denominational, and two 'slave systems'. The slave systems store visual and spatial information ('visuo-spatial sketchpad') or auditory information ('phonological loop'), and they keep it activated ('on line')⁹ for subsequent processing by the central executive. The anatomy of the central executive and slave systems is not well understood but, consistent with their distinct cognitive functions, they are thought to be anatomically segregated, with the central executive in the prefrontal cortex, and the slave systems associated with posterior cortical regions (for example, the parietal and temporal cortices).

Now, Courtney *et al.*³ have found that at least some functions of the slave systems may be carried out in the human prefrontal cortex. They presented subjects with pictures of human faces, and asked them to recall whether the picture being shown was the same, or different, from one that had been presented eight seconds earlier. The sequence of events in the task, and the time series used, allowed the authors to work out whether the activation of neurons in different regions correlated with the sequence of visual stimulation *per se*; pictures of faces in particular; or the interpolated delay periods between the presentation of stimuli (when the sequentially presented stimuli were being held 'on line'). The authors found that activations in the prefrontal areas correlated most strongly with delay periods, compared with activations in the visual areas, which were more strongly correlated with sensory stimulation. Notably, the working-memory task that was used by Courtney *et al.* mainly activated different areas of the human prefrontal cortex from those that were activated in the study by Cohen *et al.*² (Fig. 1). The one major area of overlap seems to be area 44, which is part of the rostral language zone (Broca's area). As area 44 is common to both tasks, it could be argued that it represents the central executive in the frontal lobe. Alternatively, the overlap could indicate that the subjects used verbal mediation to bridge the temporal delays in the two different tasks.

Cohen *et al.* presented subjects with written consonants, one at a time every ten seconds, and asked them to judge whether each consonant was the same as a letter presented one, two or three trials back in the sequence. This is known as the '*n*-back' task¹⁰, and it requires that subjects remember the order of consonants, as well as their identity. The farther back in the sequence the consonant to be recalled occurs, the greater the 'load' on working memory. Following the presentation of each stimulus, many scans were acquired to track the sequence of brain activations in different brain regions as the subjects processed the information in working memory — much as single-unit recording studies track neuronal activity in monkeys during the delay in a delayed-response trial.

Cohen *et al.* show that activations in the

prefrontal cortex are maintained throughout the ten-second interstimulus interval and, importantly, that the degree of prefrontal activation is higher for the conditions with the greatest memory load. By contrast, activations in the primary visual, somatosensory and motor cortices, as well as in several secondary sensory regions, are not sustained across the ten-second 'memory' interval, and they are not related to memory demand. These areas are probably responsive to the sensory or perceptual, but not the mnemonic (memory-aiding), aspects of the working-memory task. Because consonants presented two or three trials back in the sequence require a certain amount of processing, as well as maintenance of information (for example, updating the order and content of working memory), the new results², together with previous studies¹¹, indicate that the central-executive component may also be located in prefrontal areas.

The findings of Cohen *et al.*² and Courtney *et al.*³ are in close harmony with a broad basic science and clinical literature which segregate perceptual and mnemonic functions in anterior and posterior association cortices, respectively. The powerful methods used in these studies now provide a real-time analysis of the temporal dynamics of working-memory functions, in combination with brain imaging. Armed with this information about the locus and sequencing of working-memory processes which are thought to be the domain of slave systems, the next step will be to search for the elusive central executive. Given the increasingly powerful techniques available, including electroencephalography¹⁰ and magnetic source imaging¹² (which both have temporal resolutions in the millisecond range), we are ushering in a new era for understanding the cognitive processes that define human mental action. □

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1. Raichle, M. *Cereb. Cortex* **6**, iii–iv (1996).
2. Cohen, J. D. *et al.* *Nature* **386**, 604–608 (1997).
3. Courtney, S. M., Ungerleider, L. G., Keil, K. & Haxby, J. V. *Nature* **386**, 608–611 (1997).
4. Baddeley, A. & Hitch, G. in *The Psychology of Learning and Motivation: Advances in Research and Theory* (ed. Bower, G. H.) 47–89 (Academic, New York, 1974).
5. Carpenter, P. A. & Just, M. A. in *Complex Information Processing: The Impact of Herbert A. Simon* (eds Klahr, D. & Kotovsky, K.) (Erlbaum, Hillsdale, NJ, 1989).
6. Goldman-Rakic, P. S. in *Handbook of Physiology, the Nervous System, Higher Functions of the Brain* (ed. Plum, F.) 373–417 (Am. Physiol. Soc., Bethesda, MD, 1987).
7. Fuster, J. M. *Memory in the Cerebral Cortex: An Empirical Approach to Neural Networks in the Human and Nonhuman Primate* (MIT Press, Cambridge, MA, 1995).
8. Wilson, F. A. W., O'Scalaidhe, S. P. & Goldman-Rakic, P. S. *Science* **260**, 1955–1958 (1993).
9. Baddeley, A. *Working Memory* (Oxford Univ. Press, London, 1986).
10. Gevins, A. S. *et al.* *Electroenceph. Clin. Neurophysiol.* **76**, 339–350 (1990).
11. D'Esposito, M. *et al.* *Nature* **378**, 279–281 (1995).
12. Usitalo, M. A., Williamson, S. J. & Seppa, M. T. *Neurosci. Lett.* **213**, 149–152 (1996).

Daedalus

Mutable mutations

Antibiotics, those former heroes of medicine, are fast losing their power. Diseases such as tuberculosis, pneumonia and gonorrhoea, once easily cured by them, are creeping back to haunt us. We all know why. Antibiotics have been dispensed liberally and carelessly; many are routinely spread around in animal feeds. As a result, many bacteria have encountered them at low levels over long periods of time. They have evolved mutations which resist them. The worst offenders are 'hypermutable' bacteria, whose mechanisms for avoiding mutation have themselves mutated.

So Daedalus wants pharmacologists to do some mutating of their own. He points out that antibiotics are fungal metabolites or derivatives of them. The fungi — typically moulds — evolved them to discourage competing bacteria, in a chemical contest which has been going on for millions of years. Each time the fungi improved their brand of penicillin or streptomycin, the bacteria slowly mutated to become resistant to it. The fungi then had to develop an even deadlier version. The time is ripe for them to take the next step.

DREADCO biochemists are now helping them. They are putting the most accomplished moulds and the most virulent, hypermutable bacteria together in the same culture. Its medium is dense with mutagens, and irradiated from a radioactive source. The conditions will be adjusted to put the fungi at a slight disadvantage. This fierce and continuous selection pressure will force hypermutation in both fungi and bacteria. A year of such ruthless competition will advance the antibiotic art by many centuries.

The DREADCO team will then face a tricky problem. The mutated fungi will be immensely valuable, a source of a whole new stable of powerful antibiotics. The bacteria, on the other hand, will be deadlier and more antibiotic-resistant than ever. The biochemists will have to perfect some sort of filtering or centrifuging process which will permit the fungi to be harvested while reliably destroying every single one of the bacteria. DREADCO will then have a whole new range of antibiotic fungal metabolites. The old medical magic will return. But will we have learned from past experience? Daedalus is confident that his new antibiotics will once more be sprayed freely around, carelessly over-prescribed, and incorporated into numerous bulk non-medical products. In due course they will lose their potency, and DREADCO will be able to work the same trick again.

David Jones