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# The interaction between mood and cognitive function studied with PET

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## ABSTRACT

**Background.** Experimentally induced depressed mood is a suggested model for retarded depression. We describe the neural response associated with induced mood and the locus of the interaction between systems mediating mood and cognitive function.

**Methods.** Normal subjects performed a verbal fluency task during induced elated and depressed mood states. Regional cerebral blood flow (rCBF) was measured as an index of neural activity using Positron Emission Tomography (PET).

**Results.** In both elated and depressed mood state rCBF was increased in lateral orbitofrontal cortex, rCBF was also increased in the midbrain in elated mood. In the depressed condition rCBF was decreased in rostral medial prefrontal cortex. Verbal fluency produced an expected increase of rCBF in left dorsolateral prefrontal, inferior frontal and premotor cortex, anterior cingulate and insula cortex bilaterally, the left supramarginal gyrus posteriorly and the thalamus. Activation in the verbal fluency task was attenuated throughout the left prefrontal, premotor and cingulate cortex and thalamus in both elated and depressed mood conditions. An attenuation of anterior cingulate activation was specific to depressed mood.

**Conclusions.** Alteration of mood is associated with activation of orbitofrontal cortex which may be critical to the experience of emotion. The mood induced modulation of verbal fluency induced activations is consistent with resting state findings of decreased function in these regions in depressed patients. The present data suggest that resting state rCBF profile may represent the modulation of spontaneous activity in this network by a core system that is dysfunctional in depression.

## INTRODUCTION

Depressed mood and lack of emotional reactivity is pathognomic of depression. Cognitive and motivational abnormalities are also integral to depressive disorders (Weingartner *et al.* 1981). Functional imaging studies have revealed distinct patterns of abnormal resting regional cerebral blood flow (rCBF) in depression that correlate with the principal symptom profiles (Dolan *et al.* 1992; Bench *et al.* 1993).

Cognitive techniques have been widely used to alter mood in normal subjects (Gerrards-Hesse *et al.* 1994). The distinction between normal and pathological mood states has been emphasized by psychiatrists. However, a mood state characterized by negative self-evaluation and psychomotor changes analogous to those associated with clinical depression can be induced in normal subjects (Velten, 1968) and is referred to as 'depressed mood' in contrast to normal sadness. Psychologically induced depressed mood is also regarded as a valid model of retarded depression (Clarke, 1983; Riskind & Rholes, 1985). The validity of this model is

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reinforced by the associated low self-esteem (Brown & Mankowski, 1993), psychomotor retardation (Velten, 1968; Teasdale & Fogarty, 1979; Natale & Boylan, 1980) and cortisol hypersecretion (Brown *et al*. 1993). Current psychological theories of the pathogenesis of depressive disorders have emphasized the role of deviant cognitive style, characterized by self-deprecating thoughts, analogous to the some of the Velten statements, and the mood state induced by this procedure has been invoked to support cognitive models of the pathogenesis of depression (Riskind & Rholes, 1985).

An understanding of the pathophysiology of mood disorders requires specification of the neural systems that mediate normal emotional response and the neurophysiological mechanisms by which these systems influence cognitive function. Animal studies suggest a critical involvement of the ventral prefrontal cortex in the regulation of emotion (Rolls, 1994). Consistent with this, activation of the orbitofrontal cortex has been observed during recall or imagination of sad events (Pardo *et al*. 1993, George *et al*. 1995), during evoked anxiety in phobic and obsessive–compulsive disorders (Rauch *et al*. 1994, 1995) and with the dysphoria of angina pectoris (Rosen *et al*. 1994). Lesions to the orbitofrontal cortex disrupt social and emotional regulation of behaviour in humans and monkeys (Butter *et al*. 1968; Damasio *et al*. 1990). However the relationship between affective disorders and orbitofrontal dysfunction remains unclear. The surgical procedure of subcaudate tractotomy, resulting in disconnection of the orbitofrontal cortex, is reported as effective in the treatment of severe resistant depression (Bridges *et al*. 1994). Curiously, functional abnormalities are only rarely reported in this region in imaging studies of depression (e.g. Mayberg *et al*. 1990; Goodwin *et al*. 1993).

We used a combined mood induction and cognitive activation paradigm to investigate the functional anatomy of elated and depressed mood in normal subjects. Combining these tasks provides a powerful tool to determine the interaction between mood and cognitive function.

## METHOD

### Subjects

Ten male volunteers aged between 18 and 35 years took part in the study, which was approved by the Hammersmith Hospital Ethics Committee and the Advisory Committee on the Administration of Radioactive Substances (ARSAC) UK. Subjects were recruited from the staff and students at London teaching hospitals, they were screened to exclude previous psychiatric disorder and drug use and were strongly right-handed as assessed by the Edinburgh inventory. Informed consent was obtained from all subjects.

### PET scanning techniques

Regional cerebral blood flow was measured with a CTI model 953B PET Scanner (CTI, Knoxville, TN, USA), with the interplane septa retracted (Spinks *et al*. 1992). Following a 'slow bolus' infusion of $H_2{}^{15}O$, integrated counts per pixel during the 90 s acquisition frame, corrected for background counts, provided an index of rCBF. Then 11·2 mCi of $H_2{}^{15}O$ was flushed with normal saline through a cannula in an antecubital vein over 20 s at 10 ml/min by an automatic pump. After a constant delay a rise in counts at the head was detected, which peaked between 30–40 s in individual subjects. Although counts were collected for 90 s, only the activity occurring during the rising phase of the head count curve contributes significantly to the signal in the final image (Silbersweig *et al*. 1993). Each subject underwent 12 scans, with a 10 min interval between scans. Correction for attenuation was made by performing a transmission scan with an exposed $^{68}Ge/^{68}Ga$ external ring source before each session and a 30 s frame for background activity correction was acquired before each infusion.

### Study design

During each scan subjects performed either paced orthographic verbal fluency or word repetition tasks, generating or repeating one word every 5 s, in a repeated ABAB … design (Frith *et al*. 1991). In the verbal fluency condition subjects continued to generate words beginning with a given letter until they failed to respond within the time limit after which they were given a new letter. Subjects were studied in elated, neutral and depressed mood states. Mood

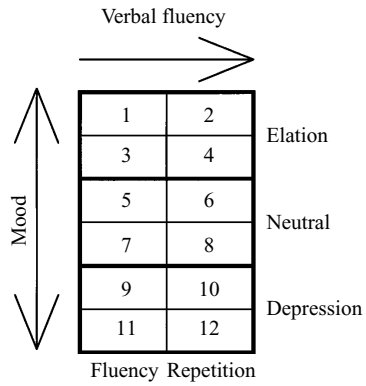


FIG. 1. Diagrammatic illustration of the study design. There are six scans in the verbal fluency condition and six in the repetition condition. These are subdivided into three blocks of four scans each in elated, neutral and depressed mood. The order of induced mood states was counterbalanced across subjects to avoid systematic time effects.

induction material was presented for 7·5 min prior to each scan. The study was divided into three blocks of four scans specific to each induced mood state (Fig. 1). This factorial design allows examination of the main effect of the verbal fluency task in the comparison of the verbal fluency and control conditions across all mood states, the main effect of mood state in the comparison of the elated and depressed mood and neutral mood states across task conditions and the interaction between verbal fluency and mood; i.e. the difference in verbal fluency activation in elated and depressed mood compared to neutral mood. The order of the mood states was counterbalanced across subjects to accommodate time dependent effects. All subjects were debriefed after the study.

## Mood induction paradigm

Subjects were studied in the presence of low background noise and dimmed ambient lighting. A combination of the Velten, musical, social interaction and gift mood induction procedures were employed (Velten, 1968; Clark & Teasdale, 1985; Gerrards-Hesse *et al.* 1994). Subjects were given explicit instructions to enter into the suggested emotional state. Elated, neutral and depressed mood induction statements, modified from Velten (1968), were presented on an Apple Macintosh microcomputer, at a rate of one statement every 30 s. Subjects were played extracts of 'Russia under the Mongolian Yoke', from Prokofiev's music for the film 'Alexander Nevsky' (Clark, 1983), at half speed in the depressed condition; 'Stressbusters', an anodyne recording of popular classics, in the neutral condition; and Delibes' 'Coppelia' in the elated condition. The investigator adopted an appropriately cheerful, neutral or solemn manner. Subjects were presented with an unexpected gift of £30 at the beginning of the elated mood condition.

## Data analysis

Image analysis was performed on a SPARC 10 workstation (Sun Microsystems Inc., Surrey, UK) using interactive image display software (ANALYZE, Biodynamic Research Unit, Mayo Clinic; Robb & Hanson, 1990) and statistical parametric mapping (SPM software, MRC Cyclotron Unit, London, UK). Calculations and image matrix manipulations were performed in PRO MATLAB (Mathworks Inc., New York, USA).

### *Image reconstruction*

Images were reconstructed into 31 slices by three-dimensional back projection using a Hanning filter with a cut-off frequency of 0·5 cycles per pixel. The resulting images consisted of $128 \times 128$ pixels of $2{\cdot}006 \times 2{\cdot}006$ mm having a resolution of $8{\cdot}5 \times 8{\cdot}5 \times 4{\cdot}3$ mm full width at half maximum (FWHM).

### *Image analysis*

The 31 original slices were interpolated to 43 planes in order to render the voxels approximately cubic. Images were automatically realigned to correct for head movement between scans (Woods *et al.* 1993) and transformed into a standard stereotactic space (Friston *et al.* 1991*a*). The stereotactically normalized images, consisting of 26 planes, correspond to the horizontal sections of the standard stereotactic atlas (Talairach & Tournoux, 1988), each pixel represents $2 \times 2$ mm with an interplanar distance of 4 mm. The field of view in all subjects extended from 8 mm below to 56 mm above a line joining the anterior and posterior commissures. Images were smoothed with a Gaussian filter 10 pixels wide in order to suppress high frequency noise in the images and accomodate normal variability in functional and gyral anatomy for group analysis.

*Stastistical analysis*

Differences in global activity within and between subjects were removed by analysis of covariance (ANCOVA) on a pixel by pixel basis with global counts as covariate and regional activity in each condition across subjects as treatment (Friston *et al*. 1990). The ANCOVA generated a mean rCBF value, normalized to 50 ml/100 ml/min, and associated error variance for every pixel in each condition. This adjusted rCBF represents a weighted mean over a sphere of approximately 20 mm. Differences between the adjusted mean pixel values across conditions were assessed using the *t* statistic (Friston *et al*. 1991*b*), the resulting images of pixel *t* values constitute a statistical parametric map (SPM(*t*)). The omnibus significance of the SPMs was assessed by comparing the expected and observed distribution of the *t* statistic under the null hypothesis of no treatment effect. The SPM(*t*)s were additionally displayed as volume images of the highest *t* values in three orthogonal projections and as surface renderings onto a standard cerebral cortex. SPM(*t*)s were transformed to the Unit Gaussian distribution using a probability integral transform so that changes could be reported as *Z* scores.

## RESULTS

### Mood induction

Nine of the 10 subjects reported subjective mood change during the mood induction procedure, reflected in highly significant change in scores on the PANAS (Watson *et al*. 1988) and ratings of elation and depression (Table 1). One subject reported no subjective change in mood and there was no change in his ratings; he was excluded from the subsequent analysis. There was no significant difference in the number of words generated in the verbal fluency task in different mood states, there were a total of six omissions in neutral and depressed mood and seven in elated mood.

### Comparison of rCBF in verbal fluency compared to repetition conditions

The main effect of the verbal fluency task was examined by comparison of all scans in the verbal fluency and control conditions. Foci of maximal change in rCBF are displayed in Fig. 2 and summarized in Table 2. Highly significant increases in rCBF ($P < 0{\cdot}001$) were observed in the verbal fluency condition in the left inferior frontal gyrus and dorsolateral prefrontal cortex, bilateral anterior cingulate and insula cortex anteriorly, the left angular gyrus posteriorly and the thalamus. There were relative decreases in rCBF ($P < 0{\cdot}001$) in right inferior and superior frontal gyri, bilaterally in superior and middle temporal gyri and in medial temporal, inferior parietal and occipital cortex.

Table 1. *Mean positive and negative affect scores on the Positive and Negative Affect Scale* (*PANAS*; *Watson* et al. 1988) *and mood ratings in depressed, neutral and elated mood conditions*

| Induced mood | PANAS scores | | Elation depression | |
|---|---|---|---|---|
| | +ve (S.D.) | −ve (S.D.) | Score (S.D.) | Score (S.D.) |
| Depressed | 17·3 (5·6)*** | 18·2 (5·7)*** | 1·3 (0·6)NS | 2·7 (1·0)*** |
| Neutral | 22·5 (7·0) | 11·7 (2·6) | 1·9 (0·7) | 1·1 (0·4) |
| Elated | 32·3 (7·6)*** | 11·0 (1·4)NS | 3·4 (0·9)*** | 1·0 (0·0)NS |

Significance of change in elated and depressed mood compared to neutral mood: *** $P < 0{\cdot}0001$; NS Not significant.

PANAS norms for college students rating current mood under standard conditions (Watson *et al*. 1988): +ve mean 29·7 S.D. 7·9, −ve mean 14·8 S.D. 5·4. Depressed and elated mood induction were both associated with significant change in rated mood from the neutral condition.

### rCBF changes in elated and depressed mood

The main effect of induced mood was examined by comparison of all scans in elated and depressed mood compared to the neutral mood. Bilateral orbitofrontal rCBF increases ($P < 0{\cdot}001$) were seen in both elated and depressed mood compared to the neutral condition (Fig. 3*a* and *b*; Tables 3 and 4), and were significantly greater in elated mood than in depressed mood ($P < 0{\cdot}0005$). rCBF increases were also observed in the superior region of the left dorsolateral prefrontal cortex and right lateral premotor area in both elated and depressed mood. In depressed mood, rCBF increases were apparent in SMA and posterior cingulate cortex. In elated mood a focal rCBF increase was also present in the region of the posterior hypothalamus and midbrain and also in left superior frontal gyrus. Posteriorly rCBF was increased in the right lateral parietal cortex.

Decreased rCBF ($P < 0{\cdot}001$) was observed in the right caudate nucleus in both elated and

Table 2. *Comparison of verbal fluency and repetition conditions: foci of significant rCBF change*

| Location | Left/ Right | Brodmann's area | Talairach coordinates | | | *Z* value |
|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | |
| rCBF increases | | | | | | |
| Anterior cingulate gyrus | L | 32 | −4 | 18 | 36 | 10·1 |
| Middle frontal gyrus | L | 46 | −32 | 44 | 20 | 6·36 |
| Middle frontal | L | 10 | −24 | 36 | −8 | 4·02 |
| gyrus | R | 10 | 20 | 34 | −4 | 3·47 |
| Inferior frontal gyrus | L | 44 | −36 | 4 | 28 | 6·94 |
| Anterior insula | L | | −30 | 18 | 4 | 7·71 |
| | R | | 22 | 16 | 4 | 4·23 |
| Medial premotor cortex (SMA) | L | 6 | −10 | 2 | 56 | 7·85 |
| Angular gyrus | L | 39 | −28 | −56 | 36 | 3·28 |
| Thalamus | | | 2 | −8 | 0 | 7·93 |
| rCBF decreases | | | | | | |
| Superior frontal | R | 10 | 6 | 58 | 4 | 3·89 |
| gyrus | R | 9 | 5 | 50 | 32 | 4·07 |
| Inferior frontal gyrus | R | 44/45 | 48 | 12 | 20 | 3·74 |
| Superior temporal | R | 22 | 46 | −12 | 4 | 7·25 |
| gyrus | L | 22 | −46 | −16 | 8 | 6·54 |
| | R | 22 | 46 | −48 | 16 | 7·84 |
| | L | 22 | −52 | −32 | 12 | 7·07 |
| Middle temporal | L | 39 | −48 | −60 | 12 | 8·40 |
| gyrus | R | 37 | 44 | −56 | 4 | 7·40 |
| Inferior parietal | L | 40 | −56 | −42 | 28 | 4·04 |
| cortex | R | 40 | 50 | −30 | 32 | 6·31 |
| Medial temporal | R | 36 | 22 | −40 | −8 | 4·73 |
| cortex | L | 19 | −32 | −44 | 0 | 3·53 |
| Occipital cortex | L | 18 | −4 | −92 | 12 | 3·16 |
| | L | 19 | −34 | −80 | 24 | 3·64 |

The co-ordinates of the foci of maximal significant change of rCBF ($P < 0{\cdot}001$) in the standard stereotaxic space of Talairach & Tournoux (1988) are given in millimeters.

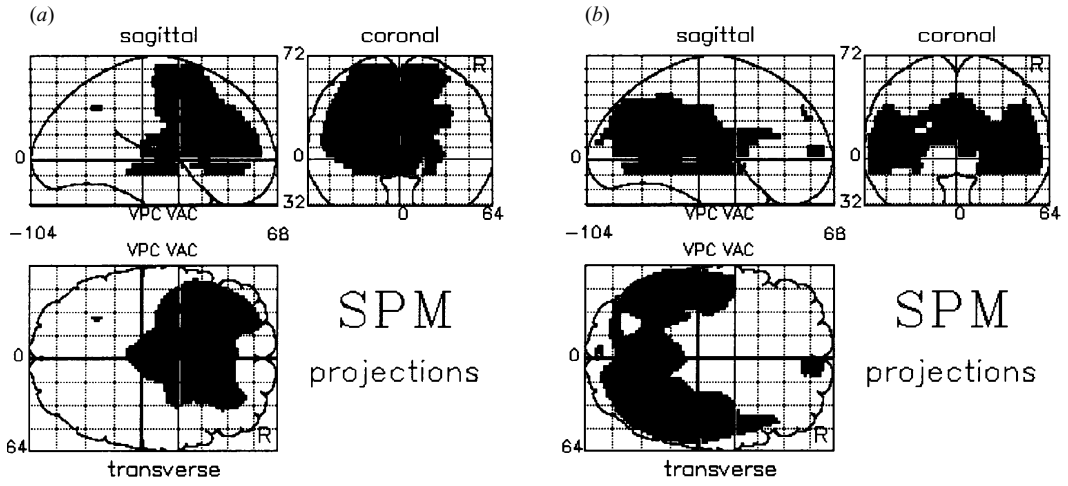


FIG. 2. Regional brain activity associated with the verbal fluency task. Statistical parametric maps (SPMs) show regional cerebral blood flow (rCBF) changes in word generation compared to word repetition scans. The SPMs illustrate: (*a*) increases; and (*b*) decreases of rCBF. Pixels exceeding an uncorrected threshold of significance $P < 0{\cdot}001$ are displayed on sagittal, coronal and transverse projections of a standard brain (Talairach & Tournoux, 1988), the left side of the brain is on the left side of the projections. The co-ordinates of the foci of maximal change of rCBF are given in Table 1.

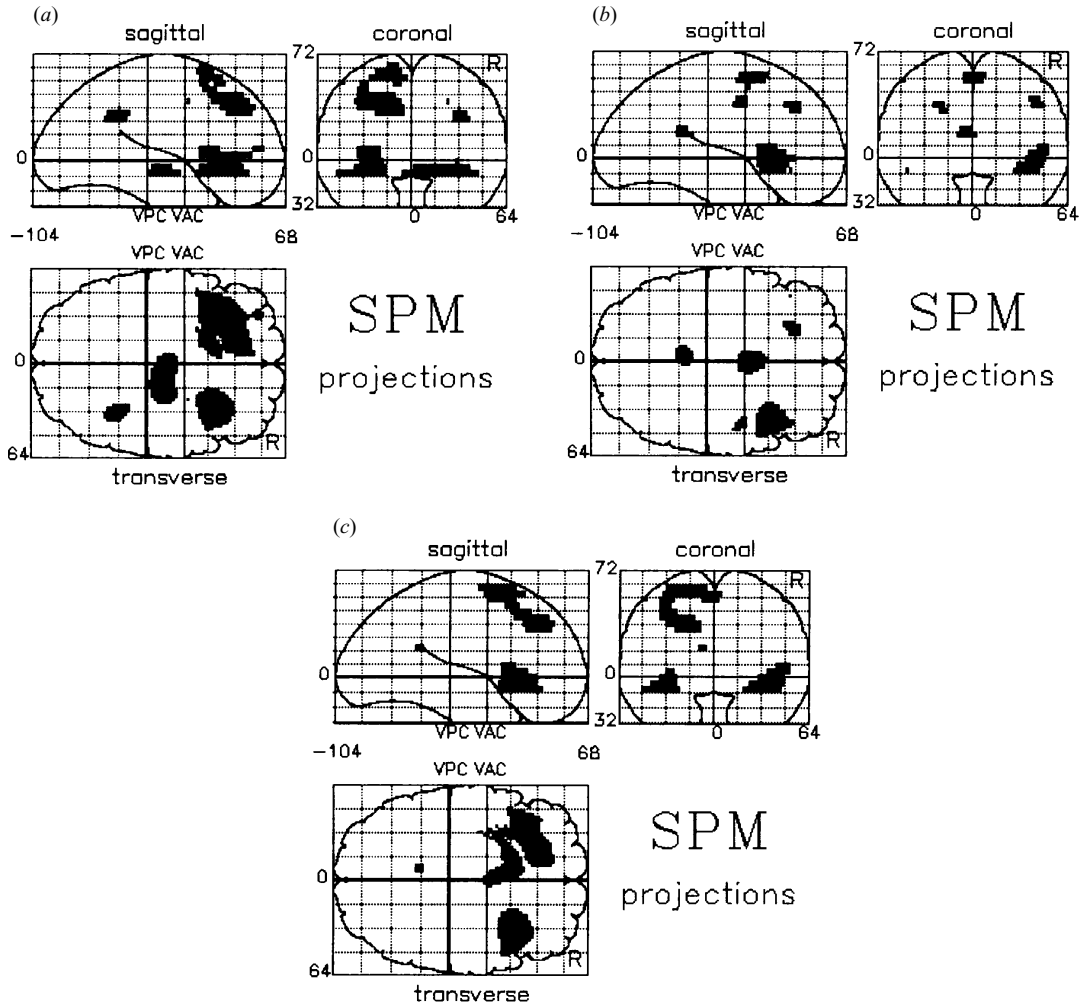


FIG. 3. Regional brain activity associated with induced mood states. SPMs illustrate increases of rCBF in: (*a*) elated mood compared to neutral mood; (*b*) depressed mood compared to neutral mood; and, (*c*) activation common to both elated and depressed mood states compared to neutral mood. Pixels exceeding an uncorrected threshold of significance $P < 0{\cdot}001$ are illustrated as in Fig. 1. The coordinates of the foci of maximal change of rCBF in elated and depressed mood compared to neutral mood are given in Table 2.

depressed mood. Depressed mood was associated with decreased rCBF in the right dorsolateral and bilateral rostral medial prefrontal cortex. Elated mood was associated with decreased rCBF in the middle and inferior temporal and posterior cingulate cortex and the thalamus.

When the combined elated and depressed mood conditions were compared with the neutral condition (Fig. 3*c*) rCBF increases attained highest significance in the lateral orbitofrontal cortex (BA 47) bilaterally.

### Interaction between induced mood and cognitive activation

To examine the interaction between mood and the cognitive task, the difference between verbal fluency activation in elated (or depressed mood) and neutral mood was determined. The network activated by the verbal fluency task defines regions in which brain activity associated with the cognitive task may be modulated by the induced mood states. These critical comparisons were therefore constrained to voxels at which

Table 3. *Comparison of depressed and neutral mood*: *foci of significant rCBF change*

| Location | Left/ Right | Brodmann's area | Talairach coordinates | | | *Z* value |
|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | |
| rCBF increases | | | | | | |
| Inferior frontal | R | 47 | 36 | 20 | −8 | 3·74 |
| gyrus | L | 47 | −44 | 32 | −8 | 3·09 |
| | R | 45 | 46 | 16 | 4 | 3·55 |
| Middle frontal gyrus | L | 9 | −24 | 32 | 36 | 3·27 |
| Lateral premotor cortex | R | 6 | 44 | 0 | 36 | 3·29 |
| SMA | | 6 | 0 | 6 | 56 | 3·77 |
| Post. cingulate | | 23 | −4 | −38 | 16 | 3·77 |
| gyrus | | 31 | 0 | −32 | 40 | 2·91 |
| rCBF decreases | | | | | | |
| Superior frontal | R | 10 | 6 | 48 | −4 | 4·06 |
| gyrus | L | 10 | −8 | 58 | −4 | 3·84 |
| Middle frontal gyrus | R | 46 | 28 | 28 | 24 | 3·30 |
| Caudate nucleus | R | | 18 | −8 | 24 | 3·09 |

The co-ordinates of the foci of maximal significant change of rCBF ($P < 0{\cdot}001$) in the standard stereotaxic space of Talairach & Tournoux (1988) are listed as in Table 2.

Table 4. *Comparison of elated and neutral mood*: *foci of significant rCBF change*

| Location value | Left/ Right | Brodmann's area | Talairach coordinates | | | *Z* |
|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | |
| rCBF increases | | | | | | |
| Inferior frontal | L | 47 | −30 | 28 | −8 | 4·17 |
| gyrus | R | 47 | 30 | 24 | −8 | 4·47 |
| | L | 47 | −26 | 28 | 0 | 3·94 |
| Middle frontal | L | 10 | −34 | 52 | 8 | 3·28 |
| gyrus | L | 8 | −30 | 32 | 40 | 4·78 |
| Superior frontal | L | 9 | −16 | 40 | 36 | 4·33 |
| gyrus | L | 8/6 | −14 | 24 | 56 | 3·59 |
| Lateral premotor | R | 6 | 24 | 4 | 40 | 3·09 |
| cortex | L | 6 | −36 | 14 | 48 | 3·24 |
| | L | 6 | −24 | 16 | 56 | 3·31 |
| Lateral parietal cortex | R | 40 | 34 | −46 | 28 | 3·85 |
| Hypothalamus | | | 2 | −12 | −8 | 3·98 |
| rCBF decreases | | | | | | |
| Fusiform gyrus | L | 37 | −32 | −44 | −8 | 3·46 |
| Middle temporal gyrus | R | 21 | 56 | −34 | −8 | 3·97 |
| Post. cingulate gyrus | R | 23/31 | 20 | −56 | 20 | 3·53 |
| Thalamus | | | 0 | −18 | 16 | 3·29 |
| Caudate nucleus | R | | 16 | −12 | 24 | 3·48 |

The co-ordinates of the foci of maximal significant change of rCBF ($P < 0{\cdot}001$) in the standard stereotaxic space of Talairach & Tournoux (1988) are listed as in Table 3.

significant rCBF increases were observed in the verbal fluency condition. Activation of the verbal fluency network was attenuated by both elated and depressed mood. No enhancement of activation in this network was observed in either induced mood state.

In the depressed mood state activation was attenuated ($P < 0{\cdot}0005$) throughout the left

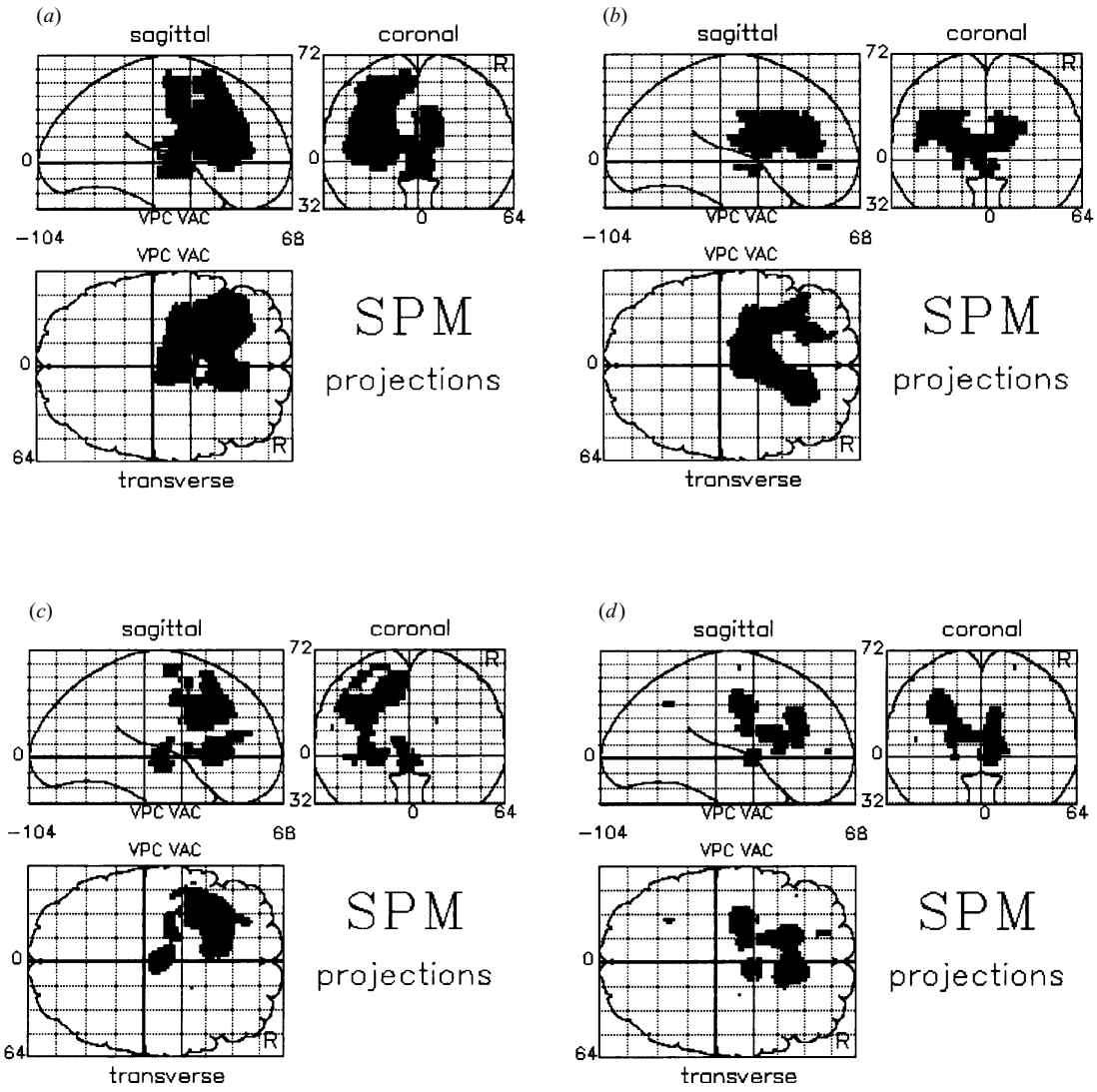


FIG. 4. Interaction between mood and cognitive activation. SPMs illustrate: (*a*) attenuation of verbal fluency activation by depressed mood (the difference between verbal fluency activation compared to repetition in depressed and neutral mood), activation of the network engaged by word generation is extensively attenuated; (*b*) direct comparison of verbal fluency scans in depressed and neutral mood, (decreased rCBF in depressed mood in this comparison is attributable exclusively to changes in the verbal fluency condition); (*c*) attenuation of verbal fluency activation by elated mood (activation is attenuated in prefrontal and premotor cortex as in depressed mood but not in the anterior cingulate cortex); (*d*) comparison of rCBF differences in (*a*) and (*c*) illustrates attenuation of verbal fluency activation in anterior cingulate cortex specific to depressed mood. Pixels exceeding an uncorrected threshold of significance $P < 0{\cdot}0005$ are illustrated as in Fig. 1.

prefrontal and premotor areas and in the right anterior cingulate cortex and thalamus (Figs. 4*a* and 5). A similar distribution of decreased rCBF in the depressed mood state ($P < 0{\cdot}005$) is observed in a direct comparison of rCBF in the verbal fluency condition in depressed and neutral mood (Fig. 4*b*). In elated mood activation of this network was also attenuated in the left prefrontal cortex, premotor cortex and thalamus (Fig. 4*c*). Comparison of these patterns of attenuated verbal fluency activation reveals that the attenuated activation in the anterior cingulate cortex is specific to depressed mood (Fig. 4*d*). Mean CBF values in the anterior cingulate

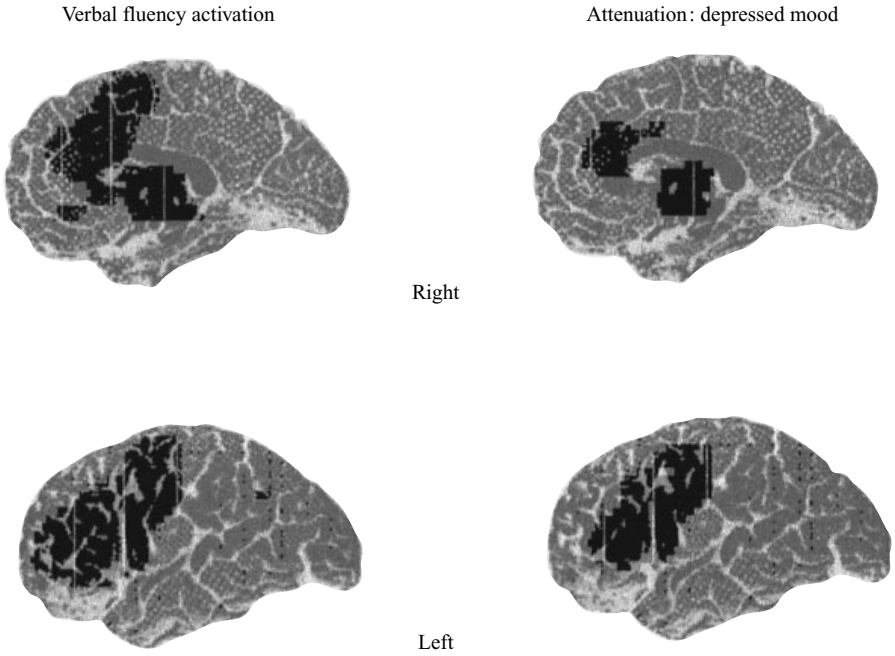


FIG. 5. Verbal fluency activation (left of figure) and areas of attenuated activation in depressed mood (right of figure) are displayed rendered onto a standard brain surface. The medial surface of the right hemisphere (top) and the lateral surface of the left hemisphere (bottom) are illustrated.

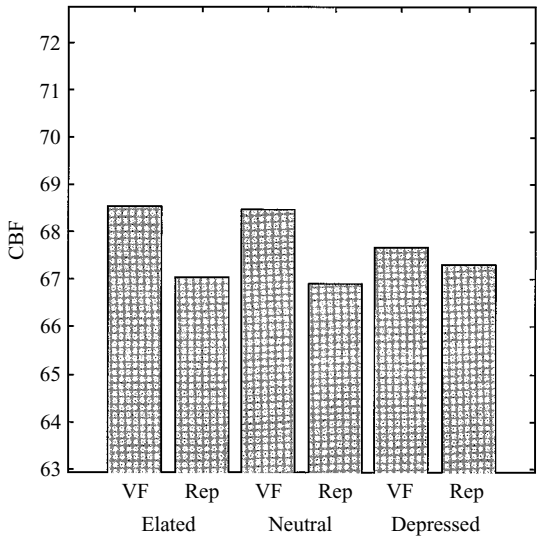


FIG. 6. Adjusted CBF values for the right anterior cingulate cortex in verbal fluency (VF) and repetition (Rep) conditions are shown in each mood state. Mean CBF values were normalized to a global mean of 50 ml/100 ml/min.

cortex at the focus of maximal significant attenuation of activation are illustrated in Fig. 6.

## DISCUSSION

The aims of the present study were to determine which neural systems mediate distinct mood states and to determine the locus of interaction, at the neurophysiological level, between affective and cognitive function. Bilateral activation of the orbitofrontal cortex in both elated and depressed mood suggests that this region is involved in the representation of emotion. The interaction of mood and cognition revealed a striking pattern of attenuation of verbal fluency induced rCBF increases, in the depressed mood state, that mirrors the decreased rCBF in patients with psychomotor retardation (Bench *et al.* 1993). These findings provide neurophysiological support for the depressed mood induction procedure as a model of the psychological and neurophysiological dysfunctions seen in retarded depression (Clark, 1983).

### Mood induction

Effective mood induction techniques rely on the co-operation and ability of subjects to 'get into' the appropriate mood state and consequently are ineffective in a proportion of subjects. The

Velten procedure has been widely employed and between 30 and 50% of subjects fail to experience a measurable change in mood (Polivy & Doyle, 1980; Teasdale & Taylor, 1981; Sutherland *et al.* 1982; Teasdale & Russell, 1983). Mood induction with music is effective in a greater proportion of subjects (Sutherland *et al.* 1982; Clark, 1983). In our study the combined mood induction procedure was ineffective in only one subject.

### rCBF correlates of induced mood

Bilateral rCBF increases were observed in lateral orbitofrontal cortex associated with both elated and depressed mood, indicating that both mood states engage a common neural substrate. This is consistent with electrophysiological studies in the monkey which demonstrate that cells responding to positive and negative affective stimuli are intermingled in the same neuronal population in the orbitofrontal cortex (Thorpe *et al.* 1983).

Activation of the orbitofrontal cortex has been found in previous functional imaging studies that have manipulated affective states. Subjects imaged in a resting state and during dysphoric mood induction using an autobiographical recollection technique (Pardo *et al.* 1993), showed bilateral activation of the lateral orbitofrontal cortex. Mood induction involving a combination of autobiographical recollection and visual inspection of mood congruent facial expression (George *et al.* 1995), is reported as activating the ventral cingulate and rostral medial prefrontal cortex during depressed mood induction compared to a control condition. No significant change in rCBF was associated with elated mood induction in the analogous comparison. However, the experimental design of the latter experiment confounds changes in neural activity associated with recollection with changes associated with the induced mood. Activation of the orbital cortex has also been reported in association with induction of anxiety and visceral pain. In phobic patients, anxiety induced by exposure to feared stimuli was associated with lateral orbitofrontal activation (Rauch *et al.* 1995) and precipitation of angina pectoris in cardiac patients (Rosen *et al.* 1994) was associated with extensive activation of the ventral cingulate and lateral orbitofrontal cortex. It should be noted that the full ventral extent of the orbitofrontal activations could not be determined in the present study due to the limited field of view of the PET camera.

The independent activation of lateral and medial orbital cortex in the present, and other, studies is strong evidence for their differential role in the regulation of emotion. A significant difference between this study and previous studies of mood induction is that we studied patients performing a cognitive task *after* the induction of a mood state. Previous experiments have all studied subjects *during* the induction of a mood state. These different findings might suggest a dissociation between the functional role of medial and lateral orbitofrontal cortex. The anterior cingulate and medial prefrontal cortex may mediate affective reactivity to emotionally salient stimuli while the lateral orbitofrontal cortex may have a more general associative function in emotional responsiveness.

A highly significant activation was also observed in the region of the posterior hypothalamus in the elated mood. This region has reciprocal anatomical connections with the orbitofrontal cortex (Neafsey *et al.* 1986) and plays an important role in emotional expression. Activation in this area has also been observed in the dysphoric state associated with induction of angina pectoris (Rosen *et al.* 1994).

Mood induction was associated with increased rCBF in medial and lateral premotor areas and superior prefrontal cortex. Although responses were paced to equate net verbal output across conditions the affective intonation and prosody of responses in induced mood states inevitably reflect the current mood. This mood congruent behaviour is an implicit response component of the mood induction procedure. Enhanced premotor activation has previously been observed in association with auditory-verbal imagery, in which subjects generated inner speech with an alien intonation (McGuire *et al.* 1996). Increased premotor rCBF in both elated and depressed mood in this study may therefore reflect activations related to the mood congruent response characteristics of the induced mood state.

### Interaction with cognitive function

A consistent finding in functional imaging studies of mood disorders has been the distributed nature of rCBF changes in brain regions

associated with sensori-motor and cognitive function. One interpretation of these changes is that they reflect the interaction between mood and baseline activity in these systems. The present study was explicitly designed to investigate the interaction between induced mood and cognitive activation by a verbal fluency task, a cognitive task that engages neural systems shown to be affected in depression (Frith *et al.* 1991*a*, *b*; Bench *et al.* 1993).

The verbal fluency task, in this and other studies, activates a network of anterior and posterior cortical areas associated with language function (Petersen *et al.* 1989; Wise *et al.* 1991; Frith *et al.* 1991*a*, *b*; Raichle *et al.* 1994; Warburton *et al.* 1995). Activation of the cortical network engaged by verbal fluency was significantly attenuated in the depressed mood state, from the inferior frontal gyrus to the precentral gyrus and SMA, and in dorsolateral prefrontal and anterior cingulate cortex. Attenuation of activation in the elated mood condition was also observed in this network, in the SMA and lateral premotor cortex and dorsolateral prefrontal cortex. Comparison of the patterns of attenuated activation in elation and depression demonstrate that the rCBF changes in the anterior cingulate cortex are specific to depression.

Both mood states were associated with orbitofrontal and dorsal prefrontal activation. Cognitive changes associated with elation have elicited less interest than those associated with depression, though pathologically elevated mood is accompanied by marked impairment of cognitive and attentional function. Faster writing speed and quicker decision times are found in elated mood states (Velten, 1968), performance on cognitive tasks, however, can be impaired (Basso *et al.* 1994). The attenuation of activation in the anterior cingulate gyrus specific to depressed mood may reflect the motivational impairment that is characteristic of depressed mood. Decreased rCBF was also apparent in the rostral medial prefrontal cortex in the depressed mood condition compared to both neutral and elated mood. rCBF decreases in this region correlated with cognitive and attentional impairment in depressed patients (Bench *et al.* 1993; Dolan *et al.* 1995).

**Depression and cognitive function**

Similar patterns of cognitive impairment have been demonstrated in both clinical depression and depressed mood and motivational and attentional impairments constitute core features of both conditions (Ellis *et al.* 1984, 1985; Radenhausen & Anker, 1988). Decreased prefrontal rCBF is a common finding in depression (Baxter *et al.* 1989; Austin *et al.* 1992; Bench *et al.* 1993). Attenuated activation in the anterior cingulate, prefrontal and premotor cortex associated with depressed mood in the present experiment corresponds to the pattern of decreased rCBF found in depressed patients (Bench *et al.* 1993). Decreased rCBF in dorsolateral prefrontal and premotor cortex correlated with psychomotor retardation whereas decreases in medial prefrontal cortex correlated with cognitive impairment. A testable hypothesis is that prefrontal rCBF decreases in depression may represent neural correlates of the subjective experience of diminished spontaneous thought and inner speech that is characteristic of a common manifestation of the condition.

Bench *et al.* (1993) also noted decreased anterior cingulate rCBF in a direct comparison of depressed and normal subjects. A similar pattern of dorsal cingulate and medial prefrontal rCBF decreases was also associated with depression in Parkinsonian patients (Ring *et al.* 1994), where the decrease in rCBF extended to the most ventral anterior cingulate gyrus. In the present study attenuation of activation in the anterior cingulate cortex was specific to depressed mood. In the light of the consistent finding of decreased cingulate rCBF in different groups of depressed patients in this laboratory we suggest that anterior cingulate dysfunction may reflect a fundamental neurophysiological component of depression.

The anterior cingulate cortex is functionally heterogenous with at least three subdivisions recognized on the basis of its anatomical connectivity; an affective, a cognitive and a motor component (Devinsky *et al.* 1995). The affective component comprises the most ventral anterior cingulate cortex corresponding to Brodmanns' areas 33, 25 and rostral areas 32 and 24. These areas project to lateral orbitofrontal cortex, limbic striatum and brainstem autonomic centres (Kunishio & Haber, 1994)

and correspond to the areas activated during mood induction and the dysphoria of angina (George *et al*. 1995; Rosen *et al*. 1994). Electrical stimulation in this area evokes prominent behavioural and autonomic responses (Kaada, 1949). Decreased resting rCBF in this region has been reported in depression associated with Parkinson's disease (Mayberg *et al*. 1990; Ring *et al*. 1994) and increased rCBF associated with recovery from depression (Goodwin *et al*. 1993). The cognitive and motor components comprise caudal areas 24 and 32. These areas are activated by somatic pain (Jones *et al*. 1991) and tasks involving attention and response selection (e.g. Pardo *et al*. 1990; Frith *et al*. 1991*a*) and correspond to the areas in which decreased rCBF has consistently been observed in depression (Bench *et al*. 1992, Ring *et al*. 1994).

Observations on patients with anterior cingulate lesions provide an important source of converging evidence to that of functional imaging data. Lesions in this structure are associated with 'diminished motivation, lethargy, loss of interest … and decreased affective range' (Devinsky *et al*. 1995) analogous to the core symptoms of depression. The function of anterior cingulate cortex is itself regulated by ascending monoaminergic systems. It receives a dopaminergic innervation from the ventral tegmental area (Lindvall & Bjorkland, 1983) and serotonergic innervation from the raphe nuclei (Anden *et al*. 1965). Dopaminergic deafferentation of the forebrain following hypothalamic lesions results in an analogous abulic syndrome that is partially reversible by dopaminergic agonists (Ross & Stewart, 1981).

Psychological theories of depression have emphasized the significance of deviant cognitive attributions in the aetiology of depression (Beck, 1967). It is self evident that both biological and psychological causes of depression must inevitably be expressed through dysfunction at the level of neurophysiology. The present study demonstrates that depressed mood in normal subjects attenuates neural activation in prefrontal and anterior cingulate areas in which decreased neural activity has been observed in depressed patients (Bench *et al*. 1992, 1993).

Activation of the lateral orbitofrontal cortex in both depressed and elated mood states is consistent with extensive previous evidence in man and other animals, indicating a central role for this region in affective behaviour (Rolls *et al*. 1994). Within this system qualitatively different emotional responses may be represented by distinct *patterns* of neural discharge, analagous to the coding of different limb movements as specific patterns of activity within the same neuronal population (Fetz, 1993). We suggest that the present findings are consistent with modulation of distant functional systems by activity in the orbitofrontal cortex associated with emotional states.

Initial exploratory studies in this laboratory have now demonstrated consistent functional abnormalities of the anterior cingulate cortex in clinical depression and induced depressed mood states. By virtue of its functional subdivisions affective, cognitive and psychomotor symptoms may reflect specific regional dysfunction of this structure.

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