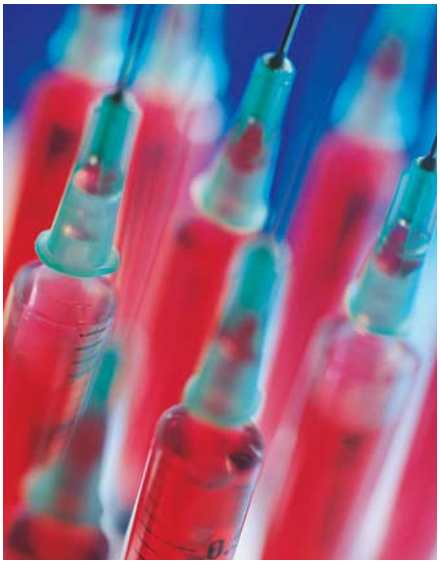
ADDICTION

True addiction



One of the obstacles to the study of drug dependence is the question of whether animals experience true addiction, rather than simply self-administering drugs. Two recently published papers in *Science* present evidence for a transition from drug taking to compulsive drug-seeking behaviour in rats — which parallels compulsive behaviour in humans — and help to explain the conditions under which this occurs.

Vanderschuren and Everitt reported that in rats trained to self-administer cocaine, there was a transition from casual drug taking to the compulsive drug seeking that is characteristic of addictive behaviour. They showed that the presentation of a conditioned harmful stimulus (the delivery of an electric shock) curbed drug-seeking behaviour in rats with a short-lived exposure to cocaine but had no effect in rats that had experienced a prolonged access to the drug. This effect was not seen when a natural reinforcer, sucrose, was used in place of the drug. Moreover, further experiments showed that an increase in incentive value of the drug and reduced fear conditioning or pain sensitivity could not explain these changes in behaviour. So, extended drug experience seems to induce compulsive, addiction-like behaviour.

Deroche-Gamonet *et al.* showed a similar transition to compulsive behaviour in rats after prolonged access to cocaine, again evident from an increase in drug seeking when the drug was not available and persistent drug taking in the face of harmful consequences (shock conditioning). Furthermore, these authors reported high levels of activity motivated towards procuring the drug. This was measured using a 'progressive-ratio schedule', whereby the number of responses required to receive the drug progressively increases until the animal reaches 'breaking point' (the maximum amount of work that an animal is prepared to do to receive the reward); the dependent rats showed higher breaking points. These three symptoms were present only in a subset (17%) of the rats — similar to the percentage of human cocaine users that are diagnosed as addicts — whereas the remainder tended to show a decrease in these addiction-like behaviours over time,

COGNITIVE NEUROSCIENCE

Synchronicity

Although many studies have shed light on the behavioural phenomena associated with visual attention, its neural mechanisms are much less well understood. A study published by Gross *et al.* in *Proceedings of the National Academy of Sciences* uses magnetoencephalography (MEG) to investigate how the different areas of the brain that have been implicated in attentional processes might interact, and how this could relate to behaviour.

The authors used a well-established effect — the 'attentional blink' — to investigate brain activity during attentional processes. Subjects have to look at a screen on which they see a stream of letters presented very rapidly (seven letters per second). The task is to spot two 'target' letters embedded in the stream among the non-target (distractor) letters. When the two targets are separated by only one distractor, so that they appear less than 500 ms apart, subjects find it harder to identify the second target. This period of reduced ability to identify the target is called the attentional blink.

Previous functional imaging studies have found several areas of the brain that seem to be involved in attention, including frontal, parietal and temporal regions. Gross and colleagues used MEG to measure the timecourse of activity in these areas, and to identify functional connections between them by looking for periods of long-range synchronization of activity.

Using a form of analysis called time–frequency representation, the authors found that presentation of visual targets, but not distractors, produced strong activity in the beta frequency band (13–18 Hz). The areas of the brain that showed high levels of activity in this band corresponded to those that had previously been implicated in attention by functional imaging studies.

By calculating the synchronization index between the individual regions, Gross *et al.* tested how the brain areas were connected into a functional network. The connections fell into two groups: in some cases (mainly connections between the occipital cortex and left hemisphere areas), synchronization depended on the presentation of any letter (target or distractor), whereas other connections showed modulation of the synchronization index only by target letters. The latter connections were between the right posterior parietal cortex and the left temporal and frontal cortex.

despite no differences in cocaine intake during the self-administration period. Importantly, a high level of drug-seeking behaviour was associated with relapse after periods of withdrawal of either 5 days or 30 days, which was not seen in rats that showed low levels of addiction-like behaviour.

These two papers present an animal model that distinguishes between drug taking and true addiction, and so opens up new avenues for the study of the biological mechanisms of drug dependence. Crucially, this might help to answer some key questions, such as why some individuals are more vulnerable to addiction than others.

Alison Rowan

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But is this synchronized activity related to behaviour? To test this, the authors compared trials in which the attentional blink prevented the subject from spotting the second target with those in which the second target was correctly identified, on the grounds that these two types of trial showed different attentional effects. They found that both overall synchronization during the trial and temporal modulation of synchronization (by targets as compared to distractors) were stronger in trials that showed no attentional blink (when subjects successfully identified the second target). The authors suggest that this enhancement of synchronization might reflect a state of higher vigilance, which allows the successful performance of the task.

These findings support the idea that different brain areas that form an 'attentional network' communicate through synchronization (in the beta band, but possibly also at other frequencies). Together with other evidence, this emphasizes the potential importance of synchronized neural activity in cognitive processes.

Rachel Jones

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PSYCHIATRIC DISORDERS

The anxious transmitter

Anxiety and sleep disorders affect millions of people around the world, but they are not well understood and often cannot be treated effectively. Reporting in *Neuron*, Xu and colleagues characterized a novel modulator, neuropeptide S (NPS), which might modulate arousal and regulate anxiety-related behaviours.

NPS was discovered as the ligand of an orphan G-protein-coupled receptor (GPCR) — a cloned GPCR with an unknown endogenous ligand. In this study, the authors analysed the pharmacological profiles of NPS and its cognate receptor, NPSR, and found that NPS binds to and activates NPSR with high potency and specificity.

Xu and colleagues then studied the tissue distribution of NPS and NPSR in rats. The mRNAs of both the NPS precursor and NPSR are expressed in various tissues, including the brain, thyroid, salivary and mammary glands. In the brain, the NPSR mRNA is widely expressed, including in the amydala and the midline thalamic nuclei. The NPS precursor mRNA is concentrated in a group of cells between the locus coeruleus and Barrington's nucleus, but its expression does not colocalize with either tyrosine hydroxylase or corticotrophin-releasing factor, which are markers of the predominant neuronal populations in these areas. The authors conclude that the NPS-expressing neurons might represent a previously unrecognized cluster of cells.

The locus coeruleus is the primary source of noradrenaline-mediated input to the cortex and has been implicated in regulating arousal and anxiety. Therefore, the authors conjectured that NPS might also be involved in arousal and anxiety. They found that intracerebroventricular injection of NPS increased locomotor activity in both naive and habituated mice. This correlated with the increased wakefulness and reduced amounts of slow wave sleep (stages 1 and 2) and REM sleep seen in rats treated with NPS.

But does NPS affect anxiety? In a test of free exploratory behaviour in a new environment, mice treated with NPS made an increased number of entries into the central zone of an open field, which could indicate an anxiolytic-like effect. To further study the effects of NPS on anxiety, the authors used another two tests — the light–dark box and the elevated plus maze — and found that mice treated with NPS showed less anxiety-related behaviour. As compounds that simulate general locomotor activity could also enhance exploration, the authors used the marble-burying test to validate the observed anxiolytic-like effects. They found that NPS reduced the number of marbles buried in a dose-dependent manner, an effect that is similar to that of several anxiolytic drugs such as the benzodiazepines.

Overall, these results support the idea that NPS might be part of a neurotransmitter system that modulates sleep–wake cycles and anxiety. This finding might shed new light on our understanding of sleep disorders such as insomnia and pathological states of anxiety.

Jane Qiu

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WEB SITE

Civelli's laboratory: http://www.ucihs.uci.edu/pharmaco/Research/laboratories/CIVELLI.html