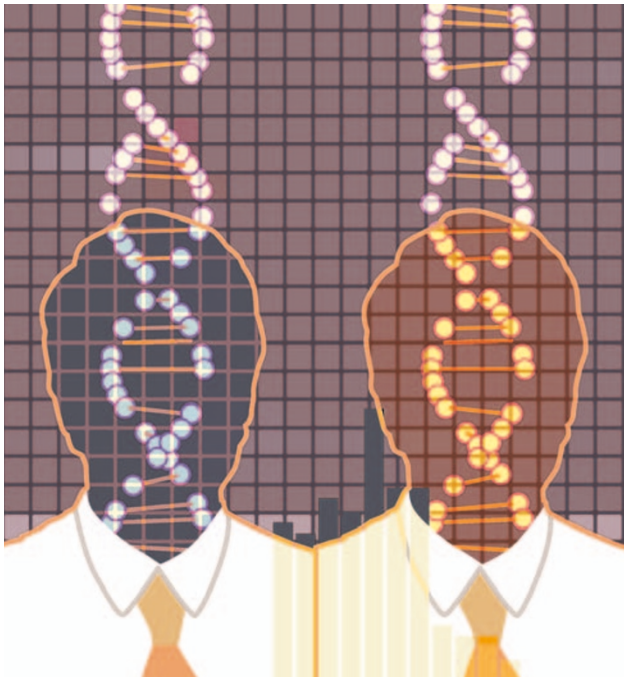
NEURODEGENERATIVE DISORDERS

Mapping multiple sclerosis genes



It is well established that multiple sclerosis is a heritable disease. Nevertheless, the susceptibility genes for this common condition have so far eluded researchers. Two studies reported in *Nature Genetics* now take us a step closer to unravelling the genetic risk factors that underlie this disorder.

The only known genomic region that has been linked to multiple sclerosis is the major histocompatibility complex (MHC) on chromosome 6, a large region that is involved in immune responses. Lincoln and colleagues used this as the starting point for their large-scale search for multiple sclerosis risk genes.

These researchers genotyped two independent samples of individuals with multiple sclerosis from Canada and Finland using a dense panel of single nucleotide polymorphisms (SNPs) that cover the MHC region. They confirmed the associations between this genomic region and multiple sclerosis. Moreover, they narrowed the candidate region to *HLA-DRB1* as the most promising susceptibility locus.

In the second study, Reich and colleagues used high-powered admixture mapping — a technique that identifies genomic regions with disease genes by exploiting differences in genetic marker frequency among different populations. Populations with combined ancestry have different frequencies of susceptibility genes that reflect the extent to which each original population has contributed to each individual's genome. As multiple sclerosis is more prevalent among European Americans than African Americans, genomic regions that contain risk genes would therefore be associated with a greater European than African contribution in African American individuals with multiple sclerosis.

Reich *et al.* studied a large group of African Americans and found a

ADDICTION

Brainwashing

For recovering addicts, the sight of drug-taking paraphernalia and other reminders of drug use can trigger intense cravings and relapses. Now, two studies report that it is possible to impair rats' memories associated with taking cocaine and that such treatments significantly reduce their drug-seeking behaviours.

Both studies are based on the belief that retrieval of some forms of memory are followed by an active 'refiling' process, known as memory reconsolidation. If this process is disrupted, memories might be weakened or even lost.

In the first study, Lee and colleagues trained rats to self-administer cocaine by nosepoking, thereby establishing a strong addiction. The animals then learned the association between nosepoking, cocaine infusion and the illumination of a light. This was followed by a 'reactivation' session, in which nosepoking resulted only in the light coming on. Before this session, the researchers blocked transcription of *Zif268* — a gene involved in reconsolidation — by infusing the antisense oligodeoxynucleotides into the amygdala. A few days later, the rats were taken to the same chamber, but this time two levers had been installed in it: pressing one lever lit the light associated with cocaine use, whereas pressing the other did nothing. Rats that had received the antisense treatment pressed the lever that illuminated the light significantly fewer times than their control counterparts.

In the second study, Miller and Marshall used the model of conditioned place preference, in which rats learned to associate the rewarding effects of cocaine with one chamber where the drug was provided, and later preferred to stay in that chamber even when no cocaine was available. Interestingly, the researchers found that this phenomenon was associated with activation of ERK, CREB, ELK1 (a member of the ETS oncogene family) and Fos in the accumbens core, which is involved in the initiation and maintenance of drug-seeking behaviours, but not in the accumbens shell, which mediates the primary rewarding effects of drugs. Infusion of an inhibitor of the ERK pathway, U0126, into the accumbens core blocks the activation of ERK, CREB, ELK1 and Fos as well as the animals' preference for the cocaine chamber.

As only drug-related memories were being recalled when the inhibitors were given, the resulting amnesia might be specific to those memories rather than having a general effect on all memories. These findings hint at an exciting new approach that might help addicts kick the habit.

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References and links

ORIGINAL RESEARCH PAPERS Lee, J. L. C. *et al.* Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. *Neuron* **47**, 795–801 (2005) | Miller, C. A. & Marshall, J. F. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* **47**, 873–884 (2005)

FURTHER READING Frankland, P. W. & Bontempi, B. The organization of recent and remote memories. *Nature Rev. Neurosci.* **6**, 119–130 (2005)