Addictions Neuroclinical Assessment: A Neuroscience-Based Framework for Addictive Disorders

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This article proposes a heuristic framework for the Addictions Neuroclinical Assessment that incorporates key functional domains derived from the neurocircuitry of addiction. We review how addictive disorders (ADs) are presently diagnosed and the need for new neuroclinical measures to differentiate patients who meet clinical criteria for addiction to the same agent while differing in etiology, prognosis, and treatment response. The need for a better understanding of the mechanisms provoking and maintaining addiction, as evidenced by the limitations of current treatments and within-diagnosis clinical heterogeneity, is articulated. In addition, recent changes in the nosology of ADs, challenges to current classification systems, and prior attempts to subtype individuals with ADs are described. Complementary initiatives, including the Research Domain Criteria project, that have established frameworks for the neuroscience of psychiatric disorders are discussed. Three domains—executive function, incentive salience, and negative emotionality—tied to different phases in the cycle of addiction form the core functional elements of ADs. Measurement of these domains in epidemiologic, genetic, clinical, and treatment studies will provide the underpinnings for an understanding of cross-population and temporal variation in addictions, shared mechanisms in addictive disorders, impact of changing environmental influences, and gene identification. Finally, we show that it is practical to implement such a deep neuroclinical assessment using a combination of neuroimaging and performance measures. Neuroclinical assessment is key to reconceptualizing the nosology of ADs on the basis of process and etiology, an advance that can lead to improved prevention and treatment.

The problem of etiologic and functional heterogeneity among patients addicted to the same agent is not new. It has long been recognized that these common diseases are etiologically heterogeneous and that dichotomous affected/unaffected classifications fail to capture severity and distinctiveness of addictive disorders (ADs). A revolution in understanding the neurobiologic basis of addiction has not been translated into the clinic. Translation of neuroscience to practice would identify the etiologic factors and functional outcomes that unify people addicted to different agents and that differentiate people addicted to the same agent. Moreover, the lack of assessments of these neurobiologic domains in people has impeded genetic, ecologic, and clinical translational research. Changes in the classification of ADs have not, arguably, advanced this nosology appreciably in several decades.

Attempts to identify meaningful subtypes of ADs have predominately focused on alcohol use disorders (AUDs). Jellinek (1), Cloninger, Babor, Lesch, and others [see (2) for a comprehensive review] have clinically subclassified alcoholism. Other addictive agents, including cocaine (3,4), opioids (5), club drugs (6), and cannabis (7,8), have been the focus of

similar efforts. Despite this work, there remains little consensus in the field regarding subtypes of various ADs. We propose this lack of agreement is because classification schemes have been limited by measures available.

This review proposes a framework and rationale for the Addictions Neuroclinical Assessment (ANA). It is our aim to establish such a framework and rationale with present knowledge of the neurobiologic basis of addiction, gleaned from humans and model organisms. Three main neurofunctional domains, executive function, incentive salience, and negative emotionality, should be assessed in patients with addictions, including behavioral addictions (process addictions as defined by the American Society of Addiction Medicine, e.g., gambling), and in individuals at risk, for purposes of better understanding the heterogeneity of ADs and eventually to improve the nosology. Other measures of exposure to addictive agents and use (e.g., impulsive, habitual, and compulsive) and related phenomena, genetics, and agent-specific outcomes would be closely integrated with measures of neuroscience domains whose importance we hypothesize transcends any particular addictive agent.

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CHANGES IN NOSOLOGY

The diagnosis of ADs has shifted over time, while adhering to a focus on clinical presentation rather than etiology. This emphasis has not been without benefit. The ability to diagnose ADs by clinical criteria has provided a reliable foundation for the practice of addiction medicine. It has also been a springboard for neuroscience and genetic studies and clinical trials that have yielded insights on ADs, e.g., neural mechanisms (9), genetics (10), and treatment (11).

In the most recent version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (12), ADs are grounded in clinical-life outcomes both because of the relevance of symptom-based diagnoses as indicators of impairment and need for intervention and because of lack of evidence-based alternatives. Properly assessed using DSM symptoms, ADs have high interrater reliabilities (13); furthermore, factor analyses show that on a statistical basis, they are internally coherent or valid (14). These virtues, while important, are insufficient. A diagnosis with high interrater reliability is not necessarily useful if the diagnosis is heterogeneous. AD diagnosis is based on endorsement of symptoms in several domains of life impact. In contrast with most medical diagnoses, the nosology and diagnosis of AD is outcome-based rather than process-based. Such a deficiency is shared by other psychiatric disorders, as discussed in Charney *et al.* (15). In identifying a research agenda for the then under development DSM-5, Charney *et al.* (15) outlined the need for a neuroscience-based framework to foster development of psychiatric nosology based on pathophysiology, rather than clinical presentation.

Translating Etiology Into Clinical Practice Across Clinical Diagnostic Categories

By way of comparison, a diagnosis of cancer affecting any particular organ is diagnosed using cellular, genetic, molecular, and imaging measures, combined with clinical history. Progress in treatment and prevention, e.g., the utility of trastuzumab (a monoclonal antibody interfering with the HER2/neu receptor) in the treatment of certain breast cancers (16) or the ability of the *BRCA1* (a gene producing tumor-suppressing proteins) genotype to predict enhanced risk of breast cancer (17), has occurred because of integration of these measures with clinical history. The clinical observations are irreplaceable but do not themselves replace the need for physiologic data in the form of an imaging, genetic, or molecular measure.

Addiction diagnoses reimagined and informed by mechanistically relevant measures, whether from neuroimaging, genetics, and/or epigenetics, are at present precluded by lack of deep data on individuals with ADs and others at risk. Pharmacotherapies to treat addictions provide one example of how present nosology impacts outcomes. For example, there are three Food and Drug Administration–approved medications to treat alcoholism: acamprosate (approved 2004), naltrexone (approved 1994), and disulfiram (approved 1951). Behavioral treatments including cognitive behavior therapy, motivational enhancement therapy, 12-step facilitated therapy, and behavioral couples/family therapies also have efficacy (18,19). To a limited extent, these behavioral treatments and medications appear to target different neurobiological components of the addiction cycle, e.g., naltrexone is an opioid antagonist and is hypothesized to target the rewarding effects of alcohol (20,21), whereas acamprosate antagonizes *N*-methyl-D-aspartate function and metabotropic glutamate receptors and is hypothesized to target craving associated with alcohol acute and protracted withdrawal (22–24). A mechanistically informed nosology may enable identification of improved treatment options and better matching to treatments.

Cloninger's tridimensional personality theory for AUDs (25), with three corresponding neurofunctional systems, was one of the first efforts to reimagine an addictions diagnosis on the basis of process and to propose a method for measuring the relevant domains. A main limitation of Cloninger's scheme (25) was that only a personality questionnaire was available to access the target processes, and as will be seen later, subsequent addiction neuroscience investigations over the past two decades have led to a somewhat different conceptualization of the neurofunctional domains involved in addiction.

The Research Domain Criteria (RDoC) (26) initiative from the National Institute of Mental Health is a broad framework relevant to multiple psychiatric disorders. RDoC is intended to advance the goal of a neuroscience-based research framework for psychiatric diseases (12). Recently, an RDoC framework modified for alcoholism, Alcohol Addiction Research Domain Criteria (AARDoC), was proposed (27). Both RDoC and AARDoc, like Cloninger's tridimensional personality structure (25), are research frameworks within which specific functional domains can be positioned and prioritized. Building on AARDoC, we propose a clinical framework for the assessment of addictions: the ANA. The ANA will provide the heuristic framework for measures of neurobiologic/neuropsychologic functions in ADs and begin to address the practical problem of specifying a panel of instruments that may be widely used by researchers.

THE NEED FOR THE ANA

Addictive disorders are a public health crisis. The 2013 National Survey on Drug Use and Health estimated that 20.3 million adults had a substance use disorder, approximately 8.5% of the population (28). Some 1.3 million adolescents, or 5.2% of the US adolescent population, had a substance use disorder (28). Behavioral addictions are similarly pervasive; between 1% and 3% of US individuals engage in pathological gambling, with high rates of comorbid psychiatric disorders among those who do (29). Availability of treatments for ADs is limited, e.g., approximately 80% of individuals with alcoholism (30) and close to 90% percent of individuals with pathological gambling do not receive treatment (31). While the Food and Drug Administration–approved medications discussed above have efficacy, less than 4% of individuals use any medication for an alcohol use disorder (32). Because of advances in technology and our understanding of neuromechanisms of addiction, meshing neuroscience-based assessments with clinical measures appears feasible and imperative. Such an approach will build upon existing treatment options to find ones that are more targeted toward the individual.

Table 1. Comparison of ANA and Related Initiatives

	ANA	RDoC	iRISA	IMAGEN	PhenX	CNTRICS
Neuroscience Domains	✓	✓	✓	✓		✓
Standardized Assessment Package	✓			✓	✓	✓
Disseminate Package to Various Settings	✓			✓	✓	✓
Identify Meaningful Subtypes of Disorder	✓	✓				✓
Describe Individualized Treatments	✓					✓

ANA, Addictions Neuroclinical Assessment; CNTRICS, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia; iRISA, Impaired Response Inhibition and Salience Attribution; RDoC, Research Domain Criteria.

SIMILAR INITIATIVES

For addictions and other psychiatric disorders, partially overlapping conceptual frameworks and approaches are in place and underway worldwide. Knowledge gained from these may be brought to bear in designing the ANA. We have identified five of particular relevance: RDoC (26), Impaired Response Inhibition and Salience Attribution (iRISA) (33), IMAGEN (34), PhenX (35), and Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (36). We discuss each briefly, and compare the initiatives in Table 1.

RDoC originated as part of the National Institute of Mental Health 2008 strategic plan. The goal of RDoC is to create a research framework for studying psychiatric disorders. Grounded in neuroscience research, this framework spans five domains: negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal and regulatory systems. The domains are further organized by units of analysis, ranging from genes to paradigms (see http://www.nimh.nih.gov/research-priorities/rdoc/research-domain-criteria-matrix.shtml for an overview of the RDoC matrix). The ANA captures information in three of five RDoC domains. A major difference between the two is that RDoC serves as a research framework rather than a clinical framework. Many publications have expanded on conceptual and methodological implications of RDoC [e.g., (26,37–40)].

iRISA, as described by Goldstein and Volkow (33,41), identifies disruptions in neural circuits that relate to ADs, with an emphasis on response inhibition and salience attribution. The iRISA model presents an addiction cycle of intoxication, bingeing, withdrawal, and craving and identifies the underlying neural disruptions with an emphasis on neuroadaptations and maladaptations in the prefrontal cortex (PFC) associated with each phase of the process. The framework presented in iRISA and emphasis on disruptions in PFC function for ADs are relevant to all three of the domains that will be assessed in the ANA.

The IMAGEN consortium, including collaborators from multiple European nations, has as its goal the identification of neurally based predictors of increased risk for developing ADs (http://www.imagen-europe.com). IMAGEN has recruited approximately 2000 adolescents, who are being longitudinally followed. The standard neuroimaging battery includes measures of reward, emotion recognition, response inhibition, and general cognition. Other measures include neuropsychological testing and blood collection for genomic analyses. Publications using the IMAGEN sample range from data analytic methods (42,43) to imaging-genetic findings related to reward, oxytocin function, and others (44–46) and behavioral findings (47,48). Unlike RDoC, IMAGEN does not seek to establish a framework of neurobiologic domains but identifies useful assessments.

PhenX seeks to standardize the measurement of 21 domains, including environmental exposures, demographics, and substance use (http://www.phenxtoolkit.org). PhenX was launched in 2007 by RTI International, with funding from the National Human Genome Research Institute. The measures were developed with input from researchers in academia, government, and scientific organizations. The PhenX toolkit includes a group of assessments specifically focused on substance abuse and addiction, identified with support from domain experts and funded by the National Institute on Drug Abuse. The PhenX Real World Implementation and Sharing consortium is a significant step forward in the practical application of PhenX measures (49). PhenX publications have been largely focused on implementation of PhenX measures (35,50–53), including a recent publication on the commonality of findings in different addictive disorders across measures of addiction (54).

CNTRICS began with the primary goal of identifying neuroscience-based treatments to improve cognitive deficits associated with schizophrenia, with principal investigators at the University of California Davis and University of Washington, along with a steering committee of scientists from academia, government, and AstraZeneca, a pharmaceutical company. Extensive details about CNTRICS may be found at its website: http://cntrics.ucdavis.edu/index.shtml. The constructs include working memory, long-term memory, executive control, social/emotional processing, attention, and perception. The CNTRICS group has published extensively on the construct and task selection process [e.g., (55–58)]. Further, the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (http://cntracs.ucdavis.edu/) consortium has grown out of CNTRICS as a way to test the practicality and applicability of the measures identified.

ANA DOMAINS

The ANA domains are derived from a conceptual framework in which ADs lead to elements of impulsivity and compulsivity dysfunction. Three functional domains, executive function, incentive salience, and negative emotionality, are involved. Changes in these domains can be staged, heuristically, as binge-intoxication (reward and incentive salience, habits, representing the incentive salience domain), withdrawal-negative affect (stress and negative emotional states, including but not limited to withdrawal, representing the negative emotionality domain), and preoccupation-anticipation (executive function) (59). It is notable that a recent review (60) identified three major domains of neurofunctional impairment related to gambling disorder, namely loss of control, craving/

withdrawal, and neglect of other areas of life. These domains closely parallel the three ANA domains.

Executive Function

The executive function domain broadly includes processes related to organizing behavior toward future goals (61). Although including the totality of executive functions under the ANA is infeasible, certain subdomains of executive function bear particular relevance for addictions. As previously described (61), we focus on executive function processes related to the cross-temporal organization of behavior, including attention, response inhibition, planning, working memory, behavioral flexibility, and valuation of future events. Taken together, these processes provide a reasonably comprehensive overview of those executive function systems disrupted in addictions.

Dysfunction in these processes is well documented among individuals addicted to various agents. Deficits in attention have been shown among individuals addicted to alcohol (62), cocaine (63), and nicotine (64). Response inhibition is impaired among heroin (65) and methamphetamine (66) addicts and in pathological gamblers (67). Further, alterations in planning are evident among those addicted to nicotine (67) and opioids (68); disruptions in working memory are evident in alcohol (62), cocaine (63), and cannabis (69) addiction. Finally, behavioral flexibility is notably impaired among those addicted to cocaine (70) and amphetamine (71), and deficits in valuation of future events are well documented in alcohol (72) and nicotine (73) addiction.

Dysfunction in executive function, producing loss of top-down control in the frontal cortex, is etiological in driving many of these deficits, and such top-down control directly impacts on incentive salience and impulsivity in the binge-intoxication stage presumably via glutamatergic connections to the basal ganglia and impacts on negative emotional states via glutamatergic connections to the extended amygdala (9).

Incentive Salience

Alterations in incentive salience are also well documented among individuals with ADs and have been intimately linked to the circuitry of the basal ganglia. The construct of incentive salience can be defined as a psychological process that transforms the perception of stimuli, imbuing them with salience, and making them attractive. Incentive salience as a construct has its roots in incentive motivation (74) and conditioned reinforcement (75) and was hypothesized to be linked directly to phasic activation of the mesocorticolimbic dopamine system (76). A series of studies was conducted in which investigators recorded from dopamine neurons in the ventral tegmental area in primates during repeated presentation of rewards and presentation of stimuli associated with reward. Dopamine cells fired upon the first exposure to a novel reward, but repeated exposure to dopamine caused the neurons to stop firing upon reward consumption and fire instead when they were exposed to stimuli that were predictive of the reward (77).

With respect to measures of various components of incentive salience, the neural responses of addicted individuals are altered to both cue and noncue targets (78–80), with increased craving for substances in response to related cues (81,82), and differences in reward learning (83). Importantly, cue reactivity to addictive agents is associated with increased risk for relapse (81,84–86), and there are strong positive correlations between cue response and attentional bias (78,87–89).

The phasic dopaminergic activation that drives incentive salience is hypothesized to also engage habit formation and compulsive-like responding for addictive agents via activation of cortical-striatal-pallidal-thalamic loops (90,91).

Negative Emotionality

Increases in negative emotional responses to various stimuli and overall self-reported dysphoria are found in individuals with ADs (92,93). Clinicians and researchers have long considered the notion that reduction of negative affect may be a primary driver for excessive consumption of addictive agents (described alternately as self-medication or tension reduction). Indeed, hypohedonia is widely documented as a clinical feature of ADs (94–98) and is highly associated with increased craving for drugs of abuse (99) and relapse (100), which may contribute significantly to the increased salience of cues associated with addictive agents and loss of interest in others [e.g., (97)]. A complete assessment of reward constructs must include measurement of hypohedonia (101).

Another key component of the negative emotional states associated with the withdrawal-negative affect stage of the addiction cycle is the engagement of the brain stress systems, including both the hypothalamic-pituitary-adrenal axis and extrahypothalamic systems (102). The brain stress systems include such neurotransmitter systems as corticotropin releasing factor, dynorphin, norepinephrine, hypocretin (orexin), substance P, and vasopressin. Equally compelling is evidence for dysregulation of the brain antistress systems such as neuropeptide Y, nociception, endocannabinoids, and oxytocin. Increased activity in brain stress systems and decreased activity in brain antistress systems are hypothesized to significantly contribute to negative emotionality (102).

OMIC INFORMATION CAPTURE IN THE ANA

The ANA is focused on capture of measures of three main neurofunctional domains; however, modern omic technologies enable the simultaneous capture of information relevant to these domains as well as information on comprehensive genetic, molecular, or neurofunctional variation, depending on the different technologies. To analyze a gene, or given set of genes, or to study their epigenetic control, it is often more cost effective, and informative, to use an omic sequencing- or array-based technology.

Although individual genes contribute a small proportion of the variance in development of addictions, they may still contribute understanding of the mechanisms leading to ADs. For this reason, genetic sampling should be a standard but ancillary part of the ANA. The present importance of the ANA for neuroassessment of addictions should not be overestimated, but the future importance of genetics for understanding heterogeneity within ADs cannot be overestimated. Identifying genetic variants underlying phenotypic differences
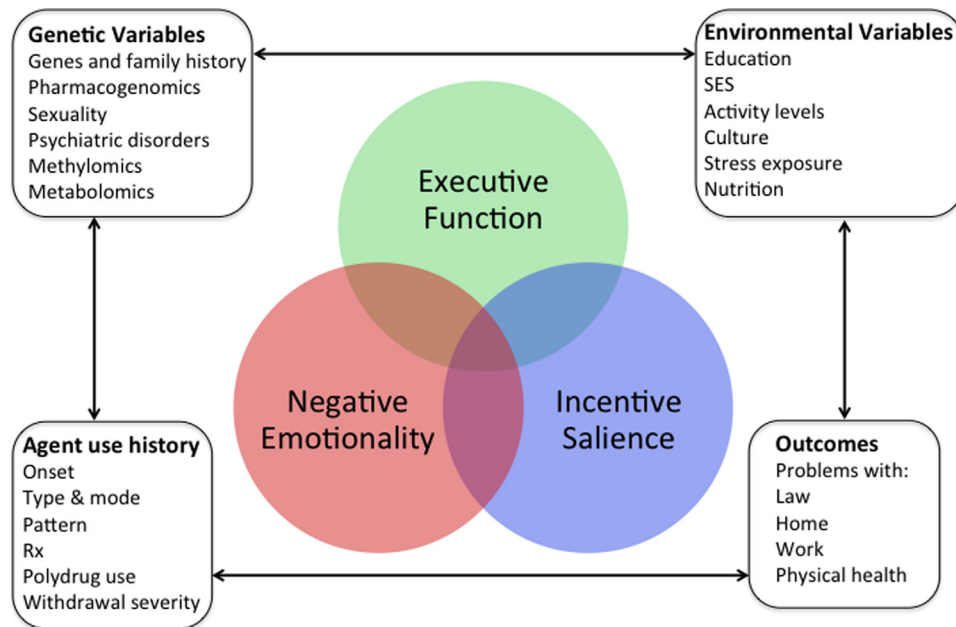
Figure 1. Addictions neuroclinical assessment primary domains and variables for ancillary assessment. Rx, prescription medications; SES, socioeconomic status.

will maximize the utility of the ANA, as will collection of DNA samples and genotyping with a one million marker array or similar tool. Further, analysis of changes in transcriptome, including microRNAs, and measurements of epigenetic changes in DNA and chromatin, may be critical for understanding neuroadaptations associated with heavy substance use (103). The goal is to use such changes as indices of function of molecular networks. It would be important to assess these changes in the context of longitudinal and/or large cross-sectional studies in which exposures and correlates of molecular responses are measured.

If feasible, exome sequencing should be performed. Whole genome single nucleotide polymorphism arrays enable comprehensive analysis for effects of common alleles of moderate or large effect. Most of these single nucleotide polymorphisms will not be strong predictors of individual outcome but may be key in understanding outcome, e.g., alcohol metabolic gene variants that predict alcohol-induced flushing, alcoholism risk, and, in moderate drinkers, esophageal cancer (104). Although pharmacogenetics is in the early stages of research, progress is being made in identifying variants that predict clinical success (105,106). For example, a common *OPRM1* polymorphism predicts response of alcoholic patients to naltrexone (107) and via reward (108), although the results are mixed (109). Such analyses will allow ANA datasets to be combined with other samples that may only have available the clinical diagnosis but with similar genomic analyses.

A critical aspect of the ANA is use of neuroimaging. The use of positron emission tomography scanning has been essential to elucidating the role of dopamine in various ADs [e.g., (110,111)]. To significantly advance the nosology and treatment of addictions, we should use neuroimaging technologies that enable multidimensional information capture to understand the mechanisms driving these disorders. The ANA will include functional magnetic resonance imaging (MRI)-based domain-specific assessments, along with imaging-based measures of brain structure (e.g., volume, morphometry, white matter integrity) and function, e.g., to assess differences in resting state functional connectivity identified in alcohol-dependent patients (112). The salience of neuroimaging to the ANA is underscored by recent imaging-genetics findings suggesting, for example, differences in neural response to alcohol cues as a function of genotype (113) and genetic modulation of neural connectivity related to nicotine addiction (114) and of resting state functional connectivity in AUDs (115).

As mentioned, many measures specific to a particular addictive agent, including behavioral addictions, or to particular exposures and outcomes would be ancillary to the ANA. Guided by clinical problems, the ANA should incorporate other measures of function and predisposition that are not included within the primary domains but vital to the etiology and treatment of ADs, e.g., habitual or compulsive use of an addictive agent. There are important distinctions in process and outcome between different addictive agents and even for the same addictive agent within different individuals. A virtue of applying the same measures across different addictive disorders, including behavioral addictions, and in people with different exposures or at different points in the clinical course of addiction is to better understand unifying mechanisms and variation at baseline and following maladaptive change. A schematic of the ANA domains and relevant ancillary assessment domains (Figure 1) illustrates the importance of core neuroassessment and the roles of other measures to improve the depth, breadth, and specificity of characterization of the individual patient. A comprehensive, although not final, list of potential measures, organized by domain, appears in Table 2. This battery would be supplemented by additional measures not included within the three domains but important for understanding ADs, including features of agent use and outcomes [e.g., the Addiction Severity Index (116)], Timeline

Table 2. Proposed Measures for ANA

Measure	Time to Complete	Type of Task
Executive Function		
Stop Signal Reaction Task (123)	10 minutes	Behavioral
Appetitive Go-NoGo (124)	10 minutes	Behavioral
Continuous Performance Test (125)	15 minutes	Behavioral
Tower of London (126)	15 minutes	Behavioral
Wisconsin Card Sorting Test (127)	15 minutes	Behavioral
Delay Discounting (128)	15 minutes	Behavioral
N-Back (129)	10 minutes	Behavioral
Beads in a Jar Task (130)	5 minutes	Behavioral
Barratt Impulsiveness Scale (131)	5 minutes	Self-report
Negative Emotionality		
Approach Avoidance Task (132)	10 minutes	Behavioral
Cyberball (133)	10 minutes	Behavioral
Trier Social Stress Test (134)	20 minutes	Behavioral
Cold Pressor Task (135)	10 minutes	Behavioral
Digit Span (136)	5 minutes	Behavioral
Two-Step Task (Model-Free Model-Based) (137)	15 minutes	Behavioral
Beck Depression Inventory (138)	5 minutes	Self-report
Beck Anxiety Inventory (139)	5 minutes	Self-report
Fawcett-Clark Pleasure Scale (140)	5 minutes	Self-report
Toronto Alexithymia Scale (141)	5 minutes	Self-report
Childhood Trauma Questionnaire (142)	5 minutes	Self-report
Facial Emotion Matching Task (143)	10 minutes	Neuroimaging
Incentive Salience		
Choice Task (Explicit Version) (144)	15 minutes	Behavioral
Dot-Probe Attentional Bias Task (Cues) (145)	10 minutes	Behavioral
Obsessive-Compulsive Drinking Scale (146)	5 minutes	Self-report
Cue Reactivity Task (80)	10 minutes	Neuroimaging
Monetary Incentive Delay Task (147)	10 minutes	Neuroimaging

ANA, Addictions Neuroclinical Assessment.

Follow-Back (117), important aspects of personality [e.g., the NEO Personality Inventory-Revised (118)], and environment [e.g., the Pittsburgh Sleep Quality Index (119) and the Inventory of Socially Supportive Behaviors (120)]. A graphic depicting the process of multidimensional information capture to data analysis to improved diagnosis appears in Figure 2.

Lastly, practical considerations regarding the implementation of the ANA must be considered. Given the breadth of potential assessments, a comprehensive battery would take approximately 10 hours. Many of the measures could be collected in any setting with access to a laptop computer, although the MRI would require specialized facilities. We have made efforts to consider measures that may be attained free or at relatively little cost; the largest cost involved would be the use of MRI. Depending on resources, these may be obtained at a local academic or hospital setting. Additional costs include data analysis and interpretation. A range of $3000 to $5000 per individual seems feasible, and if it results in significantly improved prognosis is well worth the investment.

ANA SUMMARY

A few final points about these domains and their relevance for the ANA bear mention. First, although we have highlighted significant positive findings in each domain, there is considerable variability in the literature. Not all individuals with ADs evidence disruptions in the three primary domains. This variability is symptomatic of the need to systematically understand the heterogeneity within ADs. Second, although presented independently, there is considerable overlap and interaction between domains at multiple levels of analysis. One of the most prominent examples is the relevance of PFC dysfunction for various aspects of ADs (41). These disruptions underlie deficits in executive function, emotion regulation, and reward modulation, not surprising given the neurocircuitry connections (121). These domains do not comprise the totality of disturbances related to addiction but serve as a useful starting framework for further exploration. Later studies might expand upon known differences in alcohol response, e.g., those related to acute tolerance (122), and in responses to other drugs, whether of pharmacokinetic or pharmacodynamic origin.

Finally, several factors are challenges for application of the ANA, including the magnitude of the problem of addiction, complexity of causation, and changing nature of problems that patients with ADs experience over time. Furthermore, a broad combination of collaborations and partnerships in academia, government, and private industry will be needed to realize its advantages. This review has the more modest goal of providing
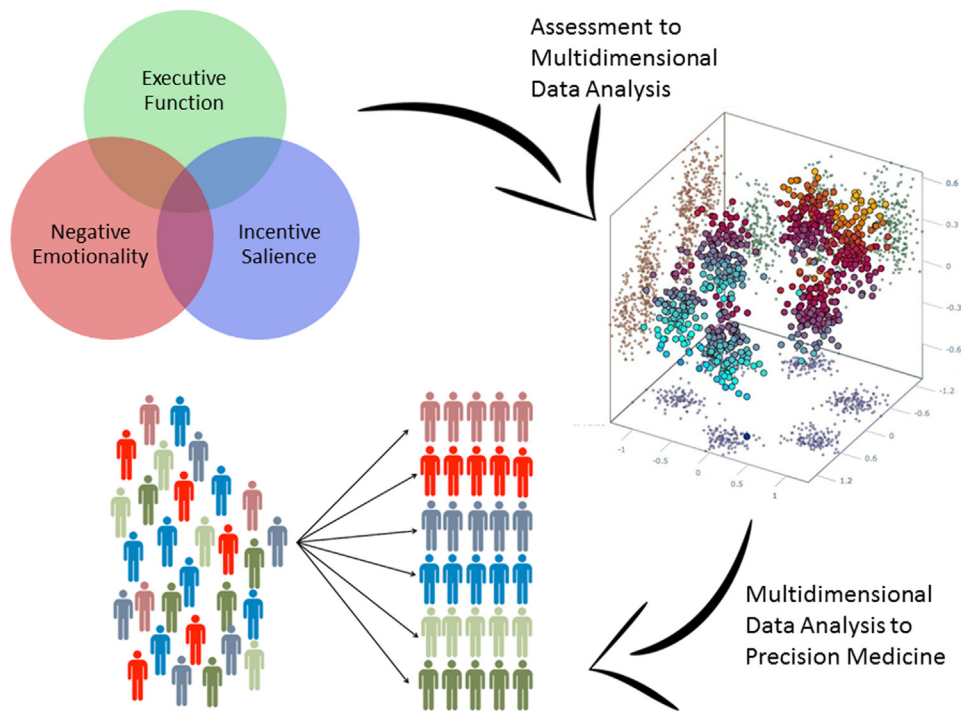
Figure 2. Proposed addictions neuroclinical assessment process from data capture to precision medicine implementation.

a heuristic framework for the ANA, with some evaluation of practicality. Given the multifactorial nature of ADs, the changing nature of exposure and response of human populations to addictive agents, the anticipated development of new methods for treatment and prevention, and the development of new, transformative technologies, we do not anticipate that any one functional domain or imaging or genetic predictor will resolve the heterogeneity of ADs or be sufficient to characterize an individual patient. Rather, it is our goal that by collecting multidimensional information and focusing on a limited number of functional domains, our understanding of the mechanisms of addiction can be improved and prevention/treatment can be better targeted. Identifying the major domains underlying ADs and how the profile of vulnerability to each domain varies among individuals and over time not only will be vital to understand the heterogeneity of the disorder but also will enable us to tailor treatment more effectively to the individual.

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ARTICLE INFORMATION

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