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Biomarkers in Substance Use Disorders

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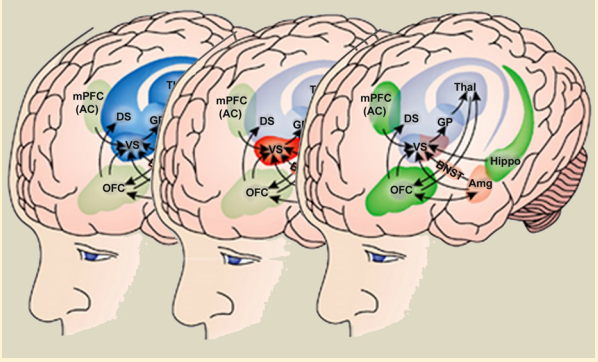
ABSTRACT: The prevention and treatment of substance use disorders (SUDs), including addiction, would benefit from having better biomarkers for the classification of patients into categories that are reproducible and have predictive validity. Direct measurement of drugs or their metabolites in various body fluids constitutes a clinically valuable biomarker but one that can only be used to corroborate acute or relatively recent drug use. Thus, there is an urgent need for biomarkers that reflect chronic drug exposure as well as biomarkers that predict or correlate with disease trajectories and treatment responses. Advances in tools and technologies to investigate genetics, epigenetics and epitranscriptomics, and human brain function and neurochemistry (brain imaging tools including EEG) offer unprecedented opportunities for the development of such biomarkers. Progress in this area will not only enhance our ability to screen and treat patients with SUDs but also accelerate research on the neurobiological processes that underlie SUDs.



KEYWORDS: *Addiction, dopamine, MRI, PET, EEG, endophenotype, genetics, epigenetics*

Substance use disorders (SUDs) are only one of the mental illnesses for which there is a clear diagnostic biomarker: quantification of drugs in bodily fluids, like urine, saliva, and plasma, is the most accurate biomarker that we currently have to determine whether a person has consumed a drug. In this respect, this biomarker has been very useful for assessing abstinence among treatment seeking substance abusers and to evaluate therapeutic benefits in clinical trials for medication development. It has also been valuable for legal purposes in evaluating the potential contribution of cognitive impairment in accidents and violent crimes. However, its value is restricted by the pharmacokinetics of drugs in the body, which limit their detection to the state of intoxication and cannot be used to differentiate between a chronic and an isolated pattern of drug use. Measurement of drugs in hair has been developed as a biomarker of chronic drug exposures, and more sensitive methods are being developed to facilitate its clinical use.[1] However, drug levels as measured in blood, urine, or hair are limited in their ability to predict clinical outcomes or processes that relate to the neurobiology of the disease. Thus, the development of biomarkers that can be used to assess chronic drug exposures as well as to identify neurobiological processes that contribute to SUD and the symptoms associated with it would be valuable both for clinical and research purposes. To be more specific, a heuristic framework is needed to link the major underlying domains of dysfunction with changes in the neurobiological circuits associated with different stages of the addiction cycle (intoxication/binge, withdrawal/negative affect, and preoccupation/rumination). Measures to be linked with brain imaging may range from biological peripheral markers of chronic drug exposures (i.e., epigenetic or epitranscriptomic marks), to genetic markers for vulnerability, to measures of performance on neurocognitive tests that reflect changes in brain circuitry.

MOLECULAR BIOMARKERS

Molecular biomarkers take advantage of advances in genomics, epigenomics, metabolomics, transcriptomics, and more recently epitranscriptomics. The investigation of genes (genomics) has strived to assess whether they could serve as biomarkers of vulnerability or resilience to SUDs or predictors of treatment responses. On the other hand, investigations of the epigenetic modifiers of gene expression (epigenomics) and of gene products (trasncriptomics, proteomics) have focused mainly on the molecular modifications and changes in expression profiles triggered by both acute and chronic drug exposures. Although most of these studies have focused on the brain, others have evaluated effects on peripheral tissue (blood cells, plasma, skin) because of their translational potential as biomarkers for chronic drug exposures and for quantifying the toxic effects of drugs.

Genetic studies have been facilitated by advances in sequencing technologies and the robust evidence that genes contribute to close to half of the risk for SUD.[2] Genetic contributions to SUD risk operate at many phenomenological levels, including developmental, physiological, and behavioral processes as well as through their interactions with environmental factors, including drug exposures. The strongest genetic

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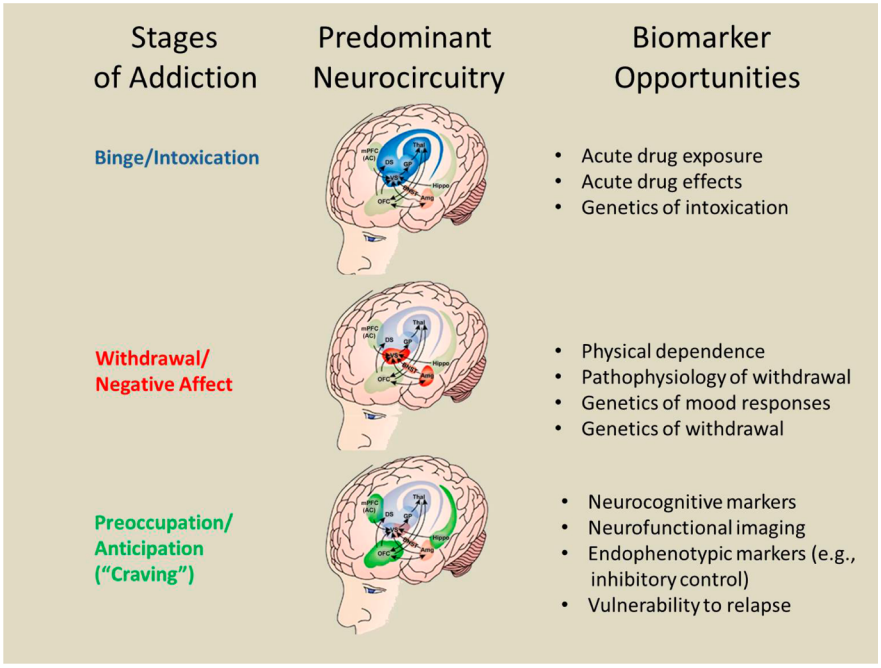

Figure 1. Schematic model of the three stages that the neural circuitry implicated in addiction can go through as it transitions from drug experimentation to addiction. *Binge/intoxication stage (blue).* Reinforcing effects of drugs may engage reward neurotransmitters and associative mechanisms in the nucleus accumbens shell and core and then engage stimulus−response habits that depend on the dorsal striatum. *Withdrawal/ negative affect stage (red).* The negative emotional state of withdrawal may engage the activation of the extended amygdala. *Preoccupation/anticipation (craving) stage (green).* This stage involves the processing of conditioned reinforcement in the BLA and the processing of contextual information by the hippocampus. Executive control depends on the prefrontal cortex and includes representation of contingencies, representation of outcomes, and their value and subjective states (i.e., craving and, presumably, feelings) associated with drugs. The subjective effects termed drug craving in humans involve activation in functional imaging studies of the orbital and anterior cingulate cortices and temporal lobe, including the amygdala. Some of the opportunities for biomarker research spurred by the delineated stages are indicated to the right of the figure. For more details on this model, see ref 41. Reprinted with permission.

signals have emerged for genes that offer protection against SUD; this is the case for genes encoding for enzymes that metabolize drugs, of which, two of the best characterized are alcohol and acetaldehyde dehydrogenases.[3] However, for genes that increase risk, studies have identified a large collection of genes or genomic regions that appear to modulate overall risk through small effects.[4] These include genes that encode molecular targets for the various substances of abuse (e.g., dopamine, GABA, glutamate, opioid, nicotinic, and cannabinoid receptors) and whose many variants constitute the frontlines in the response to drugs.[5] Genes can also modulate addiction risk through their influence on endophenotypic traits, such as stress reactivity, novelty seeking, and behavioral disinhibition/ impulsivity.[6] Genetic variation can also affect the nature or likelihood of epigenetic modifications that have emerged as a critical element for understanding how chronic drug exposure is connected to long lasting changes in synaptic strength, neurotransmitter signaling, conditioning, and cognitive performance.[7]

In parallel, ongoing efforts are being exerted to catalogue the effects of drugs on epigenetic changes (epigenome),[8] in RNA modifications (epitranscriptome),[9] protein expression (transcriptome), and other molecules (metabolome),[10] in polypeptides (proteome),[11] and in all their interactions. The potential value for biomarkers that take advantage of epigenomics and epitranscriptomics is in its infancy.

NEUROBEHAVIORAL BIOMARKERS

It is well established that drug addiction has also been associated with general hypofunction of the ventral prefrontal cortex.[12,13] Given the key role of the ventral prefrontal cortex in processing the consequences of future actions,[14] inhibition of actions,[15] and control of emotions,[14] specific neurobehavioral tests that measure various components of impulsivity and stress reactivity may also serve as biomarkers. Already in the alcohol field, specific patterns of responses on neurobehavioral tests correlate well with a diagnosis of fetal alcohol syndrome.[16] Hypothetically such a refinement of tests, combined with imaging studies and the use of big data, will allow a "composite" neurobehavioral biomarker of predictive value.

NEUROLOGICAL BIOMARKERS

The Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases are the criteria traditionally used to classify substance use disorders (SUDs) as well as the other mental illnesses and are based on symptom presentation. These criteria have heuristic value since they serve to guide the limited treatment interventions that are available for psychiatric diseases including addiction. However, these classification systems are not based on neurobiological mechanisms, which are currently unknown for most mental illnesses. Diverse neurobiological mechanisms triggering a common constellation of symptoms are likely to contribute to the heterogeneity of presentations among mental illnesses. For SUDs, the heterogeneity can manifest itself with respect to the type of drugs abused (i.e., sedative type versus stimulant

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type drugs; single drug versus drug combinations), the severity of the disorder (mild to severe), its trajectory (relapsing versus continuous), the symptoms that trigger relapse (craving versus dysphoria), and comorbid conditions (mood disorder, ADHD, PTSD). Although a better understanding of the biological and neuronal mechanisms involved in SUDs would likely facilitate personalized interventions, the lack of knowledge hinders our ability to use it for classification and research. Hence, the alternative is to do research that characterizes the biological and neuronal signatures that are associated with diverse clinical presentations and outcomes in individuals suffering from SUD.

In this respect, brain imaging has been a very valuable tool for it has helped identify many neuronal circuits implicated in the transition from drug experimentation to addiction (Figure 1). To the extent that the dysfunction of any one circuit varies from patient to patient, it can serve as a target to design interventions that either strengthen the disrupted circuits or recruit healthy ancillary circuits to help compensate the deficit. In this respect, interventions that target, for example, the strengthening of executive function via mindfulness meditation[17] or repeated transcranial magnetic stimulation (rTMS)[18] have shown promising results *vis á vis* the ability of substance abusers to decrease drug use.

Similarly, neurochemical imaging, as done with positron emission tomography (PET), has also helped identify potential biomarkers that relate to phenotypes associated with higher addiction risk, as is the case for the measurement of dopamine D2 receptors (D2Rs) in the striatum. Dopamine D2Rs in the striatum modulate the response to the rewarding effects of drugs, with high levels opposing rewarding effects and low levels enhancing them.[19−21] Indeed, low D2Rs in striatum are associated with compulsive patterns of drug use and with impulsivity,[22] whereas high levels of D2R are associated with resilience.[23,24] Moreover, chronic abusers of different drugs evince deficits in striatal D2R.[25] While it would be tempting to turn this distinct deficit into a biomarker of addiction (whether it is a cause, an effect, or some combination of both), it lacks specificity (i.e., nonabusers can show low levels of D2R and its associated with impulsive phenotypes and with stress exposures).[26,27]

Another critical goal is the discovery of surrogate markers of addiction-related processes that would allow the identification of better prognostic and therapeutic targets. For example, the anterior cingulate cortex (ACC), which is involved in error processing and conflict resolution, appears to be a particularly promising target in this regard. Results of several studies suggest that strengthening ACC function (responses or circuitry) could represent a targeted approach for enhancing top-down monitoring and emotion regulation as a strategy to reduce impulsive and compulsive behavior in addiction.[28] The utility of this finding would be greatly enhanced if *peripheral* surrogates of such markers could be found that would bypass the need to sample CNS tissue. Currently, no such peripheral surrogate markers exist for the function of prefrontal brain regions such as ACC or the orbitofrontal cortex (OFC), both of which are implicated with addiction.[29] Similarly, there are currently no peripheral biomarkers that reflect striatal levels of D2R, though eye blinking was recently associated with D2R in striatum in nonhuman primates.[30] Ongoing research is being done to develop neurocognitive tasks that are predictive of prefrontal processes associated with impulsivity and compulsive phenotypes as well as tests that might predict striatal D2R expression in humans. For example, there is preliminary evidence of a connection between the status of D2R and neurocognitive variation during an attention task that discriminates between satiated and deprived smokers.[31]

Another example of a surrogate marker with the potential to improve addiction treatment has emerged from PET studies showing that disrupted DA transmission in the striatum of cocaine addicted individuals correlates not only with impulsivity and drug seeking behaviors but also with the patient's response to behavioral treatment[32] and with their risk for relapse.[33] Brain structural and functional connectivity is yet another promising research focus since many independent studies found evidence of a robust connection between cocaine induced toxicity, disruptions in fractional anisotropy, impulsivity, and impaired decision making.[34] And so is the study of both discrete and large-scale alterations in the functional coupling of different brain circuits and networks as a way to characterize key aspects of addiction, like craving,[35] cognitive effects of abstinence,[36] cue reactivity,[37] or relapse risk.[38]

The literature in this area is growing rapidly. The results are often mixed, and both replicability and predictability issues remain a serious concern.[39] These challenges are not unexpected, however, given the complexity of the problem and the multiple sources of variability. Efforts to identify and control the relevant differences in, for example, the impact of different classes of drugs on the relationship among inhibitory control, error processing, and neural activation deficits[40] may soon begin to bear translational fruit. However, the most promising approach may lie in the harnessing of "big data" and the use of hypothesis-free machine learning to classify, and eventually subclassify, at risk individuals, individual drug users, successful abstainers, and chronic relapsers. If successful, this effort could lead to a more robust understanding of addiction-driven changes in measures of brain activity, stimulus/task response, and neural connectivity that could lay the groundwork for the development of a clinically useful, quantitative biomarker that may be employed prospectively in future clinical trials.

■ SUMMARY

At the present time, there are no biomarkers of addiction severity and no reliable set of criteria that are specific enough to identify and catalogue relevant endophenotypic traits influencing addiction trajectories or clinical subtypes nor assess or predict treatment efficacy. As a consequence, it is still not possible to design, let alone provide, the type of personalized treatments that the evidence shows would be the most effective in achieving long-term recovery. Many research avenues are being explored in parallel to fill this gap, including a vast pool of bottom level biomarkers and a growing list of promising neurophysiological and neurocognitive surrogate markers. The hope is that this richly informative menu of options will soon coalesce into predictive, reliable, and affordable platforms for the improved diagnosis and treatment of substance use disorders.

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Notes

The authors declare no competing financial interest.

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