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Parameter Space and Potential for Biomarker Development in 25 Years of fMRI Drug Cue Reactivity:

A Systematic Review

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Abstract

IMPORTANCE—In the last 25 years, functional magnetic resonance imaging drug cue reactivity (FDCR) studies have characterized some core aspects in the neurobiology of drug addiction. However, no FDCR-derived biomarkers have been approved for treatment development or clinical adoption. Traversing this translational gap requires a systematic assessment of the FDCR literature evidence, its heterogeneity, and an evaluation of possible clinical uses of FDCR-derived biomarkers.

OBJECTIVE—To summarize the state of the field of FDCR, assess their potential for biomarker development, and outline a clear process for biomarker qualification to guide future research and validation efforts.

EVIDENCE REVIEW—The PubMed and Medline databases were searched for every original FDCR investigation published from database inception until December 2022. Collected data covered study design, participant characteristics, FDCR task design, and whether each study provided evidence that might potentially help develop susceptibility, diagnostic, response, prognostic, predictive, or severity biomarkers for 1 or more addictive disorders.

FINDINGS—There were 415 FDCR studies published between 1998 and 2022. Most focused on nicotine (122 [29.6%]), alcohol (120 [29.2%]), or cocaine (46 [11.1%]), and most used visual cues (354 [85.3%]). Together, these studies recruited 19 311 participants, including 13 812 individuals with past or current substance use disorders. Most studies could potentially support biomarker development, including diagnostic (143 [32.7%]), treatment response (141 [32.3%]), severity (84 [19.2%]), prognostic (30 [6.9%]), predictive (25 [5.7%]), monitoring (12 [2.7%]), and susceptibility (2 [0.5%]) biomarkers. A total of 155 interventional studies used FDCR, mostly to investigate pharmacological (67 [43.2%]) or cognitive/behavioral (51 [32.9%]) interventions; 141 studies used FDCR as a response measure, of which 125 (88.7%) reported significant interventional FDCR alterations; and 25 studies used FDCR as an intervention outcome predictor, with 24 (96%) finding significant associations between FDCR markers and treatment outcomes.

CONCLUSIONS AND RELEVANCE—Based on this systematic review and the proposed biomarker development framework, there is a pathway for the development and regulatory qualification of FDCR-based biomarkers of addiction and recovery. Further validation could support the use of FDCR-derived measures, potentially accelerating treatment development and improving diagnostic, prognostic, and predictive clinical judgments.

The evaluation of substance use disorders (SUDs) is currently reliant on interviews, self-reported measures, and biological assays of drug metabolites that mostly reflect substance use and confound the distinction between markers of substance use and the complex pathophysiology underlying SUDs.[1] Growing recognition of this issue has led to recent interest in identifying the neurobiological underpinnings of SUDs[2] and translating this knowledge to facilitate the development of novel treatment targets and interventions and theoretically grounded, empirically sound, and clinically relevant biomarkers for patient-tailored care.[3] A particularly impactful paradigm in addiction medicine has been functional magnetic resonance imaging (fMRI) drug cue reactivity (FDCR), where brain activation patterns during an individual's exposure to addiction-related sensory stimuli are measured as a potential marker of underlying neuropathology.[4] FDCR has consistently shown that SUDs are associated with remarkable aberrations in the neural circuitry underpinning incentive salience, reward evaluation, interoception, memory, habit formation, and executive control.[5,6] The eBox in the Supplement shows a general overview of biomarkers in psychiatry and addiction medicine, and eFigure 1 in the Supplement shows an introduction to FDCR.

In the third decade of FDCR research, with consistently observed correlations between FDCR and important clinical outcomes,[7,8] biomarkers derived from FDCR paradigms could inform intervention development or clinical care of people with SUDs. Given the expense and technical difficulty of qualifying biomarkers for use in regulatory decision-making, for example, to support the approval of specific interventions, frameworks have been developed to facilitate the validation of biomarkers. According to the biomarker validation frameworks developed by organizations such as the European Medicines Agency[9] and the US Food and Drug Administration,[10] an initial step in developing FDCR-derived biomarkers with regulatory approval would be the specification of precise contexts of use (COU). Different methods and standards of validation might be required, for example, for an FDCR-derived biomarker developed to classify individuals with SUDs into different subtypes compared

with one used to predict individual responses to a specific intervention. Just as crucially, the methodological details of any FDCR-derived biomarker would need to be carefully considered and clearly specified since they may influence the FDCR signal and the interpretation of the biomarker.[11,12]

In the next stage, the defined biomarker will need to be characterized and validated within the COU. A principal step is analytical validation, establishing appropriate accuracy, repeatability, and reproducibility of the biomarker within the proposed COU.[13] Demonstrating clinical validity requires elucidating the etiological link of an FDCR biomarker to SUD symptoms and establishing that the biomarker appropriately measures a clinical feature of a disease, disease outcome, or treatment outcome.[14] Finally, the practical use of FDCR-derived biomarkers in clinical or drug development contexts requires demonstration of cost-effectiveness. These validation steps require a combination of systematic reviews, meta-analyses, and mega-analyses, expert consensus, and new studies to address potential evidentiary gaps. An overview of the overall FDCR biomarker development framework is provided in eFigure 2 in the Supplement.

Moving toward the development of clinically relevant FDCR-derived biomarkers necessitates taking stock of the current state and evolution of FDCR as a research field. While many useful systematic reviews and meta-analyses of cue reactivity fMRI studies are available,[7,15–18] these efforts have largely focused on estimating neuroimaging effect sizes rather than systematically investigating the methodological characteristics of FDCR studies and the potential of FDCR for biomarker development. We present a systematic review and synthesis of the FDCR literature, covering basic study design features, studied substances and behaviors, and methodological parameters, to outline the degree of methodological heterogeneity and to identify outstanding gaps in the evidence. We then provide a systematic assessment of the potential of FDCR studies for biomarker development under the National Institutes of Health framework in translational addiction science and discuss exemplar FDCR indices. We finally highlight a set of concrete actions and future directions in the translation of FDCR-derived biomarkers from the bench to the bedside based on the outlined biomarker development framework and the systematic review.

Methods and Results

Detailed methods and results of the systematic review sections are presented in the eMethods and eResults in the Supplement, and the search terms and syntax can be found in eTables 1 and 2 in the Supplement. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline, and the protocol for this systematic review was preregistered.[19] The annual update of this live systematic review can be found online.[20] The PRISMA flowchart can be found in eFigure 3 in the Supplement. While we refer to fMRI drug cue reactivity (including alcohol) throughout the article, behavioral addiction studies focusing on gambling and gaming were not excluded as they constitute a small portion of the cue reactivity literature and involve cue reactivity paradigms similar to DCR studies. Separate analyses of substance and behavioral addictions can be found in eFigure 11 in the Supplement.

The final database includes 415 studies from 19 countries (eFigure 4 in the Supplement) and will be continually updated, according to a registered protocol, to provide an up-to-date repository of FDCR studies and facilitate future investigations. Our results indicate a growing interest in the FDCR paradigm, with 307 FDCR studies in our database published in the last 10 years (eFigure 5 in the Supplement). We will first consider the methodological aspects of reviewed studies.

Methodological Heterogeneity and Biomarker Specification

A central element of an FDCR experiment is the selection of cues used to elicit neural reactivity, with a wide array of options available; while 345 reviewed studies (85.3%) used visual cues, others used a variety of auditory, semantic, gustatory, olfactory, or tactile reminders of drugs or drug use, alone or in various combinations (Figure 1; eFigure 6 in the Supplement). The impact of cue sensory modality in FDCR remains underexplored, but cues in different sensory modalities likely induce markedly different neural activations[21] and multisensory cues or delivering drug cues together with other rewarding stimuli may improve ecological validity and FDCR signal.[22,23]

Basic task design elements also vary considerably between studies (Figure 1). A total of 257 studies (61.9%) used blocked designs, which are popular since repeated presentations of drug-relevant stimuli may constitute more robust exposure and subsequent activation. However, event-related designs may be better able to optimally characterize the shape of the blood oxygen level–dependent response to drugcues,[11] and more sophisticated mixed designs could model interactions between cue exposure and context. Furthermore, FDCR has been combined with other task modalities to probe the interaction of cue exposure and different cognitive processes (52 studies [12.5%]). Such combined paradigms are attempted to increase ecological validity since DCR engages with multiple neurocognitive processes. For example, FDCR during response inhibition was able to predict tobacco abstinence.[24]

Methodological parameters should ideally be chosen based on evidence from meta-analyses and mega-analyses or at least empirical results, with alternative sources, such as structured expert opinion, used to address knowledge gaps.[11] Such choices also involve trade-offs: for example, simple visual FDCR paradigms may be selected since they are relatively inexpensive and already widely used,[25] while complex interactional designs and multisensory stimuli with greater ecological validity may be technically challenging and more difficult to standardize between studies.[26] On the other hand, multisensory stimuli may improve signal-to-noise ratio to increase reliability at the same scanning duration.[27] Overall, since methodological heterogeneity between studies can hamper the comparison of findings[28] and complicate meta-analyses for biomarker development,[29] it is important to promote standardized best practices and methodological harmonization to the extent that is practical.

Appropriate reporting and explanation of key methodological elements and harmonized reporting standards is essential regardless of what choices are made, for example using the COBIDAS guideline[30] and the recently developed Enhanced NeuroImaging Genetics through Meta-Analyses (ENIGMA) Addiction Cue-Reactivity Initiative (ACRI) reporting checklist.[11] Due to a lack of generally recognized and implemented standards for the quality

report in publications, FDCR studies vary widely in terms of reporting quality,[11] and there are likely substantial differences in methodological quality as well; these differences in quality, particularly in the size of study samples and appropriate correction for multiple comparisons, have been reported across fMRI studies previously[31] and in part reflect rapid improvement in imaging and analysis methods.[32] While the present study is a broad overview of FDCR research and we did not comprehensively assess methodological quality, this is important for future investigations and particularly meta-analyses for biomarker development.

Participant Characteristics

There is evidence that participant characteristics substantially impact the FDCR signal, highlighting the importance of specifying target populations for FDCR biomarkers and ensuring the diversity of populations used to develop such biomarkers. Overall, 19 311 individuals participated in FDCR studies from 1998 to 2022, including 12 950 men (67.1%) and 5130 women (26.5%), with the sex of 1231 participants (6.4%) not explicitly specified (eFigure 7 in the Supplement). The fact that only 26.5% of participants in FDCR studies have been women raises questions about the generalizability of findings and potential biomarkers informed by this literature, since men and women may have markedly distinct neural activation patterns during drug cue exposure.[33,34] While outside the scope of the present review, other demographic factors, such as age, socioeconomic status, and social determinants of health, medical and psychiatric comorbidities, and cultural background, likely impact the FDCR signal as well.[11]

Future studies would benefit from complex multivariate modeling techniques that can disambiguate the influence of various participant characteristics and other methodological choices and investigate complex FDCR patterns. Further, the median sample size of FDCR studies in our database is only 37, which may be too small to discover replicable FDCR markers.[35] Larger samples as well as meta-analyses and mega-analyses are important for developing valid and generalizable biomarkers. This systematic review aims to provide a comprehensive overview of the entire FDCR field and the broad inclusion criteria for study participants included studies of individuals who met SUD diagnostic criteria and those who used substances without meeting such criteria and did not exclude studies of participants with various comorbidities. These and the methodological heterogeneities reported in this systematic review prevent us from performing a meta-analysis across studies, but future meta-analyses and mega-analyses of clusters of studies in the database are possible and facilitated by our ongoing effort to catalog and share FDCR studies.[19]

COU of FDCR Biomarkers

Another principal consideration when developing an FDCR biomarker is its COU. First, it should be clear for what SUD(s) the biomarker is developed. This choice hinges on considering both the burden of a disorder and the extent of the FDCR literature on that disorder. To provide 2 promising examples, nicotine and alcohol use disorders are both major contributors to morbidity and mortality worldwide[5,36] and have been extensively investigated with FDCR paradigms, comprising 121 studies (29.6%) and 123 studies (29.2%), respectively, of our database (eFigure 5 in the Supplement). Then, the

COU specification should clarify whether the FDCR-derived biomarker is to be used for diagnostic or prognostic purposes, to select or assess interventions, or as an intervention target (Table; eFigure 8 in the Supplement).[23,37–52] This choice should guide the design and interpretation of the biomarker and, ultimately, its validation.

Studies with relevant evidence for developing diagnostic biomarkers constitute the largest category in our review with 143 examples, of which 134 (93.7%) have reported significant findings (Figure 2). These studies have mostly investigated differences in FDCR between individuals with SUDs and healthy controls, though some have assessed differences between clinically relevant SUD subtypes. The diagnostic studies in our database have all essentially conducted statistical comparisons of the FDCR signal between participant groups defined a priori, though in principle, researchers could start from the other end, ie, with data-driven identification of neurotypes using the fMRI data. While these provide insights into the neural correlates of SUDs, the diagnosis of SUDs currently relies on relatively inexpensive clinical interviews and drug tests, and it is unlikely that FDCR-derived biomarkers would find clinical use in identifying SUDs. Another noninterventional COU is susceptibility assessment, where there have been promising results, for example, in assessing adolescent susceptibility to SUDs based on FDCR in reward-related regions.[6,53] The other 2, and likely most promising noninterventional COUs for FDCR biomarkers, constitute prognostic evaluation and monitoring of individuals diagnosed with SUDs: there is evidence that baseline nucleus accumbens DCR, for example, can statistically predict relapse better than conventional clinical measures.[43] These latter classes of FDCR biomarkers could add to the limited repertoire of tools available to meaningfully predict the course of SUDs and monitor their progression, but their development requires expensive longitudinal studies. Only 88 studies (21.2%) in our database include more than a single time point (Figure 1).

Using FDCR biomarkers to develop, select, implement, or monitor the impact of interventions may be more cost-effective. There are 155 interventional studies in our database, most using FDCR in the context of pharmacological (67 [43.2%]; most commonly naltrexone in 10 studies) or cognitive or behavioral interventions (51 [32.9%]). These studies form a sizable evidence base to support the development of multiple types of interventional biomarkers for some SUDs, particularly alcohol and nicotine use disorders, which constitute 53 studies (34.2%) and 51 studies (32.9%), respectively, in our database (Figure 3). Individuals with SUDs are highly heterogeneous in their responses to different treatments,[54] partly since different interventions target distinct mechanisms of disease that vary between individuals. Predictive FDCR biomarkers could reflect underlying neural pathology and may predict treatment response, which could guide treatment planning and reduce poor outcomes. For example, higher ventral striatal FDCR may predict greater efficacy of naltrexone than acamprosate for alcohol use disorder, possibly since ventral striatal FDCR may reflect reward-related craving and naltrexone has craving-suppressing effects.[48] Our review indicates that the predictive biomarker category is underinvestigated, however, with only 25 relevant studies. Much more common are response biomarker studies, where postintervention FDCR or intervention-induced changes in FDCR are thought to reflect an intervention’s neurophysiological effect. There are 141 supporting pieces of evidence for response biomarker development across the 155 interventional studies in our review, and growing evidence demonstrates the sensitivity of FDCR signals to detect intervention effects

in the striatum,[46,47] amygdala[55,56], prefrontal cortical regions,[57,58] insula,[58] and cingulate cortices[59,60]—all regions widely implicated in SUDs. Given the importance of interventional FDCR studies, a more detailed breakdown of intervention types is presented in eFigure 9 in the Supplement.

Finally, an FDCR biomarker could be validated as a surrogate end point if it can be shown that FDCR causally mediates the therapeutic impact of an intervention on clinical outcomes.[10] Particularly salient examples from drug development are the use of blood pressure reduction to assess the effectiveness of antihypertensive medication or the reduction of hemoglobin A_{1c} as a surrogate marker for the effectiveness of diabetes treatments.[10] Surrogate FDCR end points would accelerate drug development, as a candidate therapeutic could be approved based on its immediate impact on the FDCR signal without the need to measure clinical outcomes over much longer time spans. Such FDCR markers may at least serve in the rapid screening of candidate therapeutics, for example, in the context of fast-failtrials, which only proceed if the intervention changes an FDCR response biomarker.[61] Relatedly, FDCR markers that are linked to clinically relevant outcomes, such as craving, may provide direct and personalized targets for direct intervention. A total of 10 studies (2.4%) in our database used neurofeedback where participants learned to directly reduce their cue reactivity in regions where they showed high FDCR, such as the striatum[62] or highly reactive cortical areas.[63] Our review includes only 12 neuromodulation studies that used FDCR. However, none used FDCR for target selection directly, which is possible in principle since the modulation of FDCR signal by brain stimulation has been shown to predict craving reduction after stimulation.[51] Indeed, 1 retrospective analysis (published shortly after the period of coverage of this systematic review) suggests that transcranial magnetic stimulation might be more clinically effective in treating alcohol used is order if the transcranial magnetic stimulation–induced electric field overlaps with an individual's endogenous alcohol cue reactivity map.[64]

Validation of FDCR Biomarkers

Specified FDCR biomarkers need validation for regulatory approval.[9,14] Clinical validation requires demonstrating etiological links between the FDCR signal and an SUD. Our reviewed studies have investigated relationships between cue exposure–associated neural activation patterns and other facets of SUDs, and this converging evidence helps buttress the clinical validity of FDCR by showing that it is linked to self-reported measures of craving (128 studies; eFigure 10 in the Supplement) and behaviors such as attentional bias and reward responsiveness,[65,66] physiological responses such as increased skin conductance during drug cue exposure,[67] and variants in genes related to glutamate, opioid, and dopamine signaling[17,68] thought to be involved in addiction. For example, neurogenetic studies suggest that the *A118G* single-nucleotide variant of the μ opioid receptor (*OPRM1*) gene and the 9R allele of the dopamine transporter gene (*DAT1*) may result in higher levels of FDCR,[69,70] and a large clinical experiment showed subsequently that both alleles interact to influence both FDCR and its reduction following naltrexone administration in alcohol-dependent individuals.[71] This body of literature can be leveraged together with future FDCR investigations using robust longitudinal designs and extensive phenotypic and clinical profiling to establish the clinical validity of an FDCR biomarker.

Next, analytical validation requires establishing that an FDCR biomarker has appropriate accuracy and reliability within the proposed COU.[13] While some recent evidence supports the reproducibility[72] and predictive accuracy[73] of certain FDCR patterns, many fMRI tasks experience low test-retest reliability,[74,75] and recent findings point to a similar challenge for FDCR.[76] This highlights the need to systematically improve FDCR measurement and identify signal patterns optimal for biomarker development. Further, moving from group-level effects to biomarkers for individual-level decision-making requires the definition of normative signal ranges across contexts and groups; for example, some FDCR studies define individuals with high FDCR as those whose FDCR value is greater than the median of study participants.[49] Such studies support further investigation to systematically establish a normative range to determine which individuals have abnormally high or low regional FDCR.

One way to establish normative FDCR bounds and design FDCR biomarkers with optimal analytic properties would be meta-analysis and mega-analysis across previous studies, exemplified by a meta-analysis that demonstrated that short-duration cues in event-related designs may induce more reliable FDCR than longer cue presentations in blocked designs.[77] However, meta-analyses of previous studies should account for publication bias, flexible reporting and interpretation of results, and the fact that published findings may be the result of posthoc, exploratory investigation. The very low rate of nonsignificant results in our database (Figure 2; eFigure 10 in the Supplement) is likely in part driven by these factors, which affect neuroscience research more broadly.[78] More insight into the analytic properties of various FDCR-derived measures would also enable appropriate task design; for example, without estimates of effect size and power analysis, it is unclear whether the median FDCR task duration of 720 seconds in our database is sufficient given usual repetition times.

Finally, practical use of FDCR-derived biomarkers in clinical or drug development contexts requires that their cost-effectiveness be demonstrated. Given the costs of fMRI and potential harms of false-negative or false-positive results, FDCR-derived biomarkers should be capable of feasibly and meaningfully complementing indicators that are often less expensive to measure, such as self-reported addiction severity or behavioral phenotypes. This requires explicit cost-benefit modeling in future FDCR biomarker development studies and attempts to make FDCR more cost-effective by optimizing study designs for sample sizes, scanning procedures, and scan durations. It is also important to select biomarker types likely to offer the greatest utility. For example, diagnostic biomarker development may be foundational but unlikely to offer clinical utility outweighing the costs, and the criterion standard of diagnosis will likely remain clinical interviewing. FDCR biomarkers may be much more cost-effective for prognosis, treatment selection, and intervention development, for which alternative markers are less available.

We discuss 2 particularly promising FDCR markers in the Box,[8,46–49,68,73,79–87] one reflecting global cue-related brain activity and the other local activation. Both examples demonstrate how validating evidence can converge across COU.

Conclusions

A growing number of biomarkers are widely used in biomedical research and clinical practice, but their role remains mostly limited in addiction medicine and psychiatry more broadly.[88] This article provides an overview of FDCR research, a promising paradigm for biomarker development for addictive disorders. FDCR biomarkers could classify patients, have prognostic value, improve treatment selection, and facilitate intervention development and personalized care. The field faces multiple important challenges, and while we have highlighted methodological heterogeneity, small sample sizes, and a lack of systematic biomarker development and validation efforts, a limitation of the present study that should be addressed in future work is that FDCR studies vary widely in reporting and methodological quality, particularly in terms of statistical practices, such as multiple comparison correction. Ultimately, biomarker specification and validation efforts will likely require moving beyond traditional single-site studies and may involve rigorous mega-analyses using in frastructure developed by initiatives such as the ENIGMA International Consortium[89] or multisite collaborations and harmonized, longitudinal assessment following examples such as the Human Connectome Project and the Adolescent Brain Cognitive Development project,[90,91] with structured expert consensus to address remaining gaps (eFigure 12 in the Supplement). Toward this aim, several of us (A. R. C., R. Z. G., A. Heinz, J. E. J., F. J. M., M. P. P., L. A. R., R. S., R. R. W., A. C. J., H. K., A. Z., and H. E.) have formed the steering committee of the ENIGMA ACRI within the ENIGMA Addiction Working Group to facilitate consensus development, methodological harmonization, and data sharing for mega-analyses.[92] Large-scale biomarker definition and validation studies would require substantial funding and resources often difficult to secure or justify for a single research institution or pharmaceutical company. This endeavor necessitates formation of diverse consortia to pool resources and guide validation efforts, develop best practices in study design and reporting, and engage in ongoing dialogue with commercial and public health stakeholders. Ultimately, there will be a need to form public-private partnerships that inform future biomarker development studies and systematically approach the arduous task of translating FDCR-derived biomarkers to clinical use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

What is the current status of functional magnetic resonance imaging drug cue reactivity (FDCR) research, and how could it support the discovery of biomarkers to facilitate intervention development and clinical care for substance use disorders?

Findings

In this systematic review including 415 FDCR studies, results from 357 studies could potentially help develop diagnostic, prognostic, susceptibility, severity, monitoring, predictive, or response biomarkers. Substantial heterogeneity in task and study design was identified that can hinder biomarker development.

Meaning

A sizable literature supports the development of FDCR-derived biomarkers, but moving forward requires large-scale collaboration, methodological harmonization and optimization, and clinical and analytical validation.

Box.

Local and Global Functional Magnetic Resonance Imaging Drug Cue Reactivity (FDCR): 2 Exemplar Cases

We highlight 2 examples of promising FDCR signals across contexts of use:

A robust FDCR biomarker would likely be useful across multiple contexts of use and would also be supported by converging avenues of validating evidence. A promising regional marker is striatal FDCR, which meets several important characteristics of a putative neural biomarker in AUD. In a diagnostic context, several studies have reported significant differences in striatal FDCR between individuals with and without AUD[79,80] and a ventral to dorsal striatum FDCR shift with more compulsive alcohol use.[81] There is support for the prognostic potential of striatal FDCR, with several studies demonstrating significant associations with subsequent alcohol use and relapse in AUD[8,47,68,82] and increases in relapse prediction accuracy of machine-learning models, over and above clinical variables.[73] In addition, converging evidence indicates that striatal FDCR is sensitive to behavioral AUD treatments, such as cue exposure therapy or drugs such as naltrexone[46,47] or nalmefene,[83] illustrating that longitudinal assessment of striatal FDCR can monitor treatment effects. Further, acquiring striatal FDCR before treatment predicts naltrexone treatment response, such that individuals with high striatal FDCR benefited more from naltrexone,[48] supporting the predictive potential of striatal FDCR. This finding was replicated in an independent sample[49] and could be expanded to positive (ie, higher response to alcohol cues) vs negative (ie, higher response to neutral cues) FDCR in striatal regions,[47] indicating that absolute levels of striatal FDCR can be used to predict treatment efficacy across datasets.

With the advent of machine learning techniques capable of discovering robust patterns of activity distributed across the brain, it is possible to develop FDCR biomarkers that reflect neural processes involved in FDCR beyond a single region. This would be in line with the growing understanding that neural processes are often under-girded by distributed brain networks[84] and that multivariate brainwide association studies may require smaller samples to discover brain-behavior relationships.[85] There have been a few attempts to date to use FDCR to create and validate a whole brain–based biomarker in SUDs.[86] In a recent example, machine learning on FDCR data from individuals with alcohol, cocaine, and tobacco use disorders identified a multivariate whole-brain marker that was reliably associated with drug craving, accurately classified individuals with SUDs from healthy controls, detected responses to interventions, and mediated the effects of intrinsic visual craving features on craving ratings.[87] While the authors noted that additional (ongoing) validation is required, current evidence supports the clinical and analytical validity of this multivariate marker as a diagnostic and response biomarker.

Abbreviations: AUD, alcohol use disorder; SUD, substance use disorder

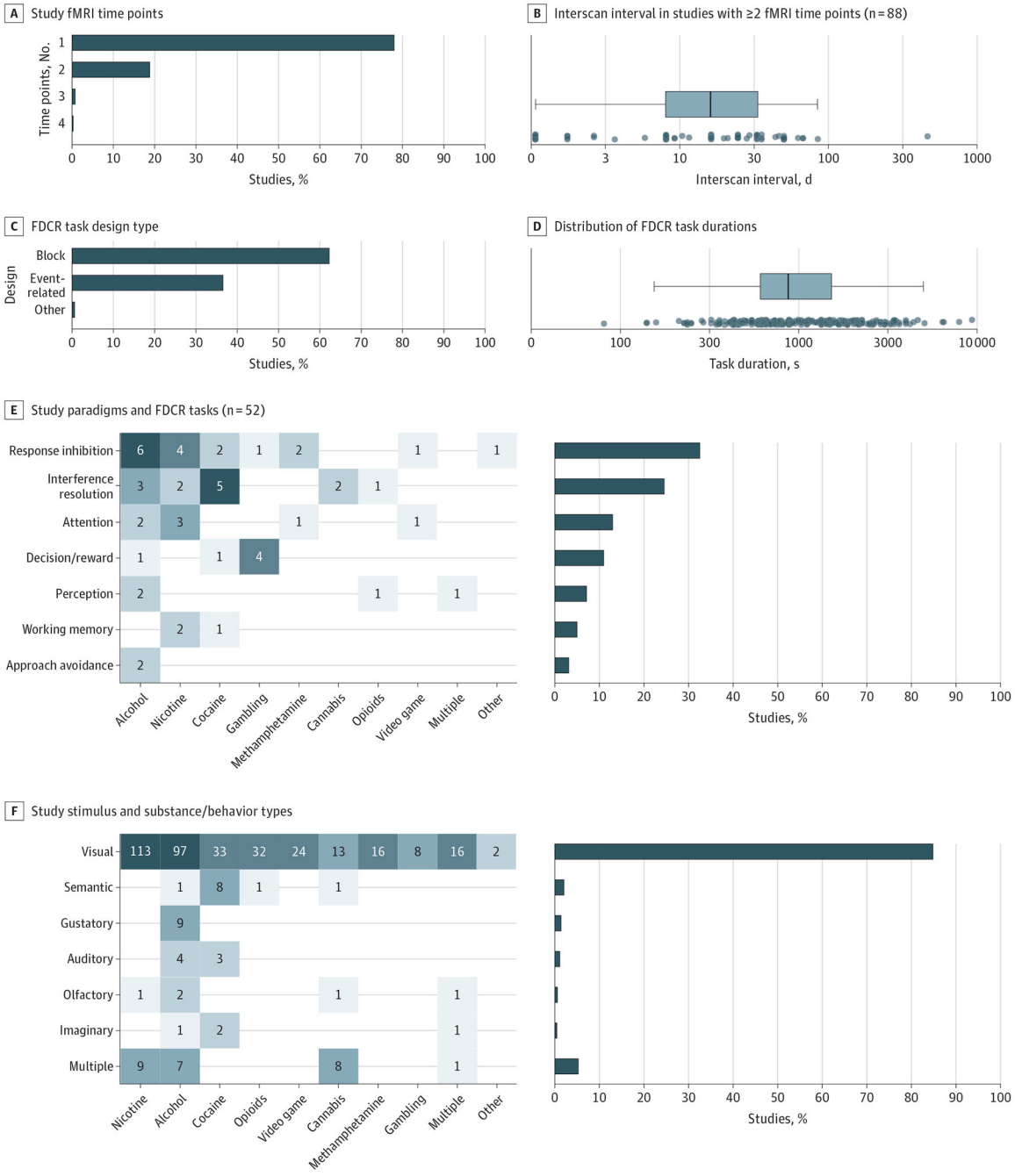

Figure 1.

Task and Study Design Features of Functional Magnetic Resonance Imaging (fMRI) Drug Cue Reactivity (FDCR) Studies

A, Number of time points in FDCR studies. A total 327 studies scanned participants at 1 time point, 81 studies at 2 time points, 6 studies at 3 time points, and 1 study at 4 time points. B, Boxplot representing the distribution of median interscan intervals (in days) for FDCR studies with more than 1 scanning session. Ten studies scanned individuals more than once within the same day (interval of 0 days). The midline indicates the median; the

box, first and third quartile; whiskers, 1.5-fold the IQR; and points, individual data. C, Main FDCR task design type. D, Boxplot of the distribution of FDCR task durations. E, Paradigms and FDCR tasks of 52 studies in the database. F, FDCR studies by stimulus and substance/behavior type. The multiple category includes studies including more than 1 type of addictive substance/behavior. The other category includes inhalants and betel quid chewing.

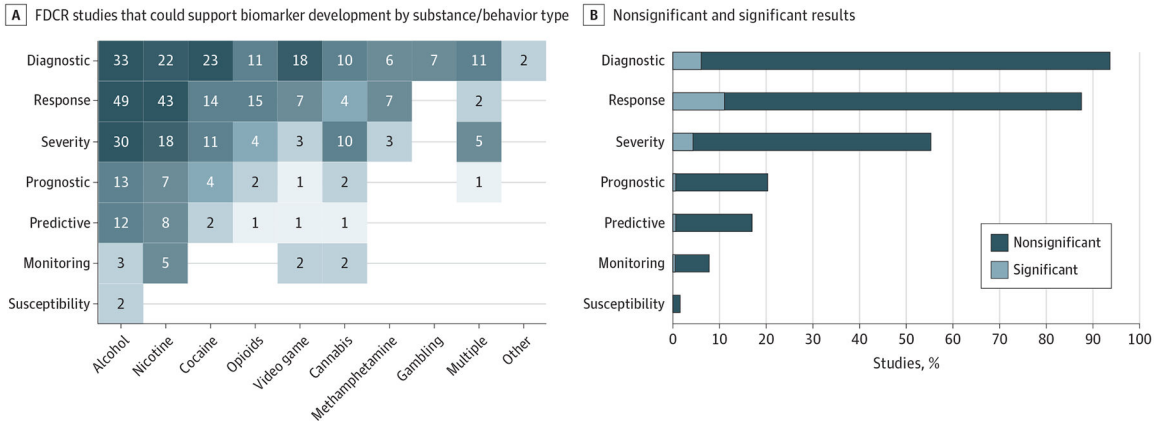

Figure 2.

Seven Functional Magnetic Resonance Imaging Drug Cue Reactivity (FDCR) Study Types A, FDCR studies that, by virtue of their study design, could theoretically support the development of each biomarker type by substance or behavior of interest. Note that all cells do not sum to 415 since some studies do not fit the biomarker framework and some studies fit multiple biomarker types. B, The number of significant and nonsignificant biomarker-related findings. The other category includes inhalants and betel quid chewing.

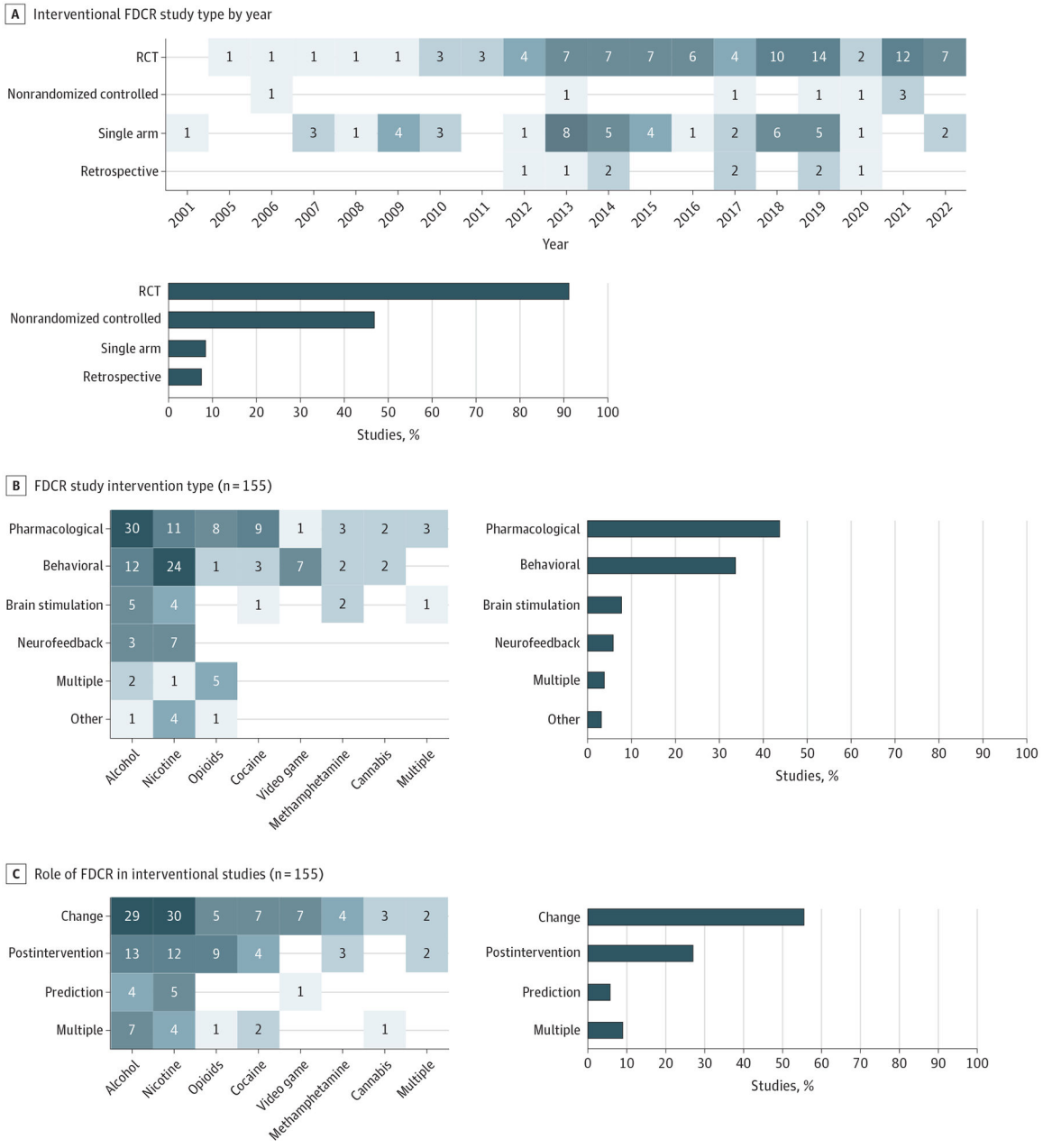

Figure 3.

Functional Magnetic Resonance Imaging Drug Cue Reactivity (FDCR) Studies With an Intervention or Manipulation

A, Types of interventional FDCR studies by year, including randomized clinical trials (RCTs), nonrandomized controlled trials, single-arm trials, and retrospective studies. B, FDCR studies intervention type. C, Role of FDCR in interventional studies. FDCR can be measured before an intervention to predict intervention results or measured after an intervention to assess impact with or without a comparison with baseline FDCR.

Table.

Potential Functional Magnetic Resonance Imaging Drug Cue Reactivity (FDRC)–Based Biomarker Domains, Their Definitions, and Sample Studies That Provide Supporting Evidence for Biomarker Development[a]

Biomarker type	Description	Examples of studies that can provide supporting evidence for biomarker development
Susceptibility	Indicates the potentialfor developing a disease or medical condition in an individual who does not currently have the clinically apparent disease or medical condition	Baseline cue reactivity in the ventromedial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, striatum, and insula was greater in individuals who subsequently transitioned from moderate to heavy drinking compared with those who did not transition[37]
Diagnostic	Detects or confirms the presence of a disease or condition of interest or identifies individuals with a subtype of the disease	Individuals with SUDs vs healthy controls • Individuals with cocaine use disorder showed higher FDCR compared with controls in a frontoparietal network[38] • Individuals with cocaine use disorder compared with people with recreational stimulant use showed greater orbitofrontal and anterior cingulate FDCR during a cocaine cue Stroop task[39] SUD subtyping • Among people with heavy alcohol consumption, relief drinking (due to negative reinforcement or habit) compared with reward drinking (due to positive reinforcement) was associated with greater dorsal striatal FDCR[40] • Individuals with cannabis use disorder and early-onset cannabis use showed FDCR in the dorsal striatum, while those with late-onset use showed FDCR in the ventral striatum[41]
Severity	Is correlated with greater intensity of the disease	In individuals with opioid use disorder, baseline FDCR in the nucleus accumbens, orbitofrontal cortex, and amygdala was associated with drug use severity (Addiction Severity Index Drug Composite Score), and withdrawal symptoms mediated the relationship between nucleus accumbens FDCR and drug use severity[42]
Prognostic	Identifies the likelihood of a clinical event, disease recurrence, or progression in patients who have the disease or medical condition of interest	Among individuals with stimulant use disorder, baseline FDCR in the nucleus accumbens was prospectively associated with time to relapse and could classify individuals into those who would relapse and those would not at 3mo after the scan, with an accuracy outperforming predictions using self-reported and clinical measures[43]
Monitoring	Is measured repeatedly for assessing the status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or environmental agent	Naturalistic monitoring • Among women with tobacco use disorder, frontal, temporal, and parietal regions showed FDCR during the follicular phase of the menstrual cycle but not the luteal phase[44] • Among participants with internet gaming disorder observed for 1 y, natural recovery from internet gaming disorder was associated with decreased anterior cingulate and lentiform FDCR and an increase in cue-related effective anterior cingulate cortex-lentiform connectivity[45] Treatment monitoring • In a randomized placebo-controlled trial of individuals with alcohol use disorder, naltrexone lowered ventral striatal FDCR from baseline, and more FDCR reduction was associated with greater clinical response[46]
Predictive	The existence or intensity of the biomarker reflects the propensity of individuals to experience favorable or unfavorable effects	• In individuals with alcohol use disorder, the existence of left putamen FDCR at baseline and the reduction of left putamen FDCR early during treatment predicted the effectiveness of naltrexone[47]

Biomarker type	Description	Examples of studies that can provide supporting evidence for biomarker development
	from exposure to a medical product or environmental agent	• In individuals with alcohol use disorder, high baseline FDCR in the ventral striatum statistically predicted response to naltrexone[48]; notably, this finding has been directly replicated[49]
Response	Shows that a biological effect has occurred in an individual exposed to a medical product or environmental agent	Biological response • In a randomized placebo-controlled trial of individuals with cocaine use disorder, modafinil acutely reduced FDCR in the ventral tegmental area and increased FDCR in the anterior cingulate and putamen, eliminating differences between participants with cocaine use disorder and healthy control participants[50] Potential surrogate end point • In a randomized sham-controlled trial involving people with tobacco use disorder, active vs sham transcranial direct current stimulation over the dorsolateral prefrontal cortex) increased cue-related functional connectivity between the dorsolateral prefrontal cortex and the parahippocampus, and this increase was correlated with decreased cigarette craving[51]
Safety[b]	Is measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxic adverse effects	Contributing to discussions on the safety of electronic cigarettes, FDCR showed that electronic cigarette smoking may immediately increase FDCR.[52] Furthermore, sweet taste and nicotine content may synergistically influence the nucleus accumbens FDCR to the sight and smell of electronic cigarettes.[23] Safety FDCR biomarkers may overlap with prognostic or response biomarkers in the context of SUDs, since SUDs involve the use of substances whose safety maybe assessed using FDCR

Abbreviation: SUD, substance use disorder.

[a]All the definitions for biomarkers have been directly adapted from the Biomarkers, Endpoints, and Other Tools Glossary, except for severity biomarkers (defined based on previous biomarker literature, as discussed).

[b]Note that potential FDCR-derived safety biomarkers were very rare in the database and thus have not been included as a separate category in other figures.