging biomarker would need to be precisely *specified*, with methodological parameters, the target population, and standard operating procedures selected with respect to its context of use. This is since measures of striatal structure, function and connections are impacted by image acquisition parameters [149] and processing and reconstruction pipelines [150], behavioral task design [151], operating parameters such as time of day [152], and participant characteristics such as sex [153] and psychiatric comorbidity [107]. Further research is required to clarify how these factors impact the clinical validity and analytical properties of striatal markers in different contexts of use and guide biomarker specification.

Lastly, a putative striatal biomarker needs to be cost-effective, but there has been virtually no cost-benefit analysis of any striatal neuroimaging biomarker. While most of the cited literature supporting the clinical use of striatal neuroimaging in SUDs has used functional neuroimaging paradigms, it is difficult to assess striatal function with

relatively inexpensive neuroimaging modalities such as EEG and structural scans are both more affordable and already in widespread clinical use. Functional striatal biomarkers would likely be most cost-effective in clinical research settings, for example in facilitating the design of novel interventions and candidate screening in drug development [104].

CHALLENGES AND FUTURE DIRECTIONS

Despite decades of research highlighting the potential of neuroimaging technologies for the development and validation of biomarkers of SUDs and the proposal of several promising biomarkers in recent years [13,154,155], critics have noted that substantial investment in biomedical addiction research has not yet led to the development of biomarkers with substantial clinical utility [156]. There is growing awareness of the myriad challenges ahead of pushing neuroimaging biomarkers through the "translational gap" and into drug development and clinical practice [54,157], and we dedicate the following sections to a reflection on these scientific, technical, and regulatory challenges and solutions which we believe are critical in developing clinically-relevant biomarkers of SUDs.

Regulatory validation of neuroimaging biomarkers

The use of neuroimaging biomarkers in clinical and drug development contexts is contingent on approval by relevant regulatory bodies. These include the FDA in the US and the EMA in the European Union, which in recent years have developed structured frameworks within which biomarkers can be approved and endorsed for use, primarily in drug development and clinical trials [158,159]. In the US, the 21st Century Cures Act adopted the process of qualification of drug development tools (including biomarkers) into US law in December 2016. Before the establishment of the drug development tool qualification program, FDA acceptance of biomarkers as drug development tools happened on a sponsor-by-sponsor, drug-by-drug basis. Biomarkers qualified under the current framework can be used by drug developers for the qualified context of use. Neuroimaging biomarkers submitted for approval through the FDA framework (and with some differences, the EMA framework) should be precisely defined with descriptions of the neuroimaging protocol, target populations, and the use context for which the biomarker is to be approved.

During the validation process, a biomarker's analytical characteristics, such as reliability, validity, and natural variation need to be established. This is particularly important since despite some supporting evidence [160], there are significant concerns about the reliability of commonly used neuroimaging paradigms [161]. Such research could also aid in the choice of biomarker: For example, a recent fMRI alcohol cue-reactivity study demonstrated that brain activations during constituting contrast conditions 'alcohol' and 'neutral' have higher reliability than the 'alcohol versus neutral' difference contrast [143]. After analytical validation, the biomarker should be "clinically validated" by elucidating its etiological link to an SUD and establishing that it is reliably associated with current or future disease or

recovery, for example by presenting evidence of the existence and role of neural aberrations in SUDs as was attempted in this manuscript. Finally, it should be demonstrated that the biomarker addresses a substantial gap and demonstrates cost-effectiveness. As an example of how these requirements can be met for a putative neuroimaging marker, Textbox 1 includes a brief discussion of the relevant evidence and important gaps in the case of markers of striatal structure and function. Besides these formal qualification pathways, the use of biomarkers in clinical contexts can be facilitated by the endorsement of a constellation of other institutions which develop relevant guidelines and best practice recommendations for SUDs. Meeting qualification standards for neuroimaging biomarkers requires broad collaboration and public-private partnerships, extensive resource sharing, and rigorous research practices. These qualification steps are outlined in Figure 7.
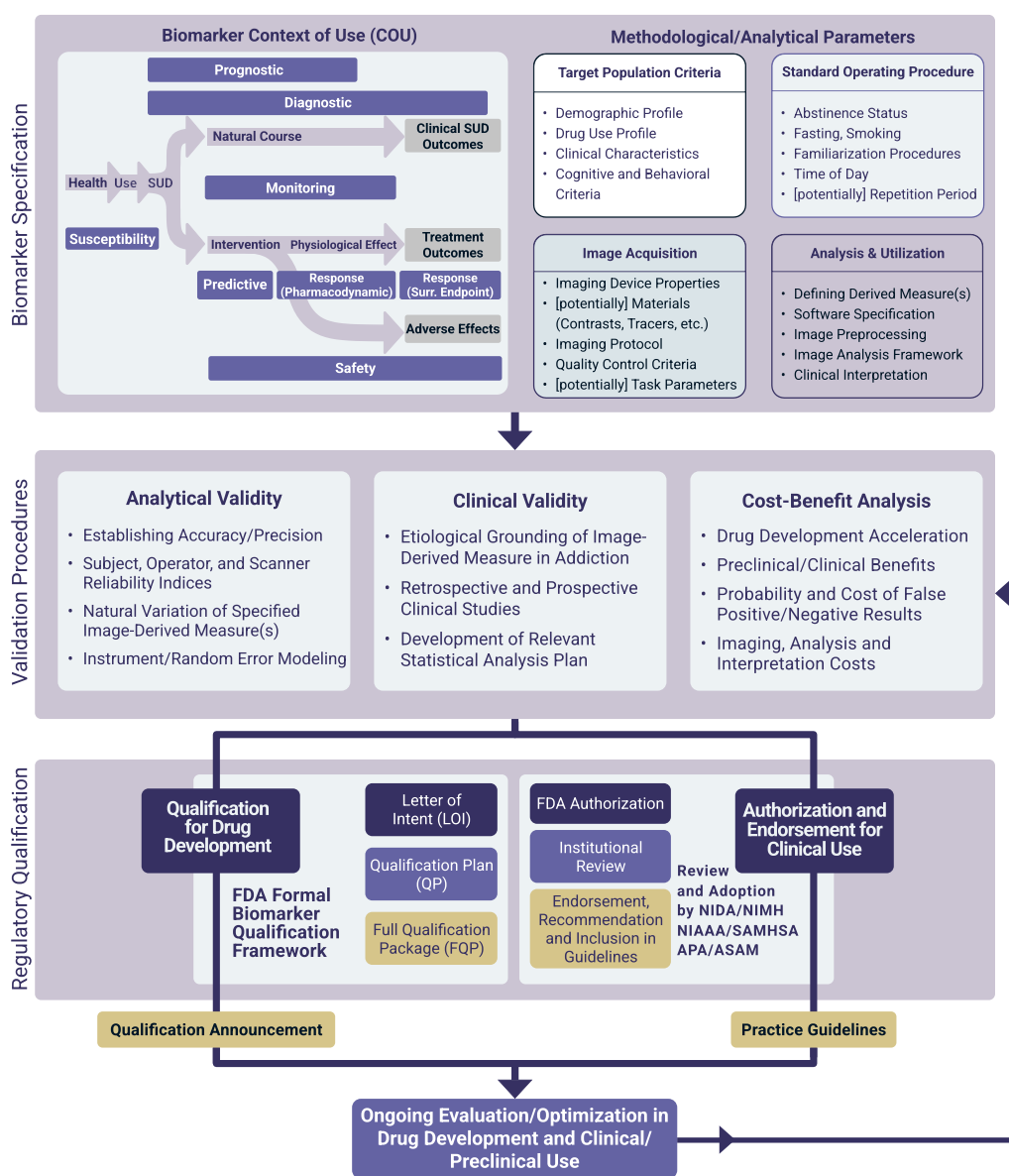
Figure 7: Major steps in the development and validation of potential neuroimaging biomarkers for SUDs. Initially, the context(s) of use for the biomarker is specified and the potential biomarker is precisely defined. Following analytical and clinical validation and cost-benefit analysis, the compiled evidence is presented for regulatory approval. The FDA evaluates the use of biomarkers for drug development through a biomarker qualification process involving submission of a Letter of Intent, a Qualification Plan, and a Full Qualification Package, though a Letter of Support may be issued by the FDA to indicate its support for a biomarker before formal qualification. The use of neuroimgaing biomarkers in clinical contexts also requires initial approval by the FDA, but also the endorsement of a constellation of other institutions (adapted from [157], reproduced with permission). Surr. Endpoint: Surrogate Endpoint, COU: Context of Use.

Large-scale collaboration and multiple stakeholders in biomarker development

The development, validation, and impactful use of neuroimaging biomarkers of SUDs will depend upon the formation of large, multi-site consortia which can effectively direct resources towards biomarker discovery with harmonized research designs, starting with the "low-hanging fruit"- biomarkers with substantial bodies of supporting evidence and greatest potential utility, such as in intervention development. Furthermore, while translational research in the field is mostly conducted by academics, the developed biomarkers need to be cost-effective from the perspective of policymakers interested in reducing the societal burden of SUDs, pharmaceutical companies developing interventions and seeking to reduce the duration and cost of drug development, and regulatory bodies interested in using scientifically validated neuroimaging markers in approval decisions [162].

Importantly, the use of neuroimaging biomarkers and the interventions that they are used to develop should also be acceptable, accessible, affordable and desirable for individuals with SUDs, and concerns about neuroscientific models of addiction should be addressed [22]. Multi-stakeholder engagement is complicated by gaps in knowledge and terminology between stakeholders, differences in expectations and interests, power imbalances and stigma associated with SUDs, and identifying representative stakeholders. Effective engagement of various stakeholders in biomarker development for SUDs requires designing engagement plans and collaboration roadmaps, developing common terminology, clarifying and communicating the purpose of the engagement and stakeholder roles, and investing in the necessary skills and resources [163–165].

Rigorous research and reporting for biomarker discovery

An essential step in the development of neuroimaging biomarkers is to harmonize best practices in study design, analysis, and reporting, especially given recent concerns about the reliability of multiple neuroimaging modalities [166–168]. While there is significant disagreement over the best neuroimaging research design practices, certain factors would likely improve overall methodological quality [18]. Larger sample sizes and appropriate statistical power analyses, for example, would improve the reproducibility of fMRI cue

reactivity studies and enable the ascertainment of substantive effects [169]. One solution is the collation of neuroimaging data into "big data" repositories, such as the structural MRI database maintained by the NeuroImaging Genetics through Meta-Analyses (ENIGMA) International Consortium [170] and task-based fMRI datasets made available on platforms such as OpenNeuro [171], which can be used for large-scale analyses, hypothesis generation, and model validation. A growing number of multi-center initiatives such as the Human Connectome Project, UK Biobank, and the Adolescent Brain Cognitive Development (ABCD) project collect neuroimaging data from thousands of individuals using harmonized scanning and data management standards across sites and may provide highly useful for the identification of neuroimaging markers [172–174]. In the absence of large-scale studies, meta-analyses can be used to synthesise data across neuroimaging studies, discover convergent findings that replicate across SUDs and contexts of use, and disambiguate the influence of study design and confounders. A summary of neural markers which have replicated across SUDs or contexts of use is presented in Table 1.

Another issue is the methodological heterogeneity of neuroimaging research. The choice of hardware, data acquisition protocol, pre-processing steps, and analysis pipelines can have unexpected and substantial effects on the results of studies using a variety of neuroimaging modalities [175–177]. While it is impossible to prescribe a similar set of best practices for every study, the design should be appropriate to specific contexts of use if the results are to contribute to biomarker development. Furthermore, the clarity, interpretability, and replicability of neuroimaging research would be enhanced with pre-registered protocols, carefully considering essential aspects of research design, and comprehensive reporting of methodological details [178]. Various guidelines for research design and reporting have been developed in recent years with various degrees of generality, such as those developed by the Committee on Best Practice in Data Analysis and Sharing (COBIDAS) and COBIDAS MEEG [179,180] and the Addiction Cue Reactivity Initiative (ACRI) of the addiction working group of ENIGMA consortium [54].

Technological advancements relevant to SUD biomarker discovery

A variety of innovations in neuroimaging technology, data management, and analysis may pave the way for SUD neuroimaging biomarkers. Among promising advances are high-field MRI with increasingly stronger magnetic fields, which can offer greater spatial resolution in structural and functional scans [181]; functional magnetic resonance spectroscopy (fMRS), which can capture dynamic changes in metabolites [182]; and new PET radiotracers, which can probe under-investigated neurotransmitter systems of interest to addiction medicine [183]. Another emerging possibility is the use of neuroimaging to derive subject-specific "fingerprints" of brain circuitry or function, such as "precision functional mapping" to identify individual-level functional connectomes with fMRI [184] or the use of EEG to identify participant-specific electrophysiological patterns [185,186]. Such subject-level (rather than group-level) neuroimaging markers are particularly useful for biomarker development since most contexts of use require biomarkers which can be used to make decisions for individual patients, and the heterogeneity of brain structure and function across individuals renders the translation of group-level findings to the individual-level problematic [187,188].

It is also increasingly possible to integrate different neuroimaging technologies concurrently or in series, and use multimodal data to probe multiple facets of brain structure and function in tandem: resting-state fMRI and MRS can be utilized together to assess the relationship between neuromodulation-associated brain network changes and neurotransmitter concentrations [189], functional diffuse correlation spectroscopy and functional near-infrared spectroscopy have been used along with EEG during and after brain stimulation to concurrently measure cerebral hemodynamics and electrical activity (Giovannella et al., 2018), simultaneous EEG and fMRI neurofeedback might improve the quality of the provided neurofeedback using bimodal data (Lioi et al., 2020), and receptor maps obtained by PET can inform resting-state fMRI functional connectivity analysis [190]. These technological advances have co-occurred with rapid developments in informatics, data analytics, and computational infrastructure which facilitate data storage and sharing, biomarker discovery with increasingly sophisticated machine learning algorithms, and reproducible analytical practices [191,192].

Theories and models of addiction

A significant challenge in biomarker development and theoretical progress in both addiction medicine and psychiatry as a whole is the fact that the DSM is a descriptive diagnostic manual, and its constructs are neither domain-based nor necessarily grounded in neurobiology [193]. SUDs are multifaceted disorders with complex comorbidity patterns and overlapping brain substrates [194,195], and neuroimaging biomarkers will likely reflect the trans-diagnostic impairment and recovery of physiological processes which undergird specific cognitive domains. This highlights the importance of mechanistic models of disease (rather than manual-based diagnostic labels) in the development of neuroimaging addiction biomarkers. Under most mechanistic accounts of addiction, addiction starts with positive reinforcement learning before other processes are involved [7]. These include excessive incentive sensitization [139] for example, which can explain heightened reactivity to drug cues in functional neuroimaging studies [96,196–200]. What happens later is subject to some contention: some emphasize a shift from initially goal-directed behavior to habitual and then compulsive substance use, reflected in neuroimaging findings of a shift in drug cue-reactivity from the ventral to the dorsal striatum [201]; while others highlight a shift from positive to negative reinforcement as withdrawal becomes more important, with some emphasizing goal-directed choice (rather than habit or compulsion) as individuals learn to relieve negative affect with substance use.

Other models focus on processes such as learning and executive control. The reward deficiency and allostasis models [202], for example, highlight the importance of suppression and disruption of reward processing circuits; while others focus on core deficits in value updates and reward learning [203]. These models can explain wide-spread neural aberrations when individuals with various SUDs process non-drug gains and losses [136] and the reduced salience of novel and surprising stimuli [204]. While the frameworks discussed above can account for frequent observations of impaired response inhibition [205] (and corresponding neuroimaging aberrations during executive control tasks [198,206–209]), recent "dual process" accounts of addiction emphasize the broad disruption of top-down, deliberative processes in prefrontal and parietal regions together with deregulation

and disinhibition of bottom-up automatic processes in mesolimbic circuits [210]. Further, recent observations suggest that general cognitive decline and a broad depletion of executive control in addiction may be particularly important to the course of disease and treatment [211], in line with broad degenerations of cortical gray and white matter [39,41,43,47,212]. It must be emphasized that many of these contructs are not mutually exclusive, and multiple interacting processes may be in play in the development, maintenance and recovery from SUDs.

Overall, the briefly discussed models (see [10] for detailed discussion) and theories have been developed in tandem with advances in addiction neuroimaging, and provide promising starting points for the development of neuroimaging biomarkers. Frameworks such as the impaired response inhibition and salience attribution model [11], the Addictions Neuroclinical Assessment framework [8], and the Alcohol and Addiction Research Domain Criteria [213] aim to map addictive disorders to specific axes of impairment and neuroimaging research by facilitating hypothesis generation and the development of interpretable neuroimaging biomarkers linked to formal theories of addiction. Despite differences, these frameworks converge on the involvement of positive valence, negative valence and cognitive control systems in SUDs, and have been used to propose neuroscience-informed classifications of interventions [10,214]. Complementing these theoretical developments, computational modeling of processes of interest in addiction neuroscience (such as drug cue-reactivity, aberrant decision-making, etc.) can mechanistically represent the interplay between neural mechanisms and behavior and link neuroimaging markers, underlying neuro-cognitive pathology, and signs and symptoms of SUDs [215,216].

CONCLUSION

Modern neuroimaging technologies can probe brain structure and function at unprecedented resolution and have already produced novel insights into the neurocognitive mechanisms of addiction and recovery. The rapid pace of technological advancement, increasing availability, and growing recognition of neuroimaging paradigms in recent years has contributed to an explosion in their use within clinical and translational addiction medicine: from 2015 to 2021, an average of 35 protocols with neuroimaging as one of the registered outcome measures in people with SUDs were registered on ClinicalTrials.gov every year, more than ten times the average number from 2000 to 2006. Especially popular are fMRI (268 protocols) and EEG (50 protocols), which dynamically assess brain function; PET (71 protocols) and MRS (35 protocols) which probe neurotransmitter systems and their interactions with radioligands; and structural MRI (35 protocols) which can be used to investigate brain structure at various scales. These paradigms can be systematically utilized to discover and develop biomarkers, measures that objectively reflect biological processes involved in both the progression of substance use and SUDs and the physiological and clinical impact of interventions for these disorders. Particularly promising are several neuroimaging markers which have replicated in meta-analyses across contexts of use and disorders. Technological and scientific advancements, rigorous research practices, and multi-stakeholder engagement can facilitate the development of institutionally approved

neuroimaging biomarkers that enable impactful, personalized interventions for SUDs to be used in clinical practice in the foreseeable future.

METHODS AND LIMITATIONS

The present manuscript is informed by two systematic reviews. The first covered SUD clinical research protocols which include neuroimaging outcome measures, obtained by querying the ClinicalTrials.gov repository between inception and November 17, 2021 (Supplementary Figure 1a). This systematic review yielded a final result of 409 protocols. The second systematic review was conducted on PubMed, focusing on meta-analyses of neuroimaging studies of SUDs and finding 61 meta-analyses from which 83 meta-analytic findings were extracted (Supplementary Figure 1b). Please refer to the methods section of the supplementary materials for more details on the methods, and to the OSF repository https://osf.io/79uc3/?view_only=1d92a6fd769f40119464b156f0c88912 for the search protocol and analysis scripts. Although we used widely-known and inclusive databases of protocols and meta-analyses, we did not triangulate the results with other databases. Our approach likely leads to some missing protocols and papers, and in particular an under-representation of protocols from countries that use registration platforms other than ClinicalTrials.gov.

DATA AVAILABILITY STATEMENT:

The protocol and data for this systematic review are available on the open science framework (OSF) website (https://osf.io/79uc3/?view_only=1d92a6fd769f40119464b156f0c88912).
The ClinicalTrials.gov search engine was used through the Study Fields query URL (https://ClinicalTrials.gov/api/gui/ref/api_urls) for searching the clinical trial protocols. For full-text screening, all available records were downloaded from the Aggregate Analysis of ClinicalTrials.gov (AACT) Database, Clinical Trials Transformation Initiative (CTTI) database [217] (https://aact.ctti-clinicaltrials.org/) for the second stage. For searching the systematic reviews and meta-analyses, studies were identified using the Medline/PubMed (https://pubmed.ncbi.nlm.nih.gov/) database.

CODE AVAILABILITY STATEMENT:

All codes are available on the study's OSF project repository at the following link:

https://osf.io/79uc3/?view_only=1d92a6fd769f40119464b156f0c88912

Data analyses and illustrations were conducted using R version 4.0.5 [218], with dplyr [219] and ggplot2 [220] packages. The codes for data illustrations are freely available on the OSF repository of this project.

ACKNOWLEDGEMENT

AUTHORS CONTRIBUTIONS STATEMENT

Kathleen Brady, Owen Carmichael, Anna Rose Childress, Hamed Ekhtiari, F. Gerard Moeller, Patricia O'Donnell, Maria Oquendo, Martin Paulus, Diego Pizzagalli, Tanya Ramey, and Joseph Schacht conceived of the presented idea and designed the study and Hamed Ekhtiari coordinated the consensus process among all authors. Arshiya Sangchooli, Mehran Zare-Bidoky, and Hamed Ekhtiari gathered data, designed the tables, and performed the initial analytic calculations. All authors discussed the results and contributed to the final manuscript.

COMPETING INTERESTS STATEMENT

O.C. has received grant funding from Eli Lilly, Inc, and Nestle, Inc. He has provided paid consulting to Novo Nordisk. Dr. Paulus is an advisor to Spring Care, Inc., a behavioral health startup, he has received royalties for an article about methamphetamine in UpToDate. M.P.P. has a consulting agreement with and receives compensation from F. Hoffmann-La Roche Ltd. P.O. is an employee and shareholder of Sage Therapeutics. Other authors report no conflicts of interest.

Disclaimer: The views and opinions expressed in this manuscript are those of the authors only and do not necessarily represent the views, official policy or position of the U.S. Department of Health and Human Services or any of its affiliated institutions or agencies.

References

1. Degenhardt L, Charlson F, Ferrari A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Psychiatry*. 2018;5(12):987-1012. doi:10.1016/S2215-0366(18)30337-7

2. Shield KD, Imtiaz S, Probst C, Rehm J. The epidemiology and public health burden of addictive disorders. In: *Integrating Psychological and Pharmacological Treatments for Addictive Disorders: An Evidence-Based Guide*. ; 2018:3-31.

3. National Institutes of Health. National Institute on Drug Abuse. Trends and Statistics. Published online 2020. Accessed May 20, 2020. https://www.drugabuse.gov/related-topics/trends-statistics/

4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition.; 2013. Accessed September 8, 2020. http://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596

5. Volkow ND, Boyle M. Neuroscience of Addiction: Relevance to Prevention and Treatment. *AJP*. 2018;175(8):729-740. doi:10.1176/appi.ajp.2018.17101174

6. Kircher J, Pierson C. Les atrophies cerebrales dans les toxicomanies: role de la pneumoencdphalographie. Essais therapeutiques. *Maroc Med*. 1956;35:668-670.

7. 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

8. Kwako LE, Bickel WK, Goldman D. Addiction Biomarkers: Dimensional Approaches to Understanding Addiction. *Trends Mol Med*. 2018;24(2):121-128. doi:10.1016/j.molmed.2017.12.007

9. Volkow ND, Koob GF, McLellan AT. Neurobiologic Advances from the Brain Disease Model of Addiction. *New England Journal of Medicine*. 2016;374(4):363-371. doi:10.1056/NEJMra1511480

10. Ekhtiari H, Zare-Bidoky M, Verdejo-Garcia A. Neurocognitive Disorders in Substance Use Disorders. In: el-Guebaly N, Carrà G, Galanter M, Baldacchino AM, eds. *Textbook of Addiction Treatment: International Perspectives*. Springer International Publishing; 2021:1159-1176. doi:10.1007/978-3-030-36391-8_81

11. Zilverstand A, Huang AS, Alia-Klein N, Goldstein RZ. Neuroimaging Impaired Response Inhibition and Salience Attribution in Human Drug Addiction: A Systematic Review. *Neuron*. 2018;98(5):886-903. doi:10.1016/j.neuron.2018.03.048

12. Ekhtiari H, Faghiri A, Oghabian MA, Paulus MP. Chapter 7 - Functional neuroimaging for addiction medicine: From mechanisms to practical considerations. In: Ekhtiari H, Paulus MP, Ekhtiari H, Paulus MP, eds. *Progress in Brain Research*. Vol 224. Neuroscience for Addiction Medicine: From Prevention to Rehabilitation - Methods and Interventions. ; 2016:129-153. Accessed February 22, 2019. http://www.sciencedirect.com/science/article/pii/S0079612315001508

13. Moeller SJ, Paulus MP. Toward biomarkers of the addicted human brain: Using neuroimaging to predict relapse and sustained abstinence in substance use disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2018;80:143-154.

14. Zakhari S, Li TK. Determinants of alcohol use and abuse: Impact of quantity and frequency patterns on liver disease. *Hepatology*. 2007;46(6):2032-2039. doi:10.1002/hep.22010

15. Bahji A, Brietzke E, Soares C, Stuart H. Recent Advances in Biomarkers of Addiction: A Narrative Review. *Canadian Journal of Addiction*. 2021;12(1):6-12. doi:10.1097/CXA.0000000000000107

16. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of "precision psychiatry." *BMC Med*. 2017;15(1):80. doi:10.1186/s12916-017-0849-x

17. Mahmood T. Biomarkers in psychiatry: a clinician's viewpoint. *Br Med Bull*. 2020;135(1):23-27. doi:10.1093/bmb/ldaa019

18. Carmichael O, Schwarz AJ, Chatham CH, et al. The role of fMRI in drug development. *Drug Discov Today*. 2018;23(2):333-348. doi:10.1016/j.drudis.2017.11.012

19. Ekhtiari H, Nasseri P, Yavari F, Mokri A, Monterosso J. Neuroscience of drug craving for addiction medicine: From circuits to therapies. *Prog Brain Res*. 2016;223:115-141. doi:10.1016/bs.pbr.2015.10.002

20. Paulus MP, Stewart JL. Neurobiology, Clinical Presentation, and Treatment of Methamphetamine Use Disorder: A Review. *JAMA Psychiatry*. 2020;77(9):959-966. doi:10.1001/jamapsychiatry.2020.0246

21. O'Donnell P, Rosen L, Alexander R, Murthy V, Davies CH, Ratti E. Strategies to Address Challenges in Neuroscience Drug Discovery and Development. *Int J Neuropsychopharmacol*. 2019;22(7):445-448. doi:10.1093/ijnp/pyz027

22. 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. *Neuropsychopharmacol*. 2021;46(10):1715-1723. doi:10.1038/s41386-020-00950-y

23. Banks ML, Negus SS. Insights from Preclinical Choice Models on Treating Drug Addiction. *Trends in Pharmacological Sciences*. 2017;38(2):181-194. doi:10.1016/j.tips.2016.11.002

24. Lewis M. Addiction and the Brain: Development, Not Disease. *Neuroethics*. 2017;10(1):7-18. doi:10.1007/s12152-016-9293-4

25. Kendler KS. Levels of explanation in psychiatric and substance use disorders: implications for the development of an etiologically based nosology. *Mol Psychiatry*. 2012;17(1):11-21. doi:10.1038/mp.2011.70

26. Heather N, Field M, Moss AC, Satel S. *Evaluating the Brain Disease Model of Addiction*. 1st ed. Routledge; 2022. doi:10.4324/9781003032762

27. Hart CL. Viewing addiction as a brain disease promotes social injustice. *Nat Hum Behav*. 2017;1(3):0055. doi:10.1038/s41562-017-0055

28. Heather N, Best D, Kawalek A, et al. Challenging the brain disease model of addiction: European launch of the addiction theory network. *Addiction Research & Theory*. 2018;26(4):249-255. doi:10.1080/16066359.2017.1399659

29. MacKillop J, Agabio R, Feldstein Ewing SW, et al. Hazardous drinking and alcohol use disorders. *Nat Rev Dis Primers*. 2022;8(1):80. doi:10.1038/s41572-022-00406-1

30. Pickard H. Is addiction a brain disease? A plea for agnosticism and heterogeneity. *Psychopharmacology*. 2022;239(4):993-1007. doi:10.1007/s00213-021-06013-4

31. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Published online 2016.

32. Brook RD, Weder AB, Rajagopalan S. "Environmental Hypertensionology" The Effects of Environmental Factors on Blood Pressure in Clinical Practice and Research. *The Journal of Clinical Hypertension*. 2011;13(11):836-842. doi:10.1111/j.1751-7176.2011.00543.x

33. Kreatsoulas C, Anand SS. The impact of social determinants on cardiovascular disease. *Canadian Journal of Cardiology*. 2010;26:8C-13C. doi:10.1016/S0828-282X(10)71075-8

34. BEST (Biomarkers E and other Tools) Resource. BEST (Biomarkers, EndpointS, and other Tools) resource. Published online 2016.

35. Verdejo-Garcia A, Lorenzetti V, Manning V, et al. A Roadmap for Integrating Neuroscience Into Addiction Treatment: A Consensus of the Neuroscience Interest Group of the International Society of Addiction Medicine. *Frontiers in Psychiatry*. 2019;10. Accessed April 22, 2022. https://www.frontiersin.org/article/10.3389/fpsyt.2019.00877

36. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Baler R. Chapter One - Neuroimaging of Addiction. In: Seeman P, Madras B, Seeman P, Madras B, eds. *Imaging of the Human Brain in Health and Disease*. ; 2014:1-26. Accessed March 29, 2022. https://www.sciencedirect.com/science/article/pii/B9780124186774000014

37. Strang J, Gurling H. Computerized tomography and neuropsychological assessment in long-term high-dose heroin addicts. *Br J Addict*. 1989;84(9):1011-1019. doi:10.1111/j.1360-0443.1989.tb00784.x

38. Whitwell JL. Voxel-Based Morphometry: An Automated Technique for Assessing Structural Changes in the Brain. *J Neurosci*. 2009;29(31):9661-9664. doi:10.1523/JNEUROSCI.2160-09.2009

39. 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):29. doi:10.1038/s41398-020-01128-2

40. Sutherland MT, Riedel MC, Flannery JS, et al. Chronic cigarette smoking is linked with structural alterations in brain regions showing acute nicotinic drug-induced functional modulations. *Behav Brain Funct*. 2016;12(1):16. doi:10.1186/s12993-016-0100-5

41. Hill-Bowen LD, Riedel MC, Salo T, et al. Convergent gray matter alterations across drugs of abuse and network-level implications: A meta-analysis of structural MRI studies. *Drug Alcohol Depend*. 2022;240:109625. doi:10.1016/j.drugalcdep.2022.109625

42. Sutherland MT, Ray KL, Riedel MC, Yanes JA, Stein EA, Laird AR. Neurobiological impact of nicotinic acetylcholine receptor agonists: an activation likelihood estimation meta-analysis of pharmacologic neuroimaging studies. *Biol Psychiatry*. 2015;78(10):711-720. doi:10.1016/j.biopsych.2014.12.021

43. Zhang M, Gao X, Yang Z, et al. Shared gray matter alterations in subtypes of addiction: a voxel-wise meta-analysis. *Psychopharmacology (Berl)*. 2021;238(9):2365-2379. doi:10.1007/s00213-021-05920-w

44. Spindler C, Trautmann S, Alexander N, et al. Meta-analysis of grey matter changes and their behavioral characterization in patients with alcohol use disorder. *Sci Rep*. 2021;11(1):5238. doi:10.1038/s41598-021-84804-7

45. Wollman SC, Alhassoon OM, Hall MG, et al. Gray matter abnormalities in opioid-dependent patients: A neuroimaging meta-analysis. *Am J Drug Alcohol Abuse*. 2017;43(5):505-517. doi:10.1080/00952990.2016.1245312

46. Mackey S, Allgaier N, Chaarani B, et al. Mega-Analysis of Gray Matter Volume in Substance Dependence: General and Substance-Specific Regional Effects. *AJP*. 2019;176(2):119-128. doi:10.1176/appi.ajp.2018.17040415

47. Beard CL, Schmitz JM, Soder HE, et al. Regional differences in white matter integrity in stimulant use disorders:A meta-analysis of diffusion tensor imaging studies. *Drug Alcohol Depend*. 2019;201:29-37. doi:10.1016/j.drugalcdep.2019.03.023

48. Monnig MA, Tonigan JS, Yeo RA, Thoma RJ, McCrady BS. White matter volume in alcohol use disorders: a meta-analysis. *Addict Biol*. 2013;18(3):581-592. doi:10.1111/j.1369-1600.2012.00441.x

49. Wollman SC, Alhassoon OM, Stern MJ, et al. White matter abnormalities in long-term heroin users: a preliminary neuroimaging meta-analysis. *Am J Drug Alcohol Abuse*. 2015;41(2):133-138. doi:10.3109/00952990.2014.985829

50. Suckling J, Nestor LJ. The neurobiology of addiction: the perspective from magnetic resonance imaging present and future. *Addiction*. 2017;112(2):360-369. doi:10.1111/add.13474

51. Duyn J. Chapter 19 - Spontaneous fMRI activity during resting wakefulness and sleep. In: Van Someren EJW, Van Der Werf YD, Roelfsema PR, et al., eds. *Progress in Brain Research*. Vol 193. Slow Brain Oscillations of Sleep, Resting State and Vigilance. ; 2011:295-305. Accessed March 28, 2022. https://www.sciencedirect.com/science/article/pii/B9780444538390000193

52. Morgenstern J, Naqvi NH, Debellis R, Breiter HC. The contributions of cognitive neuroscience and neuroimaging to understanding mechanisms of behavior change in addiction. *Psychol Addict Behav*. 2013;27(2):336-350. doi:10.1037/a0032435

53. Pariyadath V, Gowin JL, Stein EA. Chapter 8 - Resting state functional connectivity analysis for addiction medicine: From individual loci to complex networks. In: Ekhtiari H, Paulus MP, Ekhtiari H, Paulus MP, eds. *Progress in Brain Research*. Vol 224. Neuroscience for Addiction Medicine: From Prevention to Rehabilitation - Methods and Interventions. ; 2016:155-173. Accessed March 28, 2022. https://www.sciencedirect.com/science/article/pii/S0079612315001211

54. Ekhtiari H, Zare-Bidoky M, Sangchooli A, et al. A methodological checklist for fMRI drug cue reactivity studies: development and expert consensus. *Nat Protoc*. 2022;17(3):567-595. doi:10.1038/s41596-021-00649-4

55. Ekhtiari H, Nasseri P, Yavari F, Mokri A, Monterosso J. Neuroscience of drug craving for addiction medicine: From circuits to therapies. *Prog Brain Res*. 2016;223:115-141. doi:10.1016/bs.pbr.2015.10.002

56. Borogovac A, Asllani I. Arterial Spin Labeling (ASL) fMRI: Advantages, Theoretical Constrains and Experimental Challenges in Neurosciences. *International Journal of Biomedical Imaging*. 2012;2012:e818456. doi:10.1155/2012/818456

57. Gu X, Yang B, Gao S, Yan LF, Xu D, Wang W. Prefrontal fNIRS-based clinical data analysis of brain functions in individuals abusing different types of drugs. *Journal of Biomedical Semantics*. 2021;12(1):21. doi:10.1186/s13326-021-00256-y

58. Huettel SA, Song AW, McCarthy G. *Functional Magnetic Resonance Imaging*. Third Edition.; 2014.

59. Lu H, Hua J, van Zijl PCM. Noninvasive functional imaging of cerebral blood volume with vascular-space-occupancy (VASO) MRI. *NMR in Biomedicine*. 2013;26(8):932-948. doi:10.1002/nbm.2905

60. Luijten M, Schellekens AF, Kühn S, Machielse MWJ, Sescousse G. Disruption of Reward Processing in Addiction : An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies. *JAMA Psychiatry*. 2017;74(4):387-398. doi:10.1001/jamapsychiatry.2016.3084

61. Hill-Bowen LD, Riedel MC, Poudel R, et al. *The Cue-Reactivity Paradigm: An Ensemble of Networks Driving Attention and Cognition When Viewing Drug-Related and Natural-Reward Stimuli*.; 2020:2020.02.26.966549. Accessed August 13, 2021. https://www.biorxiv.org/content/10.1101/2020.02.26.966549v1

62. Wilcox CE, Abbott CC, Calhoun VD. Alterations in resting-state functional connectivity in substance use disorders and treatment implications. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;91:79-93. doi:10.1016/j.pnpbp.2018.06.011

63. Yang LZ, Shi B, Li H, et al. Electrical stimulation reduces smokers' craving by modulating the coupling between dorsal lateral prefrontal cortex and parahippocampal gyrus. *Social Cognitive and Affective Neuroscience*. 2017;12(8):1296-1302.

64. Lopes da Silva F. EEG and MEG: Relevance to Neuroscience. *Neuron*. 2013;80(5):1112-1128. doi:10.1016/j.neuron.2013.10.017

65. Singh SP. Magnetoencephalography: Basic principles. *Ann Indian Acad Neurol*. 2014;17(Suppl 1):S107-S112. doi:10.4103/0972-2327.128676

66. 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

67. Parvaz MA, Moeller SJ, Goldstein RZ. Incubation of Cue-Induced Craving in Adults Addicted to Cocaine Measured by Electroencephalography. *JAMA Psychiatry*. 2016;73(11):1127-1134. doi:10.1001/jamapsychiatry.2016.2181

68. Newson JJ, Thiagarajan TC. EEG Frequency Bands in Psychiatric Disorders: A Review of Resting State Studies. *Frontiers in Human Neuroscience*. 2019;12. Accessed April 9, 2022. https://www.frontiersin.org/article/10.3389/fnhum.2018.00521

69. Hu B, Dong Q, Hao Y, Zhao Q, Shen J, Zheng F. Effective brain network analysis with resting-state EEG data: a comparison between heroin abstinent and non-addicted subjects. *J Neural Eng*. 2017;14(4):046002. doi:10.1088/1741-2552/aa6c6f

70. Naim-Feil J, Fitzgerald PB, Rubinson M, et al. Anomalies in global network connectivity associated with early recovery from alcohol dependence: A network transcranial magnetic stimulation and electroencephalography study. *Addiction Biology*. 2022;27(2):e13146. doi:10.1111/adb.13146

71. Ceccarini J, Van Laere K, Koole M. Brain PET Quantification in Neuropsychiatric Research. In: Dierckx RAJO, Otte A, de Vries EFJ, et al., eds. *PET and SPECT in Psychiatry*. ; 2021:17-44. Accessed April 12, 2022. https://doi.org/10.1007/978-3-030-57231-0_2

72. Hellem T, Shi X, Latendresse G, Renshaw PF. The Utility of Magnetic Resonance Spectroscopy for Understanding Substance Use Disorders: A Systematic Review of the Literature. *J Am Psychiatr Nurses Assoc*. 2015;21(4):244-275. doi:10.1177/1078390315598606

73. Volkow ND, Koob G, Baler R. Biomarkers in substance use disorders. *ACS Chem Neurosci*. 2015;6(4):522-525. doi:10.1021/acschemneuro.5b00067

74. Ashok AH, Mizuno Y, Volkow ND, Howes OD. Association of Stimulants With Dopaminergic Alterations in Users of Cocaine, Amphetamine, and Methamphetamine: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2017;74(5):511-519. doi:10.1001/jamapsychiatry.2017.0135

75. Proebstl L, Kamp F, Manz K, et al. Effects of stimulant drug use on the dopaminergic system: A systematic review and meta-analysis of in vivo neuroimaging studies. *Eur Psychiatry*. 2019;59:15-24. doi:10.1016/j.eurpsy.2019.03.003

76. Darcq E, Kieffer BL. Opioid receptors: drivers to addiction? *Nat Rev Neurosci*. 2018;19(8):499-514. doi:10.1038/s41583-018-0028-x

77. Jones JA, Russell B, Dalley JW. Molecular Imaging Studies in Stimulant Addiction: A Cross-Species Perspective. In: Dierckx RAJO, Otte A, de Vries EFJ, et al., eds. *PET and SPECT in Psychiatry*. ; 2021:713-739. Accessed April 12, 2022. https://doi.org/10.1007/978-3-030-57231-0_22

78. Trick L, Butler K, Chukwueke C, et al. Abnormalities of Neurotransmission in Drug Addiction. In: Dierckx RAJO, Otte A, de Vries EFJ, et al., eds. *PET and SPECT in Psychiatry*. ; 2021:653-712. Accessed April 12, 2022. https://doi.org/10.1007/978-3-030-57231-0_21

79. Ae K, Bd B, R G, L L, Dj M, Lm S. Brain metabolite alterations related to alcohol use: a meta-analysis of proton magnetic resonance spectroscopy studies. *Molecular psychiatry*. 2022;27(8). doi:10.1038/s41380-022-01594-8

80. Smucny J, Maddock RJ. Spectroscopic meta-analyses reveal novel metabolite profiles across methamphetamine and cocaine substance use disorder. *Drug Alcohol Depend*. 2023;248:109900. doi:10.1016/j.drugalcdep.2023.109900

81. Chen T, Tan H, Lei H, Su H, Zhao M. Proton magnetic resonance spectroscopy in substance use disorder: recent advances and future clinical applications. *Sci China Inf Sci*. 2020;63(7):170101. doi:10.1007/s11432-019-2818-5

82. Chen T, Tan H, Lei H, et al. Nature of glutamate alterations in substance dependence: A systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. *Psychiatry Research: Neuroimaging*. 2021;315:111329. doi:10.1016/j.pscychresns.2021.111329

83. Califf RM. Biomarker definitions and their applications. *Exp Biol Med (Maywood)*. 2018;243(3):213-221. doi:10.1177/1535370217750088

84. Gromova M, Vaggelas A, Dallmann G, Seimetz D. Biomarkers: Opportunities and Challenges for Drug Development in the Current Regulatory Landscape. *Biomarker Insights*. 2020;15. doi:10.1177/1177271920974652

85. MacNiven KH, Jensen EL, Borg N, Padula CB, Humphreys K, Knutson B. Association of neural responses to drug cues with subsequent relapse to stimulant use. *JAMA network open*. 2018;1(8):e186466-e186466.

86. Bach P, Weil G, Pompili E, et al. FMRI-based prediction of naltrexone response in alcohol use disorder: a replication study. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(5):915-927. doi:10.1007/s00406-021-01259-7

87. Vollstädt-Klein S, Loeber S, Kirsch M, et al. Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. *Biol Psychiatry*. 2011;69(11):1060-1066. doi:10.1016/j.biopsych.2010.12.016

88. Venkatasubramanian G, Keshavan MS. Biomarkers in Psychiatry - A Critique. *Ann Neurosci*. 2016;23(1):3-5. doi:10.1159/000443549

89. Smith DG, Ersche KD. Using a drug-word Stroop task to differentiate recreational from dependent drug use. *CNS Spectrums*. 2014;19(3):247-255. doi:10.1017/S1092852914000133

90. Vollstädt-Klein S, Wichert S, Rabinstein J, et al. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. *Addiction*. 2010;105(10):1741-1749. doi:10.1111/j.1360-0443.2010.03022.x

91. Chye Y, Solowij N, Suo C, et al. Orbitofrontal and caudate volumes in cannabis users: a multi-site mega-analysis comparing dependent versus non-dependent users. *Psychopharmacology*. 2017;234(13):1985-1995. doi:10.1007/s00213-017-4606-9

92. McLellan AT, Koob GF, Volkow ND. Preaddiction-A Missing Concept for Treating Substance Use Disorders. *JAMA Psychiatry*. 2022;79(8):749-751. doi:10.1001/jamapsychiatry.2022.1652

93. Burnette EM, Grodin EN, Schacht JP, Ray LA. Clinical and Neural Correlates of Reward and Relief Drinking. *Alcohol Clin Exp Res*. 2021;45(1):194-203. doi:10.1111/acer.14495

94. Gray KM, Squeglia LM. Research Review: What have we learned about adolescent substance use? *J Child Psychol Psychiatry*. 2018;59(6):618-627. doi:10.1111/jcpp.12783

95. Heitzeg MM, Cope LM, Martz ME, Hardee JE. Neuroimaging Risk Markers for Substance Abuse: Recent Findings on Inhibitory Control and Reward System Functioning. *Curr Addict Rep*. 2015;2(2):91-103. doi:10.1007/s40429-015-0048-9

96. Tervo-Clemmens B, Quach A, Calabro FJ, Foran W, Luna B. Meta-analysis and review of functional neuroimaging differences underlying adolescent vulnerability to substance use. *NeuroImage*. 2020;209:116476. doi:10.1016/j.neuroimage.2019.116476

97. Moeller SJ, Bederson L, Alia-Klein N, Goldstein RZ. Neuroscience of inhibition for addiction medicine: From prediction of initiation to prediction of relapse. *Prog Brain Res*. 2016;223:165-188. doi:10.1016/bs.pbr.2015.07.007

98. Squeglia LM, Cservenka A. Adolescence and drug use vulnerability: findings from neuroimaging. *Current Opinion in Behavioral Sciences*. 2017;13:164-170. doi:10.1016/j.cobeha.2016.12.005

99. Camchong J, Macdonald AW, Mueller BA, et al. Changes in resting functional connectivity during abstinence in stimulant use disorder: a preliminary comparison of relapsers and abstainers. *Drug Alcohol Depend*. 2014;139:145-151. doi:10.1016/j.drugalcdep.2014.03.024

100. Parvaz MA, Moeller SJ, Uquillas d'Oleire F, et al. Prefrontal gray matter volume recovery in treatment-seeking cocaine-addicted individuals: A longitudinal study. *Addict Biol*. 2017;22(5):1391-1401. doi:10.1111/adb.12403

101. Wang X, Yu R, Zhou X, et al. Reversible brain white matter microstructure changes in heroin addicts: a longitudinal study. *Addict Biol*. 2013;18(4):727-728. doi:10.1111/j.1369-1600.2011.00316.x

102. Chou YH, Huang WS, Su TP, Lu RB, Wan FJ, Fu YK. Dopamine transporters and cognitive function in methamphetamine abuser after a short abstinence: A SPECT study. *European Neuropsychopharmacology*. 2007;17(1):46-52. doi:10.1016/j.euroneuro.2006.05.002

103. Volkow ND, Chang L, Wang GJ, et al. Loss of Dopamine Transporters in Methamphetamine Abusers Recovers with Protracted Abstinence. *J Neurosci*. 2001;21(23):9414-9418. doi:10.1523/JNEUROSCI.21-23-09414.2001

104. Grabb MC, Hillefors M, Potter WZ. The NIMH "Fast-Fail Trials" (FAST) Initiative: Rationale, Promise, and Progress. *Pharmaceut Med*. 2020;34(4):233-245. doi:10.1007/s40290-020-00343-y

105. Young KA, Franklin TR, Roberts DCS, et al. Nipping cue reactivity in the bud: baclofen prevents limbic activation elicited by subliminal drug cues. *J Neurosci*. 2014;34(14):5038-5043. doi:10.1523/JNEUROSCI.4977-13.2014

106. Beck A, Pelz P, Lorenz RC, et al. Effects of high-dose baclofen on cue reactivity in alcohol dependence: A randomized, placebo-controlled pharmaco-fMRI study. *European Neuropsychopharmacology*. 2018;28(11):1206-1216. doi:10.1016/j.euroneuro.2018.08.507

107. Wiers CE, Shumay E, Volkow ND, et al. Effects of depressive symptoms and peripheral DAT methylation on neural reactivity to alcohol cues in alcoholism. *Transl Psychiatry*. 2015;5:e648. doi:10.1038/tp.2015.141

108. Medeiros FA. Biomarkers and Surrogate Endpoints: Lessons Learned From Glaucoma. *Investigative Ophthalmology & Visual Science*. 2017;58(6):BIO20-BIO26. doi:10.1167/iovs.17-21987

109. Schacht JP, Randall PK, Latham PK, et al. Predictors of naltrexone response in a randomized trial: reward-related brain activation, OPRM1 genotype, and smoking status. *Neuropsychopharmacology*. 2017;42(13):2640-2653.

110. Nichols TT, Foulds J, Yingst JM, et al. Cue-reactivity in experienced electronic cigarette users: Novel stimulus videos and a pilot fMRI study. *Brain Res Bull*. 2016;123:23-32. doi:10.1016/j.brainresbull.2015.10.003

111. Kroemer NB, Veldhuizen MG, Delvy R, Patel BP, O'Malley SS, Small DM. Sweet taste potentiates the reinforcing effects of e-cigarettes. *Eur Neuropsychopharmacol*. 2018;28(10):1089-1102. doi:10.1016/j.euroneuro.2018.07.102

112. Coussens NP, Sittampalam GS, Jonson SG, et al. The Opioid Crisis and the Future of Addiction and Pain Therapeutics. *J Pharmacol Exp Ther*. 2019;371(2):396-408. doi:10.1124/jpet.119.259408

113. Bach P, Kirsch M, Hoffmann S, et al. The effects of single nucleotide polymorphisms in glutamatergic neurotransmission genes on neural response to alcohol cues and craving. *Addict Biol*. 2015;20(6):1022-1032. doi:10.1111/adb.12291

114. Wang W, Zhornitsky S, Le TM, et al. Cue-elicited craving, thalamic activity, and physiological arousal in adult non-dependent drinkers. *Journal of Psychiatric Research*. 2019;116:74-82. doi:10.1016/j.jpsychires.2019.06.005

115. Gouzoulis-Mayfrank E, Härtel-Petri R, Hamdorf W, Havemann-Reinecke U, Mühlig S, Wodarz N. Methamphetamine-related disorders. *Deutsches Ärzteblatt International*. 2017;114(26):455.

116. Soleimani G, Kupliki R, Bodurka J, Paulus MP, Ekhtiari H. How structural and functional MRI can inform dual-site tACS parameters: A case study in a clinical population and its pragmatic implications. *Brain Stimul*. 2022;15(2):337-351. doi:10.1016/j.brs.2022.01.008

117. Joutsa J, Moussawi K, Siddiqi SH, et al. Brain lesions disrupting addiction map to a common human brain circuit. *Nat Med*. 2022;28(6):1249-1255. doi:10.1038/s41591-022-01834-y

118. Ekhtiari H, Ghobadi-Azbari P, Thielscher A, et al. A Checklist for Assessing the Methodological Quality of Concurrent tES-fMRI Studies (ContES Checklist): A Consensus Study and Statement. *medRxiv*. Published online December 30, 2020:2020.12.23.20248579. doi:10.1101/2020.12.23.20248579

119. Esmaeilpour Z, Shereen AD, Ghobadi-Azbari P, et al. Methodology for tDCS integration with fMRI. *Human Brain Mapping*. 2020;41(7):1950-1967. doi:10.1002/hbm.24908

120. Neuling T, Ruhnau P, Fuscà M, Demarchi G, Herrmann CS, Weisz N. Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. *Neuroimage*. 2015;118:406-413. doi:10.1016/j.neuroimage.2015.06.026

121. Parks NA. Concurrent application of TMS and near-infrared optical imaging: methodological considerations and potential artifacts. *Front Hum Neurosci*. 2013;7. doi:10.3389/fnhum.2013.00592

122. Siebner HR, Bergmann TO, Bestmann S, et al. Consensus paper: combining transcranial stimulation with neuroimaging. *Brain Stimul*. 2009;2(2):58-80. doi:10.1016/j.brs.2008.11.002

123. Habelt B, Arvaneh M, Bernhardt N, Minev I. Biomarkers and neuromodulation techniques in substance use disorders. *Bioelectronic Medicine*. 2020;6(1):4. doi:10.1186/s42234-020-0040-0

124. Karch S, Keeser D, Hümmer S, et al. Modulation of Craving Related Brain Responses Using Real-Time fMRI in Patients with Alcohol Use Disorder. *PLoS ONE*. 2015;10(7):e0133034. doi:10.1371/journal.pone.0133034

125. Karch S, Paolini M, Gschwendtner S, et al. Real-Time fMRI Neurofeedback in Patients With Tobacco Use Disorder During Smoking Cessation: Functional Differences and Implications of the First Training Session in Regard to Future Abstinence or Relapse. *Front Hum Neurosci*. 2019;0.

126. Carroll KM. The profound heterogeneity of substance use disorders: Implications for treatment development. *Curr Dir Psychol Sci*. 2021;30(4):358-364. doi:10.1177/09637214211026984

127. Bach P, Weil G, Pompili E, et al. Incubation of neural alcohol cue reactivity after withdrawal and its blockade by naltrexone. *Addiction Biology*. 2020;25(1):e12717.

128. Regier PS, Jagannathan K, Franklin TR, et al. Sustained brain response to repeated drug cues is associated with poor drug-use outcomes. *Addiction Biology*. 2021;26(5). doi:10.1111/adb.13028

129. Steele VR, Maurer JM, Arbabshirani MR, et al. Machine Learning of Functional Magnetic Resonance Imaging Network Connectivity Predicts Substance Abuse Treatment Completion. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2018;3(2):141-149. doi:10.1016/j.bpsc.2017.07.003

130. Yan C, Yang X, Yang R, et al. Treatment Response Prediction and Individualized Identification of Short-Term Abstinence Methamphetamine Dependence Using Brain Graph Metrics. *Frontiers in Psychiatry*. 2021;12. Accessed May 24, 2022. https://www.frontiersin.org/article/10.3389/fpsyt.2021.583950

131. Tisdall L, MacNiven KH, Padula CB, Leong JK, Knutson B. Brain tract structure predicts relapse to stimulant drug use. *Proc Natl Acad Sci U S A*. 2022;119(26):e2116703119. doi:10.1073/pnas.2116703119

132. Xiao P, Dai Z, Zhong J, Zhu Y, Shi H, Pan P. Regional gray matter deficits in alcohol dependence: A meta-analysis of voxel-based morphometry studies. *Drug Alcohol Depend*. 2015;153:22-28. doi:10.1016/j.drugalcdep.2015.05.030

133. Yan H, Xiao S, Fu S, et al. Functional and structural brain abnormalities in substance use disorder: A multimodal meta-analysis of neuroimaging studies. *Acta Psychiatr Scand*. 2023;147(4):345-359. doi:10.1111/acps.13539

134. Klugah-Brown B, Di X, Zweerings J, Mathiak K, Becker B, Biswal B. Common and separable neural alterations in substance use disorders: A coordinate-based meta-analyses of functional neuroimaging studies in humans. *Hum Brain Mapp*. 2020;41(16):4459-4477. doi:10.1002/hbm.25085

135. Pollard AA, Hauson AO, Lackey NS, et al. Functional neuroanatomy of craving in heroin use disorder: voxel-based meta-analysis of functional magnetic resonance imaging (fMRI) drug cue reactivity studies. *Am J Drug Alcohol Abuse*. 2023;49(4):418-430. doi:10.1080/00952990.2023.2172423

136. Qiu Z, Wang J. A voxel-wise meta-analysis of task-based functional MRI studies on impaired gain and loss processing in adults with addiction. *J Psychiatry Neurosci*. 2021;46(1):E128-E146. doi:10.1503/jpn.200047

137. Schacht JP, Anton RF, Myrick H. Functional neuroimaging studies of alcohol cue reactivity: A quantitative meta-analysis and systematic review. *Addict Biol*. 2013;18(1):121-133. doi:10.1111/j.1369-1600.2012.00464.x

138. Zeng J, You L, Yang F, et al. A meta-analysis of the neural substrates of monetary reward anticipation and outcome in alcohol use disorder. *Hum Brain Mapp*. 2023;44(7):2841-2861. doi:10.1002/hbm.26249

139. Berridge KC, Robinson TE. Liking, Wanting and the Incentive-Sensitization Theory of Addiction. *Am Psychol*. 2016;71(8):670-679. doi:10.1037/amp0000059

140. Dager AD, Anderson BM, Rosen R, et al. Functional magnetic resonance imaging (fMRI) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. *Addiction*. 2014;109(4):585-595. doi:10.1111/add.12437

141. Goudriaan AE, Veltman DJ, van den Brink W, Dom G, Schmaal L. Neurophysiological effects of modafinil on cue-exposure in cocaine dependence: a randomized placebo-controlled cross-over study using pharmacological fMRI. *Addict Behav*. 2013;38(2):1509-1517. doi:10.1016/j.addbeh.2012.04.006

142. Schacht JP, Anton RF, Randall PK, Li X, Henderson S, Myrick H. Stability of fMRI striatal response to alcohol cues: A hierarchical linear modeling approach. *NeuroImage*. 2011;56(1):61-68. doi:10.1016/j.neuroimage.2011.02.004

143. Bach P, Reinhard I, Koopmann A, et al. Test–retest reliability of neural alcohol cue-reactivity: Is there light at the end of the magnetic resonance imaging tube? *Addiction Biology*. 2022;27(1):e13069. doi:10.1111/adb.13069

144. Egerton A, Demjaha A, McGuire P, Mehta MA, Howes OD. The test–retest reliability of 18F-DOPA PET in assessing striatal and extrastriatal presynaptic dopaminergic function. *NeuroImage*. 2010;50(2):524-531. doi:10.1016/j.neuroimage.2009.12.058

145. Alakurtti K, Johansson JJ, Joutsa J, et al. Long-Term Test–Retest Reliability of Striatal and Extrastriatal Dopamine D2/3 Receptor Binding: Study with [11C]Raclopride and High-Resolution PET. *J Cereb Blood Flow Metab*. 2015;35(7):1199-1205. doi:10.1038/jcbfm.2015.53

146. Khan AR, Hiebert NM, Vo A, et al. Biomarkers of Parkinson's disease: Striatal sub-regional structural morphometry and diffusion MRI. *NeuroImage: Clinical*. 2019;21:101597. doi:10.1016/j.nicl.2018.11.007

147. Albrecht J, Burke M, Haegler K, et al. Potential Impact of a 32-Channel Receiving Head Coil Technology on the Results of a Functional MRI Paradigm. *Clin Neuroradiol*. 2010;20(4):223-229. doi:10.1007/s00062-010-0029-2

148. Colizoli O, de Gee JW, van der Zwaag W, Donner TH. Functional magnetic resonance imaging responses during perceptual decision-making at 3 and 7 T in human cortex, striatum, and brainstem. *Hum Brain Mapp*. 2021;43(4):1265-1279. doi:10.1002/hbm.25719

149. Panman JL, To YY, van der Ende EL, et al. Bias Introduced by Multiple Head Coils in MRI Research: An 8 Channel and 32 Channel Coil Comparison. *Front Neurosci*. 2019;13:729. doi:10.3389/fnins.2019.00729

150. Faria D, Vale J, Tavares JMRS, Oliveira JM, Costa D. Effect of reconstruction processing methods and analysis in the quantification of brain spect studies with DaTSCAN^{TM}. *Physica Medica*. 2016;32:311. doi:10.1016/j.ejmp.2016.07.177

151. Zeng H, Su D, Wang P, et al. The Action Representation Elicited by Different Types of Drug-Related Cues in Heroin-Abstinent Individuals. *Front Behav Neurosci*. 2018;12. doi:10.3389/fnbeh.2018.00123

152. Hasler BP, Forbes EE, Franzen PL. Time-of-day differences and short-term stability of the neural response to monetary reward: A pilot study. *Psychiatry Research: Neuroimaging*. 2014;224(1):22-27. doi:10.1016/j.pscychresns.2014.07.005

153. Wetherill RR, Young KA, Jagannathan K, et al. The impact of sex on brain responses to smoking cues: a perfusion fMRI study. *Biology of Sex Differences*. 2013;4(1):9. doi:10.1186/2042-6410-4-9

154. Garrison KA, Potenza MN. Neuroimaging and Biomarkers in Addiction Treatment. *Curr Psychiatry Rep*. 2014;16(12):513. doi:10.1007/s11920-014-0513-5

155. Koban L, Wager TD, Kober H. A neuromarker for drug and food craving distinguishes drug users from non-users. *Nat Neurosci*. 2023;26(2):316-325. doi:10.1038/s41593-022-01228-w

156. Deacon BJ, McKay D. The biomedical model of psychological problems: A call for critical dialogue. *the Behavior Therapist*. 2015;38(7):231-235.

157. Addiction Cue-Reactivity Initiative (ACRI) Network. Parameter Space and Potential for Biomarker Development in 25 Years of fMRI Drug Cue Reactivity: A Systematic Review. *JAMA Psychiatry*. Published online February 7, 2024. doi:10.1001/jamapsychiatry.2023.5483

158. Bakker E, Hendrikse NM, Ehmann F, et al. Biomarker Qualification at the European Medicines Agency: A Review of Biomarker Qualification Procedures From 2008 to 2020. *Clinical Pharmacology & Therapeutics*. 2022;112(1):69-80. doi:10.1002/cpt.2554

159. Kraus VB. Biomarkers as drug development tools: discovery, validation, qualification and use. *Nature Reviews Rheumatology*. 2018;14(6):354-362.

160. Luking KR, Nelson BD, Infantolino ZP, Sauder CL, Hajcak G. Internal Consistency of Functional Magnetic Resonance Imaging and Electroencephalography Measures of Reward in Late Childhood and Early Adolescence. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017;2(3):289-297. doi:10.1016/j.bpsc.2016.12.004

161. Elliott ML, Knodt AR, Ireland D, et al. What Is the Test-Retest Reliability of Common Task-Functional MRI Measures? New Empirical Evidence and a Meta-Analysis. *Psychol Sci*. 2020;31(7):792-806. doi:10.1177/0956797620916786

162. Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. *Clin Pharmacol Ther*. 2015;98(1):34-46. doi:10.1002/cpt.136

163. Concannon TW, Grant S, Welch V, et al. Practical Guidance for Involving Stakeholders in Health Research. *J Gen Intern Med*. 2019;34(3):458-463. doi:10.1007/s11606-018-4738-6

164. Harrison JD, Auerbach AD, Anderson W, et al. Patient stakeholder engagement in research: A narrative review to describe foundational principles and best practice activities. *Health Expect*. 2019;22(3):307-316. doi:10.1111/hex.12873

165. Henderson J, Sword W, Niccols A, Dobbins M, The Connections Research Team. Implementing stakeholder-informed research in the substance abuse treatment sector: strategies used by Connections, a Canadian knowledge translation and exchange project. *Substance Abuse Treatment, Prevention, and Policy*. 2014;9(1):21. doi:10.1186/1747-597X-9-21

166. Höller Y, Uhl A, Bathke A, et al. Reliability of EEG Measures of Interaction: A Paradigm Shift Is Needed to Fight the Reproducibility Crisis. *Frontiers in Human Neuroscience*. 2017;11. Accessed January 4, 2024. https://www.frontiersin.org/articles/10.3389/fnhum.2017.00441

167. Zuo XN, Biswal BB, Poldrack RA. Editorial: Reliability and Reproducibility in Functional Connectomics. *Front Neurosci*. 2019;13:117. doi:10.3389/fnins.2019.00117

168. Hedges EP, Dimitrov M, Zahid U, et al. Reliability of structural MRI measurements: The effects of scan session, head tilt, inter-scan interval, acquisition sequence, FreeSurfer version and processing stream. *Neuroimage*. 2022;246:118751. doi:10.1016/j.neuroimage.2021.118751

169. Marek S, Tervo-Clemmens B, Calabro FJ, et al. Reproducible brain-wide association studies require thousands of individuals. *Nature*. 2022;603(7902):654-660. doi:10.1038/s41586-022-04492-9

170. Mackey S, Kan KJ, Chaarani B, et al. Chapter 10 - Genetic imaging consortium for addiction medicine: From neuroimaging to genes. In: Ekhtiari H, Paulus MP, Ekhtiari H, Paulus MP, eds. *Progress in Brain Research*. Vol 224. Neuroscience for Addiction Medicine: From Prevention to Rehabilitation - Methods and Interventions. ; 2016:203-223. Accessed June 28, 2021. https://www.sciencedirect.com/science/article/pii/S0079612315001326

171. Markiewicz CJ, Gorgolewski KJ, Feingold F, et al. OpenNeuro: An open resource for sharing of neuroimaging data. *bioRxiv*. Published online 2021.

172. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203-209. doi:10.1038/s41586-018-0579-z

173. Garavan H, Bartsch H, Conway K, et al. Recruiting the ABCD sample: Design considerations and procedures. *Developmental cognitive neuroscience*. 2018;32:16-22.

174. Van Essen DC, Ugurbil K, Auerbach E, et al. The Human Connectome Project: A data acquisition perspective. *NeuroImage*. 2012;62(4):2222-2231. doi:10.1016/j.neuroimage.2012.02.018

175. Botvinik-Nezer R, Holzmeister F, Camerer CF, et al. Variability in the analysis of a single neuroimaging dataset by many teams. *Nature*. 2020;582(7810):84-88. doi:10.1038/s41586-020-2314-9

176. Schilling KG, Tax CMW, Rheault F, et al. Fiber tractography bundle segmentation depends on scanner effects, vendor effects, acquisition resolution, diffusion sampling scheme, diffusion sensitization, and bundle segmentation workflow. *NeuroImage*. 2021;242:118451. doi:10.1016/j.neuroimage.2021.118451

177. Veronese M, Rizzo G, Belzunce M, et al. Reproducibility of findings in modern PET neuroimaging: insight from the NRM2018 grand challenge. *J Cereb Blood Flow Metab*. 2021;41(10):2778-2796. doi:10.1177/0271678X211015101

178. Poldrack RA, Baker CI, Durnez J, et al. Scanning the horizon: towards transparent and reproducible neuroimaging research. *Nat Rev Neurosci*. 2017;18(2):115-126. doi:10.1038/nrn.2016.167

179. Nichols TE, Das S, Eickhoff SB, et al. Best practices in data analysis and sharing in neuroimaging using MRI. *Nature Neuroscience*. 2017;20(3):299-303. doi:10.1038/nn.4500

180. Pernet C, Garrido MI, Gramfort A, et al. Issues and recommendations from the OHBM COBIDAS MEEG committee for reproducible EEG and MEG research. *Nature Neuroscience*. 2020;23(12):1473-1483. doi:10.1038/s41593-020-00709-0

181. Neuner I, Veselinović T, Ramkiran S, Rajkumar R, Schnellbaecher GJ, Shah NJ. 7T ultra-high-field neuroimaging for mental health: an emerging tool for precision psychiatry? *Transl Psychiatry*. 2022;12(1):1-10. doi:10.1038/s41398-022-01787-3

182. Stanley JA, Raz N. Functional Magnetic Resonance Spectroscopy: The "New" MRS for Cognitive Neuroscience and Psychiatry Research. *Frontiers in Psychiatry*. 2018;9. Accessed May 29, 2022. https://www.frontiersin.org/article/10.3389/fpsyt.2018.00076

183. Hou L, Rong J, Haider A, et al. Positron Emission Tomography Imaging of the Endocannabinoid System: Opportunities and Challenges in Radiotracer Development. *J Med Chem*. 2021;64(1):123-149. doi:10.1021/acs.jmedchem.0c01459

184. Gordon EM, Laumann TO, Gilmore AW, et al. Precision Functional Mapping of Individual Human Brains. *Neuron*. 2017;95(4):791-807.e7. doi:10.1016/j.neuron.2017.07.011

185. Demuru M, Fraschini M. EEG fingerprinting: Subject-specific signature based on the aperiodic component of power spectrum. *Computers in Biology and Medicine*. 2020;120:103748. doi:10.1016/j.compbiomed.2020.103748

186. Ozdemir RA, Tadayon E, Boucher P, et al. Cortical responses to noninvasive perturbations enable individual brain fingerprinting. *Brain Stimul*. 2021;14(2):391-403. doi:10.1016/j.brs.2021.02.005

187. Fu CHY, Costafreda SG. Neuroimaging-based biomarkers in psychiatry: clinical opportunities of a paradigm shift. *Can J Psychiatry*. 2013;58(9):499-508. doi:10.1177/070674371305800904

188. McKenna MC, Murad A, Huynh W, Lope J, Bede P. The changing landscape of neuroimaging in frontotemporal lobar degeneration: from group-level observations to single-subject data interpretation. *Expert Rev Neurother*. 2022;22(3):179-207. doi:10.1080/14737175.2022.2048648

189. Hunter MA, Coffman BA, Gasparovic C, Calhoun VD, Trumbo MC, Clark VP. Baseline effects of transcranial direct current stimulation on glutamatergic neurotransmission and large-scale network connectivity. *Brain Res*. 2015;1594:92-107. doi:10.1016/j.brainres.2014.09.066

190. Dipasquale O, Selvaggi P, Veronese M, Gabay AS, Turkheimer F, Mehta MA. Receptor-Enriched Analysis of functional connectivity by targets (REACT): A novel, multimodal analytical approach informed by PET to study the pharmacodynamic response of the brain under MDMA. *NeuroImage*. 2019;195:252-260. doi:10.1016/j.neuroimage.2019.04.007

191. Li X, Guo N, Li Q. Functional Neuroimaging in the New Era of Big Data. *Genomics, Proteomics & Bioinformatics*. 2019;17(4):393-401. doi:10.1016/j.gpb.2018.11.005

192. Poldrack RA, Gorgolewski KJ, Varoquaux G. Computational and Informatic Advances for Reproducible Data Analysis in Neuroimaging. *Annual Review of Biomedical Data Science*. 2019;2(1):119-138. doi:10.1146/annurev-biodatasci-072018-021237

193. Carvalho AF, Solmi M, Sanches M, et al. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Transl Psychiatry*. 2020;10(1):1-13. doi:10.1038/s41398-020-0835-5

194. Klugah-Brown B, Jiang C, Agoalikum E, et al. Common abnormality of gray matter integrity in substance use disorder and obsessive-compulsive disorder: A comparative voxel-based meta-analysis. *Hum Brain Mapp*. 2021;42(12):3871-3886. doi:10.1002/hbm.25471

195. Noori HR, Cosa Linan A, Spanagel R. Largely overlapping neuronal substrates of reactivity to drug, gambling, food and sexual cues: A comprehensive meta-analysis. *Eur Neuropsychopharmacol*. 2016;26(9):1419-1430. doi:10.1016/j.euroneuro.2016.06.013

196. Hogarth L. Addiction is driven by excessive goal-directed drug choice under negative affect: translational critique of habit and compulsion theory. *Neuropsychopharmacology*. 2020;45(5):720-735. doi:10.1038/s41386-020-0600-8

197. Littel M, Euser AS, Munafò MR, Franken IHA. Electrophysiological indices of biased cognitive processing of substance-related cues: a meta-analysis. *Neurosci Biobehav Rev*. 2012;36(8):1803-1816. doi:10.1016/j.neubiorev.2012.05.001

198. Zhang Y, Ou H, Yuan TF, Sun J. Electrophysiological indexes for impaired response inhibition and salience attribution in substance (stimulants and depressants) use disorders: A meta-analysis. *Int J Psychophysiol*. 2021;170:133-155. doi:10.1016/j.ijpsycho.2021.10.008

199. Zeng J, Yu S, Cao H, Su Y, Dong Z, Yang X. Neurobiological correlates of cue-reactivity in alcohol-use disorders: A voxel-wise meta-analysis of fMRI studies. *Neurosci Biobehav Rev*. 2021;128:294-310. doi:10.1016/j.neubiorev.2021.06.031

200. 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):429. doi:10.1038/s41398-020-01115-7

201. Everitt BJ, Robbins TW. From the ventral to the dorsal striatum: Devolving views of their roles in drug addiction. *Neuroscience & Biobehavioral Reviews*. 2013;37(9, Part A):1946-1954. doi:10.1016/j.neubiorev.2013.02.010

202. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*. 2001;24(2):97-129. doi:10.1016/S0893-133X(00)00195-0

203. Park SQ, Kahnt T, Beck A, et al. Prefrontal cortex fails to learn from reward prediction errors in alcohol dependence. *J Neurosci*. 2010;30(22):7749-7753. doi:10.1523/JNEUROSCI.5587-09.2010

204. Euser AS, Arends LR, Evans BE, Greaves-Lord K, Huizink AC, Franken IHA. The P300 event-related brain potential as a neurobiological endophenotype for substance use disorders: a meta-analytic investigation. *Neurosci Biobehav Rev*. 2012;36(1):572-603. doi:10.1016/j.neubiorev.2011.09.002

205. Lim TV, Ersche KD. Theory-driven computational models of drug addiction in humans: Fruitful or futile? *Addiction Neuroscience*. 2023;5:100066. doi:10.1016/j.addicn.2023.100066

206. Fairbairn CE, Kang D, Federmeier KD. Alcohol and Neural Dynamics: A Meta-Analysis of Acute Alcohol Effects on Event-Related Brain Potentials. *Biol Psychiatry*. 2021;89(10):990-1000. doi:10.1016/j.biopsych.2020.11.024

207. Cao Y, Tian F, Zeng J, Gong Q, Yang X, Jia Z. The brain activity pattern in alcohol-use disorders under inhibition response Task. *J Psychiatr Res*. 2023;163:127-134. doi:10.1016/j.jpsychires.2023.05.009

208. Le TM, Potvin S, Zhornitsky S, Li CSR. Distinct patterns of prefrontal cortical disengagement during inhibitory control in addiction: A meta-analysis based on population characteristics. *Neuroscience & Biobehavioral Reviews*. 2021;127:255-269. doi:10.1016/j.neubiorev.2021.04.028

209. Qiu Z, Wang J. Altered neural activities during response inhibition in adults with addiction: a voxel-wise meta-analysis. *Psychol Med*. 2021;51(3):387-399. doi:10.1017/S0033291721000362

210. McClure SM, Bickel WK. A dual-systems perspective on addiction: contributions from neuroimaging and cognitive training. *Ann N Y Acad Sci*. 2014;1327:62-78. doi:10.1111/nyas.12561

211. Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philos Trans R Soc Lond B Biol Sci*. 2008;363(1507):3125-3135. doi:10.1098/rstb.2008.0089

212. Rabin RA, Mackey S, Parvaz MA, et al. Common and gender-specific associations with cocaine use on gray matter volume: Data from the ENIGMA addiction working group. *Hum Brain Mapp*. 2022;43(1):543-554. doi:10.1002/hbm.25141

213. Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF. Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. *Alcohol Clin Exp Res*. 2015;39(4):579-584. doi:10.1111/acer.12669

214. Rezapour T, Rafei P, Baldacchino A, et al. *Neuroscience-Informed Classification of Prevention Interventions in Substance Use Disorders: An RDoC-Based Approach*. Addiction Medicine; 2022. doi:10.1101/2022.09.28.22280342

215. Mollick JA, Kober H. Computational models of drug use and addiction: A review. *Journal of Abnormal Psychology*. 2020;129(6):544-555. doi:10.1037/abn0000503

216. Stephan KE, Schlagenhauf F, Huys QJM, et al. Computational neuroimaging strategies for single patient predictions. *NeuroImage*. 2017;145:180-199. doi:10.1016/j.neuroimage.2016.06.038

217. Aggregate Analysis of ClinicalTrials.gov (AACT) Database. Clinical Trials Transformation Initiative (CTTI). https://aact.ctti-clinicaltrials.org

218. R Core Team. R: A language and environment for statistical computing. Published online 2013.

219. Wickham H, François R, Henry L, Müller K, Vaughan D. dplyr: A Grammar of Data Manipulation. Published online 2023. https://dplyr.tidyverse.org

220. Wickham H. ggplot2: Elegant Graphics for Data Analysis. Published online 2016. https://ggplot2.tidyverse.org

221. Spindler C, Mallien L, Trautmann S, Alexander N, Muehlhan M. A coordinate-based meta-analysis of white matter alterations in patients with alcohol use disorder. *Transl Psychiatry*. 2022;12(1):40. doi:10.1038/s41398-022-01809-0

222. Suchting R, Beard CL, Schmitz JM, et al. A meta-analysis of tract-based spatial statistics studies examining white matter integrity in cocaine use disorder. *Addict Biol*. 2021;26(2):e12902. doi:10.1111/adb.12902

223. Pan P, Shi H, Zhong J, et al. Chronic smoking and brain gray matter changes: evidence from meta-analysis of voxel-based morphometry studies. *Neurol Sci*. 2013;34(6):813-817. doi:10.1007/s10072-012-1256-x

224. Long Y, Pan N, Ji S, et al. Distinct brain structural abnormalities in attention-deficit/hyperactivity disorder and substance use disorders: A comparative meta-analysis. *Transl Psychiatry*. 2022;12(1):368. doi:10.1038/s41398-022-02130-6

225. Hall MG, Alhassoon OM, Stern MJ, et al. Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: a neuroimaging meta-analysis. *Am J Drug Alcohol Abuse*. 2015;41(4):290-299. doi:10.3109/00952990.2015.1044607

226. Rocchetti M, Crescini A, Borgwardt S, et al. Is cannabis neurotoxic for the healthy brain? A meta-analytical review of structural brain alterations in non-psychotic users. *Psychiatry Clin Neurosci*. 2013;67(7):483-492. doi:10.1111/pcn.12085

227. Li L, Yu H, Liu Y, et al. Lower regional grey matter in alcohol use disorders: evidence from a voxel-based meta-analysis. *BMC Psychiatry*. 2021;21:247. doi:10.1186/s12888-021-03244-9

228. Hahn S, Mackey S, Cousijn J, et al. Predicting alcohol dependence from multi-site brain structural measures. *Hum Brain Mapp*. 2022;43(1):555-565. doi:10.1002/hbm.25248

229. Zhong J, Shi H, Shen Y, et al. Voxelwise meta-analysis of gray matter anomalies in chronic cigarette smokers. *Behav Brain Res*. 2016;311:39-45. doi:10.1016/j.bbr.2016.05.016

230. Liu Y, Masina F, Ridderinkhof KR, Pezzetta R. Addiction as a brain disease? A meta-regression comparison of error-related brain potentials between addiction and

neurological diseases. *Neurosci Biobehav Rev*. 2023;148:105127.
doi:10.1016/j.neubiorev.2023.105127

231. Hamidovic A, Wang Y. The P300 in alcohol use disorder: A meta-analysis and meta-regression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;95:109716.
doi:10.1016/j.pnpbp.2019.109716

232. Kühn S, Gallinat J. Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. *Eur J Neurosci*. 2011;33(7):1318-1326.
doi:10.1111/j.1460-9568.2010.07590.x

233. Lin X, Deng J, Shi L, et al. Neural substrates of smoking and reward cue reactivity in smokers: a meta-analysis of fMRI studies. *Transl Psychiatry*. 2020;10(1):1-9.
doi:10.1038/s41398-020-0775-0

234. Engelmann JM, Versace F, Robinson JD, et al. Neural substrates of smoking cue reactivity: A meta-analysis of fMRI studies. *NeuroImage*. 2012;60(1):252-262.
doi:10.1016/j.neuroimage.2011.12.024

235. Chase HW, Eickhoff SB, Laird AR, Hogarth L. The Neural Basis of Drug Stimulus Processing and Craving: An Activation Likelihood Estimation Meta-Analysis. *Biological Psychiatry*.
2011;70(8):785-793. doi:10.1016/j.biopsych.2011.05.025

236. Hanlon CA, Dowdle LT, Naselaris T, Canterberry M, Cortese BM. Visual cortex activation to drug cues: a meta-analysis of functional neuroimaging papers in addiction and substance abuse literature. *Drug Alcohol Depend*. 2014;143:206-212.
doi:10.1016/j.drugalcdep.2014.07.028

237. Zeng J, You L, Sheng H, Luo Y, Yang X. The differential neural substrates for reward choice under gain-loss contexts and risk in alcohol use disorder: Evidence from a voxel-based meta-analysis. *Drug Alcohol Depend*. 2023;248:109912.
doi:10.1016/j.drugalcdep.2023.109912

238. Taebi A, Becker B, Klugah-Brown B, et al. Shared network-level functional alterations across substance use disorders: A multi-level kernel density meta-analysis of resting-state functional connectivity studies. *Addict Biol*. 2022;27(4):e13200. doi:10.1111/adb.13200

239. Dugré JR, Orban P, Potvin S. Disrupted functional connectivity of the brain reward system in substance use problems: A meta-analysis of functional neuroimaging studies. *Addict Biol*. 2023;28(1):e13257. doi:10.1111/adb.13257