nature neuroscience

Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli

Sonia Bishop, John Duncan, Matthew Brett & Andrew D Lawrence

Threat-related stimuli are strong competitors for attention, particularly in anxious individuals. We used functional magnetic resonance imaging (fMRI) with healthy human volunteers to study how the processing of threat-related distractors is controlled and whether this alters as anxiety levels increase. Our work builds upon prior analyses of the cognitive control functions of lateral prefrontal cortex (lateral PFC) and anterior cingulate cortex (ACC). We found that rostral ACC was strongly activated by infrequent threat-related distractors, consistent with a role for this area in responding to unexpected processing conflict caused by salient emotional stimuli. Participants with higher anxiety levels showed both less rostral ACC activity overall and reduced recruitment of lateral PFC as expectancy of threat-related distractors was established. This supports the proposal that anxiety is associated with reduced top-down control over threat-related distractors. Our results suggest distinct roles for rostral ACC and lateral PFC in governing the processing of task-irrelevant, threat-related stimuli, and indicate reduced recruitment of this circuitry in anxiety.

Cognitive control has been defined as the provision of top-down support for task-relevant processes, with representation of task demands being used to bias processing in favor of task-relevant stimuli and responses[1]. A number of studies have suggested that a network of cortical areas—including dorsolateral and ventrolateral prefrontal cortex (DLPFC, VLPFC) and anterior cingulate cortex (ACC)—has a role in cognitive control[1–6]. Debate continues regarding the extent to which these regions have dissociable functions[1–3,7]. It has been argued that ACC is primarily involved in signaling the presence of processing conflict, whereas lateral PFC is more directly involved in augmenting control in situations of high conflict[1,6,8].

The empirical work informing this discussion has focused primarily on the control of cognitive processing lacking an affective component. Cognitive control may, however, be equally important when the presence of emotionally salient information interferes with ongoing processing. In particular, impaired cognitive control over threat-related information may have a key role in anxiety[9]. Here we explored whether ACC and lateral PFC involvement in processing response conflict in affectively neutral tasks is paralleled in tasks where processing competition potentially arises as a result of the emotional salience of task-irrelevant stimuli. In addition, we investigated the influence of individual differences in anxiety on activity within this control circuitry.

The ACC is engaged in both cognitive and emotional processing[10,11]. It is thought that the dorsal subdivision (dorsal ACC) is primarily involved in cognitive processing, whereas the rostral-ventral subdivision (rostral ACC) is primarily involved in emotional processing[12]. In line with this, 'response conflict' tasks (where competition for processing resources is caused by information promoting an incorrect response from within the currently active response set) typically activate more dorsal areas. Rostral-ventral activity, in contrast, has been associated with emotional stimuli, pain and disordered mood states[11–15].

In response-conflict tasks, conflicting stimuli are especially disruptive when they occur infrequently[16,17]. Accompanying their greater behavioral effect, infrequent high response-conflict trials are particularly associated with increased dorsal ACC activation[6]. Such results have been taken to suggest that the ACC monitors for high levels of processing conflict, acting as a trigger for control mechanisms brought into play to prevent attentional disruption[8]. A more conservative account supports ACC involvement in the on-line response to conflicting stimuli but remains agnostic as to whether this entails conflict monitoring or the short-term trial-by-trial regulation of control.

The function of rostral ACC has not been clearly specified. Here we explore the possibility that it may be involved in responding to unexpected processing conflict arising from emotionally salient but task-irrelevant input—a role analogous to that of the dorsal ACC in simple response conflict. Previous studies have reported that rostral ACC activity is indeed associated with the processing of emotional distractors[13,18]. It is not clear, however, whether rostral ACC, like dorsal ACC, is primarily responsive to unexpected or infrequent processing conflict. We addressed this by manipulating the frequency of threat-related distractors. If rostral ACC provides an on-line response to unexpected processing conflict from task-irrelevant emotional stimuli, a greater rostral ACC response to infrequent versus frequent threat-related distractors should be seen.

In response conflict tasks, strong lateral PFC responses have been reported during the phase of expectation or preparation for high-conflict trials[1]. This has been taken to suggest a role for lateral PFC in establishing cognitive control. Following from this, the second

Medical Research Council Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK. Correspondence should be addressed to S.B. (sonia.bishop@mrc-cbu.cam.ac.uk).

Published online 4 January 2004; doi:10.1038/nn1173

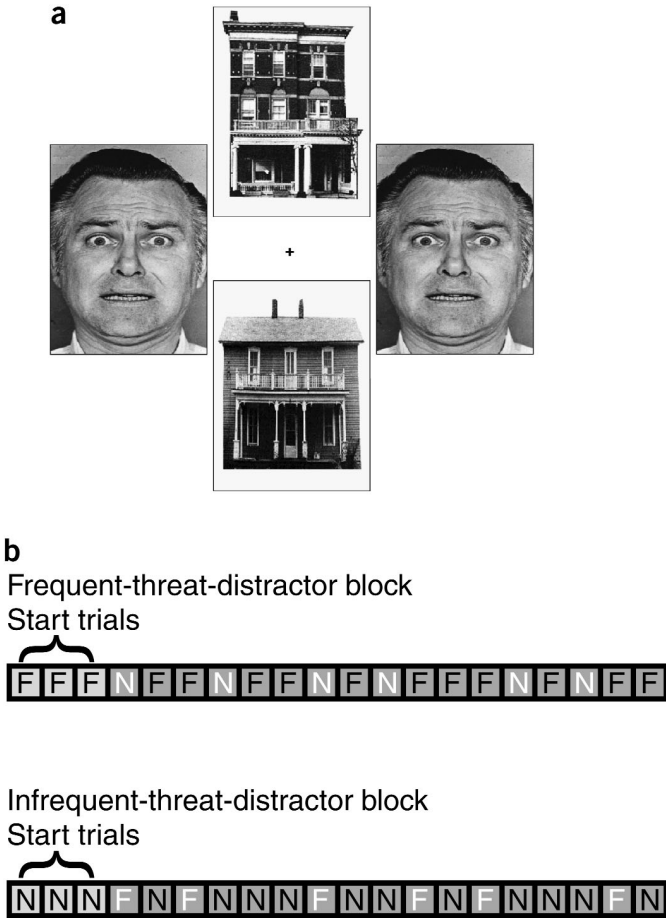

Figure 1 Stimuli and block trial composition. (**a**) Example stimuli. On each trial, two faces and two houses were presented in vertical and horizontal pairs around a central fixation cross. Participants decided whether houses were identical ($P = 0.5$) or not. Faces could also be identical or not, but were always either both neutral or both fearful in expression. (**b**) Example trial sequences. F = fearful face (threat-related) distractor, *N* = neutral face distractor. For each type of block, all trials subsequent to the three start trials were presented in a pseudo-random order that remained constant across participants.

aim of our study was to examine whether lateral PFC activation is associated with implementation of attentional control over threat-related distractors. To address this, we began each block of trials with strings of threat-related or neutral distractor trials, establishing expectancy of distractor type for that block. Activity during these start trials is taken to reflect initial establishment of attentional control settings. This was compared across threat-related versus neutral distractor start trials.

Our third concern was whether individual differences in anxiety influence the recruitment of ACC and lateral PFC in response to threat-related distractors. Within the anxiety literature, it has been suggested that the extent to which threat-related distractors capture attention may reflect competition between activation provoked by the distractor and the extent to which cognitive control supports task-focused processing[19]. This is in keeping with the proposed influence of both bottom-up salience and top-down control in biased competition models of selective visual attention[20]. While it has primarily been argued that anxiety acts to increase sensitivity to the distractor, it is also possible that heightened anxiety is associated with reduced recruitment of control mechanisms[19]. In line with this, high levels of stress have been associated with a reduction of both PFC and rostral ACC activity[21–23]. To investigate this possibility, we examined responses in lateral PFC and rostral ACC as a function of participants' level of 'state anxiety' (see Methods).

In line with the proposal that rostral ACC is particularly sensitive to unexpected processing conflict from emotional stimuli, we observed a significantly greater rostral ACC response to threat-related versus neutral distractors when threat-distractors were infrequent. In addition, heightened anxiety was associated both with lower rostral ACC activity in general and with reduced recruitment of lateral PFC circuitry as expectation of threat-related distractors was established. This supports the proposal that anxiety is characterized by weaker activation of the cognitive control mechanisms required to maintain ongoing task processing in the presence of threat-related distractors.

RESULTS

To manipulate the frequency of threat-related distractors, we adapted a matching task previously used within the fMRI literature[18]. Twenty-seven participants performed this task while functional magnetic resonance imaging (fMRI) data were collected. On each trial, they viewed a brief visual display comprising two faces and two houses in vertical and horizontal pairs (**Fig. 1a**). The faces were both either fearful or neutral in expression. Fearful facial expressions of conspecifics act as cues to potential danger and share some of the functional properties of 'prepared' (intrinsically threat-related) fear stimuli[24]. Participants attended to the two houses, deciding whether they were identical or not. The faces were distractors that were irrelevant to the task. A mixed-model design was used to implement the desired frequency manipulation. Trials were presented in blocks of 20 (**Fig. 1b**). The first three 'start' trials, used to establish the frequent face-type for each block, had either all fearful faces ('frequent-threat-distractor' blocks) or all neutral faces ('infrequent-threat-distractor' blocks). The remaining 17 trials comprised 11 trials with the frequent face-type for that block and 6 trials with the infrequent face-type (see Methods). We used these 'non-start' trials to examine whether the rostral ACC response to threat-related versus neutral distractor trials varied with the frequency of threat-related distractors.

Effects of threat-related distractor frequency

We created regions of interest (ROIs) for dorsal and rostral ACC and for left and right DLPFC and VLPFC (see Methods). Within each ROI, we examined the extent to which the differential response to threat-related versus neutral distractor trials varied by block. In line with predictions, rostral ACC activation to threat-related versus neutral distractor trials was significantly greater in the infrequent-threat-distractor versus the frequent-threat-distractor blocks: $x\ y\ z = -2\ 50\ 18$, $Z = 3.44$, P-corrected < 0.02 (**Fig. 2a**). Examining the response to threat-related versus neutral distractor trials separately by block confirmed that increased rostral ACC activity to threat-related versus neutral distractor trials was only seen in the infrequent-threat-distractor blocks ($x\ y\ z = -4\ 48\ 18$, $Z = 3.38$, P-corrected $= 0.022$) and not in the frequent-threat-distractor blocks (P-corrected > 0.5). Additionally, rostral ACC activity across trial types tended to be lower in frequent-threat-distractor blocks, though this trend was not significant. These response patterns were specific to rostral ACC and were not observed within the dorsal ACC or lateral PFC ROIs. To establish that heightened rostral ACC activity was not simply a response to the detection of infrequent threat-related stimuli *per se*, we

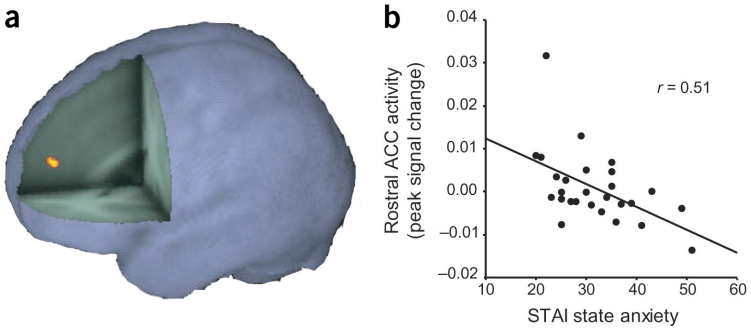

Figure 2 Activity in rostral ACC. (**a**) Rostral ACC voxels showing interaction of trial (threat-related versus neutral distractor) × block (infrequent-threat-distractor versus frequent-threat-distractor). Peak activation: –2 50 18 (*x y z*), $Z = 3.44$, $P < 0.02$ (corrected). The activation cluster includes all adjacent voxels with $Z > 3.04$ ($P < 0.05$ corrected for those voxels falling within the pre-defined ROI). No significant interaction was observed in the other ROIs (*P*-corrected > 0.1) or in any other prefrontal voxels ($P > 0.1$, whole-brain corrected). (**b**) Rostral ACC activity (peak voxel from **a**) plotted against participant state anxiety level ($P < 0.05$). Rostral ACC activity is mean signal change (% mean whole-brain signal intensity) for all trials excluding start trials. A similar relationship was observed when start trials were included.

included additional task blocks in which participants matched the identity of faces and ignored houses. Here, rostral ACC showed no selective response to infrequent fearful faces (*P*-corrected > 0.5).

State anxiety modulation of the PFC response

We next analyzed responses to the initial 'start' trials in each block, when context was being established (**Fig. 1b**). Across participants, there was no significant difference in DLPFC and VLPFC responses to the start trials in the frequent-threat-distractor versus infrequent-threat-distractor blocks. However, in both left DLPFC and left VLPFC, activity associated with this contrast showed a significant inverse relationship with state anxiety (as measured by the state subscale of the Spielberger State-Trait Anxiety Inventory[25], see Methods; **Fig. 3**). No parallel relationship was observed within the dorsal or rostral ACC ROIs. This result suggests that heightened anxiety may be associated with reduced recruitment of the lateral PFC circuitry required to augment attentional control as expectancy of threat-related distractors is established.

State anxiety modulation of the rostral ACC response

We also examined the relationship between anxiety and the magnitude of the rostral ACC response for the interaction between block and trial type. No significant association was observed. However, although low- and high-anxiety participants showed similar relative patterns of activity across trials, heightened anxiety was associated with reduced rostral ACC activity across all trial types (**Fig. 2b**).

Other brain regions

The contrasts discussed above were not associated with activation in any other neural structures (when corrected for multiple comparisons across the whole brain volume). Given the role of the amygdala in the detection of threat-related stimuli, including facial expressions of fear[26], we additionally investigated activity in this region using anatomically defined ROIs[27]. Small-volume corrected voxel-wise comparisons were conducted in line with our other ROI analyses (see Methods). There was no significant amygdala activation associated with any of our contrasts of interest. (It should be noted that our imaging protocol was not optimized for detecting amygdala signal change[28]).

Response time (RT) data

Our experiment was not primarily designed to gather response time data and participants were not asked to make speeded responses. In fact, emotional distractors often produce little RT disruption in non-clinical populations[13,29]. Our results showed the same pattern (frequent-threat-distractor blocks: threat-related distractor trials, 750 ± 102 ms (mean ± s.d.), neutral distractor trials, 746 ± 106 ms; infrequent-threat-distractor blocks: threat-related distractor trials, 744 ± 104 ms, neutral distractor trials, 742 ± 104 ms). Error rates were low and also did not vary as a function of block or trial type.

DISCUSSION

Our data suggest distinct roles for rostral ACC and lateral PFC in governing the processing of task-irrelevant threat-related stimuli. Here

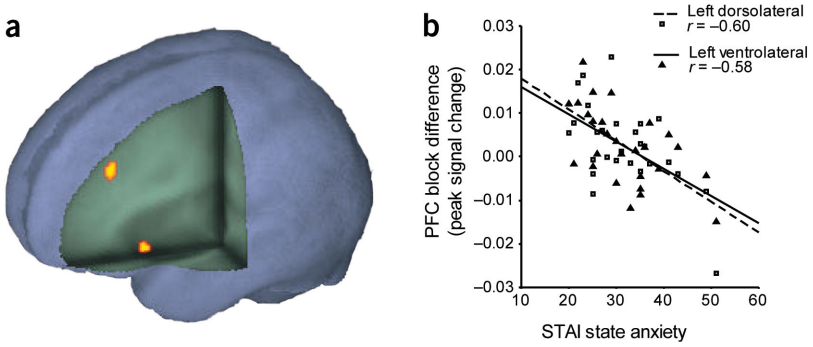

Figure 3 Activity in lateral PFC. (**a**) Left DLPFC and left VLPFC voxels showing significant inverse relationship between block difference (frequent-threat-distractor minus infrequent-threat-distractor, start trials only) and state anxiety. Peak DLPFC and VLPFC activations were, respectively: –34 36 32 (*x y z*), $Z = 3.29$, $P < 0.05$ (corrected) and –36 16 –6 (*x y z*), $Z = 3.18$, $P < 0.05$ (corrected). Conventions as **Fig. 2**. No such relationship was seen in the other ROIs (*P*-corrected > 0.1) or in any other prefrontal voxels ($P > 0.1$, whole-brain corrected). (**b**) Relationship between block difference and anxiety for peak DLPFC and VLPFC voxels. Block difference defined as in **a** (mean signal difference, % mean whole-brain signal intensity).

we also show that activity in this circuitry is modulated by state anxiety. Given our trial sequences, the expectancy of future trial type should build up over the first few trials of each block[30]. When these initial trials all contained threatening distractors, low-anxiety participants showed increased recruitment of DLPFC and VLPFC. This is consistent with lateral PFC being involved in establishing increased attentional control over expected threat-related distractors. In later trials, rostral ACC responded most strongly to unexpected (infrequent) threat-related distractors. This is consistent with a role for rostral ACC in the on-line response to processing conflict arising from emotionally salient task-irrelevant stimuli, analogous to the role of dorsal ACC in simple response conflict.

An important issue is the nature of the conflict that is processed by rostral ACC. Conflict monitoring studies of dorsal ACC function have focused fairly narrowly on conflict resulting from response competition within a specific response set (*e.g.*, in a Stroop color-naming task, the color of the word RED written in blue ink promotes the response "blue," while the meaning of the word promotes the response "red"). Proponents of the conflict monitoring model have, however, emphasized that conflict could occur at any number of points in processing[8]. In tasks with threat-related distractors, the distractors do not promote an incorrect response from within the currently active response set. Processing competition is thought to arise instead as a result of these stimuli drawing attentional resources towards themselves and associated defensive responses, thus drawing resources away from task-related stimuli[19,31]. In non-clinical populations, as in the present study, effects of threat-related distractors on response times for the primary task tend not to be reliably observed[13,29]. The potential importance of such distraction is shown, however, by the very large effects sometimes seen in clinical groups[32].

Anxiety is associated with heightened distractibility, poor concentration and increased responsivity to potential threat. Several decades of research have pointed to the centrality of disrupted attentional control over threat-related information to anxiety[9,19,32]. We report that heightened anxiety is associated with both generally lower levels of rostral ACC activity and reduced recruitment of lateral PFC as expectancy of threat-related distractors is established. According to a biased competition view of attention[20], competition among stimuli for neural representation can be influenced in several ways. One way is by 'bottom-up' sensory driven mechanisms, such as stimulus salience. Threat-related stimuli are of high salience and are strong competitors for attention. In addition, it is possible to bias the competition among stimuli by top-down control processes. Top-down control mechanisms allow objects that are less salient to win attentional competition. Here, we suggest that PFC control mechanisms may be used to bias competition toward less salient task-related stimuli in the presence of salient emotional distractors, and that heightened anxiety is associated with reduced recruitment of these top-down control mechanisms. We would hypothesize that this reduction might be even more pronounced within a clinically anxious population.

An interesting possibility is that the locus of the primary impact of anxiety on control circuitry may lie in rostral ACC. Previous studies have reported reduced rostral ACC activation in clinically anxious individuals (patients with post-traumatic stress disorder) both during task performance and at rest[22,23]. In the current study, participants with high levels of state anxiety showed a general reduction in the magnitude of the rostral ACC signal. As a consequence, though their response was still modulated by distractor valence and frequency, it was significantly reduced across the board in relation to participants with lower levels of anxiety. It is possible that a reduced-magnitude threat-related conflict detection signal from rostral ACC accounts for the reduced lateral PFC response to increases in threat-related distractors. Indeed, a general dampening of this signal could effectively increase the prioritization of fear-related responding in states of heightened anxiety. In future studies we hope to continue to elucidate the relationship between rostral ACC and lateral PFC function in anxiety.

To conclude, our present results indicate that the regulatory and control circuitry of the rostral anterior cingulate and lateral prefrontal cortex is involved in governing the processing of task-irrelevant threat-related stimuli, and suggest altered functioning of this circuitry in states of high anxiety. In bridging the gap between neuroimaging studies of cognitive control and cognitive/clinical accounts of attentional biases in anxiety, we hope to provide new insights into the neural mechanisms responsible for controlling attention in the presence of emotional stimuli.

METHODS

Behavioral protocol. The task was adapted from a previous study[18]. On each trial, two faces and two houses were presented in vertical and horizontal pairs around a central fixation cross. Stimuli were back-projected onto a translucent screen positioned in the bore of the magnet behind the head of the participant, visible via an angled mirror placed above the participant's head. In the conditions of interest, participants decided whether houses were identical ($P = 0.5$) or not. The distractor stimuli were faces[33]. These could also be identical or not, but were always either both neutral or both fearful in expression. Participants were asked to emphasize accuracy, not speed. Trials were presented in blocks of 20. The 'infrequent-threat-distractor' blocks comprised an initial 3 neutral distractor trials, followed by 11 more neutral and 6 threat-related (fearful face) distractor trials, the latter each separated by at least one neutral distractor trial. The reverse proportions applied for the 'frequent-threat-distractor' blocks. The inter-stimulus interval was randomly jittered using an exponential function with a mean of 6 s and a minimum of 5 s. Participants completed four blocks of each condition in a counterbalanced order. These house-matching blocks were interspersed with blocks where participants matched the identity of the faces, the frequency of trials with neutral or fearful facial expressions being varied in an identical manner to that for the house-matching blocks. Further details of these blocks are not reported here, as our focus was on the processing of task-irrelevant threat-related stimuli.

Twenty-seven participants (20 female, all right-handed, age 18–38 years) completed the task while both behavioral and fMRI data were collected. The study was approved by the Cambridgeshire Local Research Ethics Committee and performed in compliance with their guidelines. The standard Cambridge exclusion criteria for fMRI studies were followed (no metal, no history of neurological disease or head injury). In addition, all individuals with current or past history of inpatient psychiatric care or currently on medication for anxiety or depression were excluded from the study. Before the fMRI session informed written consent was obtained and participants completed the Spielberger State-Trait Anxiety Inventory, STAI[25]. Participants' state anxiety scores ranged from 20 to 51 (mean = 31.6, s.d. = 8.1), their trait anxiety scores from 23 to 51 (mean = 34.9, s.d. = 8.3). These scores are similar to the published norms[25] for this age group (state: mean = 36, s.d. = 10; trait: mean = 36, s.d. = 10).

Image acquisition. We acquired BOLD (blood oxygenation level dependent) signal contrast images with echo-planar T2*-weighted (EPI) imaging using a Medspec 3-tesla MR system (Bruker) with a head coil gradient set. Each image volume consisted of 21 interleaved 4-mm thick slices; interslice gap, 1 mm; field of view, 25 × 25 cm; matrix size, 64 × 64; flip angle, 90° echo time (TE), 27 ms; voxel bandwidth, 100 kHz; acquisition time (TA), 2.3 s; repetition time (TR), 3.02 s. Slice acquisition was transverse oblique, angled to avoid the eyeballs, and covering the whole brain. For each participant, data were acquired in four scanning runs of ~8 min each. The first six volumes of each run were discarded to allow for T1 equilibration effects.

Image analysis. Data were analyzed using SPM 99 software (Wellcome Department of Imaging Neuroscience). Standard pre-processing was conducted

comprising slice timing correction, realignment and masked normalization of each participant's EPI data to the Montreal Neurological Institute MNI/ICBM template. Images were resampled into this space with 2-mm isotropic voxels and smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. Trials were modeled with step functions of 0.25 s duration, convolved with the canonical hemodynamic response function to form regressors. Temporal derivatives of these regressors were also included, as were realignment parameters for each session in order to account for residual movement-related variance. A high-pass filter of 160 s was used to remove low-frequency noise. A random effects analysis was used to analyze data at a group level, modulations by anxiety being assessed by simple regression against state anxiety scores from the STAI (analyses with trait anxiety scores are not reported but produced similar results). Voxel-wise comparisons were conducted and corrected for multiple comparisons using the theory of Gaussian random fields. For dorsal ACC, rostral ACC, DLPFC and VLPFC ROIs, small volume corrections were applied[34]. We used 16-mm (diameter) spheres for all ROIs. Coordinates for the ACC ROIs were taken from the meta-analysis reported in ref. 12. The mean coordinates (*x y z*) of the response conflict (Stroop) studies included in the meta-analysis were used as the center of the dorsal ACC ROI (4 14 36). The mean coordinates (*x y z*) of the two studies that manipulated attention to emotional stimuli were used as the center of the rostral ACC ROI (–2 44 20). In both cases, precise coordinates were provided directly by G. Bush (Massachusetts General Hospital) and were converted from Talairach to MNI space[35]. The lateral PFC ROIs had the following central coordinates: DLPFC ROIs: ± 34, 36, 24; VLPFC ROIs: ± 38, 20, 0. In line with previous work[10,15], we included the cingulofrontal transition area as part of rostral ACC. Following previous reviews[2,36], the DLPFC ROIs included parts of the middle frontal gyrus and inferior frontal sulcus, whereas the VLPFC ROIs included parts of the frontal operculum and anterior insula. All activations are reported using MNI co-ordinates.

ACKNOWLEDGMENTS

This study was conducted at the University of Cambridge Wolfson Brain Imaging Centre (WBIC) and supported by the UK Medical Research Council and a Betty Behrens Research Fellowship (Clare Hall, University of Cambridge) awarded to S.B. Our thanks go to A. Andrade for statistical assistance, to B. Cox for graphical assistance and to the radiographers at the WBIC who were involved with this project: R. Bisbrown-Chippendale, V. Lupson and T. Donovan.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Received 23 July; accepted 1 December 2003
Published online at http://www.nature.com/natureneuroscience/

1. MacDonald, A.W., Cohen, J.D., Stenger, V.A. & Carter, C.S. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* **288**, 1835–1838 (2002).
2. Duncan, J. & Owen, A.M. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci.* **23**, 475–483 (2000).
3. Posner, M.I. & DiGiralomo, G.J. Executive attention: conflict, target detection, and cognitive control. in *The Attentive Brain* (ed. Parasuraman, R.) 401–423 (MIT Press, Cambridge, Massachusetts, 1998).
4. Carter, C.S. *et al.* Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* **280**, 747–749 (1998).
5. Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S. & Cohen, J.D. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* **402**, 179–181 (1999).
6. Carter, C.S. *et al.* Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proc. Natl. Acad. Sci. USA* **97**, 1944–1948 (2000).
7. Luks, T.L., Simpson, G.V., Feiwell, R.J. & Miller, W.L. Evidence for anterior cingulate cortex involvement in monitoring preparatory attentional set. *Neuroimage* **17**, 792–802 (2002).
8. Botvinick, M., Braver, T.S., Carter, C.S. & Cohen, J.D. Conflict monitoring and cognitive control. *Psychol. Rev.* **108**, 624–652 (2001).
9. Eysenck, M.W. *Anxiety and Cognition: a Unified Theory* (Psychology Press, Hove, England, 1997).
10. Vogt, B.A., Vogt, L.J., Nimchimsky, E.A. & Hof, P.R. Primate cingulate cortex chemoarchitecture and its disruption in Alzheimer's disease. in *Handbook of Chemical Neuroanatomy, the Primate Nervous System* Vol. 13, part 1 (eds. Bloom, F.E., Bjorklund, A. & Hokfelt, T.) 455–528 (Elsevier, Amsterdam,1997).
11. Drevets, W.C. & Raichle, M.E. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processing: Implications for interactions between emotion and cognition. *Cognit. Emotion* **12**, 353–385 (1998).
12. Bush, G., Luu, P. & Posner, M.I. Cognitive and emotional influences in anterior cingulate cortex. *Trends. Cogn. Sci.* **4**, 215–222 (2000).
13. Whalen, P. J. *et al.* The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division *Biol. Psychiatry* **44**, 1219–1228 (1998).
14. Mayberg, H. Limbic-cortical dysregulation: a proposed model of depression. *J. Neuropsychiatry Clin. Neurosci.* **9**, 471–481 (1997).
15. Lane, R.D., Fink, G.R., Chua, P.M. & Dolan R.J. Neural activation during selective attention to subjective emotional responses. *Neuroreport* **8**, 3969–3972 (1997).
16. Tzelgov, J., Henik, A. & Berger, J. Controlling Stroop effects by manipulating expectation for color words. *Mem. Cognit.* **20**, 727–735 (1992).
17. Logan, G.D. & Zbrodoff, N.J. When it helps to be misled: facilitative effects of increasing the frequency of conflicting stimuli in a Stroop-like task. *Mem. Cognit.* **7**, 166–174 (1979).
18. Vuilleumier, P., Armony, J.L., Driver, J. & Dolan, R.J. Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. *Neuron* **30**, 829–841 (2001).
19. Mathews, A. & Mackintosh, B. A cognitive model of selective processing in anxiety. *Cognit. Ther. Res.* **22**, 539–560 (1998).
20. Desimone, R. & Duncan, J. Neural mechanisms of selective attention. *Annu. Rev. Neurosci.* **18**, 193–222 (1995).
21. Arnsten, A.F.T. Catecholamine modulation of prefrontal cortical cognitive function.*Trends Cogn. Sci.* **2**, 436–447 (1998).
22. Lawrence, A.D. & Grasby, P.M. The functional neuroanatomy of emotional disorders. in *Handbook of Neuropsychology* 2nd edn. Vol. 5 (ed. Gainotti, G.) 235–262 (Elsevier, Amsterdam, 2001).
23. Shin, L.M. *et al.* An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol. Psychiatry* **50**, 932–942 (2001).
24. Lanzetta, J.T. & Orr, S.P. Excitatory strength of expressive faces: effects of happy and fear expressions and context on the extinction of a conditioned fear response. *J. Pers. Soc. Psychol.* **50**, 190–194 (1986).
25. Spielberger, C.D. *Manual for the State-Trait Anxiety Inventory* (Consulting Psychologists Press, Palo Alto, California, 1983).
26. Calder, A.J., Lawrence, A.D. & Young, A.W. Neuropsychology of fear and loathing. *Nat. Rev. Neurosci.* **2**, 352–363 (2001).
27. Tzourio-Mazoyer, N. *et al.* Automated anatomical labelling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single subject brain. *Neuroimage* **15**, 273–289 (2002).
28. Chen, N.K., Dickey, C.C., Yoo, S.S., Guttman, C.R.G. & Panych, L.P. Selection of voxel size and slice orientation for fMRI in the presence of susceptibility field gradients: applications to imaging of the amygdala. *NeuroImage* **19**, 817–825 (2003)
29. Compton, R.J. *et al.* Paying attention to emotion: an fMRI investigation of cognitive and emotional Stroop tasks. *Cogn. Affect. Behav. Neurosci.* **3**, 81–96 (2003).
30. Henik, A., Bibi, U., Yanai, M. & Tzelgov, J. The Stroop effect is largest during first trials. *Abstracts of the Psychonomic Society* **2**, 57 (1997).
31. Armony, J.L. & Le Doux, J.E. How danger is encoded: toward a systems, cellular, and computational understanding of cognitive-emotional interactions in fear. in *The New Cognitive Neurosciences* 2nd edn. (ed. Gazzaniga, M.) 1067–1079 (MIT Press, Cambridge, Massachusetts, 2000).
32. Williams, J.M., Mathews, A. & MacLeod, C. The emotional Stroop task and psychopathology. *Psychol. Bull.* **120**, 3–24 (1996).
33. Ekman, P. & Friesen, W.V. *Pictures of Facial Affect* (Consulting Psychologists Press, Palo Alto, California, 1976).
34. Worsley, K.J. *et al.* A unified statistical approach for determining significant signals in images of cerebral activation. *Hum. Brain Mapp.* **4**, 58–73 (1996).
35. Brett, M., Christoff, K., Cusack, R. & Lancaster, J. Using the Talairach atlas with the MNI template *Neuroimage* **13**, S85 (2001).
36. Owen, A.M. The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *Eur. J. Neurosci.* **9**, 1329–1339 (1997).