Response selection in the human anterior cingulate cortex

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The anterior cingulate cortex (ACC) has been proposed as part of the brain's attentional control network, but the exact nature of its involvement in cognitive and motor operations is under debate. Assessing effects of human ACC damage directly addresses the problem of ACC function. We report that executive control processes of a patient with a focal right hemisphere anterior cingulate lesion were not compromised. However, her performance level depended on the response modality used. Under the same task requirements, she was impaired when giving manual responses, but not vocal responses. Thus, we provide neuropsychological evidence for functional specialization within the human ACC.

The anterior cingulate cortex (ACC) has been proposed to be the neurobiological substrate for executive control of cognitive and motor processes[1]. Supporting this view, a number of neuroimaging studies demonstrate increases in blood flow to the ACC under task conditions involving high performance demands, novelty, coordination of multiple tasks, resolution of response conflicts and response monitoring[1,2], all considered to reflect the engagement of attentional control mechanisms. An alternative suggestion is that the ACC is primarily involved in premotor functions, contributing to the process of selecting, preparing and executing motor responses determined by decision-making processes mediated by the lateral prefrontal cortex[3]. Furthermore, response-selection mechanisms in the human ACC might be organized in a somatotopic fashion, with each output modality represented in distinct subdivisions of the ACC[3,4]. In particular, the caudal regions of the ACC, below the supplementary motor area, might specialize in the control of manual responses. Neuroanatomical and neurophysiological studies with nonhuman primates support the notion that the cingulate motor areas, embedded in the cingulate sulcus, have a role in the preparation and execution of motor operations[4,5].

Current views of ACC function stem mainly from neuroimaging studies and experiments with nonhuman primates. Neuropsychological studies with patients suffering focal ACC lesions can assess the importance of the ACC for the control of cognitive and motor operations. Furthermore, regions of increased ACC activity identified in the neuroimaging literature have been inconsistently localized because of variability in anatomical landmarks between subjects[6], artifacts caused by averaging across subjects[7] and differences in task requirements. Therefore, patient data can clarify the localization of functionally specialized regions within the human ACC.

Here, we tested an ACC patient with three tasks designed to investigate executive attention and motor control. The protocols were derived from neuroimaging studies that demonstrated ACC activations, such as the Stroop interference task, which consistently engages the ACC[8]. Output-modality effects were investigated by requiring the use of either manual or vocal responses while keeping other task requirements the same. If the ACC were critically involved in attentional control processes, impairments would be observed in all tasks with high attentional demands, regardless of the motor aspects of performance. On the other hand, if the ACC were mainly responsible for the control of motor responses, performance would be affected by manipulations of motor parameters, specifically the output modality involved.

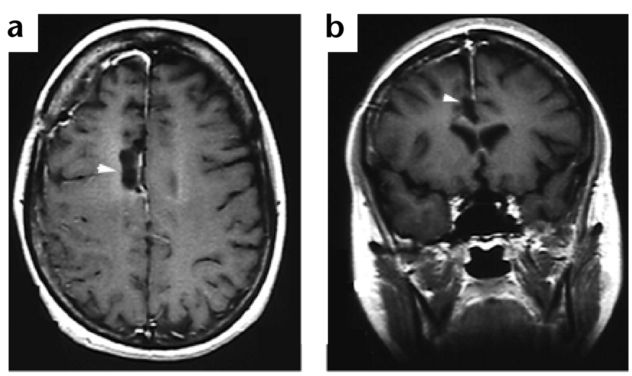

Fig. 1. MRI scans showing D.L.'s lesion. (**a**) Horizontal cross-section at the level of the cingulate sulcus. (**b**) Coronal view of caudal ACC. The lesioned area in the right hemisphere is indicated by an arrowhead, and lies on the left side of the scan. The lesion excludes the overlying supplementary motor area, and extends down to the corpus callosum. The caudal extent of the lesion coincides with the portion of the cingulate motor area reportedly involved in manual-response control. In the coronal view, the double-sulcus pattern can be seen. The paracingulate sulcus is intact, but the lesion covers both the dorsal and ventral banks of the cingulate sulcus and the surrounding gyral surface.

RESULTS

A patient with a focal ACC lesion participated in a series of studies designed to investigate attentional and motor control. Patient D.L. (a 33-year-old, right-handed female, with 12 years of education) had a portion of the ACC resected due to a glioma in 1992. She has been on antiepileptic medication (Neurontin, 900 mg and Dilantin, 300 mg, daily) to prevent seizures. On WAIS-R[9], her verbal and performance I.Q. scores were 90 and 85, respectively. Magnetic resonance imaging (MRI) revealed that her lesion extended from the middle to caudal portion of the ACC of the right hemisphere (**Fig. 1**). Neuroimaging studies demonstrating peaks of activation in the parts of ACC covered by the lesion are shown on the Talairach and Tournoux reference system[10] (**Fig. 2**).

In the first experiment, selective- or divided-attention performance was investigated using a protocol adopted from a neuroimaging study demonstrating ACC activation during divided attention[11]. The task was to detect small changes in visual stimuli (Methods, **Fig. 3a**), either along a single attribute (selective attention to color or to shape) or simultaneously along multiple attributes (divided attention). An additional condition required alternating attention between the stimulus attributes on the basis of a cue presented before each trial (precued condition). Separate sessions were conducted with manual and vocal responses. In controls ($n = 7$), accuracy did not differ significantly between task conditions ($F_{3,12} = 1.509$, $p > 0.2$) or response modalities ($F_{1,12} = 1.141$, $p > 0.3$). In contrast, D.L. showed impaired performance on all conditions ($p < 0.01$) when manual responses were required, but her performance was well within the normal range for vocal responses (**Fig. 4**). Compared to the average performance in the selective attention conditions, there was a further decrement in accuracy in the divided attention (by 11.41%, $p < 0.01$) and precued (by 7.03%, $p < 0.01$) conditions for manual responses. To control for the difficulty of the mapping between stimuli and responses, D.L. participated in an additional session requiring arbitrary vocal responses (see Methods). Her accuracy with vocal responses still remained high (95.32% and 96.88% for selective attention to color and shape, respectively, 92.97% for divided attention and 93.36% in the precued condition), comparable to her accuracy with the easier response mapping.

The relationship between response selection and output modality was assessed in a second experiment using a variant of the Stroop conflict task[17]. The patient was tested in four conditions, involving different response modalities and response selection requirements (Methods). The task was to respond to a composite display consisting of a word and an arrow, each indicating either the right or left direction, either by saying "left" or "right", or by pressing a button with the left or right hand (**Fig. 3b**). In separate conditions, subjects attended to only the word or the arrow.

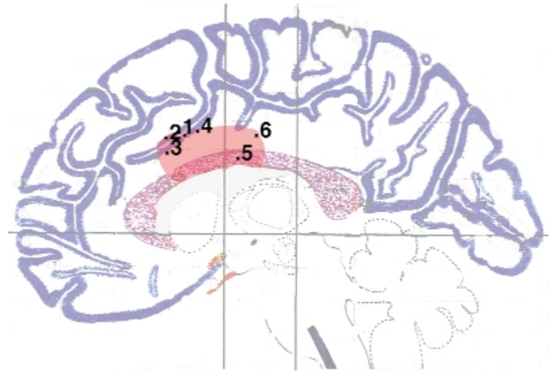

Fig. 2. The sagittal extent of the lesion is depicted in light red shading on the Talairach and Tournoux coordinate system[10]. The part of the ACC surrounding the vertical anterior commissure (VCA) line corresponds to the part of cingulate motor area reported to be involved in manual control. Peaks of activation from six neuroimaging studies are plotted inside the area of the lesion. 1, Divided attention[11]; 2, dual task[12]; 3, self-initiated finger movements[13]; 4, Stroop task (incongruent)[14]; 5, Stroop task (incongruent)[15]; 6, Stroop task (congruent)[16].

Response times (RTs) for controls ($n = 6$) were slower on incongruent trials, in which the attended and unattended stimuli did not indicate the same response ($F_{1,20} = 63.167$, $p < 0.05$, **Table 1**). Furthermore, the congruity effect interacted with the task conditions ($F_{3,20} = 9.322$, $p < 0.001$). Interference was small in the word/vocal and arrow/manual conditions, where the stimulus type and response modality were compatible, and large in the arrow/vocal and word/manual conditions, where the correct response competed with a conflicting automatic response primed by the irrelevant stimulus feature (**Fig. 5**). D.L. had high (>95%) accuracy in all conditions. Overall, her response times were slower than those of controls, but she showed a remarkably different pattern of interference across the task conditions. Compared to controls, she showed a significantly larger interference effect when giving manual responses for words ($p < 0.01$), but not in the other conditions. In the arrow/manual condition, her performance again differed from that of controls ($p < 0.01$). In this case, her congruent trials had slower RTs than incongruent trials, contrary to the pattern in control subjects. To evaluate whether overall speed of responses influenced the size of the interference effect in the arrow/vocal and word/manual conditions, six additional control subjects were included in the analysis, and data from fast and slow subjects were compared. The degree of interference in these two conditions did not depend on speed ($F_{1,10} = 1.702$, $p > 0.2$), and there was no interaction between speed and condition ($F_{1,10} = 0.01$, $p > 0.9$).

A third experiment examined response preparation using a choice RT task in which advance information about the oncoming stimulus was presented in a portion of the trials (see Methods). Cued and uncued manual responses were compared. Controls ($n = 6$) gave faster responses to the target stimulus on prepared trials ($F_{1,5} = 166.145$, $p < 0.001$), and showed no difference between left and right hand responses (109 and 120 ms improvement, respectively, $F_{1,5} = 0.003$, $p > 0.9$).

For the patient, the RT differences

Table 1. Median response times (ms) of the patient and controls in the four conditions of the Stroop-type task.

	Word (vocal)			Arrow (vocal)	
	Congruent	Incongruent		Congruent	Incongruent
D.L.	746	766	D.L.	899	954
Controls	486 ± 27	494 ± 29	Controls	514 ± 32	571 ± 38
	Word (manual)			Arrow (manual)	
	Congruent	Incongruent		Congruent	Incongruent
D.L	589	788	D.L.	771	741
Controls	382 ± 23	436 ± 24	Controls	363 ± 26	377 ± 31

Standard errors are shown for control data.

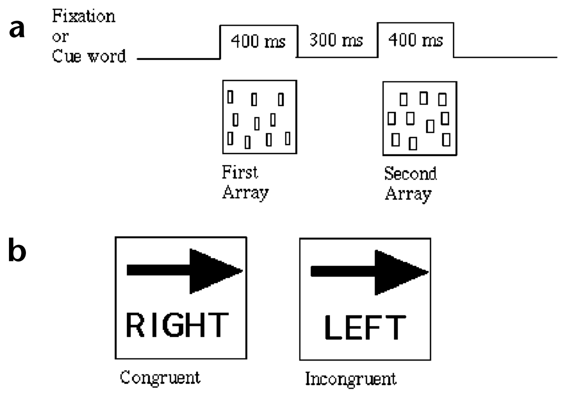

Fig. 3. Details of the stimuli and tasks. (**a**) Schematic representation of the stimulus arrays and the time course of a trial for the selective and divided attention task. In different conditions, subjects made a same-different discrimination for brightness of the color of the boxes in the array, for shape of the boxes, or both. (**b**) Example stimuli for the Stroop-type response-conflict task. Subjects responded either to the word or to the arrow by giving a vocal or a manual response. On congruent trials, the word and the arrow indicated the same response, and on incongruent trials, opposite responses.

between prepared and unprepared responses were 21 ms for the left hand and 29 ms for the right hand, significantly less than the RT benefit shown by control subjects ($p < 0.01$ in both cases, **Fig. 6**). ANOVA also confirmed that the effect of preparatory information on RT differed significantly between controls and D.L. ($F_{1,5} = 35.222$, $p < 0.005$).

Discussion

Both divided attention and Stroop-type tasks are considered tests of executive function. In both cases, the patient's performance level depended on the response modality involved although the decision requirements of the tasks remained the same. When she gave vocal responses, her performance was not compromised, indicating intact executive function. Her performance was impaired only for manual responses, and worsened with more demanding conditions. Such a dissociation between vocal and manual response modalities has not been previously reported.

Divided-attention and Stroop-interference tasks require selection between competing responses associated with different stimulus attributes, rather than allowing reliance on established stimulus–response associations. It has been proposed that command signals originating from lateral prefrontal areas are funneled to motor output systems through the ACC, where execution of correct responses is facilitated and execution of inappropriate ones is suppressed[3]. Our results are consistent with this interpretation of ACC function. The patient could produce the correct decisions in each task, as indicated by her performance with vocal responses. However, these decisions could not be successfully translated into manual output, especially when response selection was required. Her lesion included the caudal portion of the ACC, covering both banks of the cingulate sulcus. This region is involved in control of hand and arm movements in the monkey. Neuroimaging studies also indicate that different subregions of the human ACC might be specialized for the control of specific output modalities. The findings with D.L. demonstrate that the integrity of caudal ACC is necessary for manual response control.

In the response-preparation task, the patient's performance was impaired when either hand was used. A prior study with a right medial frontal patient, whose lesion included both the cingulate motor areas and the supplementary motor area (SMA), demonstrated a similar deficit[18]. In addition, the ACC is activated by conditions that involve the advance preparation of both manual and oculomotor responses[19,20]. The ACC is one of the frontal regions engaged during self-initiated actions in different modalities[21]. Extensive bilateral damage to the ACC and the SMA is known to produce 'akinetic mutism', in which spontaneous initiation of behavior is dramatically reduced[22]. In all tasks, both for manual and vocal responses, the patient had considerably slower response times than controls. This overall slowing down, together with the response-preparation impairment, indicate a general deficit in response initiation and maintaining a state of motor readiness. The gyral surface of the mid-ACC is considered to have a general role in motivation and attention[23], rather than control of specific motor processes. Damage in mid-ACC could account for these aspects of the patient's performance.

The nature of the division of labor and interactions between the ACCs of the two hemispheres has not been established[24]. It is possible that the ACCs in both hemispheres contribute equally to executive attention and, following a unilateral lesion, that the intact ACC can compensate for the damaged hemisphere. Studies with bilateral ACC patients are needed to resolve this issue. However, the current results clearly demonstrate functional specialization within the human ACC and the specific role of the caudal ACC in manual control.

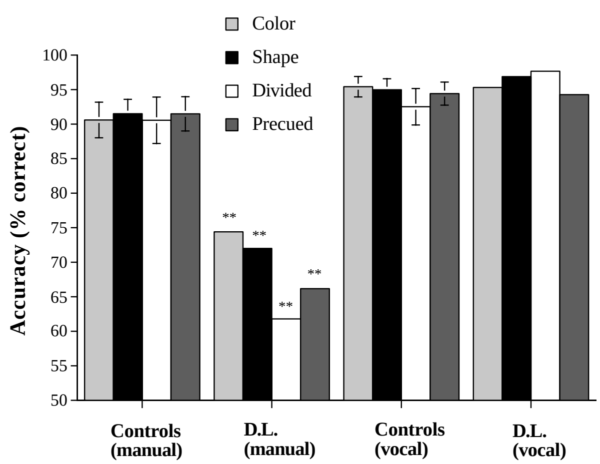

Fig. 4. Performance accuracy in the selective attention (color and shape), divided attention and precued conditions for manual and vocal responses. For manual responses, DL showed an overall impairment. Furthermore, unlike controls, she showed a significant performance decrement in the divided attention and precued conditions relative to selective attention conditions. However, for vocal responses, no performance deficit was observed. In this and the following graphs, error bars indicate s.e. Data points for the patient marked with double asterisks (**) lie outside the 99% confidence interval for controls.

Methods

All experimental sessions were conducted on a PowerMacintosh 8600/250 computer, using the Psychophysics Toolbox[25] (http://www.psych.ucsb.edu/~brainard/software/). Subjects viewed the stimuli presented on a CRT display at a viewing distance of approximately 1.50 m while seated on a chair in a dimly lit room. Manual button-press responses were registered by a response device connected to the keyboard, and vocal responses by a voice key that registered voice onset times. Age-matched normal subjects participated as controls. Three experimental tasks were

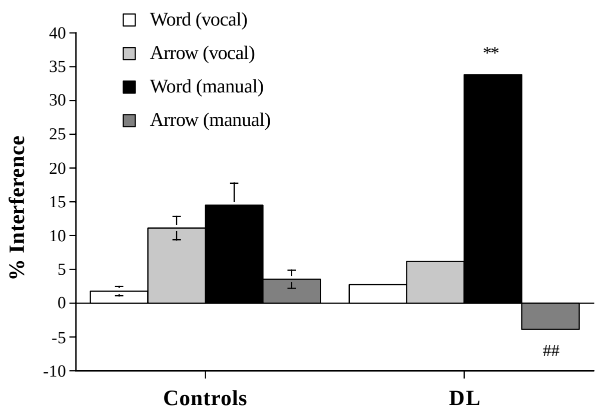

Fig. 5. Stroop-type interference and response-modality effects. For the control subjects, high interference was observed for the arrow/vocal and word/manual conditions, which have arbitrary stimulus–response mappings. D.L. showed a normal interference effect for the arrow/vocal condition, but significantly larger interference than controls in the word/manual condition. Data points for the patient marked with double asterisk (**) and double pound (##) signs lie outside the 99% confidence interval for controls.

used. The patient's performance measures on all tasks were compared with confidence intervals derived from the control subjects' data.

Selective and divided attention. The stimuli were arrays of rectangular boxes (50, each subtending approximately 0.8° × 0.5°, distributed randomly on the display). The arrays were presented in pairs, with each array shown for 400 ms and a 300 ms interval between the two displays. The boxes in each array were identical in terms of the brightness level of their colors and their shapes. Between the two arrays of the pair, the boxes could change either in shape or brightness, or both. The task was to compare the two arrays and make a same/different judgment within 2.5 s from the onset of the second array. In two conditions (selective attention to color and to shape), the instruction was to attend to only one dimension (color or shape), ignoring the other. In the divided attention condition, subjects were asked to look for a change in either dimension. In the final condition ('precued'), a cue word ("color" or "shape", displayed for 500 or 1200 ms and followed by a 500 ms delay) indicated the dimension to be used for each trial. One session comprised 2 blocks each for the selective and divided attention conditions and 4 for the precued condition, each block including 64 trials. On each block, a card placed underneath the CRT display served as a reminder for the current condition. Three sessions were held on separate dates; the first required manual button-press responses ("same" responses with the left thumb, and "different" responses with the right) and the last two vocal responses. In the second session, subjects were asked to say "same" or "different" in response to the stimuli. For the final session, in which only D.L. participated, the requirement was to say "left", instead of "same", and "right" in place of "different". In the manual condition, two labels placed on the lower left and right corners of the CRT display, reading "same" and "different" respectively, indicated the response mapping.

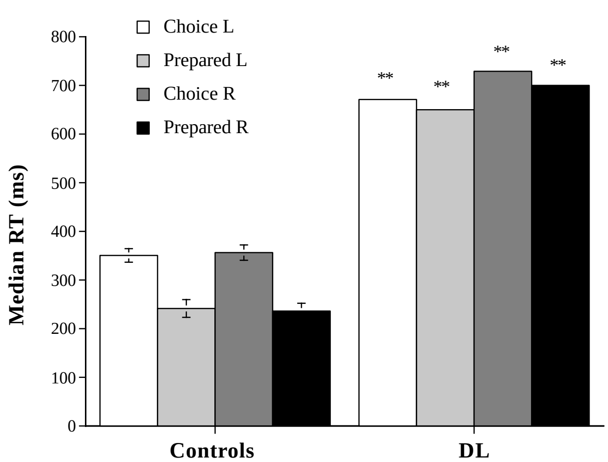

Fig. 6. Response preparation. Reaction times for choice and prepared responses with the left and the right hands are presented. For the controls, there was an RT benefit for prepared responses of equal magnitude for both hands. D.L. failed to benefit from advance preparation with either hand.

Stroop-type response conflict. The stimuli, presented following a warning signal, comprised a word and an arrow, each subtending approximately 4° × 1.5° and positioned about 2° above and below the center of the display. The arrows pointed to the left or to the right, and the words were "LEFT" or "RIGHT". The positions of the word and arrow were varied randomly from trial to trial. The stimuli remained displayed until a response was given. There were four conditions (two blocks of 48 trials each) with different instructions for the stimulus attribute to be attended to and the response modality to be used: word/vocal ("read the word"), arrow/vocal ("say 'left' or 'right' depending on the direction of the arrow"), arrow/manual ("press the left or right button with the index finger of left or right hand, corresponding to the direction of the arrow") and word/manual ("press the button indicated by the word"). In each condition, on half of the trials, the word and the arrow indicated the same response (congruent trials), and on the other half, opposite responses (incongruent trials). To obtain a measure of response interference due to incongruity of stimulus dimensions, the difference in median reaction times (RTs) for incongruent and congruent trials was expressed as a percentage of the median RT for congruent trials.

Response-preparation task. On each trial, an arrowhead pointing either to the left or to the right was presented at the center of the display for 200 ms. The task was to press a button as quickly as possible with either the left or right index finger, depending on the direction of the arrowhead. The arrowheads were preceded either by a fixation cross or one of the letters "L" or "R", displayed for 200 ms and followed by an interval of either 900 or 1400 ms. If a letter appeared, it indicated the correct response for the following stimulus ("L" for left and "R" for right). Subjects were instructed to make use of this advance cue to prepare responses, but to withhold it until the stimulus appeared. A total of 144 trials were presented in three blocks, and cue letters were presented on two-thirds of the trials. As a measure of the degree to which advance information influences RTs, the RT difference between unprepared and prepared responses was used.

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1. Posner, M. I. Attention: the mechanisms of consciousness. *Proc. Natl. Acad. Sci. USA* **91**, 7398–7403 (1994).
2. Posner, M. I. & DiGirolamo, G. J. in *The Attentive Brain* (ed. Parasuraman, R.) 401–423 (MIT Press, Cambridge, Massachusetts, 1998).
3. Paus, T., Petrides, M., Evans, A. C. & Meyer, E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J. Neurophysiol.* **70**, 453–469 (1993).
4. Picard, N. & Strick, P. L. Motor areas of the medial wall: a review of their location and functional activation. *Cereb. Cortex* **6**, 342–353 (1996).
5. Shima, K. *et al.* Two movement-related foci observed in signal-triggered and self-paced forelimb movements. *J. Neurophysiol.* **65**, 188–202 (1991).
6. Paus, T., Tomaiuolo, F., Otaky, N. & MacDonald, D. Human cingulate and

paracingulate sulci: pattern, variability, asymmetry and probabilistic map. *Cereb. Cortex* **6**, 207–214 (1996).
7. Derbyshire, S. W., Vogt, B. A. & Jones, A. K. Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex. *Exp. Brain Res.* **118**, 52–60 (1998).
8. Bush, G. *et al*. The Counting Stroop: an interference task specialized for functional neuroimaging—validation study with functional MRI. *Hum. Brain Mapp.* **6**, 270–282 (1998).
9. Wechsler, D. *Wechsler Adult Intelligence Scale—Revised* (The Psychological Corporation, San Antonio, Texas, 1981).
10. Talairach, J. & Tournoux, P. *Co-Planar Stereotaxic Atlas of the Human Brain* (Thieme, Stuttgart, 1988).
11. Corbetta, M., Miezin, F. M., Dobmeyer, S., Shulman, G. L. & Petersen, S. E. Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. *J. Neurosci.* **11**, 2383–2402 (1991).
12. Fletcher, P. C. *et al.* Brain systems for encoding and retrieval of auditory-verbal memory. *Brain* **118**, 401–416 (1995).
13. Hyder, F. *et al.* "Willed action": a functional MRI study of the human prefrontal cortex during a sensorimotor task. *Proc. Natl. Acad. Sci. USA* **94**, 6989–6994 (1997).
14. Pardo, J. V., Pardo, P. J., Janer, K. W. & Raichle, M. E. The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proc. Natl. Acad. Sci. USA* **87**, 256–259 (1990).
15. Bench, C. J. *et al.* Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia* **31**, 907–922 (1993).
16. Carter, C. S., Mintun, M. & Cohen, J. D. Interference and facilitation effects during selective attention: an $H_2^{15}O$ PET study of Stroop task performance. *Neuroimage* **2**, 264–272 (1995).
17. Baldo, J. V., Shimamura, A. P. & Prinzmetal, W. Mapping symbols to response modalities: interference effects on Stroop-like tasks. *Percept. Psychophys.* **60**, 427–437 (1998).
18. Verfaellie, M. & Heilman, K. M. Response preparation and response inhibition after lesions of the frontal lobe. *Arch. Neurol.* **44**, 1265–1271 (1987).
19. Deiber, M., Ibanez, V., Sadato, N. & Hallet, M. Cerebral structures participating in motor preparation in humans: a positron emission tomography study. *J. Neurophysiol.* **75**, 233–247 (1996).
20. Petit, L., Courtney, M. C., Ungerleider, L. G. & Haxby, J. V. Sustained activity in the medial wall during working memory delays. *J. Neurosci.* **18,** 9429–9437 (1998).
21. Frith, C. D., Friston, K., Liddle, P. F. & Frackowiak, R. S. Willed action and the prefrontal cortex in man. *Proc. R. Soc. Lond. B Biol. Sci.* **244**, 241–246 (1991).
22. Devinsky, O., Morrell, M. J. & Vogt, B. A. Contributions of anterior cingulate cortex to behaviour. *Brain* **118**, 279–306 (1995).
23. Dum, R. P. & Strick, P. L. in *Neurobiology of Limbic Cortex and Thalamus* (eds. Vogt, B. A. & Gabriel, M.) 20–70 (Birkhauser, Boston, 1993).
24. Paus, T., Koski, L., Caramanos, Z. & Westbury, C. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. *Neuroreport* **9**, R37–47 (1998).
25. Brainard, D. H. The Psychophysics Toolbox. *Spat. Vis.* **10**, 443–446 (1997).