

Affective modulation of anterior cingulate cortex in young people at increased familial risk of depression

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Background

We previously found that children of parents with depression showed impaired performance on a task of emotional categorisation.

Aims

To test the hypothesis that children of parents with depression would show abnormal neural responses in the anterior cingulate cortex, a brain region involved in the integration of emotional and cognitive information.

Method

Eighteen young people (mean age 19.8 years) with no personal history of depression but with a biological parent with a history of major depression (FH+ participants) and 16 controls (mean age 19.9 years) underwent functional

magnetic resonance imaging while completing an emotional counting Stroop task.

Results

Controls showed significant activation in the pregenual anterior cingulate cortex to both positive and negative words during the emotional Stroop task. This activation was absent in FH+ participants.

Conclusions

Our findings show that people at increased familial risk of depression demonstrate impaired modulation of the anterior cingulate cortex in response to emotionally valenced stimuli.

Declaration of interest

None. Funding detailed in Acknowledgement.

In a previous study we found that young people with a parent with depression who had not had depression themselves (FH+ participants), demonstrated abnormalities in a task of emotional categorisation,¹ suggesting a possible impairment in the integration of emotional and cognitive information. The anterior cingulate cortex is believed to play an important role in allocating attentional resources in situations of conflicting emotional and cognitive demand.^{2,3} Indeed there is now substantial evidence that the anterior cingulate cortex has functionally important divisions in which the dorsal 'cognitive' region forms part of an attentional network, while the rostral-anterior 'affective' region is involved in assessing the salience of emotional and motivational information.²

It is possible to probe the function of the anterior cingulate cortex in humans using a modified 'emotional' counting Stroop task where emotionally valenced words compete with the cognitive demands of the task.⁴ In healthy participants the emotional counting Stroop (ecStroop) activates the affective subdivision of the anterior cingulate cortex as measured by functional magnetic resonance imaging (fMRI).⁴ We therefore tested the hypothesis that, relative to age-matched controls, FH+ participants would show impaired activation in this subdivision during performance of the emotional counting Stroop.

Method

Participants and assessments

We recruited 18 young people (9 women, 9 men), mean age 19.8 years (range 19–21) who had never personally had depression but who had a biological parent with a history of major depression. Potential participants were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders Schedule (SCID-I)⁵ to exclude a personal current or previous major depression or other

Axis I disorder. The presence of major depression in a parent was assessed by the family history method using the participant as an informant.⁶ The criteria used included description of the symptoms of major depression together with the prescription of specific antidepressant treatment, either psychotherapy or medication. A history of bipolar disorder or schizophrenia in a parent was an exclusion criterion. We also recruited 16 controls (10 women, 6 men), mean age 19.9 years (range 18–21) who were determined by the same instruments to have no current or previous major depression and no history of depression in a biological parent or other first-degree relative. All participants were right-handed, according to the Edinburgh Handedness Inventory,⁷ and had normal or corrected to normal vision.

Participants were assessed on a number of measures of current emotional state, including the Mood and Feeling Questionnaire (MFQ),⁸ the Hospital Anxiety and Depression Scale (HADS)⁹ and the Perceived Stress Scale (PSS).¹⁰ We also administered the Parental Bonding Instrument (PBI)¹¹ and the Life Events Rating Scale (LERS),¹² which assesses threat and loss events in the past year and over the lifespan. All participants gave full informed consent to the study, which was approved by the local ethics committee.

Image acquisition

Imaging data were collected using a 1.5 T Siemens Sonata scanner located at the Oxford Centre for Clinical Magnetic Resonance Research. Functional imaging consisted of 35 T₂*-weighted echo-planar image slices (repetition time (TR) 3000 ms, echo time (TE) 50 ms, flip angle 90°, matrix 64 × 64, 3 mm isotropic voxels). To facilitate later co-registration of the fMRI data into standard space, we also acquired a Turbo FLASH sequence (TR 12 ms, TE 5.65 ms, voxel size 1 mm³). The first two echo-planar image

volumes in each session were discarded to avoid T_1 equilibration effects.

Emotional counting Stroop task

Participants were scanned while performing a modified version of the emotional counting Stroop called the 'name the number of words' task.⁴ Word stimuli were a subset drawn from a larger pool used in previous research¹³ examining depression and anxiety, and selected to be either neutral (e.g. mileage, molecule), physically threatening (e.g. fatal, accident), socially threatening (e.g. worthless, inferior) or positive (e.g. generous, achievement). Physically threatening and socially threatening words were combined to generate a negative word category. Words were matched for word length, frequency and imageability. (For further information see online Table DS1 and www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm.)

Participants completed one run of the task with a total of 160 words being presented across 16 blocks. Four 20-word blocks of each stimulus type were presented in a pseudo-randomised order and interspersed with 20-s blocks of fixation, free of stimulus (no motor response) as baseline. Presentation of the four conditions was counter-balanced across participants and between the two groups. Participants completed 10 trials during each presentation block (stimulus presentation 1500 ms, intertrial interval 500 ms). For each trial, participants viewed between one and four identical words and were instructed to report (via keypad response) the number of words presented in each trial. Stimuli were presented on a personal computer using E-Prime (version 1.0; Psychology Software Tools Inc., Pittsburgh, Philadelphia, USA) and projected onto an opaque screen at the foot of the scanner bore, which participants viewed using angled mirrors. Both accuracy and reaction times were recorded by E-Prime.

Functional MRI data analysis

Functional MRI data were preprocessed and analysed using the functional magnetic imaging of the Brain Software Library (FSL version 3.3; www.fmrib.ox.ac.uk/fsl), implemented in Linux SUSE, version 9.1.¹⁴ Preprocessing included within-participant image realignment,¹⁵ non-brain removal,¹⁶ spatial normalisation to a standard template (Montreal Neurological Institute (MNI) 152 stereotactic template)¹⁷ using an affine procedure and spatial smoothing using a Gaussian kernel (5 mm full-width, half-maximum). The time series in each session was high pass filtered (to a maximum of 0.007 Hz).

Analyses of data from individual participants were computed using the general linear model with local autocorrelation correction.¹⁸ Three explanatory variables were modelled: 'neutral', 'positive' and 'negative' words. In addition, temporal derivatives were included in the model as covariates of no interest to increase statistical sensitivity. All variables were modelled by convolving each block with a haemodynamic response function, using a variant of a gamma function (i.e. a normalisation of the probability density function of the gamma function) with a standard deviation of 3 s and a mean lag of 6 s.

Individual participant data were combined at the group level using full mixed effects analyses.¹⁹ Significant activations were identified using cluster-based thresholding of statistical images with a height threshold of $Z=2.0$ and a (corrected) spatial extent threshold of $P<0.05$.²⁰ Approximate Brodmann areas (BA) were identified by transformation of MNI coordinates into Talairach space (additional information available at www.mrc-cbu.cam.ac.uk/Imaging).

Results

Participant characteristics and emotional counting Stroop performance

There were no significant differences between FH+ participants and controls in age, gender, current mood state, level of perceived stress and experience of life events. Controls rated their mothers as being more overprotective (Table 1). Owing to technical difficulties, accuracy and reaction time data for 8 participants were not available and the analyses of behavioural data were therefore carried out on 26 individuals (14 FH+ and 12 controls). There were no between-group differences in accuracy and reaction time (all $P>0.40$).

Functional MRI data

Because of our interest in activation differences between FH+ participants and controls, we report significant between-group comparisons (thresholded at $Z=2.0$, $P=0.05$, whole brain corrected) rather than effects of task performance within the two groups. For the orthogonal contrast negative words *v.* neutral words, we observed significantly greater activation in controls in the anterior cingulate cortex, medial frontal and right superior frontal gyrus (BA 24/10 and 9 respectively), left middle frontal gyrus (BA 8/6) and left caudate nucleus and bilateral activation in the inferior parietal lobe (BA 7) (Table 2). Comparing positive words with neutral words, controls had significantly greater blood-oxygen-level dependent (BOLD) response in the right anterior cingulate (BA 24), left thalamus, left superior frontal gyrus (BA 10) and left precuneus (BA 19) (Table 3).

Given our *a priori* hypothesis regarding the role of the affective subdivision of the anterior cingulate cortex in the emotional counting Stroop task, we focused subsequent analyses on this brain region. To examine group \times emotion interactions we first extracted percentage signal change from the significant clusters of this subdivision identified above in the whole brain analysis (negative *v.* neutral words and positive *v.* neutral words). Further statistical analysis was implemented using a repeated measures analysis of variance (ANOVA) model with 'group' (FH+ *v.* controls) as the between-participant factors (FH+ *v.* control) and 'word type' (positive/negative/neutral words) as the within-participant factor

Table 1 Group demographic and psychosocial measures

Measure	FH+ ($n=18$) Mean (s.d.)	Controls ($n=16$) Mean (s.d.)
Age, years	19.8 (0.9)	19.9 (0.7)
Gender (male/female)	9/9	6/10
Mood and Feelings Questionnaire	8.4 (5.0)	9.5 (5.00)
Perceived Stress Scale	13.2 (5.6)	14.00 (5.3)
HADS-D	1.8 (1.7)	1.4 (1.9)
HADS-A	4.9 (3.4)	6.5 (2.7)
Parental Bonding Instrument		
Mother care	30.56 (5.00)	32.31 (3.47)
Mother protection	7.94 (4.76)	14.77 (7.85)*
Father care	26.35 (7.55)	28.33 (4.42)
Father protection	6.71 (2.82)	8.92 (6.75)
Life Events Rating Scale		
Lifetime	1.00 (1.33)	1.00 (1.18)
Past year	0.50 (0.71)	0.64 (0.63)

FH+, young person with parent with depression who has not had depression themselves; HADS-A, Hospital Anxiety and Depression Scale - Anxiety; HADS-D, Hospital Anxiety and Depression Scale - Depression.
* $P=0.005$ (all other $P>0.1$). Unpaired t-test or χ^2 as appropriate.

Table 2 Regions showing increased activation in controls compared with FH+ for the linear contrast negative v. neutral words

Region	Hemisphere	Brodman area	Talairach coordinates ^a	Z ^b	Cluster size ^c
Anterior cingulate/ medial frontal gyrus	Right	24/10	2 54 -4	3.45	1447
Superior frontal gyrus	Right	9	24 24 48	3.87	1953
Inferior parietal lobe	Left	7	-40 -64 46	3.62	974
Caudate nucleus	Left		-12 0 18	3.57	724
Middle frontal gyrus	Left	8/6	-44 14 44	3.42	633
Inferior parietal lobe	Right	7	48 -54 54	3.12	527

FH+, young person with parent with depression who has not had depression themselves.
a. Coordinates refer to the position (x, y and z, mm) for the peak voxel in each cluster according to the Montreal Neurological Institute template.
b. Clusters determined at an initial threshold of Z=2.0 and a corrected spatial extent of P=0.05.
c. Cluster size in voxels.

Table 3 Regions showing increased activation in controls compared with FH+ for the linear contrast positive v. neutral words

Region	Hemisphere	Brodman area	Talairach coordinates ^a	Z ^b	Cluster size ^c
Anterior cingulate	Right	24/32	2 26 18	3.30	729
Thalamus	Left		-6 -8 10	3.58	1998
Superior frontal gyrus	Left	10	-6 60 -2	3.73	656
Precuneus	Left	19	-2 -70 40	3.41	498

FH+, young person with parent with depression who has not had depression themselves.
a. Coordinates refer to the position (x, y and z, mm) for the peak voxel in each cluster according to the Montreal Neurological Institute template.
b. Clusters determined at an initial threshold of Z=2.0 and a corrected spatial extent of P=0.05.
c. Cluster size in voxels.

for all participants. Significant interactions were followed up using simple main effects (independent and repeated-samples *t*-tests) to elicit the degree of this differential activation.

Negative v. neutral word contrast

For this contrast we observed a significant group \times word type interaction ($F_{(1,32)}=12.63$, $P=0.001$) extending from the affective subdivision of the anterior cingulate cortex (BA 24/32) anteriorly to the medial prefrontal cortex (BA 10). As reported previously,⁴ controls showed a significantly greater activation to negative emotional words relative to neutral (repeated-samples $t_{(15)}=3.58$, $P=0.001$). By contrast, FH+ participants showed no differential response between neutral and negatively valenced words (repeated-samples $t_{(15)}=1.29$, $P=0.22$). There was a trend for controls to have a greater deactivation relative to baseline to neutral words compared with FH+ participants (independent samples $t_{(32)}=1.97$, $P=0.06$) (Fig. 1). Essentially the same findings were obtained when the negative words were analysed separately as physically threatening and socially threatening words (data not shown).

Positive v. neutral word contrast

Similar to the negative v. neutral contrast, we observed a significant group \times word type interaction ($F_{(1,32)}=12.94$, $P=0.001$) in the affective subdivision of the anterior cingulate cortex (BA 24/32). As with the negative words, controls showed a significantly greater BOLD response to positive words relative to neutral (repeated-samples $t_{(15)}=4.31$, $P=0.001$), whereas FH+ participants had similar responses to neutral and positive word types (repeated-samples $t_{(17)}=0.87$, $P=0.39$). In this comparison the deactivation from baseline seen in controls following neutral words was significantly greater than in FH+ participants (independent samples $t_{(32)}=2.35$, $P=0.03$) (Fig. 2). For both positive and negative contrasts the group by word type interaction

remained significant ($P<0.01$) when scores on the MFQ were included as a covariate in the analysis.

Discussion

The main finding of our study is that people at increased familial risk of depression show altered modulation of the anterior cingulate cortex in an emotional Stroop task compared with controls. This effect does not seem attributable to altered task performance. The anterior cingulate cortex is believed to play a key role in the regulation of emotional and cognitive processing through appropriate allocation of attentional resources.^{2,3} Our data therefore suggest that, at a neural level, increased familial risk of depression is associated with less efficient parallel monitoring of emotional and cognitive information.

Limitations

An important limitation of the study is that we did not systematically conduct personal psychiatric interviews with relatives in either FH+ or control groups and it is therefore possible that some of the parents in the FH+ group did not have depression or that some parents in the control group did. Presumably, however, misclassifications of this kind would tend to decrease rather than increase biological differences between the two groups. In addition, we have previously shown in a larger study that FH+ participants identified in this way have increased waking salivary cortisol secretion relative to controls.²¹ It has been estimated that by young adulthood up to 40% of children of parents with a clinical mood disorder will have suffered a personal episode of depression;²² however, the FH+ participants in the current study did not differ from controls in terms of current affective symptomatology and levels of perceived stress. In addition, albeit on limited data, it does not appear that their experience of parental depression is reflected in problems with parental attachment or in increased life events either recently or over the life span.

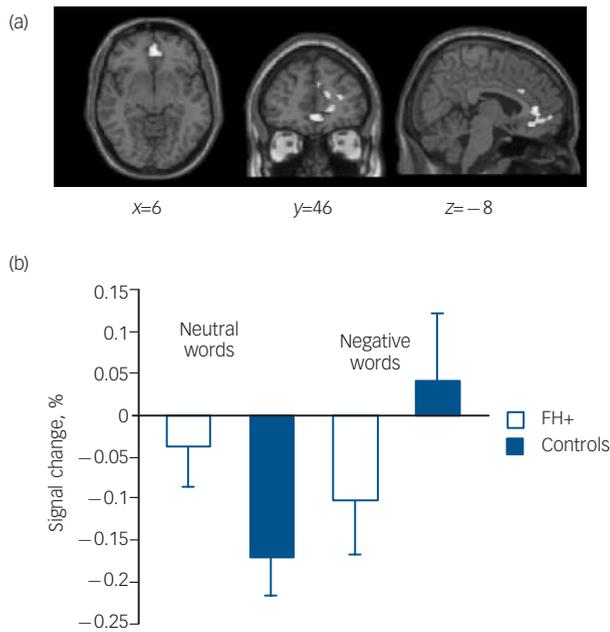


Fig. 1 Modulation of the anterior cingulate affective subdivision during performance of the emotional counting Stroop.

(a) Axial, coronal and sagittal images depicting significantly increased activation in controls for the linear contrast negative *v.* neutral words (images thresholded at $Z=2$, $P=0.05$ (corrected)) in medial prefrontal cortex extending from the rostral anterior cingulate (BA 24/32) anteriorly to medial prefrontal cortex (BA 10). Foci of activation, $x=2$, $y=54$, $z=-4$. (b) Neural response (expressed as % signal change) extracted from the above significant cluster to negative and neutral words. Error bars show standard error of the mean. FH+, young person with parent with depression who has not had depression themselves.

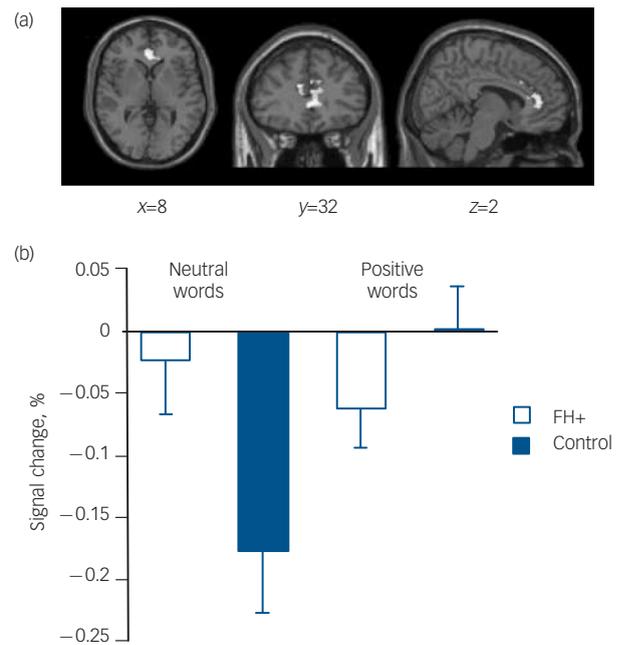


Fig. 2 Modulation of the anterior cingulate affective subdivision during performance of the emotional counting Stroop.

(a) Axial, coronal and sagittal images depicting significantly increased activation in controls for the linear contrast positive *v.* neutral words (images thresholded at $Z=2$, $P=0.05$ (corrected)). Foci of activation, $x=2$, $y=26$, $z=18$ (BA 24/32). (b) Neural response (expressed as % signal change) extracted from the above significant cluster in anterior cingulate affective division to positive and neutral words. Error bars show standard error of the mean. FH+, young person with parent with depression who has not had depression themselves.

Anterior cingulate cortex activation in controls and FH+ participants

The anterior cingulate cortex has cognitive and affective divisions that are separable both anatomically and functionally.² Previous studies in healthy individuals have shown that the affective division of the anterior cingulate cortex is activated by a number of emotional manipulations^{2,23} and our data in healthy participants confirm the findings of Whalen *et al.*,⁴ who used an emotional counting Stroop to demonstrate increased activation in the pregenual region of the affective subdivision of the anterior cingulate cortex in response to emotional relative to neutral words. Also, in agreement with Whalen *et al.*, we found that the emotional counting Stroop task was associated with an overall deactivation in this subdivision compared with fixation but that the deactivation was relatively less during presentation of emotional words. It has been suggested that the overall deactivation of the affective subdivision of the anterior cingulate cortex in response to the emotional counting Stroop reflects reciprocal inhibition from the cognitive subdivision with the purpose of maintaining cognitive performance where there is increased competition for attentional resources.^{2,4} Despite this deactivation, the relative increase in activity of the affective subdivision following presentation of emotional *v.* neutral words demonstrates the continuing ability of the anterior cingulate cortex to monitor emotional information during the emotional counting Stroop task.

In contrast to these findings in healthy participants, the affective subdivision of the anterior cingulate cortex in FH+ participants showed no difference in activation pattern to emotional *v.* neutral words. This suggests that in people at increased familial risk of depression the affective subdivision responds less efficiently

to the changing emotional valence of incoming stimuli. This difference in activation pattern appeared to be driven partly by the lessened deactivation to neutral words shown by the FH+ participants. This might imply that in people at increased familial risk of depression the affective subdivision of the anterior cingulate cortex reacts to neutral stimuli as if they had an emotional valence. Whether or not this is the case, our findings suggest that in FH+ people the affective subdivision of the anterior cingulate cortex is less efficient in detecting differences in the emotional quality of sensory input.

Changes in anterior cingulate cortex activity in acute depression

Changes in activity of the anterior cingulate cortex have been reported frequently in imaging studies of patients who are acutely depressed, particularly hypoactivity in the cognitive subdivision which may correlate with impaired performance on cognitive tasks.^{24,25} Findings in relation to the affective subdivision are more complex. Wagner *et al.*²⁶ used a counting (non-emotional) Stroop, in conjunction with fMRI, to study anterior cingulate cortex activity in patients with depression who were not receiving medication. They found no difference in either task performance or activation in the cognitive subdivision relative to controls; however, patients demonstrated less deactivation in the affective subdivision, a finding rather similar to our own. Other imaging studies in patients with acute depression have measured activation patterns in the anterior cingulate cortex in response to tasks involving the processing of emotional information. Findings have been variable, with some investigations demonstrating increased neural responses to negative emotional stimuli, consistent with

the emotional biases associated with acute depression.²⁷ However, Elliott *et al*,²⁸ using an affective go/no-go task, noted findings similar to our own, namely blunted neural activation to both positive and negative emotional stimuli in the affective subdivision of the anterior cingulate cortex.

Implications

Our data indicate that abnormalities in the neural response to emotional stimuli in the anterior cingulate cortex can exist independently of the presence of acute depression and appear to be present in those at increased familial risk of illness. The pregenual region of the affective subdivision of the anterior cingulate cortex, implicated in our study, has connections to other brain regions known to be involved in emotional experience and expression, including the orbitofrontal cortex, amygdala, hippocampus and ventral striatum.^{25,29} In this respect the pregenual affective subdivision of the anterior cingulate cortex is well placed to play a key role in the integration of emotional and cognitive information.² Hence, abnormalities in this area could be associated with impaired ability to use emotional information to influence decision-making, as we observed in an emotional categorisation task in FH+ participants.¹ It is possible that deficits of this sort could result in difficulties in making complex social decisions; this may be one mechanism through which increased familial risk of depression could be expressed.³⁰

It is important to note that we also observed differential neural activations to the emotional counting Stroop between FH+ and controls in brain regions other than the anterior cingulate cortex, including the thalamus and areas of prefrontal cortex, some of which are known to be associated with emotional processing. Although many of these brain regions have connections to the anterior cingulate cortex, these more widespread changes support the idea of a distributed circuitry underpinning both emotional processing and the risk of clinical mood disorders.^{31,32} Hence, vulnerability to depression is likely to be associated with changes across a network of areas rather than dysfunction solely in the anterior cingulate cortex. For example, reduced connectivity between thalamus and anterior cingulate cortex has been demonstrated in patients with depression compared with healthy controls.³³ Future studies investigating temporal correlations between BOLD response in the anterior cingulate cortex and the prefrontal/limbic regions reported above are warranted to examine whether altered functional integration and/or aberrant connectivity pre-date the onset of depression in at-risk individuals.

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Insane in private dwellings

The treatment of the insane in private dwellings, begun ages ago at Gheel, in Belgium, as a place of miraculous healing, entered its modern and rational phase only in the middle of the nineteenth century, when the control and administration of the colony at Gheel passed from the Commune into the hands of the State. A few years later, following the Scottish Lunacy Act of 1857, numbers of the insane were treated in private dwellings in Scotland, and are successfully so treated to-day. From Scotland the system passed to France, and from France to Russia; and from Belgium to Austria, Italy, Holland and Scandinavia. Perhaps its most remarkable development, however, is to be found in Germany to-day, for, whereas in that country there were in 1882 but two small family-colonies for the insane with scarcely more than fifty patients, ten years later there were thirty-two colonies with 1200 patients, and at the end of 1906 there were fifty-one separate colonies with 2400 patients so treated. These different countries adopted the system at the outset for diverse reasons – in Scotland for want of asylum accommodation, in France to relieve their asylums, in Holland entirely as the extension of the policy of the open door, and in Germany from a combination of these reasons; but wherever and however initiated it has been invariably found to be not only a relief to congested asylums, but in itself a valuable therapeutic aid.

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