Neuropharmacology 122 (2017) 254–264

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Addictions Neuroclinical Assessment: A reverse translational approach

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ARTICLE INFO

Article history:
Received 31 October 2016
Received in revised form
2 March 2017
Accepted 4 March 2017
Available online 7 March 2017

Keywords:
Addictions
Neuroscience
Nosology
Translational

ABSTRACT

Incentive salience, negative emotionality, and executive function are functional domains that are etiologic in the initiation and progression of addictive disorders, having been implicated in humans with addictive disorders and in animal models of addictions. Measures of these three neuroscience-based functional domains can capture much of the effects of inheritance and early exposures that lead to trait vulnerability shared across different addictive disorders. For specific addictive disorders, these measures can be supplemented by agent specific measures such as those that access pharmacodynamic and pharmacokinetic variation attributable to agent-specific gatekeeper molecules including receptors and drug-metabolizing enzymes. Herein, we focus on the translation and reverse translation of knowledge derived from animal models of addiction to the human condition via measures of neurobiological processes that are orthologous in animals and humans, and that are shared in addictions to different agents. Based on preclinical data and human studies, measures of these domains in a general framework of an Addictions Neuroclinical Assessment (ANA) can transform the assessment and nosology of addictive disorders, and can be informative for staging disease progression. We consider next steps and challenges for implementation of ANA in clinical care and research.

This article is part of the Special Issue entitled “Alcoholism”.

Published by Elsevier Ltd.

Contents

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http://dx.doi.org/10.1016/j.neuropharm.2017.03.006
0028-3908/Published by Elsevier Ltd.

1. Introduction

Psychoactive agents that are widely used tend to be widely abused. On a global basis, alcohol, nicotine, and cannabis are widely used, although quantity and qualitative aspects of use vary enormously across time and space, leading to disparities in impact on public health. On an overall basis, and for every population studied, the public health impact of addictive disorders is large. For example, alcohol is consumed worldwide, even in countries where it is illegal to sell or buy it. Correspondingly, alcohol is one of the largest preventable contributors to disease (Rehm et al., 2009), 4.6% of the global disease burden being attributable to alcohol, as measured in disability-adjusted life years. In the United States, roughly 14% of individuals are diagnosable with an alcohol use disorder (AUD) in a given year, and the lifetime prevalence rate of AUD is 29% (Grant et al., 2015). For several addictive disorders, including AUD, FDA-approved medications are available, and behavioral treatments are also helpful. Treatments for addictive disorders are partially effective, probably helping at least a third of patients who receive them, but treatment is usually not received: over 90% of individuals with AUD never receive specialized treatment (SAMHSAServices HaH, 2013). The treatment of addictions as end stage diseases in which neuroadaptive changes of addiction, and other damage to the body predominate, and may be difficult to undo, is inherently less satisfactory than prevention, and may be less efficacious than treatments targeted to specific types of vulnerability and stages of progression. However, developing new clinical approaches to addictions based on the neuroscience of addiction – a precision medicine of addictions – ultimately will require integration of relevant neuroscience-based measures into nosology.

Advances in our functional understanding of the pathophysiology of addictions are derived from studies in humans but also by investigations in animal models that capture different aspects of addictions. However, translating findings from animal models to humans, and reverse translating from humans to animal models, is hampered by the etiologic heterogeneity of addiction vulnerability in both humans and the diversity of animal models available (Belin et al., 2016). In humans, there is wide variation in progression and outcome, and limited ability to stage addiction using measures of progression emergent from studies in animal models. Animal models of addiction afford a degree of control of exposure and genotype, and access to tissue that is impossible to attain in human studies. Neuroadaptive processes (Koob and Volkow, 2016), and to a lesser extent, genes, gene transcripts, and proteins (Zhou et al., 2013), have primarily been identified in rodents, with translation to human. Translational studies at the genetic and neuroscience level reveal that mechanisms of addiction in mice, rats, and humans are orthologous, i.e., functionally similar and of a shared evolutionary origin. The roles of both genetic and environmental factors in interindividual variation in vulnerability and progression can bet traced in both humans and animal models of addiction. In rodents, genetically very similar, or identical (inbred and inbred F1) individuals can be divergent in behaviors such as novelty seeking and novelty-induced hyperlocomotion that predict addiction-like behavior, and, by extension, divergent in outcome (Belin et al., 2016), and divergent in addiction behaviors that develop subsequent to exposure. Preclinical studies are therefore an avenue to identify domains that are critical for predicting liability and staging response in human patients, provided relevant domains can be measured. Herein we link critical findings from animal models of addiction in humans to three neuroscience domains comprising the Addictions Neuroclinical Assessment (ANA) (Kwako et al., 2016), Fig. 1. While ANA focuses on addictions broadly, we have elected to focus on alcohol as an exemplar substance of abuse, with additional literature from other substances integrated throughout the manuscript as relevant.

1.1. Clinical heterogeneity

Clinical heterogeneity is the major barrier to the treatment of addictive disorders and development of better treatments. In both the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD), addictions are categorical diagnoses based on symptom counts of up to eleven intercorrelated symptoms, with a minimum of two in whatever of $(11 \times 10)/2 = 55$ combinations to meet a threshold diagnosis of DSM addictive disorder. DSM-5 (APA, 2013) estimates level of severity, also based on symptom counts. Because a diagnosis of addictive disorder under ICD and DSM criteria requires that the patient meet a limited number of criteria from a larger list of partially inter-correlated criteria, there is considerable within-diagnosis heterogeneity. Any patient can reach the endpoints represented by these behaviorally focused criteria via different destinations, and beginning from distinctly different, and even polar opposite, starting points of vulnerability. For example, both anxiety (internalizing behavior: enhanced affective response, prior sensitization to stress/trauma) and risk-taking (externalizing behavior: impulsivity, enhanced responses to novelty, novelty seeking) can predispose to addiction, liability thus arising from genetic risk factors, and exposures. The diagnostic criteria for AUD and other addictive disorders focus on overt behavioral symptoms and consequences of use rather than underlying neurobiological differences that lead to vulnerability and can define progression.

1.2. Development of research diagnostic measures, and criteria

Given the significant advances in our understanding of the neurocircuitry of addiction, e.g., (Koob and Volkow, 2016), and the neurobehavioral differences that are involved in to vulnerability, and the capacity to measure the activity and output of the brain for relevant domains, the time may be ripe for leveraging knowledge towards a more nuanced approach to diagnosis and treatment. Such an effort would align with similar initiatives in mental health, e.g., the Research Domain Criteria (RDoC) program at the National Institute of Mental Health, and in medicine more generally, e.g., the NIH Precision Medicine Initiative Cohort Program (http://www.nih.gov/about-nih/who-we-are/nih-director/statements/preparing-launch-precision-medicine-initiative-cohort-program). One major distinction between ANA and these initiatives is that ANA is focused within a particular disease category, i.e., addiction, rather than across various diseases.

1.3. Traits mediating vulnerability

Historically, most preclinical studies of addiction, including alcohol, have focused on drug reinforcement (Belin et al., 2016). However, studies in rats and mice have revealed powerful predictors of interindividual variation in liability. Several of these measures correspond to heritable, disease associated intermediate phenotypes (endophenotypes) (Gottesman and Gould, 2003) in people (Kendler and Neale, 2010). These include trait measures in the anxiety (internalizing) and impulsive-like (externalizing) domains that are the basis of a substantial portion of the quantitative inheritance of addictive disorders (Kendler et al., 2012). While an ability to recognize broad differences in externalizing and internalizing behavior has advanced genetic analyses, and has improved translational alcoholism research, better measures of these domains are needed.