Researchers test meth-addicted rats in a rodent casino

10 July 2015, by Christopher Packham

(Medical Xpress)—The altered decision-making patterns associated with neuropsychiatric disorders such as substance addiction are well documented, but it is unclear whether this dysfunction is the result of preexisting conditions or a consequence of the habitual abuse of drugs. Certainly, it's true that addiction is characterized by the continuous use of harmful substances despite negative consequences and in the absence of positive consequences.

Decision making involves three complex neural processes: (1) assessing possible options and forming preferences; (2) the selection and execution of an action; and (3) experiencing and evaluating the outcome. In a condition of methamphetamine addiction, these processes are distorted and easily lead to negative outcomes. In order to determine if pathological decision making is caused by methamphetamine addiction or is, rather, the cause of addictive behavior patterns itself, a group of Japanese researchers built a rodent casino and subjected methamphetamine-addicted rats to a gambling test. They have published their results in the *Proceedings of the National Academy of Sciences*.

A group of test animals was administered methamphetamine over a period of time intended to induce addiction. Control animals received saline instead of methamphetamine. The "slot machine" with which the animals were tested consisted of four choice arms. One of the arms was low-risk/low-reward (L-L), resulting in a small reward with high probability. It delivered one food pellet in 14 out of 16 trials, but would occasionally deliver a pellet coated in bitter quinine. Another arm was high-risk/high reward (H-H), which delivered seven food pellets in two out of 16 attempts, but which usually delivered one quinine pellet. The other two arms were empty. The conditions were similar to those of the Iowa gambling test administered to human subjects.

The researchers report that the chronic methamphetamine-treated rats chose the H-H arm more frequently than the control animals. Further, after receiving the large reward, the methamphetamine-treated rats exhibited "win-stay" behavior, choosing the H-H arm more frequently in subsequent trials than did the control rats, despite the likelier negative outcome of the quinine pellet. Additionally, when the methamphetamine-treated rats received the quinine pellet in the L-L arm, they switched to the H-H arm on the next attempt far more frequently than the control rats.

The authors conclude that chronic methamphetamine-treated rats assign higher motivational values to large rewards. There are several possible explanations for this result, including that the methamphetamine treatment altered the relative motivational values associated with a small reward. The researchers determined that this was, in fact, the cause by applying reinforcement learning models to the test data.

They further explored the neurological changes precipitated by methamphetamine treatment by subjecting the rats to c-Fos immunohistochemistry, reporting a number of results. In the

methamphetamine-treated rats, the researchers found evidence of neural activation in the insular cortex, nucleus accumbens, and striatum associated with altered decision making.

Additionally, they administered bilateral microinjections of GABA receptor agonists to suppress the insular cortical activity in methamphetamine-treated rats, finding that their H-H condition choice ratio gradually decreased. They write, "The insular cortex is also critically involved in descision making. INS activation is related to reward expectations in decision making, as are the amygdala, basal ganglia, and the orbitofrontal cortex. The INS contributes to conscious drug urges and decision-making processes that precipitate relapse."

More information: "Insular neural system controls decision-making in healthy and methamphetamine-treated rats." *PNAS* 2015 ; published ahead of print July 6, 2015, DOI: 10.1073/pnas.1418014112

Abstract
Patients suffering from neuropsychiatric disorders such as substance-related and addictive disorders exhibit altered decision-making patterns, which may be associated with their behavioral abnormalities. However, the neuronal mechanisms underlying such impairments are largely unknown. Using a gambling test, we demonstrated that methamphetamine (METH)-treated rats chose a high-risk/high-reward option more frequently and assigned higher value to high returns than control rats, suggestive of changes in decision-making choice strategy. Immunohistochemical analysis following the gambling test revealed aberrant activation of the insular cortex (INS) and nucleus accumbens in METH-treated animals. Pharmacological studies, together with in vivo microdialysis, showed that the insular neural system played a crucial role in decision-making. Moreover, manipulation of INS activation using designer receptor exclusively activated by designer drug technology resulted in alterations to decision-making. Our findings suggest that the INS is a critical region involved in decision-making and that insular neural dysfunction results in risk-taking behaviors associated with altered decision-making.