The transition to addiction defines the shift from a controlled drug use to a compulsive drug taking that culminates in loss of control over drug consumption (1, 2). This pathological behavior is observed in a restricted number of drug users after a prolonged period of drug intake (2, 3).

To uncover the biological basis of transition to addiction, substantial resources have been devoted to the study of the neurobiological effects of drugs of abuse. These investigations have identified a large number of drug-induced modifications in brain physiology (4–10) and morphological changes (11, 12). Despite these advances, which drug-induced alterations specifically underlie the transition to addiction in vulnerable individuals are currently unknown (13).

A few years ago it was discovered that addiction exists and can be studied in animals and highly specific responses to previously encountered invasive pathogens.

**References and Notes**

7. Materials and methods are available as supporting material on Science Online.
18. We thank D. Zhang, H. Roberts, J. Notarangelo, S. Armstrong, S. Compente, M. Provenza, J. Bodeuw, and R. McArthur for their technical support and B. Stecher, W.-D. Hardt, A. J. Müller, N. A. Bos, C. Mueller, R. M. Zinkernagel, A. G. Rolink, A. Lanzavecchia, and C. Reis e Sousa for their helpful comments and editing the manuscript. Grant support: Swiss National Science Foundation (310030_124732), Canadian Institutes of Health Research, Crohn’s and Colitis Foundation of Canada, Genome Canada, Fannsom Foundation, Canadian Association of Gastroenterology. This research was also supported with funding from the Canada Research Chairs program to K.D.M. and A.J.M. M.H. is a fellow of the Prof. Dr. Max Cloëtta foundation and was supported by grants of the OncoSuisse Foundation (OCS 02113-08-2007). S.H. was supported in part by a German Science Foundation fellowship, and the clean mouse facility Bern was supported by the Genaxen Foundation. The authors have no conflicts of interests to declare.

Supporting Online Material

www.sciencemag.org/cgi/content/full/328/5986/1705/DC1
Materials and Methods
Figs. S1 to S11
Tables S1 and S2
References

17 February 2010; accepted 14 May 2010 10.1126/science.1188454

---

**Transition to Addiction Is Associated with a Persistent Impairment in Synaptic Plasticity**

Fernando Kasanetz, Véronique Deroche-Gamonet, Nadège Berson, Eric Balado, Mathieu Lafourcade, Olivier Manzoni, Pier Vincenzo Piazza

Chronic exposure to drugs of abuse induces countless modifications in brain physiology. However, the neurobiological adaptations specifically associated with the transition to addiction are unknown. Cocaine self-administration rapidly suppresses long-term depression (LTD), an important form of synaptic plasticity in the nucleus accumbens. Using a rat model of addiction, we found that animals that progressively develop the behavioral hallmarks of addiction have permanently impaired LTD, whereas LTD is progressively recovered in nonaddicted rats maintaining a controlled drug intake. By making drug seeking consistently resistant to modulation by environmental contingencies and consequently more and more inflexible, a persistently impaired LTD could mediate the transition to addiction.

---

1. **INSM U862, NeuroCentre Magendie, 147 Rue Léo Saignat, 33077, Bordeaux Cedex, France.** 2. Université de Bordeaux, 147 Rue Léo Saignat, 33077, Bordeaux Cedex, France.
3. These authors contributed equally to this work.† These authors contributed equally to this work.‡ To whom correspondence should be addressed. E-mail: olivier.manzoni@insERM.fr (O.M.); pier-vincenzo.piazza@insERM.fr (P.V.P.)
most used procedure to evaluate voluntary drug intake in animals (25). As previously described (14), between 40 and 50 days of SA, we measured behaviors that are similar to the hallmarks of substance dependence in the reference diagnostic manual DSM-IV (1, 26): (i) The subject has difficulty stopping drug use and/or limiting drug intake. We measured cocaine seeking during a period in which the drug was signaled as not available. (ii) The subject has an extremely high motivation to take the drug, with activities focused on its procurement and consumption. We used a progressive ratio schedule in which the number of responses (ratio) to obtain one drug infusion progressively increases within the session, and we measured the breakpoint, the last ratio completed, which is considered a reliable index of the motivation for the drug (16). (iii) Drug use is continued despite negative consequences. We measured the persistence of the animal in seeking cocaine when it was signaled that its delivery would be associated with a punishment.

In agreement with what was previously shown (14, 27), after 50 days of SA, ~20% of the rats were positive for the three addiction-like behaviors (Addict group), whereas a large proportion of the animals (40%) were positive for none (Non-Addict group) (Fig. 1A) (26).

Addict and Non-Addict animals were compared for glutamate-dependent LTD in the nucleus accumbens core (NAC), which is an important substrate of drug seeking (4, 22). This comparison was made between 50 and 72 days of SA with NAC slices that were obtained 24 hours after the last SA session. In the NAC, basic parameters of synaptic transmission, such as the amplitude and the frequency of spontaneous excitatory postsynaptic currents (EPSCs) as well as short-term synaptic plasticity, were not modified by prolonged cocaine SA (fig. S1). In contrast, N-methyl-D-aspartate receptor (NMDAR)–dependent LTD (fig. S2), induced in medium spiny neurons with a pairing protocol (26), was suppressed in Addict rats, although it was normal in Non-Addict and control animals (Fig. 1, B and C). Strengthening this result, we also found a positive correlation between the normalized EPSC after LTD induction, an...
Fig. 3. NMDAR-dependent LTD was impaired during early stages of cocaine self-administration (SA). (A) LTD in the nucleus accumbens in animals self-administering cocaine for 7 or 17 days. LTD induction (in percent of baseline) was normal in controls (73.3 ± 3.5%, n = 8, W = 36, P < 0.01) and in Cocaine 7 days (56.7 ± 7.8%, n = 7, W = 21, P < 0.05) groups, but was absent in Cocaine 17 days animals (96.7 ± 1.5%, n = 6, W = 18, P = 0.07). Rats tested for saline SA for either 7 (n = 4) or 17 (n = 4) sessions were used for the control group. (B) After 17 days of cocaine SA, LTD was observed in controls (77.2 ± 7.2% of baseline, n = 11, W = 50, P < 0.05), but was absent in both Addiction Resistant (134.4 ± 10.6%, n = 7, W = −24, P > 0.05) and Addiction Vulnerable animals (106.8 ± 12.1%, n = 6, W = −3, P > 0.84). Rats of matching age and purchase, left undisturbed in the animal house, were used as controls. For both (A) and (B), individual experiments (top) with representative EPSC traces and averaged data (bottom) are shown. Arrows: pairing stimulations; horizontal lines: baseline levels.

Fig. 4. Persistent impairment in NMDAR-dependent LTD is associated with transition to cocaine addiction. (Top) Transition to addiction as shown by the evolution over sessions of the persistence in responding during the nondrug periods in Addict and Non-Addict animals. (Bottom) Changes in NMDAR-dependent LTD in the NAC as a function of cocaine exposure and vulnerability to addiction.
LTD, but rather its persistent impairment, that is associated with the transition to addiction.

This persistent impairment in LTD could explain the loss of control on drug intake observed in Addict rats. LTD in the NAC is considered important in rescaling synapses that were enhanced during acquisition of motor responses and cue-reward associations (31, 32), allowing those synapses to encode future associations and restore flexibility to neuronal circuits. The persistent inability to rescale synapses in Addict animals may render drug-seeking behavior consistently resistant to modulation by environmental contingencies, finally resulting in loss of control over drug intake. Thus, the major behavioral difference between Addict and Non-Addict animals, similar to that in humans (/), is their capacity to adjust their drug intake as a function of environmental contingencies. Non-Addicts can stop seeking drugs if they know that the drug is not available, if it requires an excessively high workload, or if taking the drug acquires negative consequences. Addicts have lost this ability and continue to seek drugs independently of environmental conditions.

Our results also provide unanticipated insight into the type of homeostatic alterations that characterize Addicts. We expected, as largely assumed in the field, to discover a specific pathophysiological adaptation—a particular phenotype characterizing synaptic plasticity in Addicts. In contrast, the transition to addiction was associated, at least in the NAC, with a form of LTD, but rather its persistent impairment, that is ant to modulation by environmental contingencies, similar to that observed in Addict rats. LTD in all rats. This probably corresponds to the situation when an individual engaged in sustained drug use experiences the sensation that “it is becoming too much” and that “a line is being crossed.” Fortunately, for most individuals, the brain adapts to recover a normal plasticity and allows learning to control drug intake. In contrast, the anaplasticity that characterizes addicts makes them enter a downward spiral in which drug-associated stimuli, which can no longer be overridden by other associations, gain more and more power in controlling behavior, finally leading to the compulsive drug intake that characterizes addiction.

Our results suggest that the failure of an individual to counteract the impairment in NMDAR-LTD induced by chronic cocaine administration, which results in a persistent deficit in synaptic plasticity, contributes to the transition to addiction. A clear understanding of the molecular substrates that mediate this lack of adaptation in Addicts could unravel new targets for the development of efficient therapies for drug abuse.

References and Notes
26. Materials and methods and supporting data are available on Science Online.
33. Supported by ANR (2005), EU-STREP/COMP (F6), MILDIT/INCa/INserm (2008) grants to P.V.P., O.M., and V.D.G. The authors report no conflict of interest.

Supporting Online Material
www.sciencemag.org/cgi/content/full/328/5967/1709/DC1
Materials and Methods
Figs. S1 to S4
References
2 February 2010; accepted 13 May 2010
10.1126/science.1187801

Incidental Haptic Sensations Influence Social Judgments and Decisions
Joshua M. Ackerman,1 Christopher C. Nocera,2 John A. Bargh3

Touch is both the first sense to develop and a critical means of information acquisition and environmental manipulation. Physical touch experiences may create an ontological scaffold for the development of intrapersonal and interpersonal conceptual and metaphorical knowledge, as well as a springboard for the application of this knowledge. In six experiments, holding heavy or light clipboards, solving rough or smooth puzzles, and touching hard or soft objects nonconsciously influenced impressions and decisions formed about unrelated people and situations. Among other effects, heavy objects made job candidates appear more important, rough objects made social interactions appear more difficult, and hard objects increased rigidity in negotiations. Basic tactile sensations are thus shown to influence higher social cognitive processing in dimension-specific and metaphor-specific ways.

The hand is one of the most important adaptations in our evolutionary history. From infancy, humans use their hands for two primary functions: to acquire information and to manipulate their environments. These sensory and effector capabilities facilitate learning, communication, the development of social bonds, and a host of other fundamental processes. Yet, despite the fact that tactile sensations are critical to both our intrapersonal and interpersonal lives, touch remains perhaps the most underappreciated sense in behavioral research (/).

Hands are purposive devices—they typically are used on objects (active touch) rather than objects being used on them (passive touch) (2). Active touch in particular allows for the integration of exploratory and information-processing abilities, as when sensory and motor systems exert influence over each other. That is, tactile sensations can suggest the use of specific muscle movements, whereas physically manipulating objects can enhance sensory sensitivity, improving information acquisition and making subsequent

1Sloan School of Management, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E62, Cambridge, MA 02142, USA. 2Department of Psychology, Harvard University, 3 Kirkland Street, Cambridge, MA 02138, USA. 3Department of Psychology, Yale University, Post Office Box 208205, New Haven, CT 06520, USA.