Roots of risky decisions in drug dependence

Decision-making is a key activity of everyday life. Consequently, disturbances in the ability to make appropriate decisions or anticipate their possible consequences can result in massive social, medical, and financial problems. In the Iowa gambling test developed by Bechara et al., normal healthy controls exhibit preference for long-term advantageous options associated with moderate immediate rewards over long-term disadvantageous options associated with high immediate rewards. This test is a sensitive means for detecting impairment of decision-making in patients with ventromedial prefrontal cortex lesions and other neuropsychiatric disorders. Impairment of decision-making in neuropsychiatric disorders is associated with an inability to make profitable long-term decisions that incorporate expectations of future outcomes. Thus, impaired decision-making is recognized as a core problem in the neuropsychiatric disorders, and a better understanding of the mechanisms underlying impaired decision-making should provide insights that lead to successful treatments for these diseases.

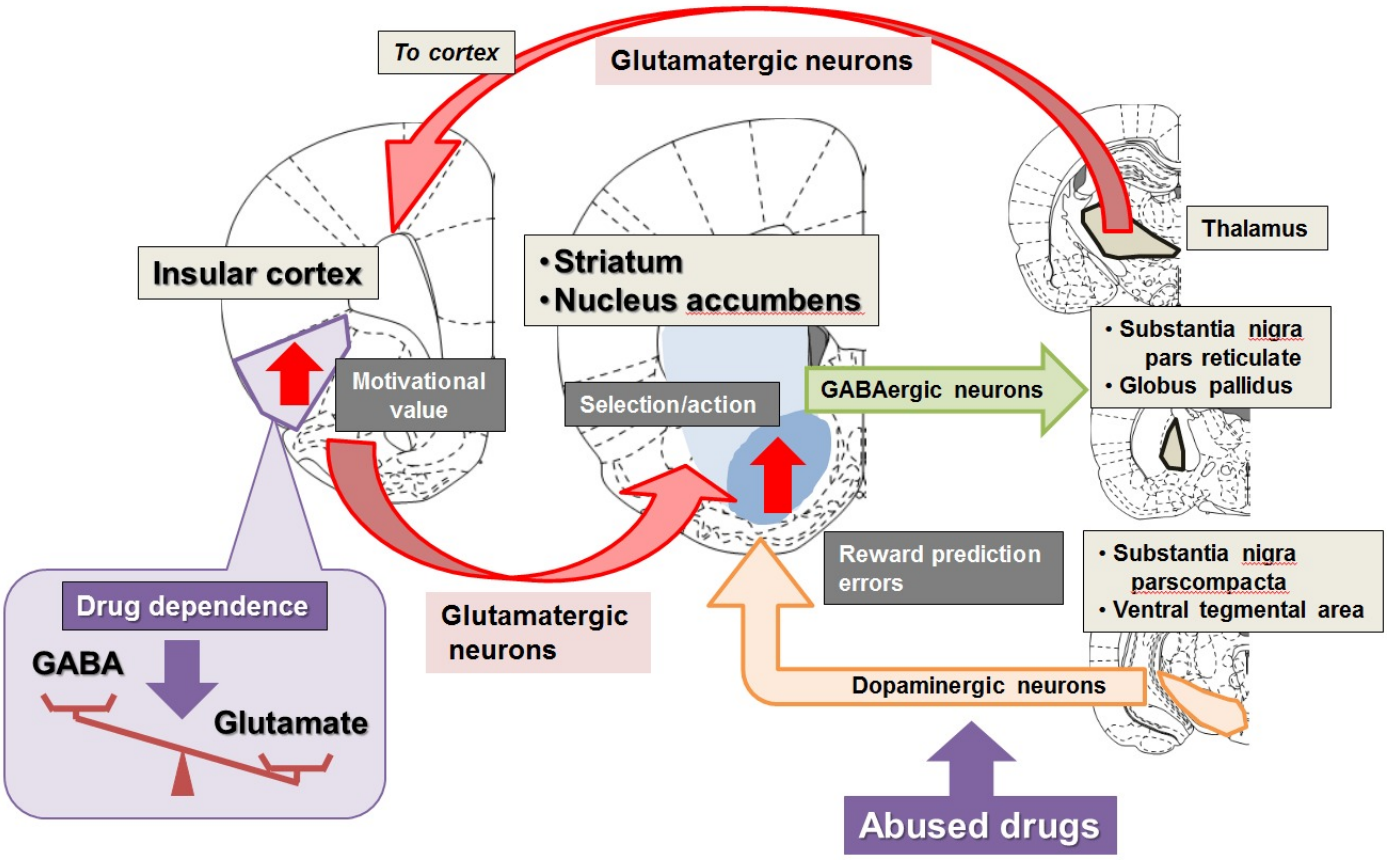

Fig. 1. Hypothesis regarding neural circuits underlying impaired decision-making in methamphetamine dependence. Treatment with a drug such as methamphetamine influences the function of dopaminergic neurons that encode reward prediction errors, as well as that of basal ganglion neurons involved in selection/action. In drug dependence, the insular GABA system is

dysfunctional, leading to disinhibition of glutamatergic neurons. Noticeably, insular cortex may determine motivational value.

Drug dependence is defined as a chronically relapsing disorder that is characterized by compulsive drug taking, inability to limit intake, and intense drug cravings. Addicts also exhibit impaired decision-making, and a hallmark of addiction is continuous use of substances despite negative consequences or the absence of positive consequences. Addicts are less able to flexibly adapt their behavior to changes in reward contingencies, have difficulties in integrating reinforcements to guide future behavior, and have a greater tendency to engage in risk-taking behaviors and to choose actions that confer short-term rewards at the cost of long-term disadvantages. However, the neural substrates underlying these deficits remain to be elucidated.

To address this issue, we sought to identify areas of the brain that play critical roles in decision-making, in particular areas in which aberrant activity is associated with deficits in this process. To this end, we developed a gambling test for use in rats, based on the Iowa gambling test, and used it to investigate the effect of chronic methamphetamine administration on decision-making in rats.

Our study revealed that rats treated with methamphetamine choose high-risk/high-reward options in decision tasks more frequently than control animals. Methamphetamine-treated rats assigned higher motivational values to large rewards, a change in decision-making that may have roots in altered activation of the brain's insular cortex and nucleus accumbens. Pharmacologic experiments combined with genetic manipulations suggest that the insular cortex may play a critical role in decision-making and risk-taking behavior. Moreover, GABAergic interneurons in the insular cortex are involved in altered decision-making in methamphetamine-treated rats, implicating insular GABA in the motivational values of rewards, similar to dopamine in the reward system, serotonin in impulsivity and patience, and noradrenaline in attention and arousal (Fig. 1). Because decision-making is a cognitive process that influences many aspects of daily living, as well as both mental and physical health, the findings of this study have broader implications. In addition, our results are of potential clinical importance: our pharmacological findings regarding the specific role of insular cortex suggest that GABA receptors might be targeted by novel therapies aimed at treating impaired decision-making in patients with neuropsychiatric or addiction disorders.

Publication

Insular neural system controls decision-making in healthy and methamphetamine-treated rats.
Mizoguchi H, Katahira K, Inutsuka A, Fukumoto K, Nakamura A, Wang T, Nagai T, Sato J, Sawada M, Ohira H, Yamanaka A, Yamada K
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