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

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sus (fig. S11). This suggests that in colonized animals persistence of a specific IgA response is limited by restimulation with other commensal bacterial species, allowing the mucosal immune system to adapt its IgA to commensals that are currently present in the intestine.

By using this system to allow transient colonization of germ-free mice in the absence of any other manipulation, we described that (i) induction of high-titer IgA can be uncoupled from permanent intestinal bacterial colonization, (ii) an intrinsic threshold exists between 10^8 and 10^9 bacteria below which the intestinal IgA system does not respond, (iii) the intestinal IgA system lacks classical immune memory characteristics, and (iv) the intestinal IgA repertoire is characterized by constant attrition and thus represents the dominant species currently present in the intestine. This deviates substantially from classical systemic immune memory paradigms and affects mucosal vaccine design and harnessing the effects of probiotic bacteria. Teleologically, intestinal IgA and serum IgG systems can be seen as complementary systems, with the intestinal IgA system continuously adapting to and protecting from the current microbiota and the systemic IgG system being capable of rapid and highly specific responses to previously encountered invasive pathogens.

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

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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.

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 morphology (*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 (*14–16*). Similar to humans, after a prolonged period of drug intake, a restricted number of rodents develop addiction-like behaviors (Addict rats), although the largest percentage maintains a controlled drug intake (Non-Addict rats). Because Addict and Non-Addict rats did not differ in the amount of drug taken (*14*), comparing these two groups of animals allows one to identify the biological changes specifically associated with the transition to addiction in vulnerable individuals.

Using this approach, we evaluated the role of synaptic plasticity in the transition to addiction. Activity-dependent long-term depression (LTD) and long-term potentiation (LTP) of synaptic transmission are the two principal forms of synaptic plasticity that permit strengthening (LTP) or weakening (LTD) of synapses in an interplay that allows the refinement of neuronal circuits necessary to adapt behavior to an ever-changing environment (*17*). Drugs of abuse modify LTP and LTD (*5, 10, 18–20*) in different areas (*21*) of the mesocorticolimbic system, one of the major substrates of drugs of abuse (*6, 19, 22, 23*). Drug-induced alterations in LTP and LTD have been proposed to be important factors leading to compulsive drug intake that they would facilitate by rendering drug taking impermeable to changes (*5, 24*). However, whether changes in synaptic plasticity occur specifically in individuals developing addiction or are nonspecific adaptations common to all the individuals exposed to drugs is currently unknown (*13*).

In the first experiment, rats were trained for cocaine intravenous self-administration (SA), the

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Fig. 1. NMDAR-dependent LTD was disrupted in Addict animals. (**A**) Differences between Addict ($n = 8$) and Non-Addict rats ($n = 8$) in (from left to right) persistence in responding when the drug is not available [$F_{(1,26)} = 9.14$, $P < 0.01$]; motivation for cocaine measured by the breakpoint in a progressive ratio schedule [$F_{(1,26)} = 70.36$, $P < 0.00001$]; responding despite negative consequences measured when cocaine infusions were associated with electric footshocks [$F_{(1,26)} = 6.15$, $P < 0.05$]; and addiction score [$F_{(1,26)} = 42.84$, $P < 0.0001$]. (**B**) Individual experiments (top) with representative excitatory postsynaptic current (EPSC) traces and averaged data (bottom) showing that LTD was induced in controls ($71.7 \pm 7.1\%$ of baseline, $n = 14$, $W = 69$, $P < 0.01$) and Non-Addict animals ($77.8 \pm 6.9\%$, $n = 13$, $W = 66$, $P < 0.005$) but not in Addicts ($118.9 \pm 17.9\%$, $n = 8$, $W = -9$, $P = 0.4$). Controls were left undisturbed for the duration of the experiments. Arrows indicate pairing stimulations; horizontal lines denote baseline levels. (**C**) Cumulative probability distribution of normalized EPSCs after LTD induction. Gray area represents LTD window. (**D**) Positive correlation (r) between the normalized EPSC after LTD and the addiction score ($r = 0.675$, $P < 0.01$). *$P < 0.05$, **$P < 0.01$ compared to Non-Addict.
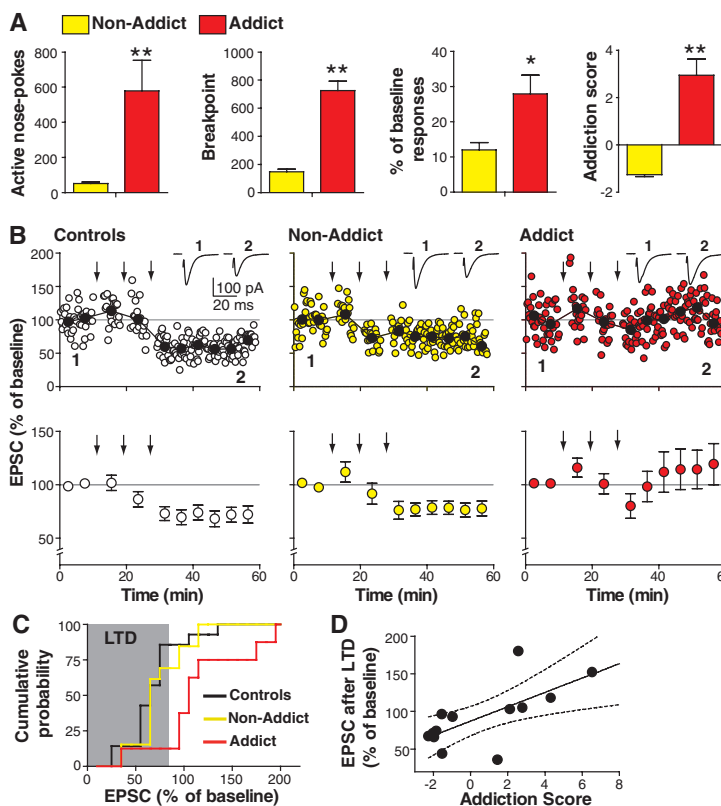
Fig. 2. Presynaptic mGluR2/3-mediated LTD in the NAC was intact after prolonged cocaine SA. Individual experiments (top) with representative field excitatory postsynaptic potential (fEPSP) traces and averaged data (bottom) showing that mGluR2/3-mediated LTD was induced in controls ($54.9 \pm 3.7\%$ of baseline, $n = 6$, $W = 21$, $P < 0.05$), Non-Addicts ($53.8 \pm 4.6\%$, $n = 7$, $W = 28$, $P < 0.05$), and Addicts ($55.8 \pm 9.1\%$, $n = 6$, $W = 21$, $P < 0.05$). Horizontal thin lines: baseline levels; LY: 10-min administration of the mGluR2/3 agonist (LY 379268, 100 nM).
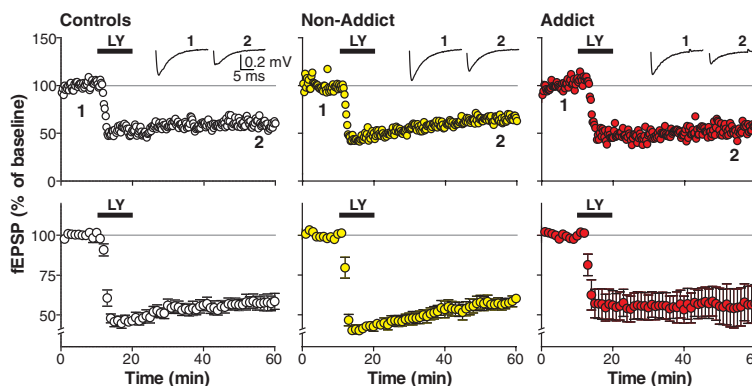
most used procedure to evaluate voluntary drug intake in animals (*25*). As previously described (*14*), between 40 and 50 days of SA, we measured behaviors that are similar to the hallmarks of substance dependence in the reference diagnostic manual DSM-IV (*1, 26*): (i) The subject has difficulty stopping 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 com-
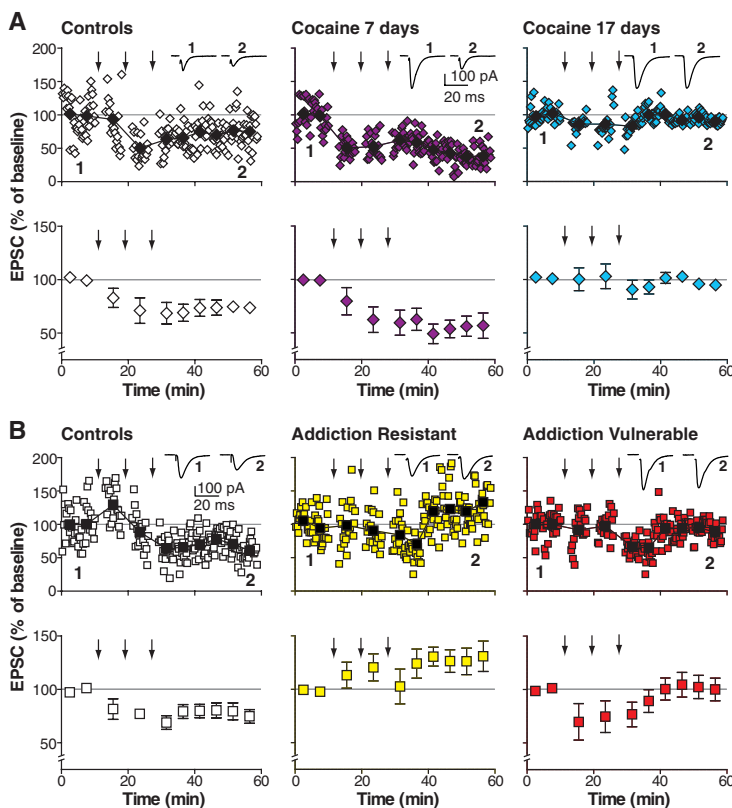
pleted, which is considered a reliable index of the motivation for the drug (*16*). (iii) Drug use is continued despite negative consequences. We measured the persistence of the animal in seeking cocaine when it was signaled that its delivery would be associated with a punishment.

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 compar-

ison 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.
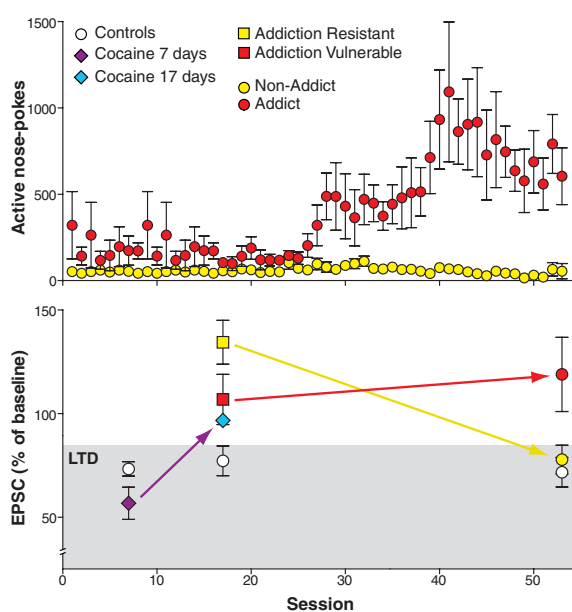
inverse measure of LTD, and the animals' addiction scores (Fig. 1D).

To evaluate if there was a general impairment of synaptic plasticity in Addict animals, we also measured the LTD mediated by mGluR2/3 receptors (28). In contrast to what was observed with NMDAR-LTD, no difference between groups was found for mGluR2/3-mediated LTD (Fig. 2).

We then studied, in our SA conditions, the evolution along time of NMDAR-LTD. One week of cocaine SA had no effect on NMDAR-LTD (Fig. 3A). However, confirming previous published observations (29, 30), NMDAR-LTD was completely abolished in rats that had self-administered cocaine for 17 days (Fig. 3A). A caveat of our and published experiments is that, after 17 days of SA, NMDAR-LTD was measured in rats that were not characterized for their vulnerability to addiction. Because in a general population only 20% of the rats belong to the Addict group, it is likely that very few future Addicts have been tested after 17 days of SA and that most of the modifications described concern Non-Addicts. To overcome this potential bias, we developed a method that allows Addict rats to be identified as early as after 17 days of SA (26) (fig. S3). We then compared animals that will (Addiction Vulnerable) or will not (Addiction Resistant) develop addiction after 17 days of SA. We found that NMDAR-LTD was suppressed in both groups of animals (Figs. 3B and 4).

Taken together, the results of the three experiments (Fig. 4) show that during the acquisition phase of SA (the first week), synaptic plasticity in the nucleus accumbens is not impaired by cocaine, supporting a role for NMDAR-LTD in the NAC in learning new reward-response associations. During the next stage (between 2 and 3 weeks of SA), once the learning has been consolidated, LTD is suppressed in all subjects. However, subsequently (between 8 and

10 weeks), a normal NMDAR-LTD is progressively recovered in animals that maintain a controlled drug intake, whereas it is persistently lost in animals undergoing the transition to addiction (Fig. 4). Because 2 weeks of SA are not sufficient for addiction-like behaviors to fully develop (Fig. 4 and fig. S4), these observations suggest that it is not a transitory loss in NMDAR-

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 (1), 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 pathological 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 anaplasticity, i.e., the incapacity of Addicts to counteract initial drug-induced impairments.

The anaplasticity of Addict rats is relevant to revising conceptualizations of the transition to addiction, currently seen as the progressive development of specific brain adaptations that lead to loss of control over drug intake. Our data suggest that instead, the transition to addiction could be mediated by the incapacity to engage the active processes that allow control of drug intake. After a prolonged exposure to drugs, all the subjects are probably at the point of losing control over drug-intake behavior, as shown by the loss of 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 intake, 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.

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Incidental Haptic Sensations Influence Social Judgments and Decisions

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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 (1).

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

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