The brain: getting ready to work

Janet Fricker, Freelance writer

Researchers from the University of Pittsburgh School of Medicine (Pittsburgh, PA, USA) have uncovered the mechanisms whereby the brain prepares itself to solve problems and then monitors its own performance. The researchers, led by Cameron Carter, believe that the activity of the two sites involved in these functions is altered in schizophrenia, and hope that their work will lead to the development of new treatments for the impaired cognitive aspects of this condition. The work was presented at the *30th Annual Meeting of the Society for Neuroscience*, held in New Orleans (LA, USA) in late 2000.

'Although people most commonly associate schizophrenia with the psychotic symptoms of hearing voices, one of the most difficult aspects for patients is disturbances in attention and memory that are associated with their ability to be organised and function independently in the community,' says Carter, Associate Professor of Psychiatry, Psychology and Neuroscience. 'The cognitive aspects of schizophrenia are currently not being addressed by any therapies in a clinically significant way.'

DLPFC and ACC

Studies using functional magnetic resonance imaging (fMRI) have related cognitive control to activity in the dorsolateral prefrontal cortex (DLPFC or Brodmann's area 9 – located on the outer surface of the frontal lobes), and the anterior cingulate cortex (ACC or Brodmann's areas 24 and 32 – located on the inner surface of the frontal lobes). DLPFC and ACC are activated when participants have to hold increasingly long sequences of items in working memory[1], or when two tasks are performed simultaneously[2]. ACC activity has been more consistently observed in tasks that require divided attention and novel or open-ended responses[3]. The relative dissociations led Carter and colleagues to hypothesise that DLPFC could be involved in representing and maintaining the attentional demands of the task, while ACC might be involved in evaluative processes such as monitoring the occurrence of errors or the presence of response conflict.

Tests in normal individuals

The team therefore tested 12 subjects, aged 20–35 years, using a modified version of the Stroop paradigm during a fMRI scanning session. All subjects showed no evidence of neurological disorders or psychiatric history and were free from substance abuse and head injury[4]. Twelve seconds prior to each trial, subjects were informed whether to read a word (an automatic response) or name the colour the word was written in when the word described a different colour (eliciting response conflict). The time delay for each task was used to separate instruction-related strategic processes from response-related processes.

Researchers found a direct correlation between the degree of increase in DLPFC activity prior to the subject being asked to name the colour (but not read the word) and their ability to perform the task, measured by the time taken to provide the correct answer. No DLPFC activity was observed when subjects were asked to read the word and no instruction-related activity was observed in the ACC. However, activity in the ACC increased when subjects had to name the colours of the words.

'A double dissociation was found between the two areas with the DLPFC being more active for colour naming than for word reading, consistent with a role in the implementation of control. By contrast, the ACC was more active when responding to incongruent stimuli, consistent with a role in monitoring performance,' says Carter. 'This work takes us a step forward in being able to test specific hypotheses about the function of these areas in relation to schizophrenia.'

DLPFC or ACC

Several studies using different cognitive paradigms in both medicated and unmedicated patients have suggested that the ACC and the DLPFC are functionally abnormal in schizophrenia[5,6]. 'We are trying to tease apart whether the problem with schizophrenia is primarily in DLPFC or ACC or whether both areas could be being disrupted simultaneously,' says Carter. The team is currently undertaking a study using the Stroop test and fMRI in patients who have just been diagnosed with first-episode schizophrenia and have yet to receive any medication, to ensure that any difference from controls is not linked to the effects of the medication.

'Functional brain imaging (both PET and fMRI) hold great promise for increasing our understanding of schizophrenia but, as yet, results using these techniques have been somewhat disappointing,' says Chris Frith (Wellcome

1359-6446/01/$ – see front matter PII: S1359-6446(00)01658-5

Department of Cognitive Neurology, University College London, UK). 'This is largely because we have little knowledge of how to map cognitive processes in the normal brain, making scan interpretation of schizophrenic patients difficult, if not impossible. Carter's group is avoiding these problems through the study of normal volunteers prior to their examination of patients with schizophrenia.'

Future hopes

Carter believes that once the fMRI changes in the activity of DLPFC and ACC have been determined in schizophrenia, it might be possible to develop a screening test. 'In the early stages, patients appear to show elements of cognitive impairment before the psychiatric symptoms. fMRI might therefore be used as a method of assessing people considered to be at genetic risk of developing schizophrenia or to adjudicate whether people are suffering from schizophrenia or some other emotional problem.'

The knowledge of the genetics of schizophrenia could then be used to define the phenotype, linking candidate genes to different patterns of brain circuitry. Finally, once these changes are known, it should be possible to use fMRI to examine the effects of different candidate drugs on the brain circuitry and decide which to pursue.

References

1 Cohen, J.D. *et al.* (1997) Temporal dynamics of brain activation during a working memory task. *Nature* 386, 604–608

2 D'Esposito, M. *et al.* (1995) The neural basis of the central executive of working memory. *Nature* 378, 279–281

3 Barch, D.M. *et al.* (1997) Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 35, 1373–1380

4 MacDonald, A.W. *et al.* (2000) Dissociating the role of dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288, 1835–1838

5 Carter, C. *et al.* (1998) Functional hypofrontality and working memory dysfunction in schizophrenia. *Am. J. Psychiatry* 155, 1285–1287

6 Fletcher, P.C. *et al.* (1996) Local and distributed effects of apomorphine on fronto-temporal function in acute unmedicated schizophrenia. *J. Neurosci.* 16, 7055–7062