Editorial

Claudia Hägele^a Werner Strik^c Andreas Heinz^{a, b}

^aDepartment of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité Universitätsmedizin Berlin, and

^bBerlin School of Mind and Brain, Berlin, Germany; ^cUniversity Hospital of Psychiatry, Bern, Switzerland

Addictive disorders rank among the most devastating mental maladies in the industrialized countries [1]. In Germany, more than 150,000 patients die from alcohol- and tobacco-related problems, which is more than 40-fold the amount of patients dying because of the use of illegal drugs [2]. There is an urgent need to improve the understanding of the mechanisms that contribute to the development and maintenance of addiction as well as therapeutic approaches that target such key mechanisms. Recent years have seen a steady increase in neurobiological research that focuses not only on the correlates of key symptoms of addiction, such as drug craving or reduced control of drug intake, but also on learning dysfunctions, which promote habitual drug intake in spite of its negative consequences [3–5]. Individual learning mechanisms include pavlovian and operant conditioning and can be computationally modelled [6, 7]. This computational approach helps to identify key steps in decision-making and their respective functional correlates, which help to bridge the gap between neural network alterations on the one hand and clinical symptoms on the other. To date, most research on such learning mechanisms has been gained in animal experiments, and computational models of specific learning mechanisms have only recently been applied to clinical studies [8, 9]. Particularly, pavlovian-to-instrumental transfer, i.e. the effect of appetitive and aversive pavlovian stimuli on approach and avoidance behaviour, appears to play a key role in cue-induced craving and relapse [10, 11]. Drug-related cues, such as pictures of alcoholic beverages, may thus facilitate approach behaviour and induce relapse [12, 13]. Other paradigms focus on the distinction between habitual and goal-directed behaviour to explain a shift from goal-directed to ha-

bitual drug intake. In healthy controls, computational models have recently been developed to distinguish between complex model-based behaviour that serves consciously chosen goals on the one hand, and habitual model-free behaviour that is mainly driven by recent reward feedback on the other [7]. The latter has mainly been associated with activation of the dorsal striatum, while the former has been associated with interactions between the prefrontal cortex and the ventral striatum [14, 15]. Such models can help to better understand the development and maintenance of habitual drug intake and its contribution to drug addiction and relapse. Improved understanding of learning mechanisms can help to individually adjust therapeutic interventions that aim at behaviour modification.

The supplement starts with a review of environmental and genetic factors that interact with learning mechanisms in the development of alcohol dependence; Hägele et al. [16] compare animal experiments and human studies and emphasize effects of e.g. early stress exposure and other risk factors on the neurobiological correlates of reward learning that promote excessive alcohol intake.

Samochowiec et al. [17] deepen the aspect of genetic risk factors for alcohol dependence. There is a high number of candidate-gene-based, linkage and genome-wide association studies that identify genetic variation underlying the risk to develop addiction. Allelic variance in several candidate genes increases the risk to develop and maintain alcohol dependence. While the respective influence of each of these variations appears to be pretty small, the relatively strongest links were found in genes associated with alcohol metabolism (e.g. alcohol dehydrogenase gene clusters). Some genetic findings also point to dopamine and related

neurotransmitters, which interact with the mesolimbic reward system, a core area of operant and habitual learning [18].

Alterations of the mesolimbic reward system and neurobiologically closely connected prefrontal areas have also been observed in gambling disorders; such similarities strengthen the idea that substance-related and non-substance-related addictions share common mechanisms. Romanczuk-Seiferth et al. [19] present a growing body of work on gambling disorder and discuss similarities and dissimilarities between alcohol dependence and pathological gambling.

A key role of learning mechanisms has also been hypothesized with respect to the maintenance of alcohol dependence, which is discussed in a review of Garbusow et al. [20]. As part of a research group funded by the Deutsche Forschungsgemeinschaft, Garbusow et al. [21] present first results from studies specifically targeting pavlovian-to-instrumental transfer, and Sebold et al. [22] present habitual versus goal-directed behaviour in patients with alcohol dependence and healthy controls. Their data suggest that there is a prominent pavlovian-to-instrumental transfer

effect in patients with alcohol dependence, which appears to be stronger than in healthy controls and may thus contribute to cue-induced relapse. Furthermore, while patients did not show an increased tendency to respond habitually in a two-step decision task, they showed alterations of goal-directed behaviour that can contribute to a reduced control of alcohol intake.

Altogether, the articles present current developments in addiction research that can help to bridge the gap between genetic findings and neurobiological alterations on the one hand and key clinical symptoms of alcohol dependence such as craving, reduced control or compulsive drug intake on the other. Comparing substance-related and non-substance-related disorders, the present findings emphasize common mechanisms contributing to addictive behaviour and their functional correlates in mesolimbic and prefrontal networks. We hope that this supplement promotes the rather new field of computational modelling in addiction research and thus helps to improve psychotherapies that are directly based on learning mechanisms, such as cue exposure or cognitive behaviour therapy, and to identify new targets for pharmacological interventions.

References

- Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T: Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *Lancet* 2013;382:1575–1586.
- Deutsche Hauptstelle für Suchtfragen: Jahrbuch Sucht 2014. Lengerich, Pabst Science Publishers, 2014.
- Kalivas PW, Volkow ND: The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* 2005;162:1403–1413.
- Robinson TE, Berridge KC: The incentive sensitization theory of addiction: some current issues. *Philos Trans R Soc Lond B Biol Sci* 2008;363:3137–3146.
- Heinz A, Beck A, Wrase J, Mohr J, Obermayer K, Gallinat J, Puls I: Neurotransmitter systems in alcohol dependence. *Pharmacopsychiatry* 2009;42:S95–S101.
- Huys QJ, Cools R, Golzer M, Friedel E, Heinz A, Dolan RJ, Dayan P: Disentangling the roles of approach, activation and valence in instrumental and pavlovian responding. *PLoS One* 2011;7:e1002028.
- Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ: Model-based influences on humans' choices and striatal prediction errors. *Neuron* 2011;69:1204–1215.
- Montague PR, Dolan RJ, Friston KJ, Dayan P: Computational psychiatry. *Trends Cogn Sci* 2012;16:72–80.
- Geurts DE, Huys QJ, den Ouden HE, Cools R: Aversive pavlovian control of instrumental behavior in humans. *J Cogn Neurosci* 2013;25:1428–1441.
- Everitt BJ, Robbins TW: Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005;8:1481–1489.
- Dolan RJ, Dayan P: Goals and habits in the brain. *Neuron* 2013;80:312–325.
- Grüsser SM, Wrase J, Klein S, Hermann D, Smolka MN, Ruf M, Weber-Fahr W, Flor H, Mann K, Braus DF, Heinz A: Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology* 2004;175:296–302.
- Beck A, Wustenberg T, Genauck A, Wrase J, Schlagenhaut F, Smolka MN, Mann K, Heinz A: Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. *Arch Gen Psychiatry* 2012;69:842–852.
- Di Chiara G, Bassareo V: Reward system and addiction: What dopamine does and doesn't do. *Curr Opin Pharmacol* 2007;7:69–76.
- Park SQ, Kahnt T, Beck A, Cohen MX, Dolan RJ, Wrase J, Heinz A: Prefrontal cortex fails to learn from reward prediction errors in alcohol dependence. *J Neurosci* 2010;30:7749–7753.
- Hägele C, Friedel E, Kienast T, Kiefer F: How do we 'learn' addiction? Risk factors and mechanisms getting addicted to alcohol. *Neuropsychobiology* 2014;70:67–76.
- Samochoń J, Samochoń A, Puls I, Bienkowski P, Schott BH: Genetics of alcohol dependence: a review of clinical studies. *Neuropsychobiology* 2014;70:77–94.
- Heinz A, Beck A, Meyer-Lindenberg A, Sterzer P, Heinz A: Cognitive and neurobiological mechanisms of alcohol-related aggression. *Nat Rev Neurosci* 2011;12:400–413.
- Romanczuk-Seiferth N, van den Brink W, Goudriaan AE: From symptoms to neurobiology: pathological gambling in the light of the new classification in DSM-5. *Neuropsychobiology* 2014;70:95–102.
- Garbusow M, Sebold M, Beck A, Heinz A: Too difficult to stop: mechanisms facilitating relapse in alcohol dependence. *Neuropsychobiology* 2014;70:103–110.
- Garbusow M, Schäd DJ, Sommer C, Jünger E, Sebold M, Friedel E, Wendt J, Kathmann N, Schlagenhaut F, Zimmermann US, Heinz A, Huys QJ, Rapp MA: Pavlovian-to-instrumental transfer in alcohol dependence: a pilot study. *Neuropsychobiology* 2014;70:111–121.
- Sebold M, Deserno L, Nebe S, Schäd DJ, Garbusow M, Hägele C, Keller J, Jünger E, Kathmann N, Smolka M, Rapp MA, Schlagenhaut F, Heinz A, Huys QJ: Model-based and model-free decisions in alcohol dependence. *Neuropsychobiology* 2014;70:122–131.