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Psychological, endocrine and neural responses to social evaluation in subclinical depression

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This study aimed to identify vulnerability patterns in psychological, physiological and neural responses to mild psychosocial challenge in a population that is at a direct risk of developing depression, but who has not as yet succumbed to the full clinical syndrome. A group of healthy and a group of subclinically depressed participants underwent a modified Montreal Imaging Stress task (MIST), a mild neuroimaging psychosocial task and completed state self-esteem and mood measures. Cortisol levels were assessed throughout the session. All participants showed a decrease in performance self-esteem levels following the MIST. Yet, the decline in performance self-esteem levels was associated with increased levels of anxiety and confusion in the healthy group, but increased levels of depression in the subclinical group, following the MIST. The subclinical group showed overall lower cortisol levels compared with the healthy group. The degree of change in activity in the subgenual anterior cingulate cortex in response to negative evaluation was associated with increased levels of depression in the whole sample. Findings suggest that even in response to a mild psychosocial challenge, those individuals vulnerable to depression already show important maladaptive response patterns at psychological and neural levels. The findings point to important targets for future interventions.

Keywords: subclinical depression; subgenual anterior cingulate cortex; social evaluation; cortisol; vulnerability

INTRODUCTION

Experiences of psychological stress and major depressive disorder (MDD) are intricately connected; indeed, onset and development of MDD is often preceded by periods of extreme, prolonged or chronic stress (e.g. Hammen, 2005). Given that worldwide, depression has been projected to become the leading cause of burden of disease over the next two decades (World Health Organization, 2008), it is of importance to understand in what ways the mechanisms that are underlying processing of psychological stress are affected in those who are at risk for developing depression. To this end, in this study, we exposed a group of young adults with subclinical levels of depression and a group of healthy young adults, to a mild psychosocial challenge task. An overall goal of the study was to identify vulnerability patterns in psychological, physiological and neural responses to social evaluation, an important aspect of psychological stress (Dickerson and Kemeny, 2004).

A thorough meta-analysis on over 200 laboratory studies of acute psychological stressors revealed that behavioral tasks that combined a motivated performance task with elements of uncontrollability and especially, social evaluative threat components induced the largest physiological stress response (Dickerson and Kemeny, 2004). The elements of social evaluative threat included permanent recording of the performance, presence of evaluative audience during the task (main experimenter and at least one more individual) and presence of negative social comparison (either real or mocked) (Dickerson and Kemeny, 2004).

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To capture some of these elements in the neuroimaging environment and be able to assess neural mechanism underlying psychosocial stress processing and regulation, we have developed the Montreal Imaging Stress task (MIST), a task that combines mental arithmetic (motivated performance) with elements of social evaluation and negative feedback (provided by immediate task feedback and the experimenter; Dedovic *et al.*, 2005). Findings from MIST studies and other neuroimaging studies on this topic suggest that, in healthy populations, psychological stress processing is associated with deactivations in the orbitofrontal cortex, medial prefrontal cortex (PFC) and the hippocampus [reviewed in Dedovic *et al.* (2009a) and Wager *et al.* (2009)]. Although, it should be noted that some studies have also observed activations in the limbic system regions (e.g. Gianaros *et al.*, 2008).

Additional studies investigating neural correlates of social evaluation reported deactivation in medial orbitofrontal cortex in response to negative evaluation on participants' performance on a math task, but only in those participants who showed an increased physiological stress response (Dedovic *et al.*, 2009b). Furthermore, people who reported lower state self-esteem over the course of receiving critical evaluation about their life goals and aspirations showed greater activity in dorsal anterior cingulate and bilateral insula, as well as dorsal medial PFC and posterior superior temporal sulcus (pSTS) (Eisenberger *et al.*, 2011). Moreover, activation in the ventral anterior cingulate cortex/medial PFC area has also been reported in response to positive feedback compared with negative feedback in healthy individuals (Somerville *et al.*, 2006) and particularly in individuals with low self-esteem (Somerville *et al.*, 2010). Finally, increased activity in dorsal ACC in response to exclusion compared with inclusion in a virtual ball tossing game, a model of social rejection, has also been repeatedly observed (Eisenberger *et al.*, 2003; Eisenberger *et al.*, 2007). Together, these studies suggest that processing psychosocial stress results in the deactivation of medial orbitofrontal cortex, medial PFC and hippocampus,

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as well as the activation of the dorsal anterior cingulate, pSTS and insula.

To date, only a few neuroimaging studies have attempted to investigate the interplay between psychological stress and depression. Specifically, a study by Masten *et al.* (2009) found that adolescents showed activation in subgenual anterior cingulate cortex (sgACC) during exclusion compared with inclusion in a virtual ball tossing game; this sgACC activation was related to higher reports of distress following exclusion. In addition, in another sample of adolescents, greater sgACC activity during exclusion was positively associated with their depressive symptoms (reported by their parents) a year later (Masten *et al.*, 2011). This is of particular interest as this region has been implicated in etiology of depression (reviewed in Drevets *et al.*, 2008) and features a prominent role in cortical-limbic dysregulation model of depression (Mayberg, 1997, 2003, 2009).

At the endocrine level, social evaluative threat triggers the main endocrine stress axis, the hypothalamic–pituitary–adrenal (HPA) axis. The HPA cascade consists of a sequential release of corticotropin-releasing hormone from the hypothalamus, adrenocorticotropic hormone from the anterior pituitary, and finally, cortisol from the adrenals (Brown, 2000). There are individual differences with respect to the HPA axis' response to social evaluative threat (e.g. Kirschbaum *et al.*, 1995; Schommer *et al.*, 2003; Kudielka *et al.*, 2004; Kudielka *et al.*, 2009). Various factors such as intensity and context of the threat, and presence of vulnerability and protective factors in an individual and social environment can influence the magnitude of the cortisol response (Dickerson and Kemeny, 2004).

Behavioral studies investigating processing of psychological stress in vulnerable and depression samples have revealed that dysregulation of the HPA axis is common in MDD. Although depressive state has been associated with a hyperactive HPA axis (Gillespie and Nemeroff, 2005; Stetler and Miller, 2011), studies using laboratory psychological stressors have reported inconsistent findings, with some studies suggesting a heightened stress response in depressed and other studies reporting blunted response (e.g. Chopra *et al.*, 2009; Handwerger, 2009; Harkness *et al.*, 2011). In a vulnerable sample, we have previously shown that participants with subclinical levels of depression show a blunted cortisol response to awakening (a natural challenge to the HPA axis; Dedovic *et al.*, 2010). Together, results to date suggest that the cortisol stress response in depressed subjects is either similar to those in control groups (if examining total plasma cortisol levels) or somewhat blunted (when levels of free cortisol are assessed in saliva) in response to a psychosocial stressor or natural challenge (reviewed in Burke *et al.*, 2005; Handwerger, 2009).

To further understand the ways in which these mechanisms that are underlying processing of social evaluation may contribute to the etiology of depression, in this study, we focused on a sample of healthy young adults who showed varying levels of depressive tendencies, at a subclinical level. We focused on subclinical depression as it has been suggested that subclinical depression may represent a milder condition on the depression severity continuum (Solomon *et al.*, 2001; Lewinsohn *et al.*, 2003; Rivas-Vazquez *et al.*, 2004) and that it may represent the precursor for the full disorder (Shankman *et al.*, 2009). Subclinical or subthreshold depression has been defined in various ways: scoring above (and below) certain cut-off points on a self-rating scale, having a depressed mood with one or more additional symptoms of a mood disorder, or as meeting the criteria for minor depression in Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (Cuijpers and Smit, 2004). In our study, subclinical depression was assessed as scoring above a cut-off point for the normal range of depressive mood and below a cut-off point for the clinical range of depressive mood on a self-rating depression inventory. A recent study revealed that assessment of subclinical depression either via symptom counting method or assessment of symptom severity was associated with functional impairment in daily life; however, the symptom severity assessment was found to be more suitable to measure clinically relevant subclinical depression (Karsten *et al.*, 2010). A subclinical depression population is indeed a population that is at a direct risk of developing depression, but who has not as yet succumbed to the full clinical syndrome; it provides a unique opportunity for investigation of potential depression vulnerability indices.

The goal of the study was to identify, at psychological, endocrine and neural levels, key response patterns to social evaluative threat that can differentiate between healthy participants and the subclinically depressed. Specifically, we examined changes in self-esteem, mood, cortisol levels and stress and mood neural networks (hippocampus, amygdala, medial PFC and sgACC) as potential early indices of vulnerability. Based on the previous literature, we hypothesized that in comparison with the healthy group, the subclinical group would show a blunted cortisol response to the psychosocial stress task. We also hypothesized that the subclinical group would show a more reactive psychological response to the task. In addition, we expected to find an association between depression levels and changes in brain activity in response to social evaluation in those brain areas that have been previously implicated in stress and mood regulation-specifically, hippocampus, medial orbitofrontal cortex and sgACC.

METHODS

Subjects

Sixty-four (30 men: 34 women) right-handed, healthy college students (mean age = 21.9 ± 2.5) were recruited. Subjects completed screening questionnaires and were excluded if they had prior and/or present neurological or psychiatric illness, if they were regular smokers, used recreational drugs on a regular basis and if they were taking any medication that could influence cortisol secretion. All subjects included met the safety requirements for participation in a functional magnetic resonance imaging (fMRI) study. Furthermore, they had no current diagnosis or history of claustrophobia or axis I disorders. The final selection was based on their score on the Beck Depression Inventory (BDI; Beck and Steer, 1987). Following the published BDI cut-off scores (Beck and Steer, 1987), the subjects were initially recruited to either a healthy group (BDI ≤ 9; $N = 33$) or a subclinically depressed group (10 ≤ BDI ≤ 18; $N = 31$).

On the scan day, subjects completed the Hamilton Depression Inventory (HDI; Reynolds, 1995), as well as the Montgomery-Asberg Depression Rating Scale Self-Assessment (MADRS-S) (Svanborg and Asberg, 1994) as a crosscheck for BDI depression levels obtained at the time of recruitment. Several subjects had scored at clinical depression levels either on the HDI or MADRS-S at that time. These subjects represented high-risk subclinical subjects and were advised to seek professional counsel and were given a referral letter. We did not include these participants for the subsequent analyses, opting to instead focus only on the healthy participants and those subjects whose levels of depression remained at subclinical levels throughout the duration of the study (27.6 days ± 11.4 passed from the recruitment in the study until completion of the testing session).

Finally, inspection of the data revealed that five subjects had to be excluded due to missing functional data, abnormal cortisol profile or an inadequate performance on the computer tasks, leaving the final number of participants as 26 healthy (12 men; 14 women) and 23 subclinical (12 men; 11 women).

Women in the sample varied with respect to their menstrual cycle and contraceptive usage. However, across the study groups, the samples were well balanced. Specifically, in the healthy group, five women were in the follicular phase, two in luteal and seven were on hormonal

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contraceptives. In the subclinical group, three were in the follicular phase, 0 in luteal and eight were on contraceptives.

The Institutional Review Board (IRB) of McGill University approved the study, and informed consent was obtained prior to participation in accordance with the requirements of the McGill IRB from all subjects.

Procedure

On the testing day, participants arrived at the Montreal Neurological Institute (MNI) in the afternoon, 1 h prior to when the scanning was scheduled. The subjects were given several psychological questionnaires to complete. Fifteen minutes prior to entering the scanning room, a research assistant explained the procedure and tasks that would be performed in the fMRI scanner. Subjects were then introduced to the study investigator and placed in the scanner where they completed an attentional bias task, followed by a structural scan and finally two runs of a modified version of the MIST (Dedovic *et al.*, 2005). The attentional bias task was a classical dot-probe attentional bias task that was adapted for neuroimaging environment. The purpose of this task was to implicitly measure participants' attentional bias for sad and happy faces. Completion of this task is unlikely to affect processing of the MIST. Behavioral and fMRI results relating to the attentional bias task will be reported elsewhere (Dedovic, K, Giebl, S., Duchesne, A., Lue, S. D., Andrews, J., Efanov, S., Engert, V., Beaudry, T., Baldwin, M., Pruessner, J. C., in preparation).

Modified Montreal Imaging Stress Task

The MIST (Dedovic *et al.*, 2005) is a psychosocial stress task that uses mental arithmetic to combine the key situational components shown to facilitate mounting of a stress response: (i) presence of social evaluative threat, (ii) atmosphere of high achievement (or challenge) and (iii) little or no controllability (Dickerson and Kemeny, 2004). Below, we describe the task and outline some of the changes that we have introduced in this version.

The MIST is based on a computer algorithm that creates mental arithmetic tasks using up to four numbers ranging from 0 to 99, and up to three operands. The algorithm has been programmed so that the solution of each task will always be an integer between 0 and 9 allowing the response to be submitted with a single number key. A difficulty gradient was built into the algorithm with seven different categories of mental arithmetic tasks, ranging from easy [e.g. $(a+b-c=d)$] to difficult [e.g. (fraction a) × (fraction b) × (fraction c) = e]; in addition, the time allowed to complete the task was manipulated (e.g. participants were given 5 s for completion of an easy task and 8 s for a difficult one). The program used probabilities to determine whether the next question should be more difficult, easy or same as the previous, and whether to reduce or increase the time allowed for answering the question (based on the subject's previous performance and on task difficulty).

In the modified MIST (Figure 1), subjects were exposed to four conditions: (1) rest (12 acquisitions), where only the task interface was shown; (2) control (20 acquisitions), where subjects were given mental arithmetic tasks to complete with plenty of time allowance; (3) experimental/evaluation stress (Exp_S) (30 acquisitions) (Figure 1A) and (4) an experimental/no evaluation, i.e. no stress condition (Exp_NS) (30 acquisitions) (Figure 1B). The conditions 3 and 4 are described in detail below.

Importantly, the Exp_S and the Exp_NS were governed by the same algorithm rules (math tasks from all categories were used, and the corresponding time limit imposed). However, in the Exp_S condition, which was outlined by a red frame, each task was presented with elements of evaluative components: (1) a performance color bar on the top of the screen indicating the subject's performance in comparison with a mock 'average' user, (2) a time advance bar indicating the amount of time the subjects had to complete the task and (3) a performance feedback window, where upon the submission of response or timeout, the subject's performance on that task was printed out and associated with the word 'RECORDED' (Figure 1A). The Exp_NS condition tasks did not contain these evaluative elements. Indeed, it was explained to the subjects that the tasks outlined by a red frame (Exp_S condition) are of greatest importance for the study, and it was emphasized that during this time subject's performance was being evaluated by the computer and the investigator outside the scanner room. All these evaluative threat components were removed for the Exp_NS condition (Figure 1B), and in fact, in the set-up appearance, the control (doing math tasks with plenty of time allowance) and the Exp_NS conditions looked the same.

Over the course of a run, these conditions were presented in a block design, and repeated three times, in a pseudo-randomized fashion (a block of one condition could not be followed by a block of that same condition).

As with the original MIST version, in between each MIST run, the subjects were exposed to additional negative feedback given directly by the study investigator when the investigator would enter the scanner room to collect the saliva samples. During the feedback, the participant would be told that the investigator had been monitoring the participant's performance during the experimental condition, the red condition, and that the participant's performance was below that of an average user during this task condition. The investigator would also tell the participant that participant's performance would need to match up to performance of an average user if the study team was to collect

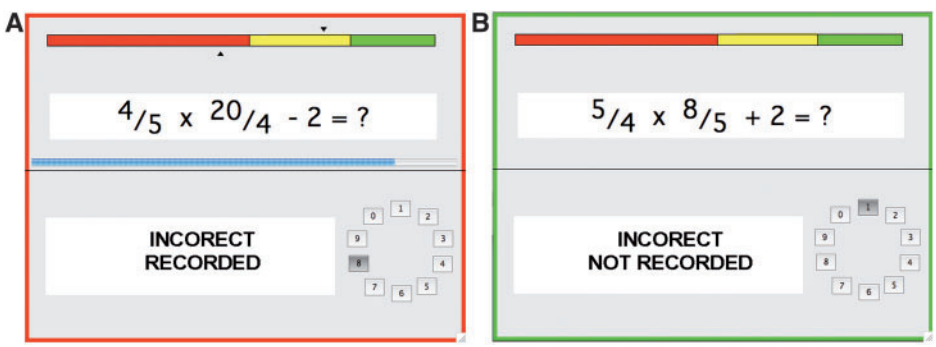

Fig. 1 The modified MIST user interface. (**A**) The experimental/stress (exp_S) condition includes performing challenging mental arithmetic in social evaluative setting: a performance color bar indicating the subject's performance (bottom arrow) in comparison to a mock 'average' user (top arrow), a time advance bar indicating the amount of time participants had to complete the task, and a performance feedback window, emphasizing that the subject's poor performance was recorded. (**B**) The experimental/non-stress (exp_NS) condition contains mental arithmetic task of same difficulty, and same time limit, but social evaluative components are removed.

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any meaningful data. Following the last MIST run, the subject was thanked for their participation and escorted by the research assistant to another testing room to complete additional questionnaires and saliva samples. The full debriefing was given only after all saliva samples were collected and questionnaires completed.

The key contrast of interest was exp_S > exp_NS, which is thought to capture the processing of social evaluative threat components—important components in psychological stress processing (Dickerson and Kemeny, 2004). The evaluative threat is stemming from the fact that participant's (inevitably poor) performance is compared to an average user, that the performance is being recorded, and that the investigator is watching participant's performance.

In a small behavioral study assessing a similar version of the MIST, 25 participants answered the following question after completing the task: 'Were you more stressed during that condition (EXPERIMENTAL) as oppose to the control condition?' Out of 20 participants, 14 said that they were, 5 said that they were equally stressed in the two conditions, one reported being more stressed during the control condition. In addition, in another study using a similar version of the MIST, we found that the participants thought more about the fact that they were being evaluated by the investigator during the ExpS compared with ExpNS condition (Duchesne A., Cooperman C., Cardoso C., Pruessner JC., submitted; Duchesne A., Cooperman C., Cardoso C., Pruessner JC., in preparation) (see also Supplementary Material). Therefore, the two conditions have been designed to differ on levels of actual and perceived evaluation.

Saliva sampling

Participants provided eight saliva samples in total to assess levels of cortisol. Saliva was collected using the salivette sampling device (Sarstedt Inc., Quebec City, Quebec, Canada). The first saliva sample was taken about an hour after the participants came into the laboratory and just prior to the scan, when subjects were seated at the scanning bench. The second saliva sample was taken during the attentional bias task prior to the last run of the attentional bias task and the structural scan, ~30 min following the first sample. Subsequently, saliva samples relevant for the MIST were taken at the following time points: right before the first MIST run, which occurred ~30 min after the second saliva sample, between 1:08 pm and 6:30 pm; then, after each MIST run (~13 min between the samples), and the final three samples were assessed outside of the scanner, at 15 min intervals, while subjects were completing additional questionnaires and resting.

Once all the saliva samples were collected and questionnaires completed, the subject was debriefed about the testing procedure. The saliva samples were stored in the laboratory freezer at −20°C until analysis. Samples were analyzed via a time-resolved fluorescence immunoassay, of which intra- and inter-assay variability have been shown to be <10% and 12%, respectively (Dressendorfer *et al.*, 1992).

As the cortisol values were not normally distributed, we log transformed data for the statistical analyses. All data points for each group were normally distributed following the transformation. Although we log transformed cortisol data for the statistical analyses, the figures reflect the non-transformed values for easier interpretation of the data.

Psychological assessment

For the fMRI and regression analyses, we created a composite score of depression severity by firstly calculating *Z* scores on BDI, MADRS-S and HDI questionnaires and then averaging these.

We investigated the impact of the MIST procedure on the subjects' state levels of performance and social self-esteem via the Current Thoughts Scale (Heatherton and Polivy, 1991). In addition, we also assessed state changes in current mood by using the Profile of Mood States that included the following subscales: depression, anxiety, anger, fatigue, vigor and confusion (McNair *et al.*, 1992). All state measures were administered twice, both at baseline and following the MIST.

Behavioral statistical analysis

Differences with respect to change in cortisol were assessed via a mixed-design ANCOVA with cortisol levels related to the MIST task as repeated measures, group and sex as between factors, and additional variables that were thought to carry influence on cortisol levels as covariates. For example, although all participants were tested in the afternoon, there was some variability in the exact time the participants were tested at, due to participant and scanner availabilities. To make sure that any observed effects on cortisol during the MIST are not due to the time of day of the testing (range 1:08 pm–6:30 pm) and do not reflect any change in cortisol that may have occurred prior to onset of the MIST (e.g. entering the scanner or completing the attentional bias task), we entered the following variables as covariates in the analysis: the time of day of start of MIST, as well as the first two cortisol measures.

For the assessment of change in mood and self-esteem across time, we applied mixed-design ANOVA, with levels of mood or self-esteem and time as repeated measures, and group and sex as between factors.

Similarly, to assess potential differences in reaction times and performance during the MIST, we conducted a mixed design ANOVA, where group and sex were always between factors.

If the sphericity assumption was violated, we applied Greenhouse-Geisser (GG) correction. In case of significant interactions, ANOVA analysis was followed up by the simple main effects tests.

Functional imaging data acquisition and processing

The subjects were scanned in a 1.5 T Siemens Magnetom SonataVision scanner. For the structural images, standard 3D gradient-echo pulse sequence was used, with the field of view of 256 mm, the voxel size of 1 × 1 × 1 mm, repetition time (TR) of 22 ms, echo time (TE) of 9.2 ms and a flip angle of 30°.

Subjects were exposed to two functional MIST runs. During each functional run, 276 whole-brain BOLD Mosaic 64 T2*-weighted echo-planar images were acquired transversely, along the direction of the anterior commissure to the posterior commissure line minus 30° (voxel size = 4 × 4 × 5 mm; slice number = 28; order of slice acquisition = interleaved; TR = 2370 ms; TE = 50 ms; flip angle = 90°; matrix = 64 × 64; field of view = 256 mm).

Preprocessing of the structural and functional data was conducted using FSL tools (Smith *et al.*, 2004; Woolrich *et al.*, 2009) and using tools contained within the Statistical Parametric Mapping software package (SPM8) (http://www.fil.ion.ucl.ac.uk/spm/).

Specifically, the Brain Extraction Tool was used to remove any non-brain tissue from both structural and functional images (Smith, 2002). Following this procedure, images were manually inspected to verify that the procedure did not affect brain tissue. The functional raw data were motion corrected by FMRIB's Linear Image Registration tool (mcflirt; http://www.fmrib.ox.ac.uk/fsl/mcflirt/index.html) which conducts linear inter-modal registration with 6 degrees of freedom, aligning each functional frame to the middle frame in each run (Jenkinson *et al.*, 2002).

The structural and functional images were then registered to a template image (MNI152_T1_2mm_brain.nii.gz) using a three-step procedure and the FMRIB's Linear Image Registration tool (flirt; http://www.fmrib.ox.ac.uk/analysis/research/flirt/) (Jenkinson *et al.*, 2002).

Finally, these normalized images were then transferred into SPM8 and smoothed using a 6 mm full-width-half-maximum Gaussian kernel to spatially smooth the data and reduce noise.

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Modeling and analysis of data was conducted using SPM8. The main contrast of interest was exp_S > exp_NS. To control for possible contribution of performance and reaction times (see 'Results' section), and movement to the changes in brain activity, we modeled one condition where we included onsets and durations for both ExpS and ExpNS condition, and then added, in the following order, reaction times, performance scores and the contrast ExpS > ExpNS as separate parametric modulators. The second modeled condition was the control condition and we also included the movement parameters as regressors of no interest.

High-pass temporal filtering of the data and the model was set to 1640s based on the power spectra of the design matrix (estimated by *cutoffcalc*; part of FSL). To account for serial correlations in fMRI time series due to aliased biorhythms and unmodeled neuronal activity we used an autoregressive AR (1) model during Classical parameter estimation. Given that we were only interested in ExpS > ExpNS comparison while controlling for all other variables, the final contrast was 0 0 0 1 0 which was additionally padded with zeros for the movement parameters.

These contrast images were then used in region of interest (ROI) and whole-brain, group-level, random-effects analyses across all participants, and for the whole-brain correlational analyses with covariates of interest. For all analyses, gender was always used as a covariate of no interest.

Regions of interest analyses

Although we planned to explore changes in response to social evaluation across the whole brain, we were particularly interested in investigating changes in activity in specific brain regions that have been previously identified as being involved in processing social evaluation or being involved in etiology of depression. These regions included the hippocampus, medial orbitofrontal cortex and sgACC. For the hippocampus, we used the structural ROI mask from the aal atlas (Tzourio-Mazoyer *et al.*, 2002) in the WFU Pickatlas toolbox (Maldjian *et al.*, 2003, 2004) in SPM. For the medial orbitofrontal cortex, we defined a region based on previous results in our study investigating processing of social evaluative components (Dedovic *et al.*, 2009b), with the center voxel being $x = -0.3$, $y = 43$, $z = -20$, and the extent set to 12 mm radius sphere. The sgACC ROI was based on work by Masten *et al.* (2009). We used the local maxima within sgACC, which was previously found to be activated during social exclusion compared with inclusion (8, 22, −4 mm) (Masten *et al.*, 2009), as the center voxel for a 10 mm radius sphere. To control for multiple comparisons across multiple ROIs, these masks were then combined into one image and used for ROI analyses.

In accordance with previous studies and to balance both type I and type II error rates, we employed the recommended combination of intensity and cluster size thresholds of $P < 0.005$, 20 voxels for establishing significance (Lieberman and Cunningham, 2009).

RESULTS

Psychological data

The two study groups differed on levels of depression. As would be expected, a two-way ANOVA (group × gender) revealed a significant effect of the group, $F(1,45) = 66.83$, $P < 0.001$, on the composite depression score, confirming that the subclinical group had higher scores compared with the healthy ($P < 0.001$). All other effects were not significant (all $F < 1$, $P > 0.51$).

Changes in mood measures following the MIST: in all participants, levels of fatigue and confusion increase, vigor decreases

We conducted a mixed design ANOVA with current mood (depression, anxiety, anger, fatigue, vigor and confusion) and time (pre-scan and post-MIST) as repeated measures, and group and gender as between factors. The mixed design ANOVA revealed a significant main effect of group [$F(1,41) = 4.72$, $P = 0.036$] and mood [$F(1.76,72.09) = 63.14$, $P < 0.001$, GG corrected], as well as significant interaction of mood by time [$F(2.23,91.56) = 13.31$, $P < 0.001$, GG corrected] and mood by group [$F(1.76,72.09) = 3.46$, $P < 0.042$, GG corrected]. Results of the significant mood by gender interaction [$F(1.76,72.09) = 7.09$, $P = 0.002$] can be found in the Supplementary Material.

The simple main effects analysis of mood × time interaction revealed no effect of time on anxiety [$F(1,41) = 2.19$, $P = 0.14$] or depression [$F(1,41) = 1.42$, $P = 0.240$]. However, anger increased over time at a trend level [$F(1,41) = 3.75$, $P = 0.060$]. In addition, fatigue and confusion increased and vigor decreased over time {vigor [$F(1,41) = 19.20$, $P < 0.001$]; fatigue [$F(1,41) = 13.76$, $P = 0.001$]; confusion [$F(1,41) = 5.03$, $P = 0.03$]}, suggesting that the MIST was psychologically taxing on the participants.

Decomposing the current mood × group interaction revealed, as would be expected, that the subclinical group showed higher levels of state levels of depression [$F(1,43) = 5.65$, $P = 0.022$] and were more fatigued than the healthy [$F(1,43) = 10.34$, $P = 0.002$]. The subclinical participants also showed higher levels of anxiety, but at a trend level only [$F(1,43) = 3.42$, $P = 0.071$]. The healthy group showed higher anger compared with the subclinical group [$F(1,43) = 4.78$, $P = 0.034$]. There were no group differences with respect to vigor [$F(1,43) = 1.39$, $P = 0.245$], or confusion [$F(1,43) = 2.28$, $P = 0.139$] levels. The findings suggest that, as would be expected, the groups did differ in levels of depression and anxiety, which is in keeping with the subclinical participants having a heightened depression risk status compared with the healthy participants. The groups also differed on levels of fatigue and anger, moods that may be more state dependent. Therefore, we controlled for levels of fatigue and anger in the fMRI analyses.

Change in state self-esteem following the MIST: performance self-esteem decreased

A mixed design ANOVA, with self-esteem type (performance, social) and time (pre- and post-MIST) as repeated measures, and group and gender as between measures, revealed a main effect of group [$F(1,45) = 6.9$, $P = 0.012$], showing that the healthy participants had overall higher self-esteem levels compared with the subclinically depressed.

In addition, we observed a main effect of self-esteem [$F(1,45) = 4.26$, $P = 0.045$, GG corrected], main effect of time [$F(1,45) = 6.56$, $P = 0.014$, GG corrected] and a time × self-esteem interaction [$F(1,45) = 19.24$, $P < 0.001$].

The simple main effects of time × self-esteem interaction revealed that specifically the state levels of performance self-esteem decreased following the MIST [$F(1,45) = 15.55$, $P < 0.001$] (Figure 2A). There was no effect of time on state levels of social self-esteem [$F(1,45) = 0.44$, $P = 0.51$]. Furthermore, prior to undergoing the MIST there was no difference in levels of performance and social self-esteem in the whole group [$F(1,45) = 0.52$, $P = 0.474$]; however, following the MIST, performance self-esteem was lower compared with the social self-esteem levels [$F(1,45) = 22.68$, $P < 0.001$], owing to the fact the performance self-esteem decreased following the MIST.

It should be noted that when controlling for the change in levels of fatigue, vigor and confusion, the time × self-esteem interaction remains significant [$F(1,40) = 9.96$, $P = 0.003$].

The main ANOVA also revealed a time × gender interaction [$F(1,45) = 4.24$, $P = 0.045$, GG corrected], and a self-esteem × gender

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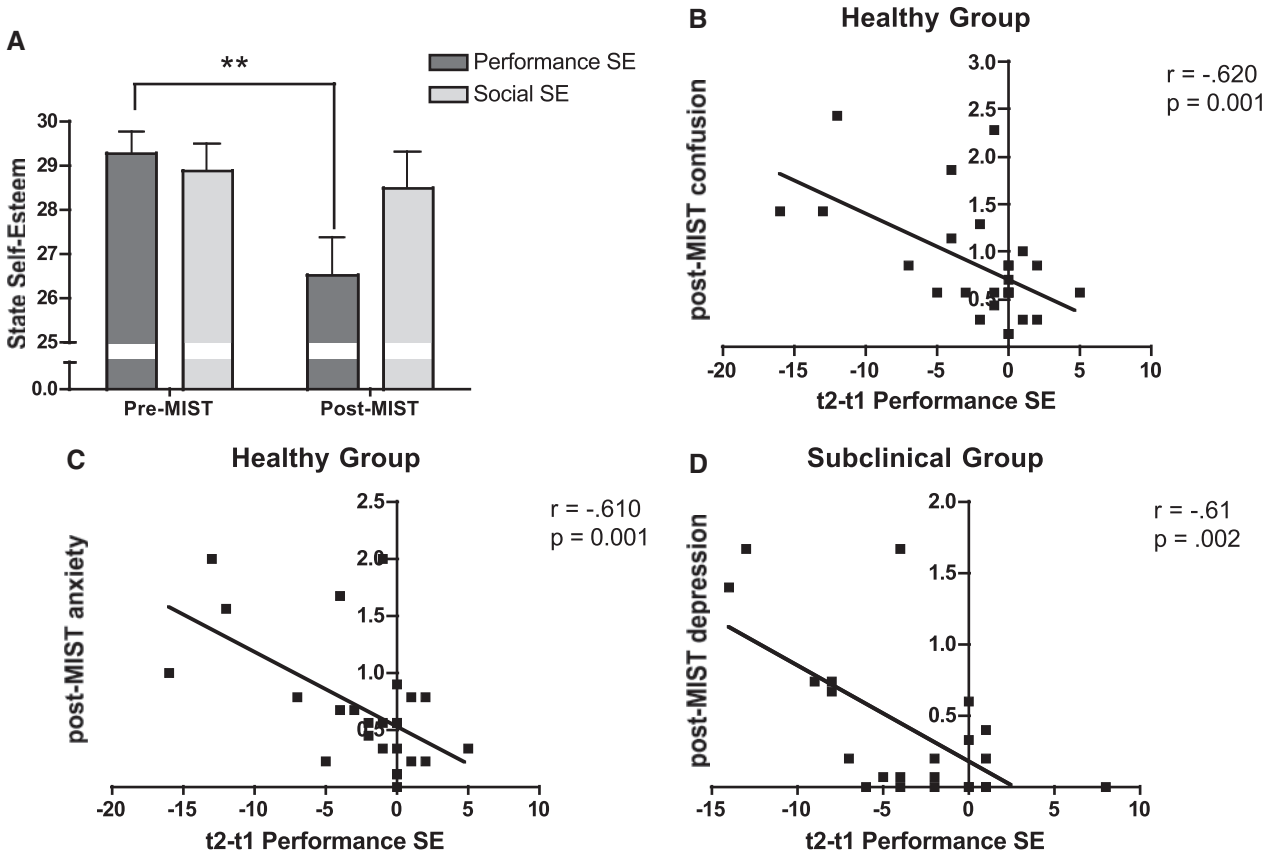

Fig. 2 Impact of social evaluative threat on performance self-esteem and its effect on mood following the MIST. (**A**) Significant decrease in performance self-esteem observed in the whole sample following the MIST. (**B**) Change in performance self-esteem associated confusion levels following the MIST in the healthy group. (**C**) Change in performance self-esteem associated with anxiety levels following the MIST in the healthy group. (**D**) Change in performance self-esteem associated with depression levels following the MIST in the subclinical group. $^{**}P < 0.001$.

interaction [$F(1,45) = 4.34$, $P = 0.043$], and decomposition of these effects can be found in the Supplementary Material.

Greater negative change in performance self-esteem is associated with higher anxiety levels in controls, but greater depression levels in subclinically depressed following the MIST

In addition, we assessed whether the change in performance self-esteem levels is associated with depression, anxiety, anger, fatigue or confusion levels either prior to the scan or post-MIST in each of the study groups. After controlling for multiple comparisons, partial correlations (controlling for gender) revealed associations with mood levels at post-MIST time point only. Specifically, the healthy group showed an inverse correlation between change in performance self-esteem and anxiety ($r = -0.610$, $P = 0.001$) and confusion levels ($r = -0.620$, $P = 0.001$) (Figure 2B and C). For the subclinical group, we found that the greater the decline in self-esteem, the higher the depression levels post-MIST ($r = -0.614$, $P = 0.002$) (Figure 2D).

Physiological data

The subclinical group shows lower overall cortisol levels during the modified MIST compared with healthy controls

We conducted a mixed design ANCOVA to examine change in cortisol levels specifically related to the MIST with the study group and sex as between variables. To make sure that any observed effects on cortisol are not due to the time of day of the testing and do not reflect any change in cortisol that may have occurred prior to onset of the MIST (e.g. entering the scanner or completing the attentional bias task; please see 'Methods' section), we entered the following variables as covariates in the analysis: the time of day of start of MIST, cortisol levels at the start of scan and cortisol levels following second run of attentional bias task {the groups did not differ on these first two cortisol samples [$F(1,45) = 1.04$, $P = 0.312$]}.

This analysis revealed a main effect of the group [$F(1,42) = 4.13$, $P = 0.048$], showing that the healthy group showed overall greater cortisol levels compared with the subclinical group (Figure 3). However, neither groups showed a typical cortisol stress response. Indeed, there were no main effects of time or any other two- or three-way interactions.

Montreal Imaging Stress Task results

Behavioral findings

MIST performance. We calculated percent correct performance (number of correct trials/total number of trials) for each condition and each run. A mixed design ANOVA with time (run 1 and run 2) and condition (control, exp_NS, exp_S) as within factors, and group and gender as between factors revealed a significant main effect of condition only [$F(1.12,50.45) = 22.24$, $P < 0.001$, GG corrected]. Simple main effects revealed that, as designed, performance during the control condition (91.7%) was better in comparison to exp_NS (52.6%) [$t(48) = 4.09$, $P < 0.001$] and exp_S condition (39.5%) [$t(48) = 4.98$, $P < 0.001$]. While the exp_S and exp_NS both induced failure, exp_S was associated with a significantly lower success rate compared to exp_NS [$t(48) = 4.34$, $P < 0.001$].

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Reaction times. A mixed design ANOVA with run (run 1 and run 2) and condition (control, exp_S, exp_NS) as within factors, and group and gender as between factors, revealed a main effect of run [$F(1,45) = 74.5$, $P < 0.001$, GG corrected], a run × gender interaction [$F(1,45) = 5.61$, $P = 0.02$, GG corrected], a main effect of condition [$F(2,50.8) = 54.3$, $P < 0.001$, GG corrected], a run × condition interaction [$F(1.47,66.05) = 14.5$, $P < 0.001$, GG corrected] and run × condition × group × gender interaction [$F(1.47,66.05) = 3.73$, $P = 0.042$, GG corrected] effect on reaction times.

We decomposed the run × condition × group × gender interaction to specifically assess whether there were any differences between groups or between conditions on all levels of other factors.

Simple main effects revealed that the subclinical males compared with healthy males had faster reaction times for the CTRL condition during the second run [$F(1,46) = 4.04$, $P = 0.05$]. There were no other significant group differences.

Furthermore, the simple main effects revealed a significant effect of condition at each level of group, gender and run (all Fs > 7, all $P < 0.001$). Simple *t*-tests assessing specifically the difference between reactions times during the ExpS and ExpNS conditions revealed that during the second run only, healthy men and women had slower reaction times during the ExpNS condition compared to Exp S condition [men: $t(10) = 2.19$, $P = 0.053$; women: $t(14) = 4.31$, $P = 0.001$]. In addition, subclinical males during both first and second run had slower reaction times for ExpNS compared to ExpS condition [run 1: $t(11) = 3.95$, $P = 0.002$; run 2: $t(11) = 7.21$, $P < 0.001$].

As previously mentioned, to account for differences in performance and reaction times between conditions, for fMRI analyses, these values were entered as parametric modulators at the first level and were controlled for. To control for any contribution of fatigue or anger in processing social evaluation, and to control for impact of gender, these variables (pre-MIST fatigue and anger levels, and gender) were included as covariates of no-interest in all contrasts at the second level.

fMRI findings

ROI analyses. The ROI analyses revealed activations in the left hippocampus and deactivations in the sgACC in the healthy group. Similarly, in the subclinical group, right hippocampus showed an increase in activity to ExpS > ExpNS, deactivations in the sgACC and deactivations in the right medial orbitofrontal cortex (Table 1). Analyses of the direct comparison between the healthy group and subclinical group did not reveal any differences within the *a priori* ROI regions. However, we observed a positive correlation between the mean depression *Z* score and change in activity in response to social evaluation in sgACC specifically (Table 2; Figure 4).

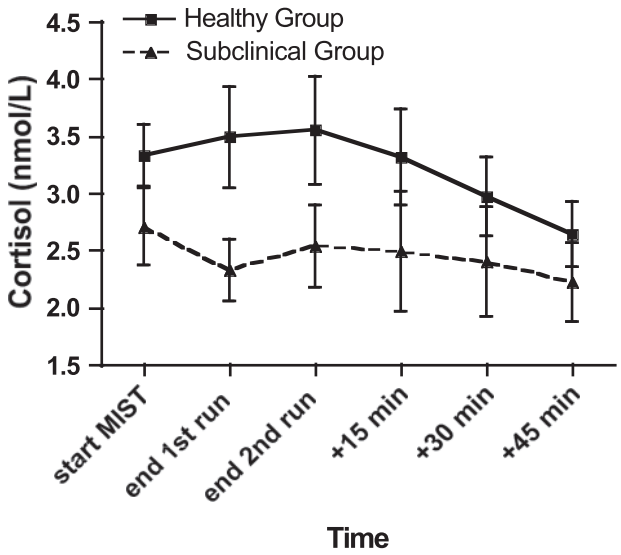

Fig. 3 Group differences with respect to cortisol response to the MIST. The subclinical group has an overall lower levels of cortisol compared with the healthy group during and following the MIST. However, neither group shows a significant cortisol response.

Whole-brain analyses. In the healthy group, whole-brain analysis revealed increased activity in response to negative feedback in a host of regions including the right posterior mid-temporal gyrus, right posterior and mid-cingulate cortex, right cuneus and insula, bilateral temporoparietal junction and cerebellum (Figure 5; Table 3). We also observed deactivations in the right lateral orbitofrontal cortex and right subgenual anterior cingulate.

In the subclinical group, the extent of activations was more constricted compared with the healthy. The activations were observed in the right precuneus and posterior cingulate, and cerebellum. Deactivations were found in the left subgenual anterior cingulate, left caudate and left nucleus accumbens (Figure 5; Table 3) in response to negative feedback compared with no evaluation.

Direct comparison between groups revealed greater activation in the healthy group compared with the subclinical group in several regions including the temporoparietal junction, right middle temporal gyrus, cuneus, thalamus and cerebellum, as well as right posterior cingulate (Figure 5; Table 4).

We also observed a positive correlation between mean depression score and changes in brain activity in response to social evaluation in the right sgACC and septal area (Table 5). No significant correlations were found in ROI analyses or whole brain with mean cortisol levels.

DISCUSSION

In this study, we focused on a sample of healthy individuals and those with subclinical depression to identify vulnerability patterns in psychological, physiological and neural responses to mild psychosocial challenge that may be present prior to the onset of clinical levels of

Table 1 ROI analyses reveal changes in brain activity in response to mild social evaluative threat in healthy and subclinical groups

	Anatomical region	*x*	*y*	*z*	*t*	*k*
Healthy group						
Activation	L hippocampus	−34	−32	−6	3.95	22
Deactivation	R sgACC	8	22	−6	4.88	110
Subclinical group						
Activation	R hippocampus	30	−36	4	4.54	31
Deactivation	R sgACC	6	20	−8	4.11	70
	R orbitofrontal cortex	4	36	−12	4.79	129

L, left; R, right; *x*, *y* and z, MNI coordinates; *t*, *t*-score at those coordinates (local maxima); *k*, cluster size (in voxels).

Table 2 ROI analyses reveal correlations between changes in brain activity in response to mild social evaluative threat and composite depression score in the study sample

	Anatomical region	*x*	*y*	*z*	*t*	*k*
All participants						
Positive correlation	R sgACC	8	26	−4	3.47	66

L, left; R, right; *x*, *y* and *z*, MNI coordinates; *t*, *t*-score at those coordinates (local maxima); *k*, cluster size (in voxels).

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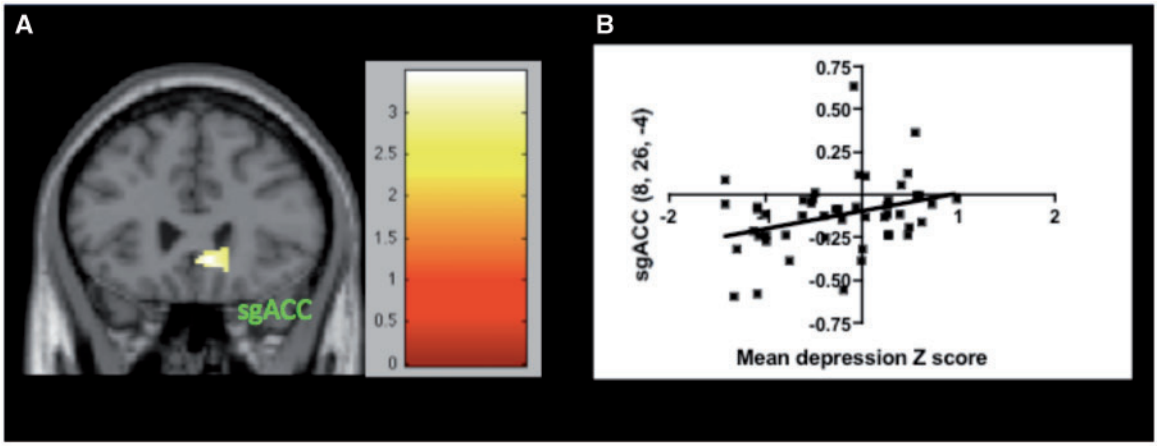

Fig. 4 Positive association between changes in the sgACC in response to social evaluation and depression levels in the whole sample. (**A**) ROI analyses of whole-brain correlational analyses revealed a positive correlation between changes in response to negative feedback in sgACC and levels of depression across the whole sample. Findings are thresholded at intensity threshold of $P < 0.005$, and extent threshold of 20 voxels. (**B**) Parameter estimates were extracted for the significant peak voxel (MNI coordinates $x = 8$, $y = 26$, $z = -4$) and entered into a graphing program to create graphs for illustrative purposes only.

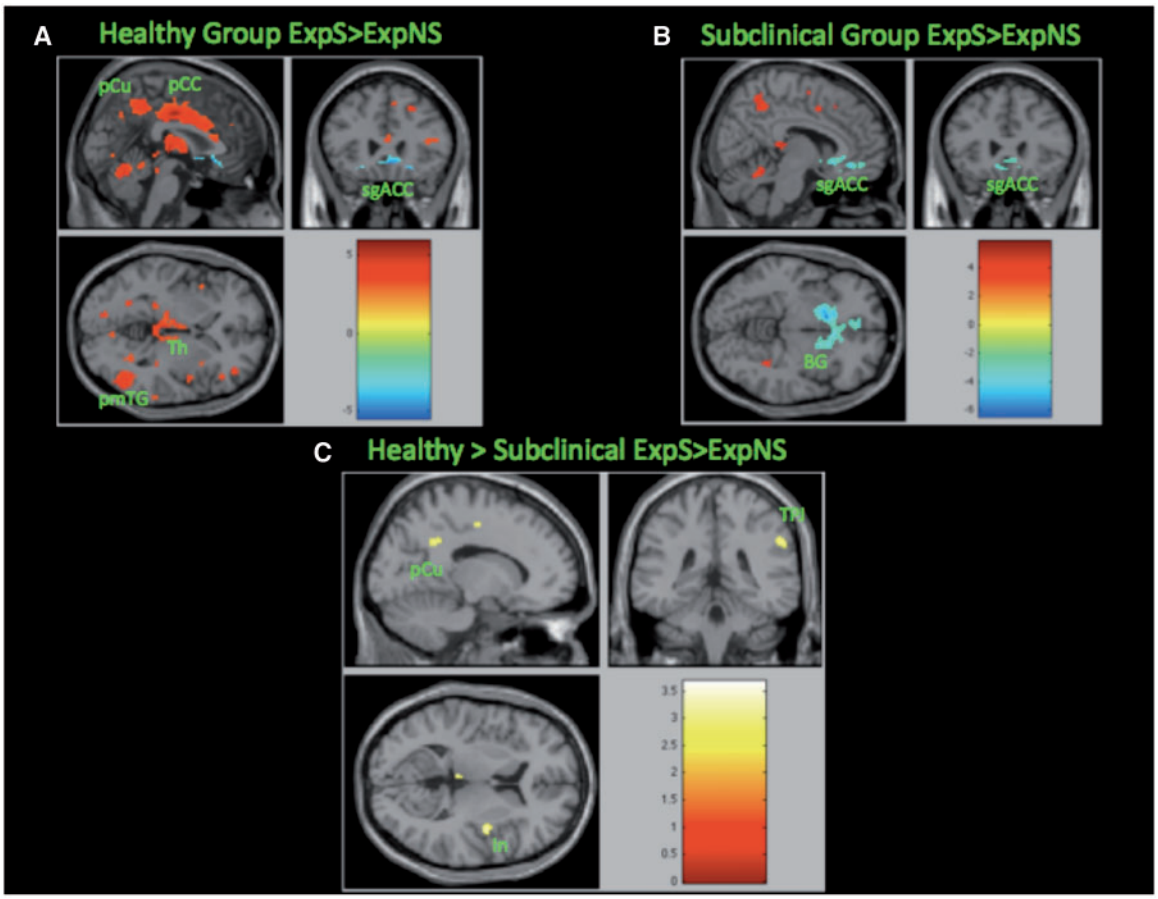

Fig. 5 Changes in brain activity in response to social evaluation in healthy and subclinical groups and healthy > subclinical direct contrast. (**A**) Whole-brain analyses in the healthy group for ExpS > ExpNS contrast revealed significant increase in precuneus (pCu), posterior cingulate (pCC), thalamus (Th) and posterior middle temporal gyrus (pmTG) and decreases in sgACC. (**B**) Whole-brain analyses in the subclinical group for ExpS > ExpNS contrast revealed significant increase in pCu and decreases in sgACC. (**C**) Direct comparison between the groups revealed primarily greater activations in healthy group in regions such as pCu, temporoparietal junction (TPJ) and insula (In). All clusters are thresholded at intensity threshold of $P < 0.005$, extent threshold of 20 voxels. ExpS, experimental stress; ExpNS, experimental non-stress.

depression. We observed that while all subjects integrated the evaluative negative feedback on their performance and showed reduction in performance self-esteem, only in the subclinical participants was this lowering of performance self-esteem associated with increased depression levels following the modified MIST; in the healthy, it was associated with increased levels of anxiety and confusion. The subclinical group showed overall reduced cortisol levels over the course of the MIST compared with the healthy group; however, none of the groups showed a typical cortisol stress response. Furthermore, the subclinically depressed group recruited select cingulate and parietal regions in

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Table 3 Whole-brain activation and deactivations in response to mild social evaluative threat in healthy and subclinical groups

	Anatomical region	x	y	z	t	k
Healthy group						
Activation	R posterior middle temporal gyrus	50	−62	8	5.82	2733[1]
	R temporoparietal junction	62	−40	28	4.68	2733[1]
	R cuneus	22	−90	16	4.42	2733[1]
	R posterior cingulate cortex	0	−12	40	5.78	3077[2]
	L mid-cingulate cortex	−4	2	32	5.38	3077[2]
	thalamus	2	−20	4	5.49	1397
	R anterior insula	34	16	16	5.37	367
	R lingual gyrus	26	−56	−4	4.27	1460[3]
	R cerebellum	4	−62	−18	4.53	1460[3]
	L posterior middle temporal gyrus	−38	−62	16	4.33	636[4]
	L temporoparietal junction	−48	−52	24	3.99	636[4]
	L precentral gyrus	−38	−26	44	4.31	432[5]
	L postcentral gyrus	−36	−36	48	4.03	432[5]
Deactivation	R lateral orbitofrontal gyrus	20	30	−14	5.39	344[6]
	R sgACC	8	22	−6	4.88	344[6]
Subclinical group						
Activation	R precuneus	10	−54	50	5.18	225
	R posterior middle temporal gyrus	46	−68	6	4.83	146
	R cerebellum	6	−50	−16	5.25	145[7]
	L cerebellum	−4	−46	−16	3.77	145[7]
Deactivation	L sgACC	−10	32	−14	5.09	1109[8]
	L caudate	−12	20	2	5.54	1109[8]
	L nucleus accumbens	−12	14	−8	6.40	1109[8]

L, left; R, right; *x*, *y* and *z*, MNI coordinates; *t*, *t*-score at those coordinates (local maxima); *k*, cluster size (in voxels), regions with *k*s that share a superscript originate from the same cluster.

Table 4 Whole-brain activation in response to mild social evaluative threat in the healthy group compared to the subclinical group

	Anatomical region	x	y	z	t	k
Healthy > subclinical						
Activation	L temporoparietal junction	−46	−52	24	3.34	35
	L superior frontal gyrus	−16	−12	48	3.34	24
	R posterior cingulate cortex	18	−22	40	3.30	31
	L postcentral gyrus	−36	−34	48	3.16	23
	R temporoparietal junction	58	−40	32	3.04	40
	Cuneus	−2	−84	24	3.03	38
	L precentral gyrus	38	−20	40	3.02	32
	L cerebellum	−8	−52	−36	3.68	50
	R lingual	26	−58	−2	3.58	62
	R middle temporal gyrus	58	−28	−14	3.57	30
	R posterior insula	40	−6	10	3.44	40
	Thalamus	−6	−28	4	3.34	81

L, left; R, right; *x*, *y* and *z*, MNI coordinates; *t*, *t*-score at those coordinates (local maxima); *k*, cluster size (in voxels).

Table 5 Whole-brain analyses reveal correlations between changes in brain activity in response to mild social evaluative threat and composite depression score in the study sample

	Anatomical region	x	y	z	t	k
All participants						
Positive correlation	R sgACC	8	26	−4	3.47	76
	Septal area	2	10	−4	3.32	27

L, left; R, right; *x*, *y* and *z*, MNI coordinates; *t*, *t*-score at those coordinates (local maxima); *k*, cluster size (in voxels).

response to ExpS > ExpNS contrast to a lower degree than the healthy group. Finally, in the whole sample, there was a positive association with depression levels and changes in deactivation within sgACC in response to processing social evaluative feedback compared to no feedback. This is the first study, to our knowledge, to investigate psychological, endocrine and neural correlates of social evaluative threat and depression in a sample showing subclinical levels of depression.

Impact of negative performance feedback on state performance self-esteem, mood *and cortisol levels*

Social evaluative threat during the MIST in this study was strong enough to elicit a decline in performance self-esteem in all subjects, yet mild enough to not lead to a significant cortisol response. As such, the task may have inadvertently modeled a situation that is common in daily life, such as, for example, receiving a bad grade on a midterm. Indeed, previous studies have shown that students, upon receiving feedback on their performance (receiving a grade), experience a significant dip in performance self-esteem without a change observed in their social self-esteem (Heatherton and Polivy, 1991). Importantly, in this study, we found that this decline in performance self-esteem in response to negative performance feedback has a differential impact on mood in the healthy and the subclinical groups. A decline in performance self-esteem was associated with an increase in anxiety in healthy, but an increase in depression levels in the subclinical group following the MIST specifically. Counter to our hypotheses, these results suggest that individuals who are at heightened risk for developing depression do not necessarily show heightened psychological response to a mild negative feedback; rather, in this population, this response has important repercussions on their mood following the challenge.

Overall, the findings related to decline in performance self-esteem in response to negative feedback suggest that, at the psychological level, the subclinical group shows a maladaptive mood response to internalizing negative feedback, and this may be one way that mild negative experiences perpetuate and maintain heightened depression levels in a subclinical sample.

Despite the absence of a significant cortisol stress response in the healthy group, we found evidence of lower cortisol levels overall in the subclinical group compared with the healthy group during the course of the MIST session. The group differences observed may possibly reflect (i) different circadian decline in each group, (ii) a possibility that the exposure to the scanner may have challenged the HPA axis during the first part of the scanning period, subsequently diminishing HPA response to threat during the MIST, (iii) something that is intrinsically different between these groups in how the HPA system dealt with mild forms of social evaluative feedback. A case can be made for the latter possibility.

The group differences in the overall cortisol output during the MIST were significant while controlling for both the two initial cortisol samples, as well as the time of day of testing for the MIST (controlling for points 1 and 2 above). In addition, previous studies on depression and cortisol circadian rhythm suggest that depressed people typically show an *increased* cortisol output in the later afternoon compared to healthy subjects (Knorr *et al.*, 2010), while another study investigating effects of MRI scanning on cortisol in healthy and depressed participants did not find any group differences (Peters *et al.*, 2011). Furthermore, we have previously observed a blunted cortisol response to the natural challenge of awakening in the subclinical group compared with the healthy group (Dedovic *et al.*, 2010), i.e. subjects showed a pattern of cortisol response to awakening that is similar to how they responded to social evaluative threat. Thus, in conjunction with these previous results, the present endocrine findings are suggestive of a hypoactive

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HPA axis in the subclinical group in response to a mild psychological stressor.

This result extends the findings from the studies of clinically depressed populations that also showed a blunted cortisol response to laboratory psychological stressors as well as daily life stressors in the depressed patient populations compared with controls (reviewed in Burke *et al.*, 2005; Handwerger, 2009). The present data suggest that a blunted cortisol output during the mild psychosocial evaluative task seems to be present prior to onset of clinical depression and may represent a vulnerability factor. This interpretation is further supported by findings from a recent study in healthy students which showed that greater trait depressive rumination was associated with a more blunted cortisol response in the condition with social evaluation present (Zoccola *et al.*, 2008). In addition, a recent study from our group has shown that participants who scored low on maternal care had a blunted cortisol response to Trier Social Stress task (TSST) compared to medium and high maternal care individuals; low maternal care participants also had greater depression scores (Engert *et al.*, 2010).

One question that arises from these findings is why there was the blunted cortisol output observed in the subclinical group? Given that the subclinical group reported greater levels of chronic stress compared to the controls (Dedovic *et al.*, 2010), one explanation could be that the blunted response reflects exhaustion of the regulatory mechanisms of the HPA axis over time (Hellhammer and Wade, 1993; Fries *et al.*, 2005). It has been suggested that blunted HPA axis activity may occur following an extensive period of hyperactivity, as in situations of chronic stress (Heim *et al.*, 2000). After such a period, the system will then either become non-responsive or may over-adjust (Fries *et al.*, 2005).

Finally, the lack of cortisol response in the healthy group suggests that a certain threshold may need to be passed with respect to the intensity of the social evaluative threat in order for an increase in cortisol or decrease in social self-esteem to be observed. Studies examining the TSST (Kirschbaum *et al.*, 1993) and manipulating levels of social evaluation have suggested this pattern of response regarding cortisol (e.g. Andrews *et al.*, 2007; Dickerson *et al.*, 2008). However, experiencing social evaluative feedback that is below such a threshold may still have impact on one's health. For example, a few studies have proposed that even if a cortisol response is not significantly increased in response to psychological stress, but is still significantly different from a typical circadian decline (which we did not assess in this study; see 'Limitations' section), this might carry important implications for one's well-being (Lovallo *et al.*, 2010; Wolfram *et al.*, 2012).

Overall, the findings related to cortisol output during the modified MIST suggest that the subclinically depressed already show a pattern of response consistent with a hypoactive HPA axis, which has been previously seen in clinical samples. In addition, even when social evaluative threat is so mild that it does not lead to significant cortisol increase in the healthy (nor the subclinically depressed), the impact on the participants' psychological well-being is still significant, and potentially relevant for development of certain psychopathologies. Intricacies of these associations should be investigated in future studies.

Neural correlates of social evaluative threat

In the healthy group, whole-brain analyses revealed activations in areas previously associated with mentalizing, theory of mind (e.g. Saxe and Kanwisher, 2003), inferences of social intentions (Decety and Grezes, 2006; Ciaramidaro *et al.*, 2007) and attentional reorienting (Decety and Lamm, 2007; Cacioppo *et al.*, 2009). Given that the negative feedback is based on performance of the subject and they are able to see how this performance is matching up to that of an average user (Figure 1), activation of these regions in processing of negative feedback is in line with their previously identified functions. No such areas were found in the subclinical group, suggesting perhaps an already compromised recruitment of higher order regions when processing social evaluative threat.

In contrast to previous findings, ROI analyses revealed activation in the hippocampal region in both the healthy group and the subclinical group. Previous studies from our laboratory have consistently found deactivation in the hippocampus in those participants who showed increased cortisol stress response to social evaluative threat; we had proposed that deactivation of the hippocampus, a region involved in the regulation of the HPA axis, may lead to a release of negative feedback on the HPA axis, thus contributing to subsequent release of cortisol (Pruessner *et al.*, 2008; Dedovic *et al.*, 2009a). In this study, given that both groups did not show increase in cortisol response, activation in hippocampus may thus represent heightened regulation of the HPA axis in response to a mild negative evaluative feedback, thus providing indirect confirmation of its regulatory role. Furthermore, the ROI analyses revealed deactivation in the medial orbitofrontal region in the subclinical group in response to social evaluative threat. We had previously proposed that the medial orbitofrontal cortex might play a role in initial stress perception and preservation of the stress response (Dedovic *et al.*, 2009b). Deactivation observed here without the presence of a cortisol stress response could suggest that perhaps the change in signal may need to pass a certain threshold to trigger the regulatory cascade that would allow for the significant increase in cortisol levels.

In both the control and the subclinical group, we observed deactivation of the sgACC in response to negative performance evaluation compared with no evaluation condition. Furthermore, in the whole sample, we observed an association with change in levels of deactivation in sgACC and depression severity, showing that the greater the depression severity, the lower the deactivation in sgACC in response to negative evaluation. This finding would suggest that it is adaptive to deactivate sgACC, and maladaptive to show activations in sgACC in response to negative feedback.

These findings are in accordance with the literature showing that increased cerebral blood flow in sgACC is associated with clinical depression (Drevets *et al.*, 2008), and correlates with induced sadness in healthy people (Mayberg *et al.*, 1999); resolution of clinical depression leads to decreases in activity in sgACC (Mayberg *et al.*, 2000). In addition, several models of emotion and mood regulation suggest that there is a disruption of balance between prefrontal regulatory areas and limbic reactive areas in depression (Mayberg, 1997; Phillips *et al.*, 2008; Disner *et al.*, 2011). Specifically, hyperactivity in limbic system (particularly sgACC) and hypoactivity of the higher order cognitive regions is a landmark of depression. Factors that disrupt the balance of the prefrontal-limbic circuit may pose particular vulnerability for depression.

In this study, healthy participants recruited both higher order areas as well as limbic system areas in response to mild negative social evaluation. The subclinical group however did not show such a pattern, suggesting that not only do they show less deactivation in sgACC to negative feedback, their 'line of defense' in higher order brain regions may also be limited. The overall association between depression severity and change in activation in sgACC replicated previous findings from Masten *et al.* (2011); although in that study, the authors observed that greater activation of sgACC in response to exclusion compared with inclusion was associated with greater depression levels in a group of adolescents. Given that brain development and maturation includes periods of time when great changes take place (Johnson, 2001; Andersen, 2003; Gogtay *et al.*, 2004)—and one such period is adolescence—it may be possible that while the overall association between depression severity and changes in the sgACC in response to evaluation

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or rejection remain similar over time, the nature of change (less deactivation *vs* more activation) might be specific to a developmental stage. A longitudinal study would be needed to assess this hypothesis.

There are other studies that have found differing effects in the sgACC. For example, a study found that people with higher levels of rejection sensitivity showed greater deactivation in sgACC in response to viewing a dissatisfied facial expression compared to a fixation (Burklund *et al.*, 2007), while another study reported that the greater the activation in this area to negative compared to neutral pictures from IAPS is associated with greater psychological well-being (van Reekum *et al.*, 2007). However, what might be an important difference in these studies compared to the present study is that the feedback presented in the present study is explicitly related to self, whereas a dissatisfied face or a negative image, while ecologically valid, are less self-relevant stimuli.

Overall, these findings suggest that when considering the intricate interplay that exists between psychological stress and onset of depression, sgACC may be an important player: sgACC underlies processing of information regarding negative performance feedback and degree of its deactivation in response to negative feedback tracks with levels of depression. This association suggests that interventions such as neurofeedback involving real-time fMRI may not only be helpful in improving one's mood (Weiskopf, 2012) but may also have beneficial effects on how one processes mild negative performance feedback. Future studies should evaluate this hypothesis further.

Limitations

This study suffers from several limitations. First, the fact that the modified MIST failed to induce a clear stress response in the healthy group limits the interpretation of group differences with respect to cortisol output. The apparent lack of cortisol stress response may be due to the changes we brought into the task. We have modified the original MIST to introduce an experimental/non-stress condition that would be exactly the same with respect to mental arithmetic and time-limit imposition as the experimental/stress condition, except for the presence of evaluative components. This, in addition to the control condition, which now contained easy math and ample time to respond, had amounted to a much longer period of time (total 5.93 min/run) during which the subjects were exposed to what they knew as the 'safe condition' compared to the evaluative condition (total 2.37 min/run). These changes have inadvertently created a task that is strong enough to elicit significant changes in state self-esteem and mood, but perhaps too mild to result in a significant increase in cortisol response. An ideal control for such a task with respect to cortisol output would involve an additional control day where subjects would come in at the same time of the day as during the stress session, but would just be required to rest. Such a control session would allow for an assessment of a pure circadian cortisol decline. As previously mentioned, studies have suggested that a non-significant cortisol stress response that is nevertheless significantly different from a typical circadian decline in cortisol might still have important implications for one's well-being (Lovallo *et al.*, 2010; Wolfram *et al.*, 2012). This should be examined in future studies. In addition, such a control session would also allow one to experimentally determine that the changes in performance self-esteem in response to the MIST are not attributable to fatigue or other characteristics of the experimental design; in this study, we account for these characteristics by statistically controlling for these in analyses.

Furthermore, cortisol levels were assessed in between each run, rather than between each condition block over the course of the scan. It is therefore possible that we might have missed some indices of interindividual variability in cortisol reactivity (Engert *et al.*, 2013) that would have revealed an additional group × time interaction. Future studies may consider sampling blood over the course of the scan to obtain total levels of cortisol, in addition to sampling saliva for free cortisol levels between each run.

Another factor that has to be addressed when considering the ExpS and ExpNS conditions is the perception of presence of social evaluation in the ExpS condition *vs* lack thereof in the ExpNS condition. While in another study in our laboratory we have established that the two conditions are perceived as different on this dimension in healthy student population (Duchesne *et al.*, submitted) (Supplementary Material), we have not assessed this aspect specifically in the current sample. Nevertheless, both the healthy and the subclinical sample are drawn from the same student population as the previous study and they also represent highly functional, university-educated individuals; it is unlikely that the participants in this study would have issues perceiving presence of evaluative components in the ExpS condition compared with the ExpNS condition.

Women in the sample were quite diverse with respect to menstrual cycle phase. Previous studies have shown that menstrual cycle and oral contraceptive usage can influence cortisol response to stress (Kudielka and Kirschbaum, 2005). However, the study groups were relatively evenly matched with respect to number of women using oral contraceptives and those in each menstrual cycle phase. Therefore, it is unlikely that the group differences observed were influenced by the diversity of menstrual cycle phase in women within this sample.

Finally, this is a population of university students and thus might differ from general population in terms of their response to academic failure; they might have higher performance self-esteem but their self-esteem might also be particularly sensitive to academic failure. A replication study with community sample of young adults with subclinical depression could address this limitation.

CONCLUSION

This is the first study to characterize psychological, endocrine and neural responses to a mild negative social evaluation in a sample of healthy individuals and those with subclinical levels of depression. Investigating these factors in subclinical populations is essential for better understanding the ways in which dysregulation of specific physiological, emotional and cognitive processes may represent a vulnerability for specific forms of psychopathology and revealing important targets for therapeutic interventions.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

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