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Emotional bias and waking salivary cortisol in relatives of patients with major depression

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ABSTRACT

Background. Biases in the processing of emotional information have been shown to be abnormal in subjects with major depression, both during an episode and after full recovery. However, it is unclear whether these biases are a cause or an effect of the depression. This study set out to explore whether such biases represent a vulnerability factor for depression by looking at unaffected first-degree relatives of those with major depressive disorder. We also measured waking salivary cortisol, as the regulation of the hypothalamo–pituitary–adrenal (HPA) axis is thought to be impaired in depressive disorder.

Method. Twenty-five female relatives and 21 age-matched controls completed a facial expression recognition task, an emotional categorization task with positive and negative personality characteristics, and had their waking salivary cortisol measured on a work day and a non-work day.

Results. The depressed relative group was significantly faster to recognize facial expressions of fear than controls. The depressed relative group also showed significantly increased reaction time to recognize positive *versus* negative personality characteristics in the categorization task. There was no difference in waking salivary cortisol between groups, although there was an effect of work day *versus* non-work day.

Conclusions. Subtle biases in the processing of emotional information may exist in the unaffected first-degree relatives of those with depression. As such, this may represent a familial vulnerability factor to developing a depressive illness.

INTRODUCTION

Patients with major depression have negative biases in the processing of various kinds of emotional information (Beck 1967; Bradley *et al*. 1995; Murphy *et al*. 1999, 2001; Harmer *et al*. 2003*b*). These biases have been demonstrated in a variety of experimental paradigms, including the recognition of emotional facial expression, as well as tasks that tap the influences of emotion on attention and memory (Gur *et al*. 1992; Bouhuys *et al*. 1999; Murphy *et al*. 1999; Sheline *et al*. 2001; Harmer *et al*. 2003*b*). Generally it has been believed that emotional biases contribute to the maintenance of the depressed state and remit with symptomatic improvement (Parker *et al*. 2003). However, we have recently found that fully recovered depressed patients, withdrawn from medication, continue to demonstrate biases in the recognition of facial expressions and also in some aspects of emotional memory (Bhagwagar *et al*. 2004; Hayward *et al*. 2005).

The origin of these persistent biases is unclear. They could represent vulnerability factors for the development of depression or be consequences of the depressive episode itself. One way to explore this question is to find out whether similar emotional biases might be present in first-degree relatives of patients with depression.

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If they are, it would suggest that negative biases in emotional processing could form part of a familial predisposition to mood disorder presumably mediated by genetic or shared family environmental factors.

In the present study we therefore assessed aspects of emotional processing in unaffected first-degree relatives of patients with depression in comparison to individuals without a personal or family history of depression. We also took the opportunity to measure the increase in morning salivary cortisol that follows waking (Wust *et al.* 2000). Abnormal activity of the hypothalamic–pituitary–adrenal (HPA) axis is a recognized abnormality in acute major depression (Holsboer *et al.* 1987) that may persist into clinical recovery (Heuser, 1998) and can also be detected in unaffected relatives of patients with depression (Holsboer *et al.* 1995). Consistent with this, we have found exaggerated salivary cortisol responses to waking in both acutely depressed and recovered depressed patients, free of medication (Bhagwagar *et al.* 2003, 2005). In the present study we hypothesized that first-degree relatives of patients with recurrent depression would show both negative bias in tests of emotional processing and elevated waking salivary cortisol.

METHOD

Subjects

A total of 46 healthy female volunteer subjects were recruited for the study through local advertisement. There were 25 in the depressed relative group (mean age 39·8 years, S.D. = 13·9; mean duration of education 15·5 years, S.D. = 1·9) and 21 in the control group (mean age 39·1 years, S.D. = 13·5; mean duration of education 15·0 years, S.D. = 2·4). Because of technical difficulties with the saliva assay, or inadequate sample volume, two subjects in the control group and four in the depressed relative group were excluded from the cortisol analysis. Thus, all subsequent cortisol analyses were performed on 21 subjects in the depressed relative group, and 19 in the control group.

Participants in the depressed relative group had at least one first-degree relative who had a diagnosis of major depression according to DSM-IV criteria based on the Family History-RDC method (Andreasen *et al.* 1977). (Mean number of episodes 2, S.D. = 1; mean duration of episodes 11·5 months, S.D. = 13. Depressed relatives had all received antidepressant treatment or electro-convulsive therapy, and a third had been hospitalized.) The Family History method has been shown to have good reliability and validity, using diagnostic criteria to detect a diagnosis of affective disorder in a first-degree relative of the interviewee. (For a list of the diagnostic criteria, see Andreasen *et al.* 1977.) The diagnosis was confirmed by a psychiatrist (M.L.M.), following an interview with each participant. Although this method is less ideal than conducting a screening interview on each proband, it has been shown to under- rather than over-diagnose affective disorders among first-degree relatives.

All participants were free of current or history of Axis I disorders, on the basis of the structured clinical interview for DSM-IV (SCID; First *et al.* 1997), administered by a psychiatrist trained in the SCID (M.L.M.). They had no current physical illness and were free of medication, with the exception of one subject in the relative group taking omeprazole, and two in each group taking oral contraceptives. All subjects gave written informed consent for participation in the study, which was approved by the local ethics committee.

All subjects completed the following psychological rating scales: the Beck Depression Inventory (BDI; Beck *et al.* 1961), the Eysenck Personality Questionnaire for Neuroticism (EPQ; Eysenck & Eysenck, 1975) and the Perceived Stress Scale (PSS; Cohen *et al.* 1983).

Sampling of salivary cortisol

Fasting saliva samples were collected in salivette tubes (Sarstedt, Leicester, UK), with the first sample taken immediately upon waking and then samples taken at 15-min intervals for the next hour. Time of waking was recorded to account for a difference between groups being a potential confounder (Kudielka & Kirschbaum, 2003). The subjects followed a standard protocol for measurement of waking salivary cortisol and remained fasting (Wust *et al.* 2000). Apart from this they followed their normal daily schedule. One collection of saliva was carried out on a work day, and another on a non-work day (Kunz-Ebrecht *et al.* 2004*a*, *b*). Salivary cortisol was measured with an in-house double

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antibody radioimmunoassay with intra- and inter-assay coefficients of variation of 3% and 10%, respectively.

Facial expression recognition

The facial expression recognition task featured six basic emotions (happiness, surprise, sadness, fear, anger and disgust), as described previously (Harmer *et al*. 2003*b*). Each image was morphed to produce an expression between 0% (neutral) and 100% of the full emotion, in 10% steps to provide a range of emotional intensities. Four examples of each emotion at each intensity were given (total of 10 individuals). Each face was also given in a neutral expression, making a total of 250 stimuli presentations. Each face was presented on a computer screen for 500 ms and was immediately replaced by a blank screen. Volunteers were asked to respond by pressing a labelled key on the keyboard as quickly and accurately as possible.

Word task

Sixty personality characteristics selected to be extremely disagreeable (e.g. domineering, untidy, hostile) or agreeable (e.g. cheerful, honest, optimistic) (Anderson, 1968) were presented on the computer screen for 500 ms (Harmer *et al*. 2003*c*, 2004). These words were matched in terms of word length and ratings of frequency and meaningfulness. Volunteers were asked to categorize these personality traits as likable or dislikable as quickly and as accurately as possible. Specifically, they were asked to imagine whether they would be pleased or upset if they overheard someone else referring to them as possessing this characteristic, so that the judgment was in part self-referring. Classifications and reaction times for correct identifications were computed for this task. After a distraction, subjects were also tested on word recall.

Statistical analysis

Salivary cortisol levels were measured as area under the curve (AUC) of cortisol secretion (from waking to 60 min) using the trapezoid method. The AUC data were analysed with a two-way repeated measures analysis of variance (ANOVA) with 'group' (relatives *versus* controls) as the main between-subjects factor and 'day' (work *versus* non-work day) as the main within-subjects factor. Baseline differences in cortisol secretion (on waking) were examined with unpaired *t* tests (two-tailed).

Facial expression recognition was analysed using a repeated measures two-way ANOVA with 'group' as the main between-subjects factor and 'facial expression' as the main within-subjects factor. Significant interactions were further analysed using unpaired *t* tests (two-tailed).

The reaction time to categorize positive and negative self-referent personality traits was analysed by calculating the ratio of speed (in ms) to correctly identify positive words divided by speed to correctly identify negative words, providing a measure of relative speed to respond to these valenced words. The groups were then compared using an unpaired *t* test (two-tailed). The number of words recalled was also compared using an unpaired *t* test.

BDI and EPQ scores and time of waking were compared using unpaired *t* tests.

RESULTS

The relatives scored slightly but significantly more on the BDI ($3{\cdot}8 \pm 4{\cdot}4$ *v.* $1{\cdot}6 \pm 1{\cdot}8$, $p = 0{\cdot}032$). However, scores on the neuroticism scale of the EPQ ($6{\cdot}8 \pm 3{\cdot}7$ *v.* $6{\cdot}4 \pm 4{\cdot}8$) and PSS (30 ± 4 *v.* 29 ± 6) did not differ significantly.

Salivary cortisol

The mean time of awakening did not differ significantly between the relatives (06:53 h ± 12 min on a work day; 07:20 h ± 15 min on a non-work day) and controls (06:53 h ± 26 min on a work day; 07:43 h ± 17 min on a non-work day; all p values $>0{\cdot}05$). On the work day, the first salivary cortisol level (taken on waking) did not differ between relatives and controls ($16{\cdot}6 \pm 6{\cdot}6$ *v.* $16{\cdot}2 \pm 5{\cdot}6$ nmol/l, $p = 0{\cdot}89$). However, on the non-work day, the waking cortisol level was significantly higher in the relatives than in controls ($17{\cdot}2 \pm 7{\cdot}5$ *v.* $12{\cdot}5 \pm 5{\cdot}9$ nmol/l, $p = 0{\cdot}036$). The ANOVA of the AUC of morning salivary cortisol (measured from waking to 60 min) showed a main effect of day ($F = 4{\cdot}71$, df = 1, 35, $p = 0{\cdot}037$), where salivary cortisol secretion was higher on the work day than on the non-work day (Fig. 1). However, there was no main effect of group ($F = 0{\cdot}68$, df = 1, 35,

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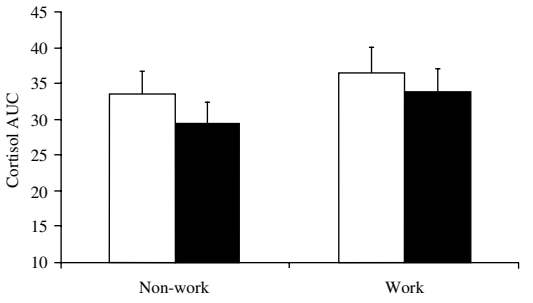

FIG. 1. Area under the curve (AUC) of salivary cortisol measured every 15 min from the point of waking for the next 60 min. Cortisol secretion is significantly greater on work days compared to non-work days ($F=4{\cdot}71$, df = 1, 35, $p=0{\cdot}037$, ANOVA). ■, Control; □, relative.

$p=0{\cdot}42$) or group by day interaction ($F=0{\cdot}00$, df = 1, 35, $p=0{\cdot}99$). There were no significant correlations (all p values $>0{\cdot}05$) between cortisol AUC on work and non-work days and EPQ, BDI and PSS in either the total group or each group considered separately.

Facial expression recognition

There was no interaction between group and facial expression recognition accuracy (two-way ANOVA with repeated measures: df = 5, 220, $F=0{\cdot}43$, $p=0{\cdot}82$), nor were there any differences in accuracy between groups (df = 1, 44, $F=0{\cdot}59$, $p=0{\cdot}45$). However, there was a significant interaction between group and emotion in terms of reaction time (two-way ANOVA with repeated measures: df = 5, 215, $F=3{\cdot}1$, $p=0{\cdot}014$) (Fig. 2). The *post hoc* independent samples t test showed that the depressed relative group specifically identified the facial expression for fear significantly faster than the controls ($t=2{\cdot}2$, df = 44, $p=0{\cdot}037$) (Fig. 2). There was no correlation between BDI score and reaction time to fear ($r=-0{\cdot}17$, $p=0{\cdot}3$). Groups did not differ on performance indices for emotional recognition categories other than fear (all p values $>0{\cdot}05$). No other individual differences were apparent.

Word task

Both depressed relatives and control groups responded to positive personality characteristics faster than to negative ones (Table 1; main effect of valence: $F=133$, df = 1, 44, $p=0{\cdot}0001$). However, this difference was reduced in the depressed relative group (see Table 1). This decreased relative speed to identify the positive characteristics was significantly different in the two groups (unpaired t test: df = 43, t value $=-2{\cdot}37$, $p=0{\cdot}022$). There was no difference in word recall between the two groups (unpaired t test: $F=0{\cdot}034$, df = 33, $p=0{\cdot}39$), and there was no correlation between reaction time difference and BDI ($r=0{\cdot}003$, $p>0{\cdot}9$).

DISCUSSION

The current study suggests trait-like differences in some aspects of emotional processing in volunteers with a family (but not personal) history of depression. In particular, the depressed relative group showed a specific increase in speed to identify facial expressions of fear. Furthermore, this group showed reduced positive bias in the emotional categorization task. These results suggest that negative emotional processing may be increased in volunteers with a family history of depression even in the absence of personal experience of depression. As such, these biases may represent a familial vulnerability factor for depression.

Negative biases in depression have been demonstrated across different cognitive paradigms including facial expression perception. Studies using schematic facial expressions displaying positive, negative or neutral faces have reported that depressed patients are more likely to mislabel neutral faces as negative and positive as neutral in depression (Gur *et al.* 1992). We have also reported increased recognition of negative facial expressions, most notably fear (Bhagwagar *et al.* 2004) and disgust (Hayward *et al.* 2005), in unmedicated recovered depressed patients. The persistence of this negative bias into remission from depression suggested that it could represent either a trait vulnerability marker or a 'scar' effect of depression and its treatment. In the current study, the speed of fearful face recognition was also facilitated in unaffected first-degree relatives of depressed patients, suggesting that this kind of negative bias may be a risk factor for mood disorder, rather than simply a consequence of having been ill in the past. Although the current study found an effect on speed of recognition, previous studies have tended to find effects on accuracy of recognition. However, both processes are likely to be involved in the recognition of

Table 1. *Mean reaction times to designate a word as positive or negative, and ratios of speed to positive words versus negative words*

Group	Mean reaction time to negative words (±S.D.), ms	Mean reaction time to positive words (± S.D.), ms	Ratio of positive reaction time to negative reaction time (±S.D.)
Depressed relative	973±207	642±268	0·67±0·27
Control	973±232	514±300	0·50±0·22

S.D., Standard deviation.

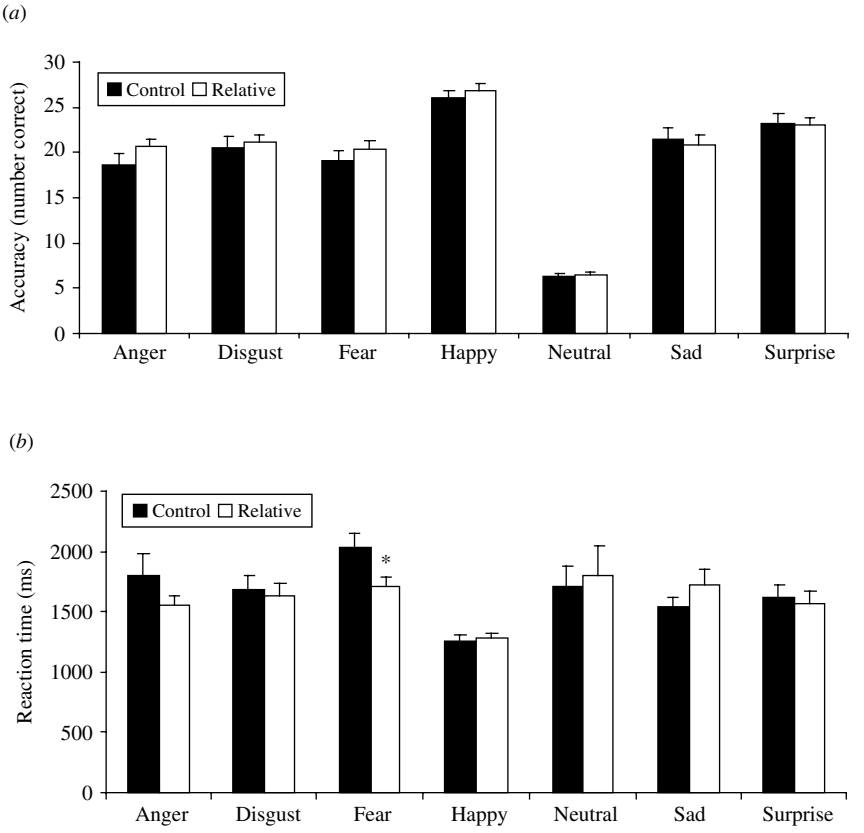

FIG. 2. (*a*) Accuracy and (*b*) reaction time for facial expression recognition in group with a depressed relative compared to controls. Significant interaction between group and emotion in terms of reaction time (two-way ANOVA with repeated measures df=5, 215, $F=3{\cdot}1$, $p=0{\cdot}014$). * $p=0{\cdot}037$ (*post hoc* independent samples *t* test).

different emotional states. Indeed, in studies looking at the effects of neurochemical manipulations on fearful facial expression recognition, we have typically seen interchangeable effects on both speed and accuracy (Harmer *et al.* 2003*a*, *b*).

The unaffected relatives of depressed patients also showed a relative slowing of reaction time to categorize positive adjectives in this study. An increased reaction time to identify positive words has also been reported in depression in a go/no-go task (Murphy *et al.* 1999) and we have

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reported the opposite effect (increased relative speed of responding to positive adjectives) following antidepressant drug administration in healthy volunteers (Harmer *et al.* 2003*a*, 2004). Again, these results suggest that subtle changes in the way in which emotional information is processed may be involved in vulnerability to depression, presumably as a result of genetic factors or shared family experience.

It is unlikely that the differences seen between the two groups were due to confounding factors such as low-grade depression or neuroticism in the group with a family history, as no correlation was found between BDI or EPQ scores and reaction times.

Evidence for these kinds of negative biases in unaffected relatives of depressed patients are consistent with Beck's cognitive model of depression (Beck, 1967), which proposes that latent negative schema are apparent before the onset of depression and are involved in the risk of developing this disorder, usually following a life event or stressor. While the existence of biases prior to depression has been questioned, the current data set suggests that subtle changes in emotional processing are associated with risk for depression, even in the absence of depression itself. However, the changes in emotional processing seen here are relatively modest compared to the biases reported in depression, and their functional effects on mood and depression remain unclear. The biases seen in major depression may therefore be a combination of pre-morbid biases and greater activation and consolidation of negative schema following life events, stress and previous episodes of depression.

Abnormalities in various aspects of HPA axis function have been reported in depressed patients (Holsboer *et al.* 1987). While some of these abnormalities remit with clinical recovery, others seem to be more enduring (Holsboer *et al.* 1995; Bhagwagar *et al.* 2003). For example, the corticotrophin (ACTH) and cortisol responses to the combined dexamethasone/corticotrophin-releasing hormone (CRH) test continue to be abnormal in remitted depressed patients at high risk of relapse (Heuser 1998; Zobel *et al.* 1999, 2001; Ising *et al.* 2005). In addition, abnormal ACTH and cortisol responses to these challenges have been reported in the first-degree relatives of depressed patients who have not themselves been depressed (Holsboer *et al.* 1995).

The increase in salivary cortisol that follows waking is thought to reflect increased endogenous activity of the HPA axis. This cortisol response is exaggerated both in patients with acute major depression and in fully recovered subjects withdrawn from medication (Bhagwagar *et al.* 2003, 2005). In the present study, however, no increase in waking salivary cortisol was seen in the first-degree relatives of depressed patients. This suggests that shared familial genetic or environmental factors are unlikely to account solely for the abnormal cortisol response to waking in recovered depressed patients. Neuroticism is also an important risk factor for depression and we have recently found that healthy subjects with high neuroticism scores on the EPQ also show exaggerated waking salivary cortisol responses (Portella *et al.* 2005). In the present study, neuroticism scores did not differ between relatives and controls. This raises the possibility that the abnormal HPA axis function detected by waking salivary cortisol levels in recovered depressed subjects may be more dependent on environmental and genetic factors linked to neuroticism than a family history of depression. Another possibility is that elevated waking cortisol levels may relate more to specific individual risk factors for depression such as childhood adversity. Finally, increased morning cortisol secretion could be a consequence of having suffered depression. It should be noted, however, that our study was powered to detect a difference in AUC cortisol secretion between relatives and controls of about 25%; this is somewhat less than the difference found by Bhagwagar *et al.* (2003) in recovered depressed subjects. However, our study would have lacked sufficient power to detect differences less than this.

As reported previously, waking salivary cortisol was slightly but significantly greater on work compared to non-work days (Kunz-Ebrecht *et al.* 2004*a*). While controls had a lower cortisol level on the point of waking on their non-work day relative to their work day, this pattern was not apparent in the relatives who therefore had higher salivary cortisol levels than controls on the point of waking on their non-work day. Clearly this could be a chance

finding. However, it might suggest that in people at risk of depression, salivary cortisol secretion at the point of waking may not show a decline in response to what might be perceived cognitively as a less stressful day.

We acknowledge that this study had limitations in its design. These included its small size, the lack of a depressed comparison group, and the fact that the subjects had only one depressed relative. The latter was for ease of recruitment, although using subjects with a greater degree of genetic loading may well have increased the robustness of our findings. It is possible, for example, that some of the affected relatives did not in fact suffer from depression or that some of the first-degree relatives of the control group did. Such effects would presumably tend to diminish possible cognitive and endocrine differences between the two groups.

In summary, the present study has revealed subtle but clear negative biases in processing of emotional information in unaffected subjects with a family history of depression. These results suggest that subtle negative biases in emotional information processing may represent vulnerability factors that predispose individuals to develop depression in the presence of adverse life circumstances.

DECLARATION OF INTEREST

None.

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