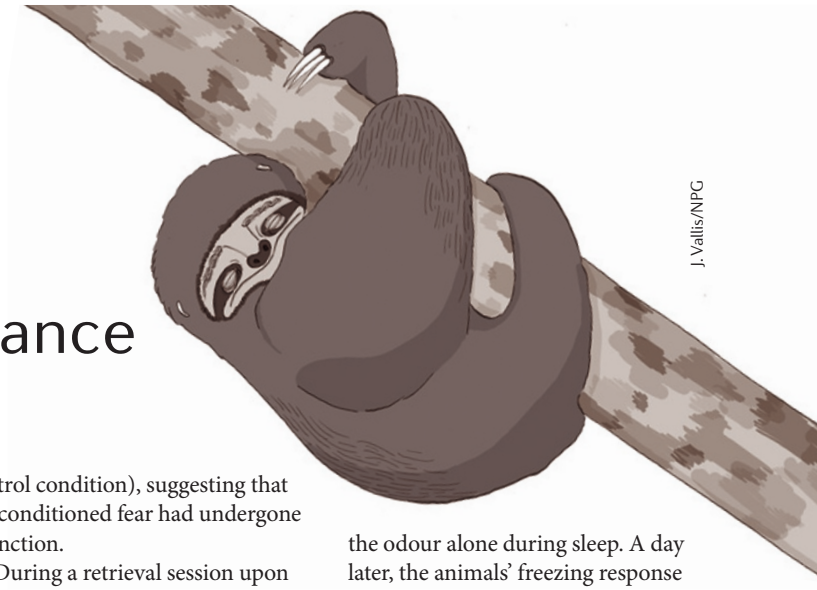

J. Vallis/NPG

LEARNING AND MEMORY

To sleep, perchance to forget

> Odour re-exposure during sleep had induced the formation of a new, 'safe' memory trace in the amygdala

Sleep has an important role in memory, and recent studies have shown that presentation of smells or sounds that accompanied learning can enhance procedural and episodic memories when re-presented in sleep. Two new studies now show that sleep can also be harnessed to manipulate specific fear memories.

In one study, Hauner *et al.* repeatedly showed human subjects two different face images (conditioned stimuli (CS+)), which were accompanied by delivery of either one odour (the target odour) or another (non-target) odour. Both target and non-target CS+ were paired with a mild shock on 50% of the trials to induce fear memories for the face image–odour combinations.

Immediately after the conditioning phase, subjects' skin conductance responses (SCRs) to the CS+ were higher than SCRs to images that had not been paired with a shock (CS–). In addition, exposure to CS+ increased functional MRI (fMRI) activation in the orbitofrontal cortex (OFC), insula, anterior cingulate cortex (ACC), hippocampus and amygdala — areas that have a role in olfactory and contextual conditioning.

About 1 hour after conditioning, the subjects took a brief nap, and the target odour was re-presented during slow-wave sleep. Presentation of the target odour caused a robust SCR during the first half of slow-wave sleep, but the SCR decreased in the second half (compared with a control condition), suggesting that the conditioned fear had undergone extinction.

During a retrieval session upon waking, the SCR to both CS+ faces was smaller than before sleep, but notably, the decrease was greatest for the target CS+; that is, for the CS+ whose associated odour had been delivered during sleep. This indicates that odour re-exposure had weakened the fear memory. Interestingly, re-exposure to the target odour in awake control subjects (who were asked to watch a documentary film) had the opposite effect.

After sleep, the fMRI response to the target CS+ was reduced (compared with pre-sleep) in the right anterior hippocampus, entorhinal cortex, ACC and amygdala. Moreover, multivariate fMRI pattern analysis revealed that distributed pattern activity in the left amygdala evoked by the target CS+ post-sleep was qualitatively distinct from pre-sleep, whereas this difference was less pronounced for the non-target CS+. This suggests that odour re-exposure during sleep had induced the formation of a new, 'safe' memory trace in the amygdala rather than simply a weakening of the original fear memory.

In a separate study, Rolls *et al.* exposed mice to a fear-conditioning session in which an odour (acting as the CS+) was paired with a footshock. The mice then stayed in their home cages for 24 hours, after which they were exposed to the odour alone during sleep. A day later, the animals' freezing response to presentation of the odour CS+ lasted longer than it did before sleep, indicating that odour-re-exposure had strengthened the fear memory. In a second experiment, the authors injected a protein synthesis inhibitor into the basolateral nucleus of the amygdala after fear conditioning and before re-exposing the mice to the odour during sleep. In contrast to the first experiment, this manipulation reduced the freezing response to the odour on the subsequent day.

Design differences between the two studies may explain the opposite effects of odour re-exposure: in the first, the odour served as the conditioning context, and odour re-exposure during sleep occurred immediately after fear conditioning; in the second, the odour served as the CS+, and odour re-exposure was delayed by 24 hours. Nevertheless, both studies show that specific emotional memories can be selectively manipulated during sleep by sensory stimuli. This idea has potential implications for the treatment of conditions such as specific phobias.

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ORIGINAL RESEARCH PAPERS
Hauner, K. K. *et al.* Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.3527 (2013) | Rolls, A. *et al.* Sleep to forget: interference of fear memories during sleep. *Mol. Psychiatry* http://dx.doi.org/10.1038/mp.2013.121 (2013)