Selective attention to emotional stimuli in a verbal go/no-go task: an fMRI study

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Tasks requiring subjects to attend emotional attributes of words have been used to study mood-congruent information processing biases in anxiety and affective disorders. In this study we adapted an emotional go/no-go task, for use with fMRI to assess the neural substrates of focusing on emotional attributes of words in normal subjects. The key findings were that responding to targets defined on the basis of meaning of words compared to targets defined on the basis of perceptual features was associated with response in inferior frontal gyrus and dorsal anterior cingulate. Further, selecting emotional targets, whether happy or sad, was associated with enhanced response in the subgenual cingulate, while happy targets elicited enhanced neural response in ventral anterior cingulate. These findings reaffirm the importance of medial prefrontal regions in normal emotional processing. *NeuroReport* 11:1739–1744 © 2000 Lippincott Williams & Wilkins.

Key words: Anterior cingulate; Attention; Depression; Mood

INTRODUCTION

Neuroimaging studies investigating the neural substrates of human emotion have focused mainly on responses to facial expressions [1–3], affective pictures or film clips [4–6]. Diverse regions of the brain have been activated in these studies, particularly medial prefrontal cortex, including anterior cingulate, the amygdala and insula and orbitofrontal cortices. A striking finding of these studies is the high degree of overlap between neural responses engendered by pleasant and unpleasant emotions. For example, the anterior cingulate responds to happy, sad or fearful faces [1,2] and to both positive and negative emotional pictures [4,7]. It has been suggested [7] that anterior cingulate response mediates the processing of affect-related meanings in general, rather than any individual emotion.

Responses to the emotional properties of words have been less widely studied, perhaps because words are considered less potent affective stimuli than faces or pictures. However, there is neuropsychological evidence that patients with affective disorders show differential responses to the emotional valence of words, indicating an important processing bias in these patient groups. Biases towards the processing of negatively toned information in depressed patients has been demonstrated in several attentional studies [8,9]. For example, depression-related words cause interference in a Stroop task, while neutral and happy words do not [10,11]. In one of the few neuroimaging studies using emotional verbal stimuli, Whalen *et al.* [12] found that the ventral portion of the anterior cingulate responded preferentially to emotionally toned words in a version of the Stroop paradigm, suggesting a possible neural substrate for the observed processing bias.

A recent study of an emotional go/no-go task also found a bias towards negative information in patients with depression [13] and, interestingly, a contrasting bias towards positive information in patients with mania. Depressed patients were slower to respond to happy target words than sad or neutral words, while manic patients showed the converse pattern. This is a potentially important dissociation between the performance of patients with depression and mania, disorders that have been difficult to distinguish neuropsychologically. The present study was motivated by this finding suggesting that the emotional go/no-go task may be a probe for differential function in patients with affective disorders. A first stage to investigate this is to use the same emotional go/no-go task in conjunction with fMRI in normal subjects to determine the brain regions normally involved in responding to targets of different emotional valence. This study in controls can potentially provide a baseline for studies that explore the neural basis of mood-congruent processing biases in patients with affective disorders.

However, the study also allowed us to assess whether neural responses to affectively valenced visual stimuli extended to the verbal domain in the context of a different attentional task to those used in previous studies. This addresses the general question of whether responses to emotional stimuli are modulated by the exact nature of the stimulus and the demands of the tasks used. Our *a priori* prediction was that attention to emotional targets would

elicit neural responses in similar regions to those seen in previous neuroimaging studies of emotion; particularly the medial prefrontal cortex, insula and regions of the classic 'limbic system'. We also predicted that there would be more commonalities than differences between the regions mediating response to positive and negative verbal stimuli.

MATERIALS AND METHODS

Subjects: Twelve right-handed volunteers were recruited, eight female and four male, aged between 24 and 59 years. Prior to scanning, a medical history was obtained and subjects were excluded if they reported any neurological or psychiatric history, closed head injury or substance abuse. A structural MRI scan was taken before fMRI scanning (see below) to exclude subjects who showed any evidence of structural abnormality. One male subject was excluded from the subsequent analysis on this basis. The study was approved by the local research ethics committee (Joint ethics Committee of National Hospitals and Institute of Neurology) and informed written consent was obtained from all subjects.

Cognitive activation paradigm: Subjects were scanned during performance of 24 blocks of task interspersed with rest blocks. In each block they performed one of a number of variants of a classic go/no-go task. The task was adapted for imaging purposes from that used by Murphy *et al.* [13]. This task compared two conditions; happy targets with sad distractors and sad targets with happy distractors. The words were drawn from a carefully selected cohort as described by Murphy *et al.* [13]. Representative examples of happy words included joyful, success and confident, while representative sad words included gloomy, hopeless and failure. In the present study, we also introduced a cohort of neutral words as this allows us to distinguish between neural responses specific to happy or sad emotions from those seen for all emotionally toned words. Neutral words were selected to match the emotional words for imageability, word length and frequency; representative examples include range, vary and directly. The task was presented in blocks and prior to the start of a block, subjects were given an instruction to respond (go) to certain targets but ignore (no go) distractors. The different conditions were as follows: (1) targets happy words, distractors sad words; (2) targets happy words, distractors neutral; (3) targets sad words, distractors happy words; (4) targets sad words, distractors neutral words; (5) targets neutral words, distractors happy words; (6) targets neutral words, distractors sad words; (7) all words neutral, targets in italic text, distractors in plain text; (8) all words neutral, targets in plain text, distractors in italic text

Conditions 1–6 assessed the effects of attending to words of different emotional tone. We expected significant effects to be due to the differences between emotional tone of target words. Note however that the above design also enabled us to assess whether differences may also be due to the emotional tone of distractors. Thus, for example, condition 1 compared with 2 assesses the effect of sad compared to neutral distractors for happy targets. Conditions 7 and 8 were included as low level controls where

subjects were not required to make any semantic judgment.

In all conditions, subjects were shown a series of 20 words, flashed on the screen for 300 ms. Ten of the words were targets and 10 were distractors, presented in a randomized order. Between words there was a 900 ms interval during which subjects made their response. Thus each 20 word block was 24 s long. Between test blocks were rest blocks where subjects relaxed for 24 s. Rest blocks were used partly to provide subjects with breaks from the intensive active task and partly to provide a repeating baseline condition to model low frequency drift in signal (see below). Four seconds before the end of the rest blocks, a written instruction for the next task block appeared on the screen. Subjects were told to respond by pressing a button as quickly as possible every time they detected a target. The task was fully explained and demonstrated to subjects prior to scanning to ensure they fully understood the requirements of the different conditions.

MRI scanning: MRI data were acquired using a 2 T Siemens VISION system. Structural images were acquired with a T1 weighted sequence and functional images with a gradient echo, echo-planar T2* sequence using BOLD (Blood Oxygenation Level Dependency) contrast. A total of 294 functional images were taken for each subject, each comprising a full brain volume of 48 3 mm axial slices with 3 mm in plane resolution. Volumes were acquired continuously with a Tr of 4 s. Thus each 24 s task block corresponded to 6 volumes. The run began with 6 dummy volumes to allow for T1 equilibration effects; these volumes were subsequently discarded.

Data analysis: Data were analysed using statistical parametric mapping (SPM98; Wellcome Dept. of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks Inc, Sherborn, MA, USA) and run on a SPARC workstation (Sun Microsystems Inc, Surrey, UK). The SPM methodology is discussed in detail elsewhere [14]. Scans were realigned, normalised and spatially smoothed, using the standard SPM approach. Statistical analysis of these data was then carried out using a random effects model to account for intra-subject variability to generate statistical parametric maps of the *t*-statistic (SPM{t}) which was transformed to a normal distribution (SPM{Z}). For descriptive purposes, and in line with the conventions of the functional imaging literature, we report neural responses seen at an uncorrected threshold of $p < 0.001$. This is an acceptable threshold for reporting neural response in regions about which there is an *a priori* hypothesis. For regions about which there was no *a priori* hypothesis, we applied the more stringent threshold of $p < 0.05$, corrected for multiple comparisons. Designation of anatomical localizations are based on the individual structural MRIs of the group and the atlas of Duvernoy [15].

RESULTS

Behavioural data: Mean performance data are given in Table 1. Reaction times did not differ significantly for different emotional valence, although there was a trend towards subjects being slower for neutral targets ($p < 0.1$). As expected, the responses to targets on the basis of font

Table 1. Performance data. The mean behavioural scores on three performance measures; reaction times, mean (s.e.m.) error rate (false positives) per 20 word block and mean omissions (non-response to targets) per 20 word block.

	Happy targets	Sad targets	Neutral targets
Mean reaction time (ms)	535 (8.8)	549 (7.9)	554 (9.3)
Mean error rate (/block)	1.3 (0.14)	1.2 (0.11)	1.4 (0.16)
Mean omissions (/block)	0.63 (0.09)	0.67 (0.07)	0.59 (0.07)

were significantly quicker: mean ($\pm$ s.e.m.) reaction time 338 ± 5.4 ms. Subjects made minimal errors (responding to distractor words) with no significant differences between conditions. There were also minimal omissions (failures to respond to targets), again with no significant differences between conditions.

All active tasks compared with rest: This comparison represents conditions 1–8 above compared with condition 9 and assesses the neural substrates of a verbal go no-go paradigm (see Table 2). Highly significant ($p < 0.05$, corrected) neural responses were seen in bilateral lateral orbitofrontal cortex (BA 47), bilateral inferior frontal gyrus (BA 44), bilateral medial occipital gyrus (BA 19) and dorsal anterior cingulate (BA 32). Less significant ($p < 0.001$, uncorrected) responses were seen in the left inferior parietal lobe (BA 40) and pulvinar.

All semantic tasks compared with orthographic control: This comparison represented conditions 1–6 above, compared with conditions 7 and 8 (see Table 2). Highly significant neural responses (p < 0.05, corrected) were observed

in left inferior frontal gyrus (BA 47 extending dorsally to BA 45). Less significant response ($p < 0.001$, uncorrected) was seen in dorsal anterior cingulate (BA 32).
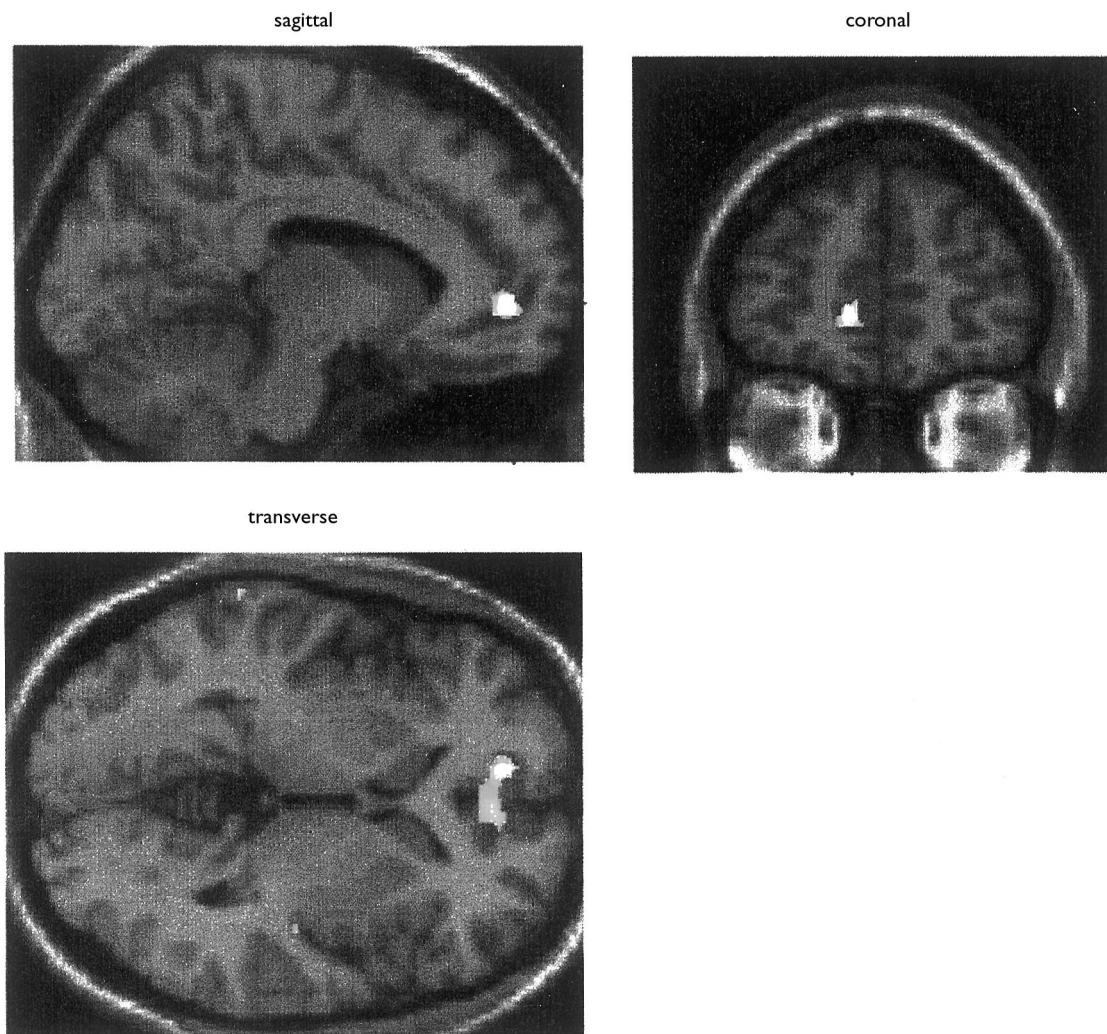
Emotional targets compared with neutral targets: This comparison represented conditions 1–4 above, compared with conditions 5 and 6. There were no neural responses that survived correction for multiple comparisons. However, at the lower threshold of $p < 0.001$, uncorrected, neural responses were seen in hippocampal gyrus bilaterally (BA 27), right insula and subgenual cingulate (BA 32; Fig. 1, Table 2).

Happy compared with sad targets: Greater neural response for happy than sad targets was assessed by comparing conditions 1 and 2 with 3 and 4. The only neural response that was significant at a threshold of $p < 0.001$, uncorrected, was in a restricted region of relatively ventral anterior cingulate (Table 2). The reverse comparison, assessing where there was greater neural response to sad than to happy words, revealed no areas significant at the $p < 0.001$ uncorrected threshold.

Table 2. Regions responding to contrasts between cognitive conditions.

Region	Left/Right	Brodmann's area	Talairach coords			Z value
All go/no-go *vs* rest						
Lateral orbitofrontal cortex	R	47	36	27	−6	5.02*
	L		−54	18	−9	4.85*
Medial occipital gyrus	R	19	45	−78	0	5.53*
	L		−48	−72	−6	5.34*
Inferior frontal gyrus	R	44	45	12	27	6.42*
	L		−45	9	27	6.78*
Dorsal anterior cingulate	R	32	3	21	48	4.56*
	L		−3	15	45	5.67*
Inferior parietal lobule	L	40/7	−27	−57	51	4.23
All semantic *vs* orthographic						
Inferior frontal gyrus	L	47	−51	30	6	5.36*
	L	45	−48	21	21	4.61*
Dorsal anterior cingulate	L	32	−3	21	45	4.05
Pulvinar	L		−12	−15	6	3.57
Emotional *vs* neutral targets						
Hippocampal gyrus	L	27	−6	−36	0	4.37
	R	27	12	−36	3	4.00
Subgenual cingulate		24	−6	36	−3	3.49
Insula	R		48	−8	6	3.88
Happy *vs* sad targets						
Ventral anterior cingulate	R	32/24	6	30	21	3.60

Z values are thresholded at 3.09, corresponding to a significance level of $p < 0.001$, uncorrected. * $p < 0.05$ corrected.

sagittal

coronal

transverse

Fig. 1. Neural response in the subgenual cingulate region associated with responding to emotional targets compared to neutral targets. The group response is shown rendered onto a standard MRI template and is thresholded at p < 0.001, uncorrected.

Effects of distractors: There were no significant differences in neural response to happy, sad and neutral distractors.

DISCUSSION

The results indicate an involvement of regions including bilateral orbitofrontal cortices in a verbal go/no-go paradigm. When targets were defined by semantic, as opposed to orthographic properties, there were significant neural responses in other prefrontal regions; left ventrolateral prefrontal cortex and dorsal anterior cingulate cortex. Emotional compared to neutral targets were associated with neural response in regions that include hippocampal gyri, insula and subgenual cingulate cortex. Ventral anterior cingulate response (although dorsal to the subgenual region) was more pronounced for happy than sad targets. There were no differential neural responses reflecting differences in the emotional valence of distractors.

An involvement of lateral orbitofrontal cortices in a go/no-go paradigm is consistent with previous studies. In the classic lesion literature, orbitofrontal damage has been associated with impaired performance of go/no-go tasks in animals [16]. In a recent fMRI study, Casey *et al.* [17] reported lateral orbitofrontal cortex response associated with a letter-based go/no-go task. A key component of go/no-go paradigms is response inhibition and the lateral orbitofrontal cortex may mediate this process. Consistent with this hypothesis is the finding of Nobre *et al.* [18] that lateral orbitofrontal cortex response is associated with a covert orienting task with invalid cues. In this task subjects were cued to prepare a particular response which they subsequently had to inhibit. Similarly, for go/no-go tasks such as that used here, the requirement to respond quickly to targets creates a strong preparatory motor set that must be inhibited when the word is not a target.

Lateral orbitofrontal response was seen in all go/no-go

conditions compared to rest. For conditions where the decision to go or no-go was based on a semantic judgement, the neural responses were in more dorsal prefrontal regions. Most significant was response in left ventrolateral frontal cortex extending from BA 47 to BA 44/45. This is a region that has been consistently activated in PET studies of semantic compared to visual processing [19]. While the precise role of this region remains unclear, one prominent theory [20] is that it is involved with the selection of semantic material rather than actual semantic processing. In the task used here, selection of response on the basis of semantics is a key component. A dorsal region of anterior cingulate also responded more strongly in the semantic than the orthographic task. This is a region that has been shown to respond in a range of cognitive activation paradigms, with differentially greater activation in more difficult or attention-demanding conditions [21], leading to the suggestion that this region mediates enhanced cognitive effort. In the task used here, subjects found the semantic conditions more difficult than the orthographic condition, as evidenced by the elevated reaction times and the dorsal cingulate response can be accounted for on this basis.

The key findings of this study were of differential neural responses associated with responding to emotional compared to neutral targets. As previous studies have also reported, we observed a number of regions where neural response was associated with both positive and negative emotional tone, compared to neutral tone. The regions involved were a subset of those that were predicted on the basis of previous research. Notably absent in the present study is the amygdala, a region traditionally associated with response to emotional stimuli. It is possible that this reflects a lower affective salience of words compared to the facial expressions or emotive pictures used in previous studies. Expressive faces or graphic pictures may activate more automatic or visceral emotional processes, critically mediated by the amygdala [6,22]. Interestingly, an earlier fMRI study by Teasdale et al. [7] using a combination of pictures and captions to generate affect, but with the affective component only explicit in the words, also failed to report amygdala activation.

The modality of emotional material (words compared to faces or pictures) is one important difference between this study and previous studies of emotional processing. However another difference is in the task demands; here, emotional processing is being studied in the particular context of a response inhibition task. Our results do not allow us to state clearly whether the modality of stimuli or the task demands are the critical factor distinguishing our activation paradigm from those used previously, however it seems plausible that both factors may be important. In the go/no-go task used here, emotional salience is used to define targets in a classic cognitive task. Thus the observed neural responses are not to emotion *per se* but to the modulation of performance of a cognitive task by emotional tone. Emotional salience of targets was associated with hippocampal gyrus, insula and subgenual cingulate and one interpretation of our findings is that these regions represent an interface between emotion and cognition, that is activated when emotional information must be used to guide cognitive processing.

A critical region in this comparison was the subgenual cingulate cortex. This is an area that has recently aroused a great deal of interest in the context of the pathophysiology of depression and mania [23]. The subgenual cingulate has been demonstrated to be both structurally and functionally abnormal in unipolar and bipolar depression, disorders characterized by disturbances of emotional processing and biases in cognitive processing by emotional tone of material. Specifically, it has been demonstrated that patients with affective disorders show significant mood congruent biases on a go/ no-go task similar to that used here [13]. This suggests that the paradigm, in its fMRI compatible form, may be a cognitive activation probe for subgenual dysfunction in patient populations. The control subjects, in both the study of Murphy *et al.* [13] and the present study, show no significant bias towards either positive or negative information and the subgenual cingulate is equally responsive under both emotional conditions. However, it is a reasonable prediction that the mood-congruent biases reported in depressed and manic patients may be mediated by differential response in this region.

Consistent with previous studies of neural response to emotional material, we observed more commonalities than differences in the regions responding to pleasant compared with unpleasant emotions. The only differential neural response to different targets was in a region of ventral anterior cingulate that responded to happy but not sad emotional tone. It is unlikely that this is an effect of difficulty. Firstly the focus is more ventral than typical difficulty-related neural response, and secondly, there is no evidence from performance data to suggest that detecting happy targets is harder than detecting sad ones. The more ventral region of anterior cingulate is principally interconnected with classical limbic structures including the amygdala [24], and also projects to brainstem regions involved in control of autonomic function [25]. The ventral cingulate region is thus often considered as part of an extended limbic system and its differential response under emotional conditions is therefore entirely plausible. It is less clear why this region should be more responsive to happy than to sad targets, since previous studies have not reported such a differentiation [4,7]. One possible explanation is that positive stimuli in this study may be more arousing to control subjects.

A possible confound of studies of attentional bias is that while the effects may represent enhanced or reduced processing of targets, they may also represent reduced or enhanced interference by distractors. The design employed here allowed us to look at neural responses to distractors as well as to targets and confirm that, to the extent to which neural response is an index of information processing, there is no differential effect of the emotional valence of distractors. This does not mean that the distractors are not being processed since subjects must clearly process all the words as a prerequisite of deciding whether or not to respond. Rather, it means that the difference between the conditions depends on the valence of the targets rather than distractors. This suggests that the difference operates at a top-down level of processing. That is, the neural response depends on the target-defined attentional set formed by the subject in each block and not on the actual words that appear on the screen.

CONCLUSION

These findings therefore provide evidence that differential neural responses to the emotional tone of verbal material in a simple go/no-go task can be distinguished using fMRI, in the absence of measurable performance differences. Further, they demonstrate that it is the nature of the targets rather than the distractors that determine this differential response. The regions mediating response to emotional tone include foci within the medial prefrontal cortex, including the subgenual cingulate, that have been shown to be abnormal in affective disorders. Murphy *et al.* [13] have demonstrated behaviourally, that an emotional go/no-go task is sensitive to mood-congruent biases in mania and depression. The paradigm used here therefore provides a means of assessing the functional anatomy of these biases and has potential implications for our understanding of the mood disturbance that is central to affective disorders.

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