authors' study — the light from the first half experiences a negative time delay (it accelerates) compared with the original green light, whereas that from the second half experiences a positive time delay (it slows down). This opens up a time gap of approximately 50 picoseconds in the transmitted light intensity. Afterwards, the time gap is closed seamlessly using similar techniques involving an oppositely dispersive medium from the first one and a second split time-lens (Fig. 1).

To demonstrate temporal cloaking in this system, Fridman *et al.*[7] created an 'event' in the form of a light pulse, at the centre of the time gap, that has a different frequency from that of the light passing through the system. The temporal cloaking is turned on or off by controlling the operation of the split time-lenses using additional laser light. The authors found that the detected signal associated with this event becomes more than tenfold weaker than the event's original signal. This result demonstrates that the event has been cloaked.

The distinction between temporal and spatial cloaking can be understood in terms of a metaphor involving automobile traffic. A spatial cloak acts like a junction in the form of a 'cloverleaf' interchange or flyover, in which the traffic is guided (by slip roads) to bend around a certain region of space. After passing through the junction, the traffic continues in the same direction as if the junction did not exist. By contrast, a temporal cloak behaves like a railway crossing. Traffic is stopped when a train passes, forming a gap in the traffic. After the train has passed the crossing, the stopped cars speed up until they catch up with the traffic in front of them, and the fact that a train has crossed the intersection cannot be deduced by observing the traffic flow.

Because spatial and temporal cloaking work in different physical dimensions — space and time, respectively — there is no fundamental reason why the two techniques cannot be combined so that full spatial–temporal cloaking could be turned on or off at will. Nonetheless, what Fridman *et al.* have demonstrated as a first unidirectional temporal cloaking device could already be useful in some applications, such as enhancing the security of communication in fibre-optic systems. Future directions may include increasing the cloaking time towards the order of microseconds to milliseconds, and building a device that can work simultaneously for incident light coming from different directions. ■

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NEUROSCIENCE

Behavioural effects of cocaine reversed

Cocaine use causes lasting changes in behaviour by altering the strength of connections between neurons. The finding that these changes can be reversed in mice suggests strategies that could be used to treat drug addiction. SEE LETTER P.71

MARINA E. WOLF

Synaptic plasticity — the process by which connections (synapses) between nerve cells grow stronger or weaker depending on their activity level — is essential to normal development and learning. But synaptic plasticity also has a role in brain disease, including that resulting from drug abuse. Understanding this role is a challenging problem. Over the past decade, drug-addiction researchers have made progress towards this goal, aided by the fact that different facets of addiction can be modelled in animals and involve well-characterized brain circuits. From these studies, we know that drugs of abuse produce synaptic plasticity in the brain's 'reward circuitry' and that this contributes to addiction-related behaviours. On page 71 of this issue, Pascoli *et al.*[1] report that reversal of cocaine-induced synaptic plasticity in mice resets such behaviours to the pre-cocaine baseline.

Pascoli *et al.* studied synaptic plasticity associated with cocaine-induced behavioural sensitization — the increased behavioural response to a drug that occurs over the course of repeated administration and which persists long after drug exposure is discontinued. Even a single cocaine exposure in mice can cause sensitization to the drug's locomotor stimulatory effects (hyperactivity), thereby enhancing the locomotor response to a subsequent 'challenge' injection of cocaine. Opinions differ about the clinical relevance of sensitization, but according to one influential addiction theory, cocaine's incentive motivational properties (which make users want it) undergo sensitization[2].

The authors focused on part of the brain known as the nucleus accumbens and its major cell type, the medium spiny neuron (MSN). These neurons receive and integrate input signals — in the form of glutamate molecules — from cortical and limbic brain regions that control motivated behaviours, and then signal the motor circuitry to trigger a behavioural response (Fig. 1). There is evidence that glutamate synapses to MSNs are strengthened in cocaine-sensitized rodents[3], but exactly which synapses are strengthened, and how this relates to sensitization, is controversial.

To address these fundamental questions, Pascoli *et al.* gave mice a single injection of saline or cocaine, using enough of the drug to produce 'one-shot' locomotor sensitization. They took brain slices from the mice 7 days later, and used high-frequency stimulation (HFS; a series of electrical pulses) to produce long-term potentiation of glutamate synapses onto MSNs of the nucleus accumbens in the slices. Long-term potentiation (LTP) is a form of synaptic plasticity in which increased activity strengthens glutamate synapses, often through insertion into the neuronal membrane of additional glutamate receptors known as AMPA receptors. The authors found that the magnitude of HFS-induced LTP produced in cocaine-exposed neurons was approximately half of that observed in saline-treated controls. This could be explained if cocaine selectively eliminates HFS-induced LTP in a subpopulation of MSNs. But which one?

MSNs can be classified according to whether they express the D1 or D2 subtype of dopamine receptor (D1R or D2R). These subpopulations generally have distinct projection targets and different functions, although the distinctions are less clear in the nucleus accumbens than in the neighbouring dorsal striatum[4]. To distinguish between these subpopulations, Pascoli *et al.*[1] used transgenic mice that express green fluorescent protein in either D1R- or D2R-expressing MSNs. They thus observed that a single exposure to cocaine abolished HFS-induced LTP selectively in D1R neurons.

Crucially, the authors found that the abolition was not caused by impairment of mechanisms

that elicit LTP. Rather, they showed that synapses in the D1R neurons had been strengthened by cocaine, and therefore could not be further potentiated by HFS. This cocaine-induced potentiation depended on the same mechanisms that underlie HFS-induced LTP in the nucleus accumbens, namely activation of a subgroup of glutamate receptors called NMDA receptors, and the ERK signalling pathway. So, when Pascoli *et al.* gave mice an inhibitor of the ERK pathway before cocaine injection, no cocaine-induced potentiation occurred, allowing HFS-induced LTP to be elicited.

The authors also observed that the time course of cocaine-induced potentiation in D1R MSNs mirrored that of locomotor sensitization: both sensitization and synaptic potentiation were observed a week after cocaine injection, but were absent after a month. The million-dollar question is whether synaptic potentiation is causally involved in sensitization. To find out, Pascoli *et al.* tested whether reversal of synaptic potentiation — a process known as depotentiation — would also reverse locomotor sensitization. To do this, they used an optogenetic method in which nerve terminals projecting from the infralimbic cortex to the nucleus accumbens in mice were modified so that they could be depolarized by light pulses. The authors gave these mice a single injection of cocaine, and applied light pulses 7 days later using a protocol that produces depotentiation at MSN synapses. Remarkably, when they gave the mice a challenge injection of cocaine 45 minutes after depotentiation, the 'depotentiated' mice did not exhibit locomotor sensitization.

Pascoli *et al.* confirmed these findings by using a different protocol (consisting of five daily cocaine injections) that produces more robust sensitization in mice. They found that when optogenetic depotentiation was performed on withdrawal day 10, just before a cocaine challenge, the expression of locomotor sensitization in the animals was prevented. In a key experiment, the authors then showed that this effect was long-lasting — a challenge injection of cocaine given to the mice 5 days after depotentiation was still unable to elicit a sensitized locomotor response.

These results are exciting because they offer hope that some of the neuroadaptations associated with cocaine exposure are reversible. This would not necessarily have been predicted, given that addicts exhibit extremely persistent changes in the brain and a lifelong vulnerability to relapse[5]. Furthermore, Pascoli and colleagues' approach differs in a subtle but important way from previous studies that have targeted plasticity mechanisms to inhibit cocaine seeking. Typically, a particular abnormality at a cocaine-exposed synapse has been identified and then normalized using an exogenous reagent (see, for example, refs 6, 7). By contrast, the current approach[1] normalized nucleus-accumbens synapses by altering their level of synaptic activation — that is, through the same physiological mechanism that the brain uses to regulate synaptic strength. Harnessing this physiological mechanism may make it possible to produce a more global and lasting normalization of synapses and behaviour. In humans, this might be accomplished using deep brain stimulation or transcranial magnetic stimulation, rather than optogenetics. Indeed, these approaches have shown some promise in animal studies[8].

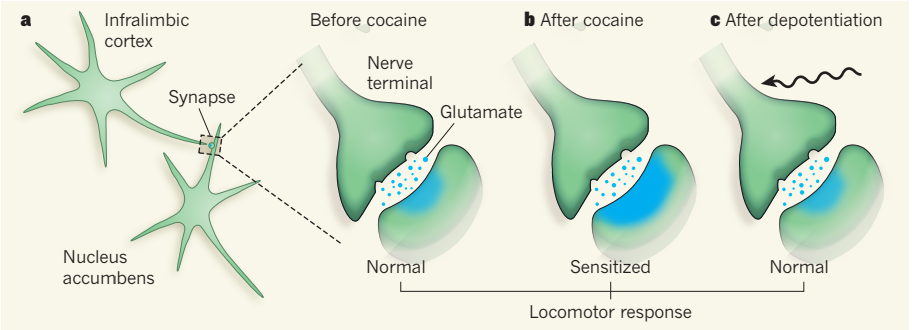

Figure 1 | Normalizing the locomotor response to cocaine in mice. **a**, Glutamate-releasing nerve terminals originating in the infralimbic cortex make excitatory connections (synapses) with medium spiny neurons that express D1 dopamine receptors in the shell subregion of the nucleus accumbens. These synapses regulate locomotor behaviour in mice. The blue region represents the postsynaptic density — the location of AMPA-type receptors that respond to glutamate released by the infralimbic nerve terminals. **b**, Cocaine injections strengthen these synapses (represented by a larger blue area). This synaptic potentiation is associated with a sensitized locomotor response — increased hyperactivity — in mice that are given a subsequent 'challenge' injection of cocaine. **c**, Pascoli *et al.*[1] report that depotentiation of these synapses using an optogenetic strategy (represented by the wavy arrow) resets the synaptic strength and normalizes the locomotor response to cocaine.

The next step should be evaluation of the depotentiation strategy in more sophisticated animal models that involve voluntary drug self-administration. These models measure an animal's motivation to obtain a drug based on the effort it is willing to expend — or even its willingness to tolerate punishment — in order to do so. Complexities in the neuroanatomy of the reward system will no doubt be important. For example, neurons in the nucleus accumbens receive glutamate projections from regions other than the infralimbic cortex, regions that also have critical roles in drug seeking[5]. So, although depotentiating a single pathway is sufficient to block locomotor sensitization[1], more complex approaches may be needed in self-administration experiments.

Similarly, although differentiating between D1R- and D2R-expressing cells is a useful starting point for studying functionally distinct MSN subpopulations in the nucleus accumbens, the issue of dopamine-receptor segregation is complex[4]. For example, the target regions of these subpopulations overlap[4], and many studies have uncovered cooperative effects of D1Rs and D2Rs on nucleus-accumbens firing and related behaviours[9,10]. Furthermore, within any neuronal population defined by the expression of a particular protein marker (such as the D1R), only a few neurons may actually contribute to behavioural output in a particular situation[11]. Finally, given that LTP in the nucleus accumbens is presumably caused by an increase in the number of synaptic AMPA receptors, it is logical to infer that depotentiation and reversal of sensitization reflect AMPA-receptor removal. Yet this inference is difficult to reconcile with previous studies[3] in cocaine-sensitized rodents, which showed that locomotor sensitization can be expressed under conditions in which AMPA-receptor levels are not elevated — at early withdrawal times, for example, before there is any increase in AMPA-receptor number.

Nevertheless, Pascoli and colleagues' paper[1] is a landmark in our understanding of cocaine-related plasticity and of how such plasticity might be harnessed in the development of addiction therapies. Their experimental approach provides a strategy for future studies: targeting a particular synapse, determining the stimulation parameters for its potentiation or depotentiation, and then developing a method to accomplish a desired adjustment in an intact animal. ■

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