Received: 7 June 2019 | Revised: 24 October 2019 | Accepted: 4 December 2019

DOI: 10.1111/adb.12866

ORIGINAL ARTICLE

Addiction Biology SSA WILEY

Addiction Research Consortium: Losing and regaining control over drug intake (ReCoDe)—From trajectories to mechanisms and interventions

Andreas Heinz[1] | Falk Kiefer[2] | Michael N. Smolka[3] | Tanja Endrass[4] | Christian Beste[5] | Anne Beck[1] | Shuyan Liu[1] | Alexander Genauck[1] | Lydia Romund[1] | Tobias Banaschewski[6] | Felix Bermpohl[1] | Lorenz Deserno[3,7] | Raymond J. Dolan[7] | Daniel Durstewitz[8] | Ulrich Ebner-Priemer[9] | Herta Flor[10,11] | Anita C. Hansson[12] | Christine Heim[13,14] | Derik Hermann[2,15] | Stefan Kiebel[3,16] | Peter Kirsch[17] | Clemens Kirschbaum[18] | Georgia Koppe[8] | Michael Marxen[3] | Andreas Meyer-Lindenberg[19] | Wolfgang E. Nagel[20] | Hamid R. Noori[12,21] | Maximilian Pilhatsch[22] | Josef Priller[23,24] | Marcella Rietschel[25] | Nina Romanczuk-Seiferth[1] | Florian Schlagenhauf[1] | Wolfgang H. Sommer[2,12] | Jan Stallkamp[26] | Andreas Ströhle[1] | Ann-Kathrin Stock[5] | Georg Winterer[27] | Christine Winter[1] | Henrik Walter[1] | Stephanie Witt[25] | Sabine Vollstädt-Klein[2] | Michael A. Rapp[28] | Heike Tost[19] | Rainer Spanagel[12]

[1]Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin (Campus Charité Mitte), Berlin, Germany

[2]Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[3]Department of Psychiatry and Neuroimaging Centre, Technische Universität Dresden, Dresden, Germany

[4]Institute for Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany

[5]Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, Technische Universität Dresden, Dresden, Germany

[6]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[7]Max Planck Centre for Computational Psychiatry and Ageing Research & Wellcome Centre for Human Neuroimaging, University College London, London, UK

[8]Department of Theoretical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[9]Department of Sports and Sports Science, Karlsruhe Institute of Technology (KIT), Karlsruhe, Germany

[10]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[11]Department of Psychology, School of Social Sciences, University of Mannheim, Mannheim, Germany

[12]Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[13]Institute of Medical Psychology, Charité – Universitätsmedizin Berlin, Berlin, Germany

[14]Department of Biobehavioral Health, Pennsylvania State University, University Park, Pennsylvania

[15]Feuerlein Center on Translational Addiction Medicine (FCTS), University of Heidelberg, Heidelberg, Germany

[16]Department of Psychology and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany

[17]Department of Clinical Psychology, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[18]Department of Psychology, Biological Psychology, Technische Universität Dresden, Dresden, Germany

[19]Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[20]Center for Information Services and High Performance Computing, Technische Universität Dresden, Dresden, Germany

[21]Max Planck Institute for Biological Cybernetics, Tübingen, Germany

[22]Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany

[23]Department of Neuropsychiatry and Laboratory of Molecular Psychiatry, Charité-Universitätsmedizin Berlin, Berlin, Germany

[24]UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK

[25]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[26]Project Group for Automation in Medicine and Biotechnology, Fraunhofer IPA, Mannheim, Germany

[27]Experimental and Clinical Research Center (ECRC), Department of Anesthesiology and Intensive Care Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany

[28]Social and Preventive Medicine, Universität Potsdam, Potsdam, Germany

Correspondence
Andreas Heinz, Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin (Campus Charité Mitte), Charitéplatz 1, 10117 Berlin, Germany.
Email: andreas.heinz@charite.de

Rainer Spanagel, Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, J5 Mannheim, Germany.
Email: rainer.spanagel@zi-mannheim.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: TRR265; German Research Foundation

Abstract

One of the major risk factors for global death and disability is alcohol, tobacco, and illicit drug use. While there is increasing knowledge with respect to individual factors promoting the initiation and maintenance of substance use disorders (SUDs), disease trajectories involved in losing and regaining control over drug intake (ReCoDe) are still not well described. Our newly formed German Collaborative Research Centre (CRC) on ReCoDe has an interdisciplinary approach funded by the German Research Foundation (DFG) with a 12-year perspective. The main goals of our research consortium are (i) to identify triggers and modifying factors that longitudinally modulate the trajectories of losing and regaining control over drug consumption in real life, (ii) to study underlying behavioral, cognitive, and neurobiological mechanisms, and (iii) to implicate mechanism-based interventions. These goals will be achieved by: (i) using mobile health (m-health) tools to longitudinally monitor the effects of triggers (drug cues, stressors, and priming doses) and modify factors (eg, age, gender, physical activity, and cognitive control) on drug consumption patterns in real-life conditions and in animal models of addiction; (ii) the identification and computational modeling of key mechanisms mediating the effects of such triggers and modifying factors on goal-directed, habitual, and compulsive aspects of behavior from human studies and animal models; and (iii) developing and testing interventions that specifically target the underlying mechanisms for regaining control over drug intake.

KEYWORDS
addiction, alternative rewards, animal and computational models, cognitive-behavioral control, craving and relapse, habit formation

1 | INTRODUCTION

We established a collaborative research center (CRC) in mid-2019, which brings together scientists with complementary expertise in addiction research from three internationally recognized centers (Charité Berlin, Technical University of Dresden, and Central Institute of Mental Health in Mannheim) in Germany. Our multidisciplinary *Losing and Regaining Control over Drug Intake* (ReCoDe) consortium consists of 40 principal investigators (PIs) and it will be substantially funded for up to 12 years (three 4-year funding periods) by the German Research Foundation (DFG). The consortium integrates a range of fields, including psychology, medicine, computation and machine learning, and neurobiology, allowing experts (for clinical and animal studies) to move basic science discoveries into practice.

2 | KEY AIMS AND RESEARCH DOMAINS OF THE RECODE CONSORTIUM

The main goals of our research consortium are (a) to identify triggers and modifying factors that longitudinally modulate the trajectories of

losing and regaining control over drug consumption in real life (Research Domain A), (b) to study underlying behavioral, cognitive, and neurobiological mechanisms (Research Domain B), and (c) to develop mechanism-based interventions (Research Domain C) (Figure 1).

We build a work plan and design the methodology to investigate the following core research domains:

1. Domain A: Defining individual trajectories of ReCoDe requires a holistic approach, which longitudinally assesses the interactions between triggers (drug cues, stressors, and priming doses) and modifying factors (eg, age, gender, physical activity, and cognitive functions) in real life in substance use disorder (SUD) subjects and in animal models of addiction. Technically, we will use mobile health (m-health) tools such as individual assessment devices fitted with mobile sensors (wearables) and accelerometers. The former technology will acquire geolocation and additional data on psychological and physiological cue and stress reactivity and on alcohol intake, while the latter will collect intensive longitudinal datasets (ILDs). These data will be combined with app-based tests for key cognitive control and learning mechanisms in real-life settings. We will analyze the data using new multiscale analysis tools from statistical physics and biosignal processing to identify tipping points in substance use trajectories.
2. Domain B: The effects of the above-mentioned triggers and modifying factors on goal-directed, habitual, and compulsive aspects of addictive behaviors are mediated by distinct processes (eg, cue reactivity, habitization, reduced choice of alternative rewards, and reduced cognitive control). Here, we will build computational models by using animal and human data. The goal of our models are to understand the corticolimbic control mechanisms as well as aberrant learning mechanisms and their interaction with triggers and modifying factors, which bias behavior towards drug seeking and intake.
3. Domain C: Based on the prediction of individual trajectories of losing and regaining control, we will develop mechanism-based interventions that specifically match the above-mentioned key processes (eg, cue reactivity, habitization, reduced choice of alternative rewards, and reduced cognitive control).

3 | RESEARCH DOMAIN A: DESCRIPTION OF ANTECEDENTS AND TRAJECTORIES OF LOSING AND REGAINING CONTROL AND MODULATING FACTORS

The first goal of this joint research effort is to identify triggers and modifying factors that longitudinally modulate the trajectories of losing and regaining control over drug consumption in real life across the lifespan.

Losing control over drug intake is a gradual and dimensional process, which starts with goal-directed drug intake and proceeds to habitual and ultimately compulsive drug use. Interestingly, a limited number of addicted subjects manage to regain behavioral control over compulsive drug intake without professional help, either by becoming abstinent (up to 19% of untreated alcohol-dependent patients) or by substantially reducing drug intake, for example, by decreasing tobacco or alcohol consumption.[1-4] Even in patients with severe stages of alcohol dependence who require detoxification, a few percent manage to drink small amounts of alcohol for a longer period of time without again losing control.[5] Regaining behavioral control over drug intake has been attributed to mindful selection of goals replacing habitual behavior, extinction of drug cue-induced behavioral tendencies, regulation of drug craving and prioritization of alternative nondrug rewards, and increased cognitive control over behavior including inhibitory control.[3,6-8]

In Domain A of our CRC, we will identify common, as well as age- and gender-specific factors that contribute to losing and regaining control over consumption of alcohol (and other drugs of abuse), by a systematic longitudinal assessment of a large sample of persons with mild to moderate alcohol use disorder (AUD), who do not (yet) require detoxification. This traditional longitudinal cohort study approach

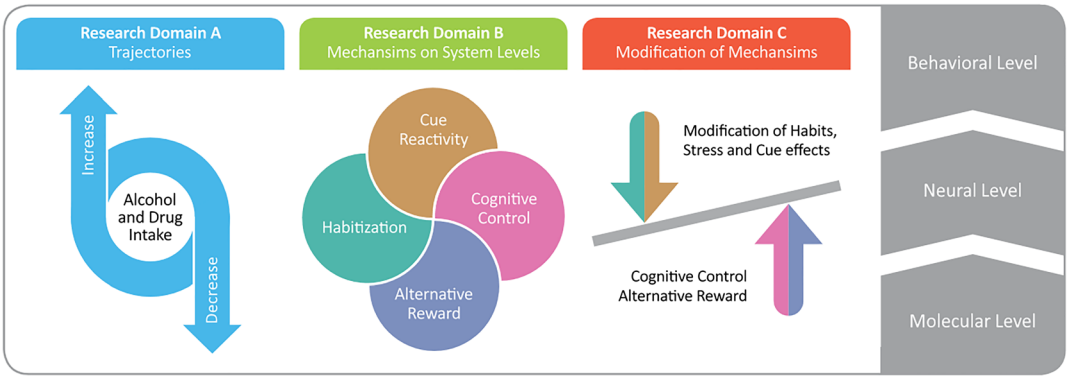

FIGURE 1 The losing and regaining control over drug intake (ReCoDe) framework to study losing and regaining control over drug intake over a 12-year perspective: Our 19 projects are divided into three research domains. Research domain A relates to trajectories of alcohol and drug intake. Research domain B relates to mechanisms (eg, cue reactivity) on different system levels (behavioral, neural, and molecular) and research domain C focusses on the modification of mechanisms (eg, by increasing cognitive control via physical activity or neurofeedback)

using latent growth curve and growth mixture models[9] will be combined with in-depth ambulatory assessments several times a week. We will use Ambulatory Assessment including Ecological Momentary Assessment (EMA)[10] to acquire ILDs over several months in AUD patients with and without additional tobacco and cannabis use. For EMA, we will use smartphones with additional mobile sensors (wearables) which will be used to measure physical activity, data on location (GPS), geolocation-based triggering of e-diaries, self-reported stress reactivity, cue exposure (encounter with drug-related stimuli in real life), drug craving, impulsivity, and drug consumption (priming doses, binges, and continuous use of all drugs of abuse). App-based brief questionnaires and cognitive[11] tasks that allow the assessment of momentary emotional, motivational, and cognitive states, including new brief games to assess Pavlovian and instrumental (model-based and model-free) learning mechanisms as well as sensors to detect physiological stress responses will be applied (Figure 2).

The ILDs will undergo multiscale statistical analysis to identify early warning signs and critical phases[12] indicative for craving and drug use as reported online and as assessed in animal models of addiction. ILDs will also be collected to acquire predictive models of single subjects and their behavioral dynamics, using cutting-edge AI techniques like deep recurrent neural networks.[13] The influence of age and gender, as well as adverse life events on the occurrence of early warning signs and critical phases, will be studied in humans and in related animal experiments. DSM-IV/5-based animal models of addictive-like behavior[14,15] will be run in parallel for sampling ILDs and for running modulating factors under more controlled conditions. Such translational animal models will be also key to studying neurobiological and molecular mechanisms underlying loss of control (Domain B) and new interventions (Domain C).

To take into account the variance explained by genetic factors which ranges between 40% and 70% for the different SUDs,[16] as well as epigenetic factors, biomaterial will be assessed from all participants at all time points. In an innovative approach, the data from genome- and epigenome-wide analyses will be integrated into the computational models mentioned above.

4 | RESEARCH DOMAIN B: BEHAVIORAL AND COGNITIVE CONTROL MECHANISMS AND THEIR MOLECULAR/NEUROBIOLOGICAL CORRELATES UNDERLYING LOSING AND REGAINING CONTROL

The second goal is to identify and to computationally model key mechanisms mediating the effects of such triggers and modifying factors on goal-directed, habitual, and compulsive aspects of behavior in corresponding human studies and animal experiments. In Domain B,

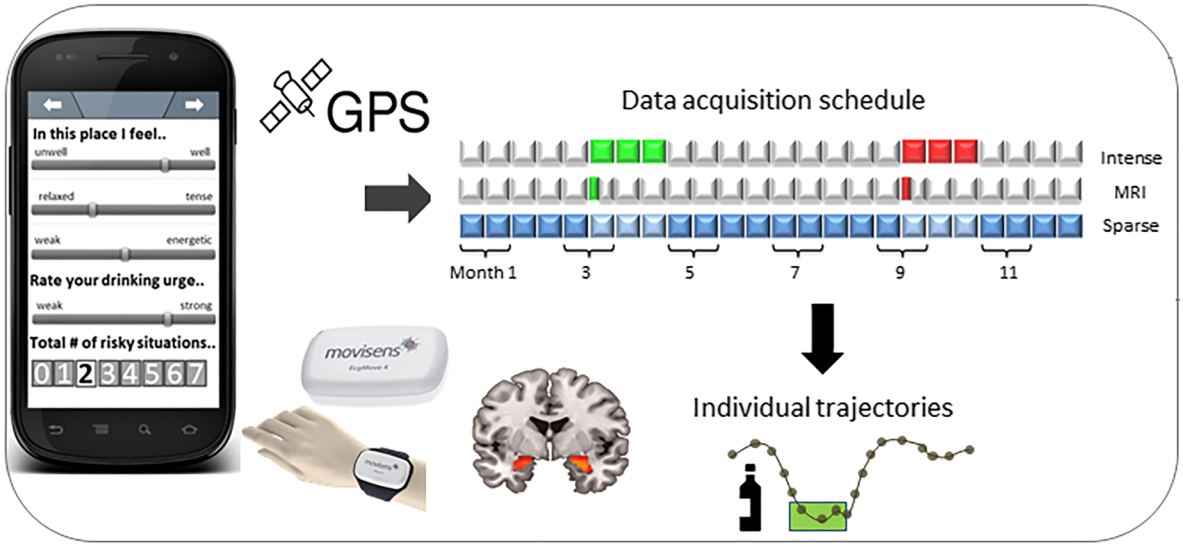

FIGURE 2 We will acquire a highly phenotyped cohort of female and male subjects with substance use disorder (SUD) (N = 900 patients plus 150 age-matched controls) focusing on alcohol use but allowing comorbidity with other drugs of abuse. Subjects with SUD will use apps and handheld devices for Ecological Momentary Assessment (EMA) including accelerometers to measure physical activity. Stress and drug exposure, supportive social encounters, and trajectories of increasing or decreasing drug intake, as well as binging, will regularly be monitored over the observation time of one year (sparse sampling). Multi-modal neuroimaging will be acquired at months 3 and 9. For in-depth assessment of cognitive control, we will use additional apps to assess working memory and other executive functions in real life with respect to drug intake ort. In addition, we will assess stress reactivity profiles and explore their interaction with trajectories of craving and alcohol intake. Besides this sparse data sampling approach, we will use specialized apps for intensive EMA to collect e-Diaries, sensor, and geolocation data in subjects at course transition points, ie, with substantial increases and decreases of alcohol intake (intense sampling). This intensive data sampling will provide detailed information on momentary effects of triggers on subjective craving, mood, impulsivity, physiological responses, and alcohol consumption in real-world settings, identify their neural correlates, and test the predictive value of the identified mechanisms for subsequent course trajectories. Finally, data integration and postprocessing will yield early warning signs and tipping points in drug consumption and will allow us to computational model trajectories of alcohol consumption

the impact of triggers and modulating factors on the proposed learning and control mechanisms in subjects with AUD deriving from our longitudinal real-life assessment (such as stress, cue exposure, and physical activity) will be assessed in laboratory experiments and compared with tobacco use disorder (TUD) in order to achieve generalizability of our conclusions. Closely linked human studies and animal experiments will assess key learning and control mechanisms and measure their neurobiological and molecular correlates that contribute to a shift from goal-directed to habitual and ultimately compulsive drug consumption and their potential readjustment when regaining goal-directed control. In particular, we will examine and build computational models for specific learning mechanisms, such as Pavlovian mechanisms including Pavlovian-to-instrumental transfer (PIT) that energizes ongoing drug-seeking, for goal-directed vs habitual decision making and for corticolimbic control mechanisms of craving and behavior and their respective effects on prospective drug intake.

5 | RESEARCH DOMAIN C: SPECIFIC INTERVENTIONS FOR REGAINING CONTROL

The third aim is to develop and test interventions that specifically target the underlying mechanisms for regaining control over drug intake. Domain C focuses on the modification of learning and cognitive control mechanisms in subjects with SUD. In the first 4-year funding period, the interventions will begin by examining the modification of learning processes and the effects of physical exercise on cognitive control. In particular, we will use (a) cognitive remediation treatment and implicit computer-based habit-modifying training aiming at habitual vs goal-directed control of behavior. (b) We will focus on modifying Pavlovian and instrumental learning parameters by specific alterations of Pavlovian cue value and general stress reduction techniques. (c) We will measure effects of physical exercise training on working memory and craving regulation and their respective impact on drug intake, and (iv) we will use neurofeedback to modulate key brain areas associated with cue-reactivity and control over drug intake.[17]

In a 12-year perspective, we will assess cognitive, emotional, and behavioral trainings as well as neurobiological interventions such as brain stimulation or specific pharmacological therapies addressing mechanisms identified in Domains A and B. To do so, Domain C will use information on risk and protective factors from Domain A observed under real-life conditions, as well as the learning and executive control paradigms from Domain B and their computational modeling. Domain C will thus increasingly be able to identify the most efficient intervention strategies to strengthen control mechanisms and to alter aberrant learning mechanisms. This will result in specific mechanism-based intervention strategies for alcohol-dependent patients and patients suffering from other addictions.

5.1 | Summary and outlook

Here, we suggest a set of approaches in addiction research which can promote understanding the mechanisms underlying losing versus regaining control over drug intake. Specifically, a dimensional approach can help to facilitate long-term assessment of subjects with mild to moderate AUD who do not need to be detoxified. Among these subjects with AUD, technical advances in m-health tools such as EMA, GPS-based geolocation, and mobile sensors allow monitoring of behavior, cognitive-emotional states, stress reactivity, and environmental exposures under real-life conditions. Computational and AI-based models can then be applied to these data in order to identify key computational steps in goal-directed and habitual decision-making and their neurobiological correlates in reward-related learning, stress-reactivity, and cognitive control.

A long-term aim of our ReCoDe consortium is to amend impaired control or even loss of control and thereby to reduce drug seeking and intake by identifying common and specific cognitive and neurobiological mechanisms and by probing specific interventions for addictive behavior in men and women across the lifespan. Synergistic effects and added value will be achieved by using translational animal models, applying the same learning paradigms and computational models in animal experiments and human studies, and by building tandem projects between basic and clinical addiction researchers to maximize the translational nature of this work. Clinical relevance will be ensured by using a complementary set of approaches, from computational modeling, to tightly coordinated animal experiments and human studies, to pilot testing interventions. In a 12-year perspective, our ReCoDe initiative will assess cognitive, emotional, and behavioral trainings, as well as neurobiological interventions such as brain stimulation or specific pharmacological therapies addressing mechanisms identified in Domains A and B, working towards the ultimate goal of developing mechanism-based individualized treatments.

ACKNOWLEDGEMENTS

The Collaborative Research Center (CRC) (Transregio - TRR 265 - Losing and regaining control over drug intake—from trajectories to mechanisms and interventions) is funded by the German Research Foundation (Deutsche Forschungsgemeinschaft DFG).

ORCID

Falk Kiefer https://orcid.org/0000-0001-7213-0398
Michael N. Smolka https://orcid.org/0000-0001-5398-5569
Tanja Endrass https://orcid.org/0000-0002-8845-8803
Anne Beck https://orcid.org/0000-0002-6215-7295
Shuyan Liu https://orcid.org/0000-0002-6948-5734
Alexander Genauck https://orcid.org/0000-0002-9159-0709
Peter Kirsch https://orcid.org/0000-0002-0817-1248
Michael Marxen https://orcid.org/0000-0001-8870-0041
Hamid R. Noori https://orcid.org/0000-0002-2592-247X
Ann-Kathrin Stock https://orcid.org/0000-0001-7113-4020
Rainer Spanagel https://orcid.org/0000-0003-2151-4521

REFERENCES

1. Helzer JE, Robins LN, Taylor JR, et al. The extent of long-term moderate drinking among alcoholics discharged from medical and psychiatric treatment facilities. *N Engl J Med*. 1985;312(26):1678-1682.

2. Imber S, Schultz E, Funderburk F, Allen R, Flamer R. The fate of the untreated alcoholic. Toward a natural history of the disorder. *J Nerv Ment Dis*. 1976;162(4):238-247.
3. Sobell LC, Ellingstad TP, Sobell MB. Natural recovery from alcohol and drug problems: methodological review of the research with suggestions for future directions. *Addiction*. 2000;95(5):749-764.
4. Swift W, Coffey C, Degenhardt L, Carlin JB, Romaniuk H, Patton GC. Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. *J Epidemiol Community Health*. 2012;66(7):e26.
5. Mann K, Schafer DR, Langle G, Ackermann K, Croissant B. The long-term course of alcoholism, 5, 10 and 16 years after treatment. *Addiction*. 2005;100(6):797-805.
6. Gladwin TE, Wiers CE, Wiers RW. Cognitive neuroscience of cognitive retraining for addiction medicine: from mediating mechanisms to questions of efficacy. *Prog Brain Res*. 2016;224:323-344.
7. Rezapour T, DeVito EE, Sofuoglu M, Ekhtiari H. Perspectives on neurocognitive rehabilitation as an adjunct treatment for addictive disorders: from cognitive improvement to relapse prevention. *Prog Brain Res*. 2016;224:345-369.
8. Heinz A, Beck A, Halil MG, Pilhatsch M, Smolka MN, Liu S. Addiction as learned behavior patterns. *J Clin Med*. 2019;8:1086-1095.
9. Rapp MA, Schnaider-Beeri M, Wysocki M, et al. Cognitive decline in patients with dementia as a function of depression. *Am J Geriatr Psychiatry*. 2011;19(4):357-363.
10. Serre F, Fatseas M, Swendsen J, Auriacombe M. Ecological momentary assessment in the investigation of craving and substance use in daily life: a systematic review. *Drug Alcohol Depend*. 2015;148:1-20.
11. Brown HR, Zeidman P, Smittenaar P, et al. Crowdsourcing for cognitive science—the utility of smartphones. *PLoS One*. 2014;9:e100662.
12. Foo JC, Noori HR, Yamaguchi I, et al. Dynamical state transitions into addictive behaviour and their early-warning signals. *Proc Biol Sci*. 2017;284.
13. Durstewitz D, Koppe G, Meyer-Lindenberg A. Deep neural networks in psychiatry. *Mol Psychiatry*. 2019;24(11):1583-1598.
14. Meinhardt MW, Sommer WH. Postdependent state in rats as a model for medication development in alcoholism. *Addict Biol*. 2015;20(1):1-21.
15. Spanagel R. Animal models of addiction. *Dialogues Clin Neurosci*. 2017;19(3):247-258.
16. Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. *Nat Rev Genet*. 2005;6:521-532.
17. Kirsch M, Gruber I, Ruf M, Kiefer F, Kirsch P. Real-time functional magnetic resonance imaging neurofeedback can reduce striatal cue-reactivity to alcohol stimuli. *Addict Biol*. 2016;21(4):982-992.

How to cite this article: Heinz A, Kiefer F, Smolka MN, et al. Addiction Research Consortium: Losing and regaining control over drug intake (ReCoDe)—From trajectories to mechanisms and interventions. *Addiction Biology*. 2020;25:e12866. https://doi.org/10.1111/adb.12866