

Acknowledgment

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References

1. Volkow N. D., Li T. K. Drug addiction: the neurobiology of behaviour gone awry. *Nat Rev Neurosci* 2004; **5**: 963–70.
2. Kalant H. What neurobiology cannot tell us about addiction. *Addiction* 2010; **105**: 780–9.
3. Hall W. D. Avoiding potential misuses of addiction brain science. *Addiction* 2006; **101**: 1529–32.
4. Midanik L. *Biomedicalization of Alcohol Studies: Methodological Shifts and Institutional Challenges*. New Brunswick, NJ: Transaction Publishers; 2006.
5. Room R. Social policy and psychoactive substances. In: Nutt D., Robbins T., Stimson G., Ince M., Jackson A., editors. *Drugs and the Future: Brain Science, Addiction and Society*. London: Academic Press; 2007, p. 337–58.
6. Carter A., Capps B., Hall W. D., editors. *Addiction Neurobiology: Ethical and Social Implications*. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2009.
7. Hall W. D. Stereotactic neurosurgical treatment of addiction: minimizing the chances of another 'great and desperate cure'. *Addiction* 2006; **101**: 1–3.
8. Stelten B. M., Noblesse L. H., Ackermans L., Temel Y., Visser-Vandewalle V. The neurosurgical treatment of addiction. *Neurosurg Focus* 2008; **25**: E5.
9. Carter A., Hall W. D. The issue of consent in research that administers drugs of addiction to addicted persons. *Account Res* 2008; **15**: 209–25.
10. Goodman A. Neurobiology of addiction: an integrative review. *Biochem Pharmacol* 2008; **75**: 266–322.
11. Koob G. F., Le Moal M. *Neurobiology of Addiction*. New York: Academic Press; 2006.
12. West R. *Theory of Addiction*. Carlton, Victoria: Blackwell Publishing; 2006.
13. Levy N. The social: a missing term in the debate over addiction and voluntary control. *Am J Bioeth* 2007; **7**: 35.

A CALL FOR SYSTEMS APPROACHES IN ADDICTION RESEARCH

In his review about neurobiology and addiction, Harold Kalant comes to an important conclusion: 'It is inherently impossible to explain addiction by pursuing only the analytical study of drug interactions with the nervous system at ever finer levels of molecular structure and function' [1]. Instead of the classical reductive scientific approach in addiction research, he proposes to take a systems approach for achieving a better understanding of addictive behaviour. Thus, only by studying the interaction of drug effects with the different system levels, i.e. from the genetic to the molecular level, from the synaptic to the neuronal network level, and finally from the behavioural level to its interactions with the environment, will we be able to detangle the multi-dimensional puzzle of addictive behaviour [2,3]. Harold Kalant is most probably right in

his conclusion. However, before I deconstruct the classical reductive approach I would like to offer my appreciation to the fascinating research field of neurobiology. Neurobiology is the greatest playground for curious scientists, and the methodological progresses in this field are breathtaking. I would like to give just one example of how advanced neuroscience can be: only recently, optogenetic tools have been introduced to brain research. Optogenetics is an emerging field, combining optical and genetic techniques to probe neural circuits within freely moving laboratory animals, at the millisecond-timescale needed to understand brain information processing [4]. This technique is based on a group of light-sensitive ion channels called channelrhodopsins that can be integrated by genetic engineering into the neuronal cell membrane. By a laser-diode-coupled optical fibre targeting a specific neuronal population of interest, a brief light pulse can then activate those neurones. The Deisseroth laboratory from Stanford University has now applied this fascinating technique to stimulate the reward system and to induce conditioned place preference [5,6]. They introduced the light-sensitive proteins to different parts of the reward system. The animals then underwent a conditioned place preference study [7]. Instead of presenting a drug reward or any other reward, they applied pulses of light to either the ventral tegmental area or the nucleus accumbens via an optical fibre. Thus, whenever the mice moved into the designated location of the conditioning box, the light activated the light-sensitive proteins and switched on the biochemical signalling pathways which would normally be initiated when the animals are given a drug. Remarkably, the optical stimulation was sufficient to replace a drug reward, and as a result the mice spent more time the following day in the location at which the stimulation had been delivered than in other parts of the conditioning box [5,6]. From a technical viewpoint these studies are outstanding, but what have we learned from these studies? Not more, as we have already known from the classical studies by James Olds in the early 1950s. Following electrical stimulation of several brain sites he could also induce a conditioned place preference and thereby discovered the reward system [8]. Hence, in line with the conclusion from Harold Kalant, optogenetic studies are a much finer analysis of the molecular structure and function of the reward system than the initial studies by James Olds, but will not help us to understand why, in some individuals, repeated drug administration leads to an allostatic decrease in reward function [9], and thereby induces a compulsive drug-taking behaviour. Instead, a systems approach might be more helpful to understand the switch to compulsive drug use: a molecular oscillator model has been described where levels of oscillations are changed by repetitive drug administration, leading to set-point adjustments that may underlie allostatic shifts in drug reinforcement processes

[2,10]. Although systems approaches in addiction research are still in its infancy, they might eventually be useful for a better understanding of the addicted brain.

Declaration of interest

None.

Keywords Allostatic shift, drug reinforcement, optogenetics, systems approach.

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References

1. Kalant H. What neurobiology cannot tell us about addiction. *Addiction* 2010; **105**: 780–9.
2. Gebicke-Haerter P. J., Tretter F. The systems view in addiction research. *Addict Biol* 2008; **13**: 449–54.
3. Spanagel R. Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiol Rev* 2009; **89**: 649–705.
4. Zhang F., Wang L. P., Boyden E. S., Deisseroth K. Channelrhodopsin-2 and optical control of excitable cells. *Nat Meth* 2006; **3**: 785–92.
5. Tsai H. C., Zhang F., Adamantidis A., Stuber G. D., Bonci A., de Lecea L. *et al.* Phasic firing in dopaminergic neurons is sufficient for behavioural conditioning. *Science* 2009; **324**: 1080–4.
6. Airan R. D., Thompson K. R., Fenno L. E., Bernstein H., Deisseroth K. Temporally precise *in vivo* control of intracellular signalling. *Nature* 2009; **458**: 1025–9.
7. Tzschentke T. M. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. *Addict Biol* 2007; **12**: 227–462.
8. Olds J., Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 1954; **47**: 419–27.
9. Ahmed S. H., Koob G. E. Transition to drug addiction: a negative reinforcement model based on an allostatic decrease in reward function. *Psychopharmacology (Berl)* 2005; **180**: 473–90.
10. Ahmed S. H., Graupner M., Gutkin B. Computational approaches to the neurobiology of drug addiction. *Pharmacopsychiatry* 2009; **42**: S144–52.

WHAT INTEGRATED INTERDISCIPLINARY AND TRANSLATIONAL RESEARCH MAY TELL US ABOUT ADDICTION

In his paper [1], Kalant raises important points regarding how addiction is conceptualized and researched. This topic seems particularly timely, given current preparations for the next editions of the International Classifica-

tion of Diseases and Diagnostic and Statistical Manual (DSM). At the paper's onset, Kalant provides a definition for addiction: 'compulsive use of the drug despite the occurrence of adverse consequences'. Although this definition was widely agreed upon in prior iterations of the DSM including the current DSM-IV-TR [2], several DSM-V research work-groups (including those relating to substance use disorders and obsessive-compulsive spectrum disorders) have recently discussed at length the extent to which non-substance behaviors or disorders (e.g. related to gambling) should be considered addictions [3].

Kalant cites the importance to studies of addiction of the decision to self-administer drug (or by extension engage in the potentially addictive behavior) by individuals who become addicted. Decision-making represents an important and arguably central component of addiction [4], and performance of individuals with addictions on neurocognitive tasks assessing decision-making has been associated with treatment outcome [5] and real-life measures such as the ability to maintain employment [6]. Precisely how decision-making relates to addictions, however, is less clear. For example, individual differences in decision-making prior to substance exposure could lead to initial engagement in substance use and substance use may generate suboptimal decision-making. Animal models seem particularly well suited to investigate such questions, and pre-clinical studies indicate that not only does substance-naive impulsive decision-making predict substance self-administration [7,8], but also that substance intake, probably in a developmentally sensitive fashion, influences decision-making [9].

Decision-making and related processes (e.g. impulsivity) represent complex, multi-faceted constructs [10], with their expression influenced by genetic and environmental factors in a dynamic and complicated fashion. Multiple individual differences, including those relating to gender, emotional reactivity and stress responsiveness, among others, represent important considerations with respect to addictions and frequently co-occurring disorders, and an improved understanding of how individual differences relate to decision-making, and addiction will probably be facilitated by an integrative translational research approach involving multiple disciplines [11]. Such approaches ideally might involve studying behaviors (e.g. through analogous tasks in pre-clinical and clinical settings) and using assessments (e.g. relating to brain imaging or genetics) across species such that findings from each study might be linked directly with one another, while at the same time affording unique insight through the utilization of 'species-specific' techniques (e.g. through self-report, diagnostic and real-life measures in human studies and genetic manipulation and neurochemical measurements from brain tissues in pre-clinical