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# Non-human primate models in drug addiction deserve more attention

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**Dear Editor,**

The process of relapse involves firm or aberrant memories of environmental cues associated with drug craving or addiction. To date, it is not known where these memories are stored in the brain, what kinds of regulatory biological factors or molecules are involved, nor why it is so difficult to stop addiction psychologically. Currently, rodent animal models, such as the self-administration and conditioning place preference / aversion paradigm are still widely used in the studies of drug withdrawal syndromes or drug-associate memories. However, the differences between humans and rodents—particularly in terms of genetics, and pathology and pharmacology—have significantly limited the application of further studies on this topic. Essentially, rodents lack the long-term or life-time memories humans possess and lose their drug-associated memory only after a few weeks of withdrawal.

Compared to rodents, non-human primates have numerous intrinsic advantages that make them an irreplaceable animal model for studying drug addiction, especial relapse. Non-human primates are not only closely related to humans in terms of taxonomic status, but also possess a sophisticated developed prefrontal cortex (PFC) and experience patterns of addictions similar to humans. For example, similar to humans, rhesus monkeys (*Macaca mulatta*) are able to remember morphine-associated cues for at least 36.3±1.3 months after six injections of morphine (Wang et al, 2012; Wu et al, 2012). Some laboratories have also applied monkeys in drug addictive self-administration paradigm (Foltin & Evans 2001) and have combined it with brain imaging techniques (MRI and PET) to explore the changes in the white matter, gray matter, and other brain regions, especially the PFC (Nader& Banks，2014; Smith et al, 2014). Non-human primates have also been used in screening genes of addiction vulnerability, molecules and pathways in addiction memory (e.g., CREB, ΔFosB, PKMzeta, ERK pathway, etc.) (Nestler, 2013;Shema et al, 2011), as well as epigenetic alterations to drug addiction (DNA methylation, histone acetylation/methylation, non-coding RNA, etc.; Nestler, 2014).

Addiction is a complicated process involving both brain malfunction and homeostatic dysfunction (Naqvi, 2014; Paulus et al, 2013). Previous studies indicated that insula and viscerosensory responses play active roles in addiction (Contreras et al, 2007; Naqvi et al, 2007). Alongside PFC, which is one of the most highly focused areas in addiction research (Chen, 2013), other brain areas such as the orbito-frotal cortex (OFC), limbic system and striatum, are increasingly becoming research targets in non-human primate studies. Similarly, other key aspects of addiction including interoceptive reflexes, emotional and environmental contexts, and social status, are being examined using non-human primates.

In addition, as another close relative to human, tree shrews (*Tupaia belangeri chinensis*) are quickly becoming a common animal model in biomedical research (Xu et al, 2013). Wiens et al (2008) reported that the pentailed tree shrew (*Ptilocercus lowii*) evolves a specific metabolic system to avoid alcohol intoxication, while Sun et al (2012) found that tree shrews can develop morphine addiction. Therefore, tree shrews may be considered as a viable animal model in addiction studies.

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## References


Contreras M, Ceric F, Torrealba F. 2007. Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium. *Science*, **318**(5850): 655-658.

Chen BT, Yau HJ, Hatch C, Kusumoto-Yoshida I, Cho SL, Hopf FW, Bonci A. 2013. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature*, **496**(7445): 359-362. doi:10.1038/nature12024.

Foltin RW, Evans SM. 2001. Location preference related to smoked heroin self-administration by rhesus monkeys. *Psychopharmacology*, **155**(4): 419-425.

Nader MA, Banks ML. 2014. Environmental modulation of drug taking: Nonhuman primate models of cocaine abuse and PET neuroimaging. *Neuropharmacology*, **76**: 510-517.

Naqvi NH, Rudrauf D, Damasio H, Bechara A. 2007. Damage to the insula disrupts addiction to cigarette smoking. *Science*, **315**(5811): 531-534.

Naqvi NH, Gaznick N, Tranel D, Bechara A. 2014. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. *Annuals of the New York Academy of Sciences*. doi: 10.1111/ nyas.12415.

Nestler EJ. 2013. Cellular basis of memory for addiction. *Dialogues in Clinical Neuroscience*, **15**(4): 431-443.

Nestler EJ. 2014. Epigenetic mechanisms of drug addiction. *Neuropharmacology*, **76**: 259-268.

Paulus MP, Stewart JL, Haase L. 2013. Treatment approaches for interoceptive dysfunctions in drug addiction. *Frontiers in Psychiatry*, **4**: 137-144.

Shema R, Haramati S, Ron S, Hazvi S, Chen A, Sacktor TC, Dudai Y. 2011. Enhancement of consolidated long-term memory by overexpression of protein kinase Mzeta in the neocortex. *Science*, **331**(6021): 1207-1210.

Smith HR, Beveridge TJB, Nader MA, Porrino LJ. 2014. Regionally-specific alterations in myelin proteins in nonhuman primate white matter following prolonged cocaine self-administration. *Drug and Alcohol Dependence*, **137**:143-147.

Sun YM, Yang JZ, Sun HY, MA YY, Wang JH. 2012. Establishment of tree shrew chronic morphine dependent model. *Zoological Research*, **33**(1): 14-18.

Wang JH, Wu XJ, Li CY, Wei JK, Jiang HH, Liu CR. 2012. Effect of morphine on conditioned place preference in rhesus monkeys. *Addiction Biology*, **17**(3): 539-546.

Wiens F, Zitzmann A, Lachance M-A, Yegles M, Pragst F, Wurst FM, von Holst D, Guan SL, Spanagel R. 2008. Chronic intake of fermented floral nectar by wild treeshrews. *Proceedings of the National Academy of Sciences*, **105**(30): 10426-10431.

Wu XJ, Zong W, Sun YM, Hu XT, Ma YY, Wang JH. 2012. Morphine addiction in non-human primates using rhesus monkeys. *Zoological Research*, **33**(1): 89-91. (in Chinese)

Xu L, Zhang Y, Liang B, LV LB, Chen CS, Chen YB, Zhou JM, Yao YG. 2013. Tree shrews under the spot light: emerging model of human diseases. *Zoological Research*, **34**(2): 59-69. (in Chinese)