Disrupting addiction through the loss of drug-associated internal states

John A Dani & P Read Montague

Damage to the insula enables some smokers to quit easily and without relapse, reports a recent paper. The lesion may disrupt a a representation of internal bodily urges that is normally cued by learned drug associations.

Tobacco use is the second leading cause of death worldwide, responsible for five million deaths each year[1]. Of the 650 million people who smoke, half of those who do not quit will be killed by tobacco eventually. Coupled to this devastating loss of life are enormous economic costs. Tobacco use decreases productivity by producing illness, and it kills people after years of investment in training and while they are still productive. In 1994, tobacco use was estimated to cause an annual net loss of $200,000 million worldwide, with one third of the loss in developing countries[1].

Nicotine is the main addictive component of tobacco[2,3]. Without tobacco, nicotine supports self-administration, reinforces place preference and produces a withdrawal syndrome that is relieved by nicotine replacement. The addictive power of tobacco is exemplified by the difficulty of quitting[2,3]. Most smokers wish to quit and try repeatedly to do so. About one third attempt to quit each year, but less than 10% of those succeed. A recent paper in *Science*, however, showed that some stroke patients with damage to their insula can easily stop smoking[4].

The insula (**Fig. 1**) lies on an inward fold of the cerebral cortex, beneath the junction where the frontal, temporal and inferior parietal lobes of the cortex meet. It receives diverse cortical inputs and thalamic afferents that convey emotional and homeostatic information and projects to a variety of cortical regions, including sensory and association areas and orbitofrontal and cingulate cortex[5]. The insula also projects down to brainstem and limbic structures, including the amygdala, hypothalamus and nucleus accumbens of the ventral striatum. Thus, the insula is positioned to be, and appears to function as, an integrative center that links sensory information from the body, emotional information from limbic structures and conscious feelings arising in cortical regions. The insula is proposed to participate in the process of establishing a continually updated representation of our internal state[6].

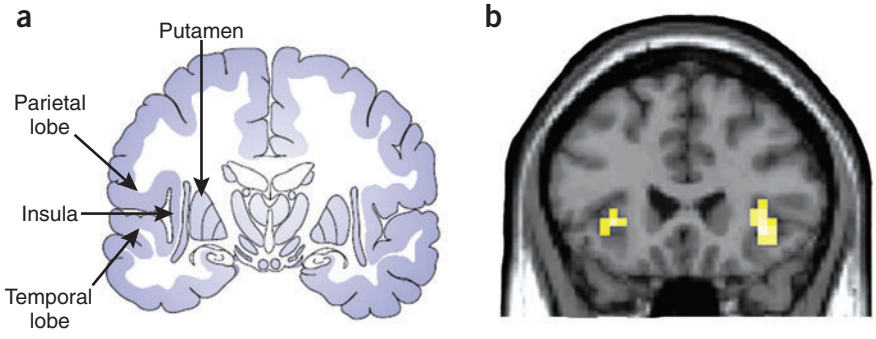

Figure 1 Drawing and fMRI image of the insula. (**a**) Coronal brain section depicting the insula. Reprinted by permission from Macmillan Publishers Ltd: Craig, A.D. *Nat. Rev. Neurosci.* **3**, 655–666 (2002). (**b**) Activation of the insula in a brain imaging study. Deviations from normal expectations activate the insula in just the fashion illustrated here. This kind of activation can arise for something as primal as the surprising delivery of disgusting stimuli to unfairness in monetary exchange games (image courtesy of B. King-Casas, Baylor College of Medicine).

In the new study, 69 patients with brain lesions (most due to stroke) were selected because they had similar smoking histories[4]. Nineteen of the 69 smokers had damage to the insula. Although there was a trend, damage to the insula, when compared with other regions, did not statistically alter the likelihood that a smoker quit smoking. However, damage to the insula seemed to be important for the subjective experiences associated with quitting. Twelve of the 13 patients with insula damage who quit smoking reported that they quit immediately and easily after acquiring the brain lesion. More importantly, they did not relapse and had lost their desire to smoke. Those with brain lesions outside of the insula were much less likely to have lost the urge to smoke or to have quit smoking with such ease. These results are consistent with other studies showing that cue-induced drug cravings correlate with insula activity[7,8]. Thus, the insula may participate in the representation of the internal bodily state recognized as the desire, urge or craving to smoke[5,6].

This interpretation of the insula is consistent with the emerging view that memories associated with addictive behaviors become internal motivational drives to relapse[2,7–10]. That is, environmental cues elicit internal states (bodily memories) that motivate cravings and, potentially, relapse. Although there is little direct evidence to support this hypothesis, this point of view is consistent with indications that the addiction process shares many commonalities with the synaptic plasticity associated with learning and memory[11].

Evidence is accumulating that events associated with addictive drugs can spur continued use, induce cravings and make long-term abstinence difficult. There are systems in the brain that normally function to help us learn how to exploit our environments successfully. Operating beneath our consciousness, these systems associate environmental situations with behavioral sequences that produce success[12]. Ultimately, those same environmental situations cue internal states that motivate the successful behaviors. For example, a pizza advertisement cues the internal state of hunger, which motivates the behavior of eating. That behavior, eating, successfully relieves the internal state, hunger.

Addictive drugs usurp these normally adaptive systems, which include the dopaminergic system originating in the ventral tegmental area of the midbrain. Whenever an addictive drug is used, there are associated

The authors are in the Department of Neuroscience, Menninger Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, USA.
e-mail: jdani@bcm.tmc.edu

events obligatorily linked to the usage. Smoking can be considered a learned (conditioned) behavior reinforced by nicotine. Those events associated with nicotine are also subject to conditioning. For smoking, the drug-taking behavior is associated with common events of the day, such as waking in the morning or the evening meal. After repeated conditioning, these drug-associated cues themselves motivate smoking. A recent functional magnetic resonance imaging study of addicted smokers showed that cues related to smoking elicit neural activity in regions linked to attention, memory, emotion and motivation[13]. In rats, presentation of nicotine-associated cues reinstated previously extinguished nicotine-seeking behavior, providing evidence that links nicotine-associated cues to relapse[14].

The drug-related associations that motivate use can also be aversive. For example, environmental cues linked to the acute symptoms of withdrawal may stimulate ongoing drug use. Withdrawal from chronic nicotine administration decreases 'reward' signaling, as detected by decreases in evoked dopamine release and elevated thresholds for intracranial self stimulation in rats[10,15]. Stimuli repeatedly paired with withdrawal discomfort come to elevate reward thresholds on their own. Thus, the changes in reward pathways normally caused by nicotine withdrawal eventually arise from conditioned stimuli that then cue drug use to relieve the symptoms[10]. The conditioned, neutral stimuli gain incentive salience that prompts continued nicotine use. Also, in human addicts, exposure to environmental situations previously paired with withdrawal provides a powerful cue for drug use. The withdrawal cue induces an aversive internal state that prompts normally adaptive behaviors to relieve that state. In this case, unfortunately, the behavior is continued drug use.

In summary, drug addiction subverts normal mechanisms of neuronal adaptation, learning and memory; leading to long-lasting changes in behavior that accrue with the ongoing progression of addiction[9,11]. Normal behavior develops as a function of experiences, such as those associated with adaptive reward-based learning, which is the essential process subverted by addiction[11]. Events and processes associated with the addictive drug (for example, the environment during drug-taking) become linked to the acquisition and delivery of drug, making them salient cues that prompt the desire for the drug[9].

Patients with lesions to the insula often quit smoking easily and lose the subsequent desire to smoke[4], and the insula is active during the urge for drugs[7,8]. Thus, a lesion to the insula seems to disrupt the representation of internal states[5,6] that underlie the motivation or urge for the drug (nicotine in this case). The accumulating evidence (albeit indirect) indicates that learned drug associates can cue internal states that perpetuate addiction. After the insula is lesioned, learned associations to the drug experience no longer produce the internal bodily states that drive drug use, particularly during periods of abstinence.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

1. WHO. World Health Organization, http://www.who.int/tobacco/health_priority/en/print.html (2007).
2. Balfour, D.J. *Nicotine Tob. Res.* **6**, 899–912 (2004).
3. Dani, J.A. & Harris, R.A. *Nat. Neurosci.* **8**, 1465–1470 (2005).
4. Naqvi, N.H., Rudrauf, D., Damasio, H. & Bechara, A. *Science* **315**, 531–534 (2007).
5. Craig, A.D. *Nat. Rev. Neurosci.* **3**, 655–666 (2002).
6. Damasio, A.R. *et al. Nat. Neurosci.* **3**, 1049–1056 (2000).
7. Bonson, K.R. *et al. Neuropsychopharmacology* **26**, 376–386 (2002).
8. Kilts, C.D. *et al. Arch. Gen. Psychiatry* **58**, 334–341 (2001).
9. Everitt, B.J., Dickinson, A. & Robbins, T.W. *Brain Res. Brain Res. Rev.* **36**, 129–138 (2001).
10. Kenny, P.J. & Markou, A. *J. Neurosci.* **25**, 6208–6212 (2005).
11. Hyman, S.E., Malenka, R.C. & Nestler, E.J. *Annu. Rev. Neurosci.* **29**, 565–598 (2006).
12. Schultz, W., Dayan, P. & Montague, P.R. *Science* **275**, 1593–1599 (1997).
13. Smolka, M.N. *et al. Psychopharmacology (Berl.)* **184**, 577–588 (2005).
14. Paterson, N.E., Froestl, W. & Markou, A. *Neuropsychopharmacology* **30**, 119–128 (2005).
15. Volkow, N.D., Fowler, J.S., Wang, G.J. & Goldstein, R.Z. *Neurobiol. Learn. Mem.* **78**, 610–624 (2002).

Developing recognition of faces and places

In adults, high-level visual cortex includes several regions that seem to be specialized for processing different classes of stimuli, such as faces or objects. However, little is known about the developmental trajectory of these areas or how this progression relates to aptitude in object, face or scene recognition. A paper on page 512 by Golijeh Golarai and colleagues provides an elegant demonstration of the concurrent changes in these specialized cortical regions and recognition memory during development. Their findings suggest that cortical maturation varies temporally across functional regions and is correlated with the development of category-specific recognition memory.

The authors used fMRI to identify areas of the occipito-temporal cortex that preferentially respond to objects (lateral occipital complex, LOC), faces (fusiform face area, FFA) or places (parahippocampal place area, PPA) in children, adolescents and adults. They found that children had smaller face-sensitive and place-sensitive cortical areas than adults, but no age-related changes in the size of object-selective cortical areas. In these same subjects, tests of recognition memory for faces, objects and places revealed that age was correlated with face and place recognition memory, whereas there were no effects of age on memory for objects. Finally, the authors went a step further to show that face recognition memory correlated with the size of the right FFA, and that place recognition memory correlated with the size of the left PPA. Object recognition memory was not correlated with the size of any of the cortical areas of interest.

These changes were specifically associated with improvements in recognition memory for faces and places, but not for objects, suggesting a more prolonged development of the FFA and PPA than the LOC, lasting at least until children reached the age of 11. One possible implication of this finding is that there may be an important role for experience even in the development of high-level visual cortex. In addition, the finding that better recognition memory was associated with increases in the size of specific cortical areas provides hints about the potential coding schemes that could be used in these areas to represent complex stimuli.

Hannah Bayer