Psychological Medicine (2008), **38**, 247–256. © 2007 Cambridge University Press
doi:10.1017/S0033291707001523 Printed in the United Kingdom

ORIGINAL ARTICLE

Neural basis of the emotional Stroop interference effect in major depression

M. T. Mitterschiffthaler[1]*, S. C. R. Williams[1], N. D. Walsh[2], A. J. Cleare[1], C. Donaldson[1], J. Scott[1,3] and C. H. Y. Fu[1]

[1] *Institute of Psychiatry, King's College London, UK*
[2] *University of Pittsburgh, School of Medicine, Department of Psychiatry, Pittsburgh, PA, USA*
[3] *University Department of Psychiatry, Royal Victoria Infirmary, Newcastle upon Tyne, UK*

Background. A mood-congruent sensitivity towards negative stimuli has been associated with development and maintenance of major depressive disorder (MDD). The emotional Stroop task assesses interference effects arising from the conflict of emotional expressions consistent with disorder-specific self-schemata and cognitive colour-naming instructions. Functional neuroimaging studies of the emotional Stroop effect advocate a critical involvement of the anterior cingulate cortex (ACC) during these processes.

Method. Subjects were 17 medication-free individuals with unipolar MDD in an acute depressive episode (mean age 39 years), and 17 age-, gender- and IQ-matched healthy volunteers. In an emotional Stroop task, sad and neutral words were presented in various colours, and subjects were required to name the colour of words whilst undergoing functional magnetic resonance imaging (fMRI). Overt verbal responses were acquired with a clustered fMRI acquisition sequence.

Results. Individuals with depression showed greater increases in response time from neutral to sad words relative to controls. fMRI data showed a significant engagement of left rostral ACC (BA 32) and right precuneus during sad words in patients relative to controls. Additionally, rostral ACC activation was positively correlated with latencies of negative words in MDD patients. Healthy controls did not have any regions of increased activation compared to MDD patients.

Conclusions. These findings provide evidence for a behavioural and neural emotional Stroop effect in MDD and highlight the importance of the ACC during monitoring of conflicting cognitive processes and mood-congruent processing in depression.

Received 26 March 2006; Revised 5 July 2007; Accepted 11 July 2007; First published online 10 September 2007

Key words: Anterior cingulate cortex, depression, emotional Stroop.

Introduction

Increased levels of negative mood has been related to a processing and recall bias for negative information (Teasdale & Fogarty, 1979; Teasdale & Russell, 1983). This processing bias has been shown in experimentally induced transient sadness in healthy individuals as well as in clinical depression. This mood-congruent heightened sensitivity towards negative stimuli and prolonged processing of emotionally negative information has been proposed to play an important role in the development and maintenance of unipolar depression. Cognitive theories of mood-biased processing, such as schema theory (Beck *et al*. 1979) and network theory of affect (Bower, 1981) postulate that during a depressive state memory resources are bound to negative stimuli, which leads to an attenuation in memory capacity for incoming information of a positive emotional value (Ellis & Ashbrook, 1988).

Some corroborative evidence for these theories comes from behavioural studies investigating processing of negative stimuli (Gotlib & McCann, 1984; Williams & Broadbent, 1986; Gotlib & Cane, 1987) and mood-congruent memory biases in depression (Lloyd & Lishman, 1975; Clark & Teasdale, 1982; Bradley *et al*. 1996).

The emotional Stroop task is a potentially useful tool to assess mood-congruent processing, by measuring the attentional bias towards negative stimuli. In this task affective words are presented in various colours, and subjects are required to name the colour of words rather than perform the automatic and overlearned response of reading the word itself. Interference effects arise when attention drawn to disorder-specific emotional expressions trigger memories of personal loss and failure. These

* Address for correspondence: M. T. Mitterschiffthaler, Ph.D., Neuroimaging Research Group, Clinical Neuroscience, PO Box 89; Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.
(Email: m.mitterschiffthaler@iop.kcl.ac.uk)

disorder-specific self-schemas are then in conflict with a cognitive colour-naming instruction (MacLeod, 1991; Segal *et al*. 1995). Increased latencies are the result of this process.

A number of behavioural studies of emotional Stroop paradigms have observed these interference effects in depression (Williams & Broadbent, 1986; Gotlib & Cane, 1987; Segal *et al*. 1995; Kerr *et al*. 2005). Negative, positive and neutral words have been used to investigate, whether these interferences are elicited simply through the affect component rather than the negative information *per se*. Although a few studies report interference to affective material in general (Taylor & John, 2004), the majority of reports support the notion that depressed individuals display a memory bias for negative material centred around loss and failure (Watkins *et al*. 1996; Neshat-Doost *et al*. 1998; Dudley *et al*. 2002; Koster *et al*. 2005).

Neuroimaging studies suggest that the anterior cingulate cortex (ACC) plays a major role in Stroop task performance (Pardo *et al*. 1990; Bench *et al*. 1993; Taylor *et al*. 1994, 1997; George *et al*. 1994; Carter *et al*. 1995; Bush *et al*. 1998; Peterson *et al*. 1999; Banich *et al*. 2000; Mead *et al*. 2002; Gruber *et al*. 2002; Langenecker *et al*. 2004; Kerns *et al*. 2004). The ACC is at the core of organizing endogenous, individual-driven control processes and exogenous control processes, that are influenced by environmental distractions (Posner, 1980). It is implicated in error monitoring and attentional processes (Paus, 2001), coordinating cognitive control and conflict processes experienced during incompatible conditions (Carter *et al*. 2000), and it is further involved in the elicitation of autonomic responses during cognitive challenges (Critchley *et al*. 2004).

In healthy individuals, during performance of an emotional Stroop task Whalen and colleagues (1998) observed greater neural activity in the ACC with negative words and in absence of a behavioural interference effect. In individuals with a mood disorder, George and colleagues (1997) found greater latencies during a sad word condition relative to healthy controls but did not observe any significant differences in their neural activity. However, the patient group had a number of diagnoses and their affective state varied from euthymic to moderate depression. In individuals with bipolar disorder during a euthymic state, Malhi and colleagues (2005) reported an emotional Stroop effect and increased ACC engagement, although all patients were taking medication.

A further, related, method of assessing a mood-influenced bias is through emotional go/no-go tasks. Sets of target and distractor words are presented and participants are instructed to respond to target words immediately by pressing a corresponding button. In these paradigms low latencies are a direct measure of a mood-congruent bias (Murphy *et al*. 1999). These tasks have been used in behavioural as well as functional magnetic resonance imaging (fMRI) research (Murphy *et al*. 1999; Elliott *et al*. 2002; Erickson *et al*. 2005). Increased activation during sad target words has been found for major depressive disorder (MDD) patients, relative to positive words and to controls, in the rostral ACC and medial prefrontal cortices (Elliott *et al*. 2002), further supporting the role of the ACC in selective attention and mood-congruent processing.

In a fMRI study utilizing an original Stroop task, increased activation was found in the rostral ACC and the dorsolateral prefrontal cortex in unmedicated MDD patients, compared to controls (Wagner *et al*. 2006). Dorsal ACC activation did not differ between groups.

Due to a high variability in sample characteristics and paradigm specifications findings of previous research are not always easy to interpret and compare. The present study aimed to control some factors, such as treatment effects and co-morbidity to investigate the relationship between attentional biases and mood-congruent processing in a group of medication-free patients with unipolar MDD. All MDD subjects were experiencing an acute depressive episode of moderate severity. We hypothesized that MDD patients would show an attentional bias in response to negative words which would be expressed in increased latencies during colour-naming emotional words. On a neural level, we expected an engagement of the ACC during processing of negative emotional words. As we did not use positive emotional stimuli our study cannot answer the question of effects of emotional arousal *per se*; however, as outlined above, emotional Stroop effects in depression have been shown to be mostly specific to negative stimuli.

Method and materials

Participants

After full explanation of the study procedures, all participants provided written, informed consent. The study was approved by the South London and Maudsley NHS Trust Research Ethics Committee.

Seventeen right-handed individuals (mean age 39.3 years, S.D. = 9.4) meeting DSM-IV criteria for a diagnosis of unipolar major depression, acute depressive episode, were recruited through local newspaper advertisement. The diagnosis was obtained through the SCID-I, patient version (First *et al*. 1997) and a clinical interview with a board-certified psychiatrist. Inclusion criteria included a score of $\geqslant$18 on the 17-item Hamilton Depression Rating Scale (HAMD; Hamilton,

https://doi.org/10.1017/S0033291707001523 Published online by Cambridge University Press

Table 1. *Demographics and mean scores of depression measures (HAMD, BDI)*

	MDD patients ($n=17$)	Controls ($n=17$)
Mean age (years)	39.3 (9.4)	39.4 (9.2)
Gender	14 F/3 M	14 F/3 M
Full Scale IQ	116.4 (15.9)	124.4 (10.8)
HAMD	20.88 (1.83)	0.35 (0.70)
BDI	38.00 (11.28)	2.76 (3.80)

MDD, Major depressive disorder; HAMD, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory.

1960). All participants were free of psychotropic medication for a minimum of 4 weeks at the time of inclusion into the study or a minimum of 8 weeks if the previous medication had been fluoxetine. Apart from psychotropic medication, one patient took trimethoprim, one received treatment for high cholesterol, one had an oestrogen patch, one patient had a nicotine patch and one patient sporadically used a nasal spray for hay fever. Exclusion criteria were co-morbidity with other Axis I disorders, current or past neurological disorders, history of neurological trauma resulting in loss of consciousness, reported substance or alcohol abuse within 2 months prior to study participation, and criteria that are contra-indicative for having a MRI scan. Seventeen right-handed volunteers, matched by age, gender and IQ (mean age 39.4 years, S.D. = 9.2), without a personal or family history of psychiatric disorders, head injury resulting in unconsciousness, neurological disorder and current substance abuse were recruited through local advertisements. The ratio of smokers per group was 3:2, with three smokers in the patient group.

All participants completed the Beck Depression Inventory (BDI; Beck *et al*. 1961), and were assessed with the HAMD (Hamilton, 1960) and the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) (Table 1).

Experimental paradigm

Selection and assessment of words

A pilot study was first carried out to confirm the appropriateness of 40 negative and 40 neutral words and to assess their suitability in a clinical population. Fifteen healthy individuals (mean age 27.9 years, S.D. = 7.8) and 15 medication-free individuals with mild depression (mean age 32.6, S.D. = 10.9; mean BDI score 15.4, S.D. = 2.9) participated in the pilot study. Eighty words were chosen from two lists of emotional and non-emotional words (John, 1988; Bradley & Lang, 1999) and divided into two groups based on sad or neutral valence. Stimulus groups were matched for standardized lexical word frequency (Francis & Kucera, 1982), pronounceability (expressed in number of syllables) and word length. The John (1988) list contained word associations, and words were chosen that produced the lowest number of negative and happy associations for neutral words and the lowest number of happy associations for sad words. The Bradley & Lang (1999) affective word norms were used to determine emotional valence and word frequency. Mean *sad* word frequency was 28.20 (S.D. = 35.21) and mean word length was 6.75 (S.D. = 1.81). Mean *neutral* word frequency was 33.95 (S.D. = 47.03) and mean word length was 6.83 (S.D. = 1.82). Independent-sample t tests confirmed that words did not differ significantly on frequency, pronounceability, or word lengths (all $p > 0.54$), but did differ in emotional valence.

Forty negative and 40 neutral words (see Appendix) were presented on a laptop computer. Words were collated into blocks of eight words per emotional category, repeated five times whereby each word was presented only once with a presentation time of 700 ms per word. All words appeared on black background in red, blue, green or yellow colour, pseudo-randomized across the two valence categories.

Participants were informed that they would see words appearing individually on the screen, coloured in red, green, yellow or blue. They were instructed to name the colour of the word as quickly as possible, rather than reading the word. Reaction time recordings were done through onset of speech.

Reaction times were evaluated using a valence × group (2 × 2) repeated-measures ANOVA. The analysis revealed main effects of valence [$F(1,28) = 21.98$, $p < 0.001$] and group [$F(1,28) = 5.60$, $p = 0.03$] and a valence × group interaction effect [$F(1,28) = 8.07$, $p = 0.01$]. This preliminary study confirmed an emotional interference effect for sad emotional stimuli in the patient group through prolonged latencies in colour naming of emotionally charged words.

fMRI experiment

The emotional Stroop task was projected onto a mirror inside the scanner. Head movement was restricted with foam padding and a Velcro strap across participant's forehead. Participants were required to name the colour of the presented word. Stimuli were then presented in a blocked design of ten alternating blocks of eight sad and eight neutral words, as described above. Volunteers' vocal responses were recorded by using a MRI compatible microphone and software that monitors the input to the computer soundcard. As

https://doi.org/10.1017/S0033291707001523 Published online by Cambridge University Press

soon as a vocal response was detected reaction times were measured. For each subject microphone settings were adjusted in order to account for individual differences in loudness of speaking voice. Each word was presented for 700 ms within a 2000 ms quiet period which allowed recording of their vocal responses in the relative absence of scanner noise. After 2000 ms (700 ms word presentation + 1300 ms blank screen) image collection was carried out. The clustered/sparse image acquisition process has been used previously and has been found suitable for recording of vocal responses and minimizing the effects of head movement artefacts associated with verbal responses in healthy and patient groups (Fu *et al*. 2006). An auditory (.wav) file was recorded for each individual to ensure accuracy of response. Additionally, volunteers' responses were monitored by a researcher (M.T.M. or N.D.W.) through headphones and by pressing a corresponding coloured button on a button box.

Image acquisition

A 1.5 T General Electric Signa MR Imaging system (General Electric Medical Systems, Milwaukee, WI, USA) was used to acquire 84 T2-weighted echoplanar images depicting blood-oxygen-level dependent (BOLD) contrast. For each acquired volume 22 near-axial slices parallel to the intercommissural plane were collected over 2000 ms allowing for a silent period of 2000 ms (repetition time 4000 ms, echo time 40 ms, flip angle 90°, slice thickness 5 mm, interslice gap 0.5 mm, matrix size 64×64).

Statistical analysis

Behavioural data

MANOVA was carried out using group (MDD, controls) as independent variable to investigate differences between MDD patients and controls on psychometric measures (dependent variables: HAMD, BDI, WASI).

To test differences in reaction time and stimulus category between patients and controls, repeated-measures ANOVA was carried out using valence (sad, neutral) as within-group variable, group (MDD, controls) as between-group variable and reaction time (in ms) as dependent variable. *Post-hoc t* tests were carried out to follow-up significant main and interaction effects, two independent-sample *t* tests (sad and neutral) and two paired-sample *t* tests (MDD and controls). The α-level was set at 0.025 for each pair of tests.

fMRI data

Images were pre-processed and analysed using the Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London) software package on a Matlab platform. The 84 images functional time series was realigned, normalized into a standard stereotaxic space using a Montreal Neurological Institute EPI template and the coordinate system of Talairach & Tournoux (1988) and smoothed using an 8 mm Gaussian kernel filter full-width-at-half-maximum to permit application of Gaussian random-field theory and to facilitate inter-subject averaging. The first four images were then discarded.

Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure. The first level analysis allowed computation of individual mean images that corresponded to the main contrasts of interest. The time series was modelled as a block-design with the temporal delay in BOLD response corrected for by a canonical haemodynamic response function. Contrasts were performed of the main effect of each affective state: negative > neutral and neutral > negative.

The significance of individual observations was tested in two second-level analyses by combining contrast images using one-sample *t* tests [$p < 0.05$, family-wise error (FWE)] to assess groups individually and a two-sample *t* test. A two-sample *t* test examined differences between groups on key contrasts. A threshold of $p < 0.05$, FWE was used to discuss brain areas without an *a priori* hypothesis. To discuss activation in the ACC, an uncorrected threshold of $p < 0.001$ and small-volume correction (SVC) were applied. A general linear model was used to determine voxel-wise *t* statistics. This model estimates the error variance for each condition of interest across subjects, rather than across scans and therefore provides a stronger generalization to the population from which data are acquired. The *t* statistics were normalized to *Z* scores and significant clusters of activation were determined. To confirm validity of results acquired through an uncorrected $p < 0.001$, region of interest (ROI) analysis using the Marsbar toolbox implemented in SPM2 was performed to identify significant activation levels in the ACC. Extracted data were analysed with SPSS software (SPSS Inc., Chicago, IL, USA) using an independent-sample *t* test. Furthermore, ROI data was used to investigate relations between latency and clinical measures (BDI, HAMD). Pearson correlations were calculated on activation levels, mean latencies as well as clinical variables.

Results

Behavioural data

Analysis of clinical measures revealed significant differences between the two groups in HAMD

https://doi.org/10.1017/S0033291707001523 Published online by Cambridge University Press

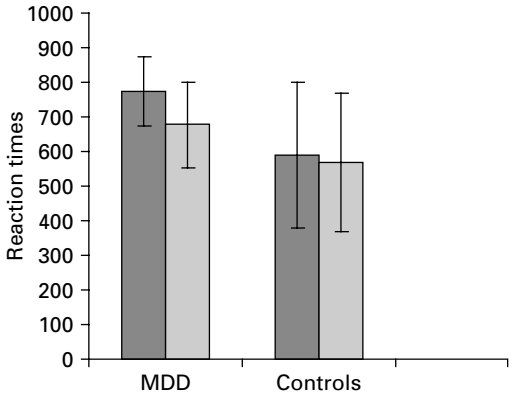

Fig. 1. Mean latencies and standard deviations for major depressive disorder (MDD) patients and controls during colour-naming negative (■) and neutral (□) words during the fMRI experiment.

[$F(1,27)=1550.47$, $p<0.001$] and BDI [$F(1,27)=128.69$, $p<0.001$].

An ANOVA of reaction times of 30 datasets (four datasets could not be analysed due to problems with response recordings during neuroimaging) revealed significant main effects of valence [$F(1,28)=25.01$, $p\leqslant 0.001$], indicating that both groups showed an increased reaction time with sad words relative to neutral words, a main effect of group [$F(1,28)=0.02$], indicating that depressed patients displayed increased latencies in response compared to controls, and an interaction effect of valence × group [$F(1,28)=10.27$, $p=0.03$], suggesting a greater difference in latency between neutral and negative stimuli in patients than in controls (Fig. 1). *Post-hoc* analyses to explain the interaction effect revealed that the two groups differed significantly on negative ($t=3.89$, df = 28, $p=0.004$) but not neutral ($t=1.81$, df = 28, $p=0.08$) stimuli. *Post-hoc* analyses also revealed significant effects of valence in both the MDD ($t=4.59$, df = 14, $p<0.001$) and the control ($t=2.90$, df = 14, $p=0.01$) groups.

For the purpose of completeness results are reported from the individual group analysis and between-group analysis. Results from between-group comparisons are discussed.

fMRI results

Effect of affect: negative words > neutral words

Controls. There was a significant bilateral increase in activation in the middle frontal/superior frontal gyrus (BA 10, BA 46: x = −30, y = 62, z = 14; $p=0.003$, $Z=2.73$).

MDD patients. In this group sad words were associated with a significant increase in activation in the left ACC (BA 32: x = −10, y = 32, z = 28; $p=0.001$, $Z=4.05$), right precuneus (BA 7: x = 6, y = −60, z = 42; $p=0.01$, $Z=4.55$), left middle temporal gyrus (BA 39: x = −52, y = −72, z = 24; $p=0.02$, $Z=3.89$), left thalamus (x = −26, y = 32, z = 4; $p=0.05$, $Z=3.68$), right cerebellum (x = 8, y = −46, z = −6; $p=0.02$, $Z=3.60$) and left middle frontal gyrus (BA 6: x = −26, y = 10, z = 58; $p=0.01$, $Z=3.55$).

Main effect of group: negative words > neutral words

MDD patients relative to controls activated the left ACC (BA 32: x = −5, y = 30, z = 24; $p<0.000$, $Z=3.68$; after SVC: $p=0.004$, Z = 3.68) and right precuneus (BA 7: x = 2, y = −60, z = 44; $p=0.02$; FWE: $Z=4.75$) more strongly. Controls, relative to MDD patients, displayed no significant increase in activation in response to sad word stimuli (Fig. 2).

Results from ROI analysis confirmed a significant difference between patients and controls on ACC activation ($t=3.97$, df = 32, $p\leqslant 0.001$).

Correlations with clinical measures and latencies

There was a significant correlation between mean signal change in the rostral ACC and latencies in response to negative emotional words ($r=0.68$, $p=0.003$) in MDD patients only (Fig. 2). We did not find significant correlations between negative word latencies and rostral ACC activation in healthy controls. Furthermore, correlations with clinical measures (HAMD, BDI) and brain activation in the rostral ACC did not produce significant results ($r=1.39$, $p=0.98$). This could be due to the small range of HAMD and BDI scores, since all patients were acutely depressed.

Discussion

The present study investigated an emotional Stroop interference effect at a behavioural and a neural level in medication-free individuals with unipolar depression, during an acute depressive episode of moderate severity. We observed greater response latencies with negative compared to neutral words in MDD patients compared to healthy controls, which was associated with greater activity in the rostral ACC and precuneus.

Increased latencies in patients probably reflect an interference effect in response to self-referent schemas (Beck *et al*. 1979) and networks (Bower, 1981). The negative self-referent schema in depressed patients provides a facilitating basis for incoming negative information resulting in prolonged and sustained processing of mood-congruent information reflected in longer reaction times. Although there was also an overall increase in reaction time across both word

https://doi.org/10.1017/S0033291707001523 Published online by Cambridge University Press

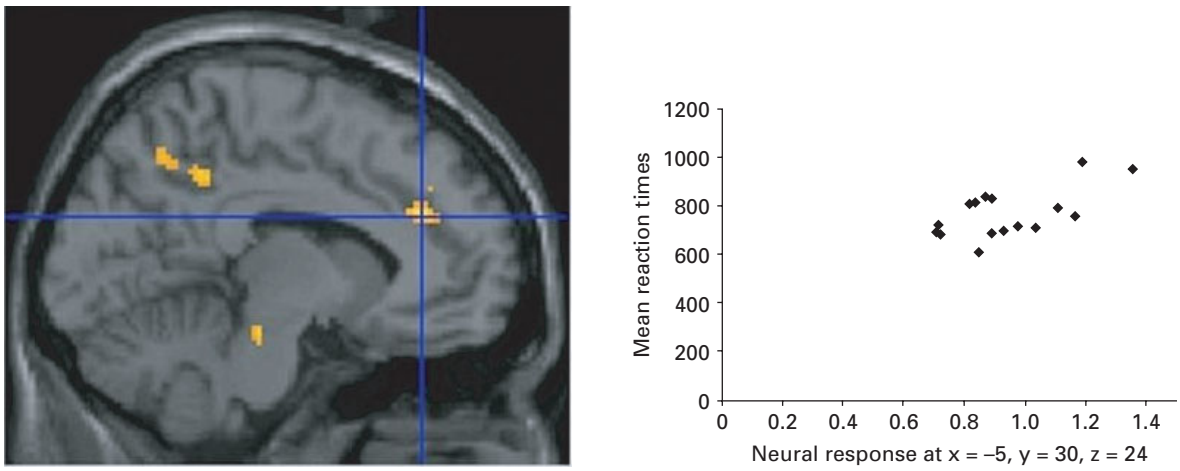

Fig. 2. Sagittal view of significantly increased activation in the left anterior cingulate cortex (ACC) (x = −5, y = 30, z = 24) in a between-group comparison, superimposed on a single-subject template. The graph on the right shows the correlation between activation in the ACC and latencies for colour-naming negative words in major depressive disorder patients ($r = 0.68$, $p = 0.003$).

types in MDD patients compared to controls, psychomotor slowing and information processing is typical of depression (Caligiuri & Ellwanger, 2000; Tsourtos *et al*. 2002; Rogers *et al*. 2004). However, the group × valence interaction effect indicates an even greater emotional Stroop effect in depressed patients relative to healthy controls.

The fMRI data revealed greater engagement in the rostral ACC with negative words relative to neutral words in depressed individuals. The overactive rostral ACC in response to negative words suggests a contribution to the attentional bias towards mood-congruent information. This interpretation is further supported by the finding of a positive correlation between ACC activation and latencies of negative words. This finding suggests that the rostral ACC is associated with the interference process. MDD patients may be less able to disregard the emotional content of the presented words resulting in increased reaction times. The rostral ACC is a critical component in the pathology of depression with a role in assessing emotional salience which is thought to be dysfunctional in depression (Mayberg, 1997).

Elliott and colleagues (2002) similarly found greater ACC activation with sad words in depressed patients and during happy words in controls. In a counting Stroop paradigm, Whalen and colleagues (1998) found that the emotional condition led to signal increase in the rostral ACC in healthy controls. Moreover, a hyperfunction of the rostral ACC has recently been observed in a fMRI study of an original Stroop task (Wagner *et al*. 2006). During an incongruent colour-naming condition MDD patients displayed signal increase in the rostral ACC compared to healthy controls (Wagner *et al*. 2006).

The rostral ACC is involved in attention allocation and conflict monitoring. The emotional Stroop task presents a cognitively demanding challenge to participants, as it requires suppression of a highly trained and therefore very early (in terms of information processing) response, i.e. naming the word, in favour of a more complex process, i.e. naming the colour. Resolving this conflict relies heavily on response selection and executive control. In these circumstances an initial response has to be overridden by a correct response. This overriding process could be reflected in an engagement of the rostral ACC (Botvinick *et al*. 1999) as mood-congruent trials that withdrew attention from the task instructions led to signal increase in this region. Neutral word conditions did not conflict with the highly overlearned and automated colour- naming procedure in depression.

A recent study in healthy volunteers employing a modified version of an emotional Stroop task also found both rostral ACC and amygdala activation associated with emotional conflict (Etkin *et al*. 2006). Rostral ACC signals increased when conflict resolutions were found while amygdala activation was seen during emotionally conflicting conditions. Etkin and colleagues (2006) conclude that the rostral ACC could be a key regulator of amygdalar activity. Amygdala activation is seen during emotional Stroop tasks in other patient groups in relation to disorder-specific words (van den Heuvel *et al*. 2005). In the present study, we did not observe greater amygdala activity in depressed patients relative to healthy controls, which may have reflected a top-down suppressive processing from the ACC to the amygdala. This may be examined further in an effective connectivity analysis.

https://doi.org/10.1017/S0033291707001523 Published online by Cambridge University Press

An additional region that was significantly activated in MDD patients during the affective condition was the precuneus. The precuneus holds widespread connections with the prefrontal cortex (Goldman-Rakic, 1988) and shows a direct connectivity relationship with the dorsal ACC. Its involvement has been reported in a range of cognitive processes such as response selection (Banich *et al*. 2001), working memory (LaBar *et al*. 1999), problem solving and reasoning (Elliott & Dolan, 1998) and verbal processing (Pinel *et al*. 2001; Fu *et al*. 2006). Engagement of both the rostral ACC and the precuneus probably reflect increased exogenous attention in the ACC to negative words and simultaneously heightened endogenous attention (Posner, 1980) to memory retrieval (Nyberg *et al*. 2000), visual imagery (Krause *et al*. 1999) and phonological processes (Cabeza & Nyberg, 2000).

A number of limitations of this study have to be discussed. First, all emotional word stimuli had a negative valence. The observed behavioural and neural effects in patients could have been due to the emotional content rather than the negative valence of the words, although the findings are consistent with neuropsychological theories of Beck (Beck *et al*. 1979) and Bower (1981). Previous research has also shown that emotional interference in depression is mainly linked to negative word processing. Second, both patients and controls displayed increased latencies in response to negative words (although only very weak in controls), the finding could simply reflect induced conflict rather than a pathological feature of depression. This finding could further imply that negative words had a greater neuronal demand, rather then reflecting greater interference in depressed patients. Future studies should address this caveat by using comparison groups with comparable amounts of cognitive interference as well as words across different emotional categories, to investigate whether neural demands are generally higher during emotional words. This issue touches upon a general problem in fMRI research, namely that of the relationship between brain functional and behavioural measures. In the present study it is difficult to disentangle whether the increased processing of sad stimuli in depressed patients caused enhanced brain activation or vice versa. A final potential limitation of the current study could be the application of an uncorrected significance level. However, as our analysis was hypothesis driven and the findings were confirmed in a ROI analysis this approach is accepted and in accordance with previous MRI literature (Elliott *et al*. 2002; Wagner *et al*. 2006).

To summarize, depression is associated with an emotional interference effect in response to emotionally salient word stimuli on a behavioural and neural level. The behavioural interference effect was reflected in significantly prolonged latencies in response to negative adjectives and verbs in patients with MDD relative to healthy controls. On a neural level, increased engagement of the rostral ACC and precuneus in MDD patients was observed during processing of sad word stimuli. These findings underline the role of the rostral ACC in the determination of the degree of emotional conflict or mood-biased cognitions, particularly in depression. However, further research should be conducted addressing more specifically behavioural and neural interference effects in response to words of different emotional categories.

Appendix. *Negative and neutral word stimuli*

Sad words		Neutral words	
ashamed	selfish	acquaint	note
avoided	sick	amended	parking
blamed	sorrowful	arrange	participate
crying	tearful	brushing	placed
dead	tired	categorized	rendered
despair	tragic	decide	reside
desperate	troubled	deduct	retrieved
discouraged	unhappy	delegate	revise
doomed	unlovable	delegate	run
dying	unlucky	dial	shaving
failed	unwanted	doubled	spin
gloomy	unworthy	drawn	tabulate
grieving	upset	enlist	transfer
helpless	useless	expand	translate
hopeless	vulnerable	follow	underline
hurt	weak	generate	walk
lonely	widowed	indirect	washing
poor	woeful	invent	willing
rejected	worried	locate	writing
sad	worthless	navigate	zoom

Acknowledgements

This study was supported by a NARSAD Young Investigator Award to Cynthia Fu. The authors thank the volunteers and the staff of the MRI Unit, Maudsley Hospital, London.

Declaration of Interest

None.

References

Banich MT, Milham MP, Atchley R, Cohen NJ, Webb A, Wszalek T, Kramer AF, Liang ZP, Wright A, Shenker J, Magin R (2000). fMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. *Journal of Cognitive Neuroscience* **12**, 988–1000.

Banich MT, Milham MP, Jacobson BL, Webb A, Wszalek T, Cohen NJ, Kramer AF (2001). Attentional selection and the processing of task-irrelevant information: insights from fMRI examinations of the Stroop task. *Progress in Brain Research* **134**, 459–470.

Beck AT, Rush AJ, Shaw BF, Emery Y (1979). *Cognitive Therapy of Depression*. Guilford Press: New York.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

Bench CJ, Frith CD, Grasby PM, Friston KJ, Paulesu E, Frackowiak RS, Dolan RJ (1993). Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia* **31**, 907–922.

Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* **402**, 179–181.

Bower GH (1981). Mood and memory. *American Psychologist* **36**, 129–148.

Bradley BP, Mogg K, Millar N (1996). Implicit memory bias in clinical and non-clinical depression. *Behaviour Research and Therapy* **34**, 865–879.

Bradley MM, Lang PJ (1999). *Affective Norms for English Words* (*ANEW*). The NIMH Center for the Study of Emotion and Attention, University of Florida: Gainesville, FL.

Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL (1998). The counting Stroop: an interference task specialized for functional neuroimaging – validation study with functional MRI. *Human Brain Mapping* **6**, 270–282.

Cabeza R, Nyberg L (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience* **12**, 1–47.

Caligiuri MP, Ellwanger J (2000). Motor and cognitive aspects of motor retardation in depression. *Journal of Affective Disorders* **57**, 83–93.

Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, Cohen JD (2000). Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences USA* **97**, 1944–1948.

Carter CS, Mintun M, Cohen JD (1995). Interference and facilitation effects during selective attention: an $H_2{}^{15}O$ PET study of Stroop task performance. *NeuroImage* **2**, 264–272.

Clark DM, Teasdale JD (1982). Diurnal variation in clinical depression and accessibility of memories of positive and negative experiences. *Journal of Abnormal Psychology* **91**, 87–95.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience* **7**, 189–195.

Dudley R, O'Brien J, Barnett N, McGuckin L, Britton P (2002). Distinguishing depression from dementia in later life: a pilot study employing the Emotional Stroop task. *International Journal of Geriatric Psychiatry* **17**, 48–53.

Elliott R, Dolan RJ (1998). Activation of different anterior cingulate foci in association with hypothesis testing and response selection. *NeuroImage* **8**, 17–29.

Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ (2002). The neural basis of mood-congruent processing biases in depression. *Archives of General Psychiatry* **59**, 597–604.

Ellis HC, Ashbrook PW (1988). Resource allocation model of the effects of depressed mood states on memory. In *Affect, Cognition and Social Behaviour* (ed. K. Fiedler and J. P. Forgas), pp. 25–43. Hogrefe: Goettingen.

Erickson K, Drevets WC, Clark L, Cannon DM, Bain EE, Zarate Jr. CA, Charney DS, Sahakian BJ (2005). Mood-congruent bias in affective go/no-go performance of unmedicated patients with major depressive disorder. *American Journal of Psychiatry* **162**, 2171–2173.

Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J (2006). resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* **51**, 871–882.

First MB, Spitzer RL, Gibbon M, Williams JBW (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition* (*SCID-P*). Biometrics Research, New York State Psychiatric Institute: New York.

Francis WN, Kucera H (1982). *Frequency Analysis of English Usage*. Houghton Mifflin: Boston, MA.

Fu CH, Vythelingum GN, Brammer MJ, Williams SC, Amaro Jr. E, Andrew CM, Yaguez L, van Haren NE, Matsumoto K, McGuire PK (2006). An fMRI study of verbal self-monitoring: neural correlates of auditory verbal feedback. *Cerebral Cortex* **16**, 969–977.

George MS, Ketter TA, Parekh PI, Rosinsky N, Ring HA, Casey BJ (1994). Regional brain activity when selecting a response despite interference: An $H_2{}^{15}O$ PET study of the Stroop and the emotional Stroop. *Human Brain Mapping* **1**, 194–209.

George MS, Ketter TA, Parekh PI, Rosinsky N, Ring HA, Pazzaglia PJ, Marangell LB, Callahan AM, Post RM (1997). Blunted left cingulate activation in mood disorder subjects during a response interference task (the Stroop). *Journal of Neuropsychiatry and Clinical Neuroscience* **9**, 55–63.

Goldman-Rakic PS (1988). Topography of cognition: parallel distributed networks in primate association cortex. *Annual Review of Neuroscience* **11**, 137–156.

Gotlib IH, Cane DB (1987). Construct accessibility and clinical depression: a longitudinal investigation. *Journal of Abnormal Psychology* **96**, 199–204.

Gotlib IH, McCann CD (1984). Construct accessibility and depression: an examination of cognitive and affective factors. *Journal of Personality and Social Psychology* **47**, 427–439.

Gruber SA, Rogowska J, Holcomb P, Soraci S, Yurgelun-Todd D (2002). Stroop performance in normal control subjects: an fMRI study. *NeuroImage* **16**, 349–360.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

John CH (1988). Emotionality ratings and free-association norms of 240 emotional and non-emotional words. *Cognition & Emotion* **2**, 49–70.

Kerns JG, Cohen JD, MacDonald III AW, Cho RY, Stenger VA, Carter CS (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science* **303**, 1023–1026.

Kerr N, Scott J, Phillips ML (2005). Patterns of attentional deficits and emotional bias in bipolar and major depressive disorder. *British Journal of Clinical Psychology* **44**, 343–356.

Koster EH, De RR, Goeleven E, Franck E, Crombez G (2005). Mood-congruent attentional bias in dysphoria: maintained attention to and impaired disengagement from negative information. *Emotion* **5**, 446–455.

Krause BJ, Schmidt D, Mottaghy FM, Taylor J, Halsband U, Herzog H, Tellmann L, Muller-Gartner HW (1999). Episodic retrieval activates the precuneus irrespective of the imagery content of word pair associates. A PET study. *Brain* **122**, 255–263.

LaBar KS, Gitelman DR, Parrish TB, Mesulam M (1999). Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *NeuroImage* **10**, 695–704.

Langenecker SA, Nielson KA, Rao SM (2004). fMRI of healthy older adults during Stroop interference. *NeuroImage* **21**, 192–200.

Lloyd GG, Lishman WA (1975). Effect of depression on the speed of recall of pleasant and unpleasant experiences. *Psychological Medicine* **5**, 173–180.

MacLeod CM (1991). Half a century of research on the Stroop effect: an integrative review. *Psycholollgical Bulletin* **109**, 163–203.

Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R (2005). An emotional Stroop functional MRI study of euthymic bipolar disorder. *Bipolar Disorder* **7** (Suppl. 5), 58–69.

Mayberg HS (1997). Limbic-cortical dysregulation: a proposed model of depression. *Journal of Neuropsychiatry and Clinical Neuroscience* **9**, 471–481.

Mead LA, Mayer AR, Bobholz JA, Woodley SJ, Cunningham JM, Hammeke TA, Rao SM (2002). Neural basis of the Stroop interference task: response competition or selective attention? *Journal of the International Neuropsychological Society* **8**, 735–742.

Murphy FC, Sahakian BJ, Rubinsztein JS, Michael A, Rogers RD, Robbins TW, Paykel ES (1999). Emotional bias and inhibitory control processes in mania and depression. *Psychological Medicine* **29**, 1307–1321.

Neshat-Doost HT, Taghavi MR, Moradi AR, Yule W, Dalgleish T (1998). Memory for emotional trait adjectives in clinically depressed youth. *Journal of Abnormal Psychology* **107**, 642–650.

Nyberg L, Persson J, Habib R, Tulving E, McIntosh AR, Cabeza R, Houle S (2000). Large scale neurocognitive networks underlying episodic memory. *Journal of Cognitive Neuroscience* **12**, 163–173.

Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990). The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proceedings of the National Academy of Sciences USA* **87**, 256–259.

Paus T (2001). Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nature Review Neuroscience* **2**, 417–424.

Peterson BS, Skudlarski P, Gatenby JC, Zhang H, Anderson AW, Gore JC (1999). An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. *Biological Psychiatry* **45**, 1237–1258.

Pinel P, Dehaene S, Riviere D, LeBihan D (2001). Modulation of parietal activation by semantic distance in a number comparison task. *NeuroImage* **14**, 1013–1026.

Posner MI (1980). *Attention and Consciousness*. Lawrence Erlbaum Associates: Mahwah, NJ.

Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, Fukuda M, Kato N (2004). Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neuroscience Research* **50**, 1–11.

Segal ZV, Gemar M, Truchon C, Guirguis M, Horowitz LM (1995). A priming methodology for studying self-representation in major depressive disorder. *Journal of Abnormal Psychology* **104**, 205–213.

Talairach J, Tournoux P (1988). *Co-planar Sterotaxic Atlas of the Human Brain*. Thieme Medical Publishers Inc.: New York.

Taylor JL, John CH (2004). Attentional and memory bias in persecutory delusions and depression. *Psychopathology* **37**, 233–241.

Taylor SF, Kornblum S, Lauber EJ, Minoshima S, Koeppe RA (1997). Isolation of specific interference processing in the Stroop task: PET activation studies. *NeuroImage* **6**, 81–92.

Taylor SF, Kornblum S, Minoshima S, Oliver LM, Koeppe RA (1994). Changes in medial cortical blood flow with a stimulus-response compatibility task. *Neuropsychologia* **32**, 249–255.

Teasdale JD, Fogarty SJ (1979). Differential effects of induced mood on retrieval of pleasant and unpleasant events from episodic memory. *Journal of Abnormal Psychology* **88**, 248–257.

Teasdale JD, Russell ML (1983). Differential effects of induced mood on the recall of positive, negative and neutral words. *British Journal of Clinical Psychology* **22**, 163–171.

Tsourtos G, Thompson JC, Stough C (2002). Evidence of an early information processing speed deficit in unipolar major depression. *Psychological Medicine* **32**, 259–265.

van den Heuvel OA, Veltman DJ, Groenewegen HJ, Witter MP, Merkelbach J, Cath DC, van Balkom AJ, van Oppen P, van Dyck R (2005). Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Archives of General Psychiatry* **62**, 922–933.

Wagner G, Sinsel E, Sobanski T, Kohler S, Marinou V, Mentzel HJ, Sauer H, Schlosser RGM (2006). Cortical inefficiency in patients with unipolar depression: an event-related fMRI study with the Stroop task. *Biological Psychiatry* **59** 958–965.

Watkins PC, Vache K, Verney SP, Muller S, Mathews A (1996). Unconscious mood-congruent memory bias in depression. *Journal of Abnormal Psychology* **105**, 34–41.

Wechsler D (1999). *Wechsler Abbreviated Scale of Intelligence* (*WASI*). Psychological Corporation. Harcourt Brace & Co.: San Antonio, TX.

Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL (1998). The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biological Psychiatry* **44**, 1219–1228.

Williams JM, Broadbent K (1986). Distraction by emotional stimuli: use of a Stroop task with suicide attempters. *British Journal of Clinical Psychology* **25**, 101–110.