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RESEARCH HIGHLIGHT

Getting to the core of relapse: The role of the nucleus accumbens core in the incubation of methamphetamine seeking after choice-based abstinence

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Methamphetamine is currently the most widely abused psychostimulant drug in the world, its use being especially prevalent in North America and East Asia. Addiction to methamphetamine is characterised by high rates of relapse after detoxification. At present, contingency management is probably the most effective treatment for methamphetamine addiction. Contingency management treatment is based on operant conditioning principles, whereby desired behaviour from the participant, such as treatment adherence, is positively (reward) or negatively (punishment) reinforced. In the context of addiction treatment, contingency management treatment typically comprises rewarding abstinence from drug use with non-drug commodities like monetary vouchers. However, after cessation of contingency management, the risk of relapse remains high [1]. It is therefore important to understand the neurobehavioural mechanisms by which contingency management reduces drug use, and how relapse after its discontinuation comes about.

Here, Rossi et al. [2] used a discrete-choice setup to emulate how contingency management promotes abstinence from methamphetamine use in rats. This model is based on fascinating findings from Ahmed and colleagues [3], who showed about a decade ago that when given a mutually exclusive choice between palatable food and cocaine, the majority of rats on the majority of occasions preferred food over drug. The intriguing implication of these observations is that if animals forego drugs if alternative non-drug rewards are simultaneously available, it can be used as a preclinical model of contingency management treatment. Another important feature of addictive behaviour in the Rossi et al. study [2] is based on the observation that drug cue-controlled reinstatement of responding increases after abstinence, a phenomenon called 'incubation of craving' [4]. In their study, Rossi and colleagues investigated the role of the nucleus accumbens, a forebrain structure widely implicated in appetitive behaviour, subjective pleasure and addiction [5], in the incubation of responding for a methamphetamine-associated cue after food choice-based abstinence.

In the first experiment, expression of the neuronal activity-associated immediate early gene product Fos was investigated after 1 and 15 days of testing for methamphetamine vs. palatable food choice—virtually equivalent to abstinence from drug. Consistent with previous findings [6, 7], methamphetamine taking in the choice procedure declined to very low levels, and responding for the methamphetamine-cue was markedly higher after 15 days vs. 1 day of testing, confirming the incubation effect. Since anatomically and functionally distinct core and shell subregions can be distinguished in the nucleus accumbens [5], Rossi et al. investigated these two regions separately. The data were clear-cut: in the core, the expression of Fos protein was profoundly increased after 15 days of abstinence, i.e. in animals that showed incubation of methamphetamine seeking, whereas no changes in cellular activity in the accumbens shell region were found. The increased Fos expression was not specific to a particular set of output neurons, as co-labelling with both dopamine D1 and D2 receptors was observed. This latter observation is important, since nucleus accumbens GABAergic output neurons that express D1 vs. D2 receptors project to distinct output regions [5]. To test whether functional activity in the core vs. shell underlies the incubation of methamphetamine seeking, the authors next pharmacologically inactivated these regions with a mixture of the GABA receptor agonists muscimol and baclofen. Consistent with the previous experiment, functional inactivation of the core, but not the shell reduced incubated methamphetamine seeking on day 15. Methamphetamine seeking on day 1 was not affected, although this may be the result of a floor effect. To gauge the role of dopamine in incubated methamphetamine seeking, in the final experiments Rossi et al. infused a dopamine D1-, dopamine D2-, or a non-selective dopamine receptor antagonist into the core. Treatment with all three antagonists reduced methamphetamine seeking on day 15, but not on day 1 (although rates of responding on day 1 were again low).

The study by Rossi et al. [2] thus implicates the nucleus accumbens core in incubated methamphetamine seeking in a rat model of contingency management. Two important observations in this study should be highlighted. First, the selective involvement of the core region is noticeable. Both the nucleus accumbens core and shell have been implicated in relapse-like behaviour, and the present findings resonate particularly well with the notion that the core is important for the influence of appetitive cues on behaviour [5, 8]. In addition, the present findings add to our knowledge of how distinct output channels of the nucleus accumbens, that express either dopamine D1 or D2 receptors, steer behaviour. Both co-operative and opposing roles for D1-receptor and D2-receptor expressing cells have been postulated [5], and the data from Rossi et al. are consistent with the former notion, implicating both types of dopamine receptors— and the cells that express them—in incubated methamphetamine seeking.

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Clearly, the findings by Rossi et al. also raise questions for future research, for example about the generalisability of the findings. First, a particular strength of the choice model used here, emulating voluntary abstinence during contingency management, is its high translational value. It would therefore be of great interest to know whether comparable neural mechanisms underlie relapse after another form of voluntary abstinence, that uses punishment to model negative consequences of addictive behaviour [9]. Second, it is important to know whether the mechanisms reported here also underlie relapse to the use of other substances of abuse. For example, both common and distinct mechanisms have been implicated in the incubation of methamphetamine vs. cocaine seeking [10]. Identification of a common neural circuit of relapse would be an enormous step forward, not least since co-abuse of different drugs is widespread among addicts, and motivations for abstinence will also differ between individuals. The third question relates to the associative structure of behaviour measured here. On test, the animals receive response-contingent presentations of the drug-associated cue, which effectively is a test for conditioned reinforcement. However, it is unclear to what extent humans receive the cues that drive their addictive behaviour in a response-dependent, instrumental way or a passive, Pavlovian manner. Since the influence of Pavlovian vs. instrumental cues—and their interaction, in so-called Pavlovian-to-instrumental transfer—on behaviour is different, and relies on dissociable neural mechanisms [8], it is important to distinguish these, as this will further enhance the translatability of findings in relapse models.

In sum, the study by Rossi et al. [2], together with previous findings [6, 7], begins to outline a neural network underlying relapse to drug use after contingency management-based abstinence, that includes the anterior insular cortex, central amygdala, dorsomedial striatum and nucleus accumbens core. Further extension of this network, and elucidating the functional flow of information in it may reveal the neural underpinnings of relapse. This knowledge can ultimately aid in the treatment of addiction, by identifying targets for deep brain stimulation, transcranial magnetic stimulation, or drug development.

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ADDITIONAL INFORMATION

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