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Distinct but overlapping neural networks subserve depression and insecure attachment

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Insecure attachment has been linked to depression and to outcome in psychotherapy. The neural mechanisms subserving the relationship between attachment security and depression are not well understood. We have developed a method to examine attachment-related brain activity in depression. Twenty-eight women, half depressed, viewed images of their mother, a female friend, and female strangers during fMRI scanning. The effects of depression and insecure attachment were determined with whole-brain multiple linear regression of blood-oxygen-level-dependent response against subjects' Beck Depression Inventory and Adult Attachment Interview (AAI) coherence of mind scores. Interaction effects were analyzed with ANOVA. Activity associated with depression and with insecure attachment was found in the cortico-striato-thalamic circuits of affect regulation. For early attachment (mother–friend contrast), depression scores correlated with activation of cortical and sub-cortical components of these circuits, while attachment insecurity correlated with sub-cortical activity in the same circuitry. Depression and attachment insecurity correlated with both cortical and sub-cortical activities for mother–stranger, and areas of overlap and of enhancing interactions between depression and insecure attachment were found. For late attachment (friend–stranger contrast), only cortical effects were found. Depression and attachment insecurity may be subserved by similar but distinct components of affect regulating circuits. Their interactions may explain the greater difficulty of treating depression in insecurely attached patients and suggest a contributing role for insecure attachment in depression. Further, differential sub-cortical *vs* cortical encoding of early *vs* late attachment suggests a top-down model of late attachment, potentially relevant to psychotherapeutic outcome.

Keywords: depression; attachment; attachment security; insecure attachment; AAI; mother

INTRODUCTION

Depression and insecure attachment are linked

Depression is a leading cause of morbidity and mortality worldwide; however, our understanding of its etiology remains incomplete (Greenberg *et al.*, 2003; Mathers and Loncar, 2006; Moussavi *et al.*, 2007). Growing evidence has linked failures in early attachment experience to depression (Oakley-Browne *et al.*, 1995; Agid *et al.*, 1999; Kendler *et al.*, 2002; Edwards *et al.*, 2003; Heim *et al.*, 2004; Anda *et al.*, 2006). In animals, separation and neglect result in changes to gene transcription in limbic and paralimbic structures correlating with alterations in behavior and stress reactivity (Ladd *et al.*, 2000; Meaney, 2001). In humans, dysregulation in similar paralimbic cortical regions differentiates depressed from non-depressed subjects (Mayberg, 2003), and linkage between insecure attachment and depression in humans may likewise be related to developmental processes affecting these regions.

Indeed, a causal role for insecure attachment in the development of depression has been proposed (Selcuk and Gillath 2009). Attachment style and security are thought to be relatively stable characteristics that develop in infancy and describe a working model of others and their response to one's distress (Wallin, 2007). Depression, on the other hand is an episodic syndrome of depressed mood, negative affect, negative cognitions/cognitive bias and withdrawal behavior, which may be provoked by life events, such as loss of an attachment figure, or occur spontaneously (Levitan *et al.*, 2009; American Psychiatric Association, 2000). Linkage between depression and attachment style is suggested both by correlations of specific attachment styles with personality disorders comorbid with depression, and by linkage of attachment insecurity to specific depressive symptoms (Brennan and Shaver, 1998; Crawford *et al.*, 2006; Levitan *et al.*, 2009). Nonetheless, our understanding of the

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relationship between attachment insecurity and depression and of the mechanisms underlying the observed linkage remains incomplete (Selcuk and Gillath, 2009).

Linkage of depression and insecure attachment may impact treatment

Understanding how insecure attachment affects depression could have significant treatment implications for psychotherapy. For example, psychotherapy can induce change in attachment style toward greater security, and such change has been linked to therapeutic outcome (Fonagy *et al.*, 1996; Levy *et al.*, 2006; Toth *et al.*, 2006), yet treatment of depression in insecurely attached patients is more difficult (Ciechanowski *et al.*, 2003; Levy *et al.*, 2011).

So, while psychotherapy can be at least as effective as pharmacotherapy (DeRubeis *et al.*, 2005; Miklowitz *et al.*, 2007; Thase *et al.*, 2007), outcome is significantly dependent on individual patient–therapist interactions, which in turn derive from attachment relations between patient and therapist, and thus on their attachment style and security (Safran and Muran, 2000; Bruck *et al.*, 2006; Karver *et al.*, 2006). In fact, two elements central to the psychotherapeutic process—transference and corrective emotional experience – may be significantly affected by attachment style and security (Wallin, 2007). Thus, ultimately, psychotherapeutic efficacy may be improved by understanding the neural networks subserving insecure attachment in depressed subjects and the interactions between insecure attachment and depression.

The neural mechanisms underlying the link between depression and insecure attachment have not been fully explored

Functional neuroimaging is a powerful method used to elucidate neural networks subserving complex emotional phenomena in humans. However, the neural relations between attachment and depression have just begun to be explored (Moses-Kolko *et al.*, 2010), and no study has yet examined the neural correlates of the interaction between insecure attachment and depression in adults. To date, studies examining the neural correlates of adult attachment have focused on healthy subjects' response to their own or others' children or romantic partners (Bartels and Zeki, 2004; Aron *et al.*, 2005; Strathearn *et al.*, 2008, 2009), or healthy and borderline personality disordered adults' responses to the Adult Attachment Projective (Buchheim *et al.*, 2008).

Neural correlates of non-depressed mothers' attachment responses to their infants under non-stress conditions have been reported in orbito-frontal cortex (OFC) (Nitschke *et al.*, 2004; Noriuchi *et al.*, 2008) and in nigro-striatal circuitry, in association with positive attachment responses and attachment security (Bartels and Zeki, 2004; Noriuchi *et al.*, 2008; Strathearn *et al.*, 2008, 2009). Neural correlates of mothers' attachment responses to their infants in distress have been reported in orbito-lateral and medial PFC structures, caudate nucleus and thalamus, as well as posterior superior temporal sulcus, posterior cingulate and substantia nigra (Lorberbaum *et al.*, 1999; Leibenluft *et al.*, 2004; Noriuchi *et al.*, 2008; Strathearn *et al.*, 2009). Just one study (Ramasubbu *et al.*, 2007) has examined adult healthy subjects' responses to their own mothers' faces, which might be most relevant to psychotherapeutic processes of transference and corrective emotional experience (Lewis, 1998; Kernberg *et al.*, 2008).

Other relevant neuroimaging studies, also in euthymic subjects, examined relationships between attachment style and affective response. In these studies, insecure attachment styles associated with increased limbic response to negative affect (Gillath *et al.*, 2005; Lemche *et al.*, 2006; Vrticka *et al.*, 2008). In contrast, insecure avoidant attachment style was linked to decreased striatal reactivity to reward and decreased lateral prefrontal cortex (PFC) and subgenual anterior cingulate deactivation in response to negative affect (Gillath *et al.*, 2005; Vrticka *et al.*, 2008).

Goals of the present study

In this context, we aimed to develop and test an fMRI method that examines the neural correlates of insecure attachment in subjects with depression. Further, as both early and late attachment relations can have significant bearing on depression, the psychotherapeutic process and its outcome (Lewis 1998; Wallin, 2007; Kernberg *et al.*, 2008), our method examined neural responses to both mother (early attachment figure) and close friend (late attachment figure).

We proposed and tested three hypotheses in this study.

(i) Depression and insecure attachment will be subserved by distinct but overlapping neural networks previously identified in studies of depression (Price and Drevets, 2010) and mothers' affective responses to infants (Lorberbaum *et al.*, 1999; Leibenluft *et al.*, 2004; Noriuchi *et al.*, 2008; Strathearn *et al.*, 2009). We expect the overlap (indicating additive effects) in the cortico-striato-thalamic circuitry of affect regulation. We expect greater associations between OFC activity and attachment, and greater associations between inferior ACG activity and depression.

(ii) Interaction effects between depression and insecure attachment will be found in the cortico-striato-thalamic circuitry of affect regulation in addition to the additive effects posited for depression and attachment security in the areas of overlap. Specifically, as distress activates the attachment system, we predict that mother images, acting as early-attachment cues, would induce reciprocally increased activity in the striatum (Strathearn *et al.*, 2009) with increased approach regulating activity in the OFC (Roelofs *et al.*, 2009) in insecurely attached subjects.

(iii) Attachment-associated activations due to mother *vs* close friend (early *vs* late attachment figure) will differ in depressed subjects, as has been reported in healthy subjects (Ramasubbu *et al.*, 2007). Specifically, as early attachment formation appears to be mediated by close physical contact involved in physical care during infancy, while non-romantic late attachment relationships tend to be formed more through verbal interaction under conditions of much greater independence (Wallin, 2007), we predict that mother-associated brain activity will have a stronger sub-cortical component than friend-associated brain activity.

To test these hypotheses, we measured healthy and depressed subjects' blood oxygenation-level-dependent (BOLD) responses to pictures of their mothers' and close female friends' faces contrasted with images of female strangers, regressing brain activity against measures of depression and attachment security.

METHODS

Participants

The study was approved by the Beth Israel Medical Center Institutional Review Board. All participants signed the informed consent.

Depressed and healthy participants were recruited through Craigslist advertisements, and screened by telephone and then in person by trained researchers. To ensure adequate recruitment of subjects with living mothers and to minimize major demographic variability in our sample, we limited recruitment to females aged 18–30 years.

Other inclusion criteria were as follows:

(i) Right-handed;
(ii) able to understand and sign the informed consent
(iii) raised (birth to at least 14 years old) in a household with their biological mother
(iv) mother living and able to provide recent photographs
(v) fluency in English, and normal or corrected to normal visual acuity
(vi) for depressed subjects, current depression defined by the Mini-International Neuropsychiatric Interview.

Exclusion criteria were as follows:

(i) current and lifetime substance abuse;
(ii) history of head trauma or mental retardation
(iii) history of Schizophrenia, Schizoaffective Disorder, OCD, or serious medical illness;
(iv) use of psychotropic medications: current or past year (depressed); lifetime (controls);
(v) acute suicidality.

Instruments and subject evaluations

The Mini-International Neuropsychiatric Interview (MINI), a short, structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders, was used to establish subjects' clinical diagnosis of depression (Sheehan *et al.*, 1998).

The Beck Depression Inventory II (BDI-II) was used to assess depression. Scores of 14–19 are considered mild, 20–28 moderate and 29–63 severe depression (Beck *et al.*, 1996). Attachment security was assessed with the Adult Attachment Interview (AAI). The AAI is a structured semi-clinical interview focusing upon early attachment experiences and their effects. From these interviews, the Coherence of Mind index is derived as a measure of attachment security with values ranging from 1 to 9. Scores (henceforth referred to as 'AAI scores') 6–9 indicate secure attachment, scores 1–3 indicate insecure attachment and scores 4–5 are indeterminate (George *et al.*, 1996). AAI interviews were administered, audiotaped and transcribed by trained research assistants (George and West, 2001). The transcripts were scored by trained and certified raters (Bakermans-Kranenburga and van Ijzendoorn, 1993).

Recruitment and evaluation procedure

Of 47 depressed women responding to our advertisement for depressed subjects, 21 passed the telephone screen for inclusion/exclusion criteria and were interviewed onsite. Of these, 14 depressed subjects met inclusion criteria and successfully underwent the complete fMRI scanning procedure.

Of 64 women who responded to our advertisement for control subjects, 36 passed the telephone screen and were interviewed on site. Fifteen were determined to be without current or lifetime psychiatric disorder, met inclusion/exclusion criteria and underwent the fMRI scanning procedure. One subject was excluded due to excessive movement (>5 mm) in scanning.

All MINI evaluations were conducted in the research office at the Beth Israel Medical Center 1–4 weeks prior to the scan. AAI and BDI were administered on the morning of the scan at the Hatch Imaging Center at Columbia Presbyterian Medical Center.

Stimuli

Stimuli were color photographs of the subject's mother (M), a close female friend (F) and two strangers, one age matched to the mother and the other to the friend (S1 and S2). The subject selected the photographs (straight on and shoulders up, taken within the past year) as most characteristic of the person being represented. Stranger photographs were selected from other subjects' mother and friend photographs. Four different photographs of each person were provided. Facial expressions ranged from neutral to smiling. All images were processed using Photoshop to conform to approximately uniform head size, brightness and contrast, and backgrounds were blacked-out.

Scanning procedure

There were four 12.6-min fMRI scans per subject. Each scan consisted of three blocks. For each block, one of three tasks was defined for the subject with a written prompt. At the beginning of each block, this prompt was shown for 10 s. The prompts were as follows: 'How much can you relate to this picture?' (Salience block), 'How pleasant do you feel when you look at this picture?' (Valence block) and 'Press any button when you see the picture' (Neutral block). Each block consisted of 16 trials, with a picture viewed through goggles for 4 s followed by a fixation cross shown for 10 s. While each picture was viewed, subjects used their right hands to rate the viewed picture according to the prompt on a 1–4 Likert scale by a recorded button-press. Both type of picture and sequence of task were pseudo-randomized.

Image acquisition

Scanning was performed on a Philips Intera 3 T scanner using a Philips SENSE head coil. To measure the blood oxygenation-level dependent (BOLD) signal, whole-brain functional scans were acquired parallel to the AC-PC line (gradient echo EPI, TR/TE = 2 s/25 ms, 77° flip angle). Voxel size was $2 \times 2 \times 3$ mm. Following the functional scans, a T1-weighted high-resolution structural scan was acquired.

fMRI data analysis

Functional data were preprocessed and analyzed with FSL (FMRIB Software Library). Data were first corrected for motion. Motion correction parameters and global average of the BOLD for white matter were entered as covariates to control for movement and global BOLD signal fluctuation. Images were smoothed with a 9-mm FWHM Gaussian kernel. Individual data were then co-registered to the standard Montreal Neurological Institute (MNI) template. There were three event-related models, viewing the picture of the mother (M), the friend (F) and both strangers (S), respectively. Exposure to mother images was intended to elicit mother-associated brain activity, including early-attachment representations. Exposure to friend images was intended to elicit friend-associated brain activity, including late-attachment representations, and to serve as a control for familiarity *vs* mother images. Finally, exposure to stranger images was used as a control female face processing. For this report, the data for relatedness, valence and neutral tasks were combined. Models were convolved with the canonical hemodynamic response function. The data for each subject were averaged using fixed effects analysis, and group analysis was done using mixed effects analysis (Smith *et al.*, 2004; Woolrich *et al.*, 2009).

Three contrasts, mother *vs* friend (M–F), mother *vs* strangers (M–S) and friend *vs* strangers (F–S) were carried to high-level analyses. M–F contrast was interpreted as a measure of mother response, controlled for familiarity. M–S and F–S contrasts were interpreted as measures of mother and friend responses, respectively, controlled for female face viewing. Control for familiarity in F-S late attachment response was thus obtained by comparison with M-S and reference to the published literature. The threshold determining significant activity was absolute Z-score >2.32 ($P < 0.01$) for activation maps, corrected for multiple comparisons by removal of false positive voxels using a $3 \times 3 \times 3$ mm Gaussian filter applied to the Z-score image, which provided a more conservative threshold criterion than the cluster criterion obtained using the Gaussian random field theory to correct for the family-wise error rate (FWER) with threshold $P < 0.05$ provided by FSL. This approach was adopted to preserve detection of activity in anatomically smaller subcortical regions while rejecting activities that do not follow a Gaussian profile.

Only clusters with size >10 voxels, and peak voxel Z-score >2.57 ($P < 0.005$) were listed in the result tables.

Statistical analysis

To test our hypotheses, we conducted a three-step primary analysis. In the first step, we examined the main effect of contrast. In the second step, for each contrast, we assessed the main effects of depression and attachment security as measured by BDI and AAI scores, respectively. In the third step, for each contrast, we examined the interaction between depression and attachment security. Multiple linear regression was used to determine the distinct correlations of BDI and AAI scores with the BOLD signal for each contrast. For the analysis of interaction effects, depression and attachment security were converted into categorical variables, and the binarized BDI × AAI was added as an independent variable to the regression. Depression categories were assigned values −1 (non-depressed) for BDI ≤ 13 and +1 (depressed) for BDI ≥ 14. Attachment security categories were assigned values of −1 (secure) for AAI score ≥ 6 and +1(insecure) for AAI score <6. In a secondary analysis, to measure correlations (R^2) between BDI or AAI and the BOLD activity in the regions of interest (ROIs) determined by the primary analyses, median voxel Z-scores for conservatively transformed ROIs were used to avoid inflation of correlations by peak voxel Z-scores; ROIs were expanded using a Z-score threshold of $Z > 1.65$ and intersected with the corresponding atlas-defined anatomical ROI.

RESULTS

Subject characteristics and behavioral data

Subject characteristics and behavioral data are summarized in Table 1. Of the depressed subjects, 13 had BDI scores of ≥ 14 and one had a BDI score of 11. Five depressed subjects received AAI coherence of mind scores 6 or greater (secure) and four had scores of ≤ 3 (insecure), with six in the indeterminate range. Of the non-depressed subjects, all had BDI scores <13. Nine received AAI scores 6 or greater (secure) and none had scores of ≤ 3 (insecure). Correlation between BDI and AAI scores was found in the expected negative direction, $r = -0.25$, but was not statistically significant (two-tailed $P = 0.19$).

There were no significant between-group differences in behavioral data or demographics. However, for both subject groups, valence and salience rating were higher for mother and friend than for stranger (unpaired t-test $P < 0.005$).

Three contrasts, mother *vs* friend (M–F), mother *vs* strangers (M–S) and friend *vs* strangers (F–S), were carried to high-level analyses. In addition to the results below,

Table 1 Socio-demographic and clinical and behavioral characteristics

	Control group ($n = 14$)	Depressed group ($n = 14$)
Age (years)	24.50 (2.47)	24.85 (3.10)
Years of education	16.79 (1.89)	16.63 (2.12)
BDI score*	3.86 (4.09)	29.92 (12.53)
BAI score*	3.07 (2.84)	18.71 (11.44)
RSQ general secure**	3.69 (0.52)	2.99 (0.81)
AAI score**	6.25 (1.75)	4.62 (1.76)
AAI score categories, *n* (%)		
1,2,3 (insecure)	0 (0)	4 (28.58)
4,5 (intermediate)	5 (35.71)	5 (35.71)
6,7,8,9 (secure)	9 (64.29)	5 (35.71)
Race/ethnicity, *n* (%)		
Caucasian	10 (71.43)	11 (78.57)
African American	1 (7.14)	0 (0.00)
Hispanic/Latino	1 (7.14)	2 (14.29)
Asian	2 (14.29)	0 (0.00)
Other[a]	0 (0.00)	1 (7.14)
Image ratings[b,c]		
Mother salience	3.80 (0.24)	3.38 (0.82)
Mother valence	3.64 (0.34)	3.10 (1.01)
Mother neutral	2.83 (0.78)	2.28 (0.83)
Friend salience	3.86 (0.18)	3.94 (0.12)
Friend valence	3.78 (0.25)	3.94 (0.17)
Friend neutral	2.77 (0.76)	2.48 (1.08)
Stranger salience	2.15 (0.46)	1.98 (0.93)
Stranger valence	2.26 (0.63)	2.13 (0.72)
Stranger neutral	2.22 (0.57)	1.99 (0.69)

Values are represented as mean (s.d.), unless otherwise specified.
[a]Pacific Islander, Alaskan Native or Native American.
[b]Salience ratings (1–4 Likert scale) refer to the prompt 'How much can you relate to this picture?' Valence ratings (1–4 Likert scale) refer to the prompt 'How pleasant do you feel when you look at this picture?' Neutral ratings (1–4 button press) to the prompt 'Press any button when you see the picture'.
[c]Between-group difference of means were not significant for any stimulus.
*Between-group difference of means $P < 0.005$, $^{**}P < 0.05$.

we observed significant clusters of activation and deactivation in posterior cortical regions related to visual processing of familiar faces (e.g. calcarine cortex, cuneus, precuneus, fusiform and lingual gyri) and of sensorimotor areas (pre-and postcentral gyri and cerebellum) (Skinner and Fernandes, 2007). In line with the published literature, our analysis focused on anterior and sub-cortical brain areas previously reported in studies of depressed mood, emotion and attachment. The complete lists of coordinates, *Z*-scores and *P*-values for these regions are listed in the Supplementary Tables.

Main effects of contrast

In the proof-of-method analysis, whole-brain analysis demonstrated significant contrast by BOLD signal intensity interactions for all three contrasts (Supplementary Table S1). For the M–F contrast, clusters with significant activity were found in the left anterior paracingulate gyrus and right middle and inferior frontal gyri. Significant deactivation clusters were found in the right PFC and the left lateral ventricular pole.

For the M–S contrast, widespread activation clusters were also found primarily in the left lateral PFC, temporal cortex, bilateral anterior and left posterior cingulate gyri. Significant deactivation clusters were found in lateral frontal cortical regions, including insula, bilaterally, as well as in right sensorimotor areas.

The F–S contrast showed clusters of significant activation in the left visual cortical areas, and superior medial frontal cortex, bilateral anterior and left posterior cingulate gyri, and the right parahippocampal gyrus. The F–S contrast showed clusters of significant deactivation in right sensorimotor and visual cortical areas, and bilateral anterolateral prefrontal cortical areas.

Effects of depression

Effects of depression were seen both sub-cortically and cortically in the cortico-striato-thalamic circuits of affect regulation for M–F and M–S contrasts, but only cortically for the F–S contrast (Table 2, Supplementary Table S2). Brain activity generally demonstrated linearity with BDI score (Figure 1, Supplementary Table S4). The results are summarized below.

For the M–F contrast, after covarying for attachment security, increased depression was associated with significant clusters of relative cortical activation in the bilateral middle frontal gyri, right superior medial frontal cortex, left middle temporal gyrus, and sub-cortical activation in the right medial thalamus and left ventral putamen. Scatter plots demonstrated particularly strong linear relationships ($R^2 \geq 0.25$) between relative activation and BDI in the left putamen, caudate and bilateral thalamus, sub-cortically, and left insula, right middle frontal gyrus and bilateral paracingulate gyri, cortically. (These findings are illustrated in part in Figure 1A.)

Excepting the left middle temporal gyrus, similar regional changes were seen for the M–S contrast also. Additionally, significant activation clusters were seen in the putamen and orbitofrontal cortices bilaterally. Significant clusters of relative deactivation were seen in the right superior temporal gyrus, right insula and left superior frontal gyrus. As with the M–F contrast, scatter plots demonstrated strongly linear relationships between relative activation and BDI in most regions (These findings are illustrated, in part, in Figure 1B.)

For the F–S contrast, significant cortical activation was found in the left anterior insula and right superior medial frontal cortex.

Effects of attachment security

Effects of insecure attachment were also found in the cortico-striato-thalamic circuits. For M–F contrast, significant activity was exclusively sub-cortical, whereas for F–S contrast it was exclusively cortical (Table 3, Supplementary Table S3). Brain activity generally demonstrated linearity

Table 2 Regions of significant variation with BDI score

Brain region	*X*	*Y*	*Z*	*Z*-score	*P*-value	Cluster size
M-F activations: mother > friend						
L paracingulate gyrus	0	24	48	3.7	0.0001	996
R superior medial frontal cortex	4	42	50	2.81	0.0025	996
R middle frontal gyrus	30	22	52	2.86	0.0021	240
L middle temporal gyrus	−60	−44	2	2.77	0.0028	153
L middle frontal gyrus	−30	60	4	2.64	0.0041	35
L putamen	−22	18	−2	2.85	0.0022	246
R thalamus	6	−10	6	2.61	0.0045	40
M-F deactivations: mother < friend						
R posterior cingulate gyrus	16	−28	32	2.75	0.003	53
M-S activations: mother > stranger						
L paracingulate gyrus	0	22	54	4.39	0	3483
L superior medial frontal cortex	−2	28	46	4.3	0	3483
R anterior cingulate gyrus	2	22	22	3.35	0.0004	3483
L middle cingulate gyrus	−10	8	40	2.95	0.0016	3483
L insula	−34	20	−8	3.42	0.0003	1486
L inferior frontal gyrus	−44	46	0	2.89	0.0019	1486
L insula	−48	14	−6	2.86	0.0021	1486
L inferior orbitofrontal cortex	−50	36	−6	2.84	0.0023	1486
L insula	−34	18	12	2.56	0.0052	1486
L middle frontal gyrus	−44	8	50	2.95	0.0016	420
L middle frontal gyrus	−34	4	56	2.67	0.0038	420
R insula	34	16	−4	2.59	0.0048	271
R middle frontal gyrus	48	6	40	2.99	0.0014	215
R middle orbitofrontal cortex	4	48	−8	2.58	0.0049	190
R operculum	54	18	−4	2.67	0.0038	43
R middle frontal gyrus	24	50	26	2.67	0.0038	42
L putamen	−24	22	−2	3.49	0.0002	1486
R thalamus	6	−12	4	3.43	0.0003	848
R putamen	18	14	−4	2.89	0.0019	271
M-S deactivations: mother < stranger						
R superior temporal gyrus	50	−16	20	3.10	0.0010	885
R superior temporal gyrus	50	−16	12	3.01	0.0013	885
R insula	42	−4	6	2.79	0.0026	885
L superior frontal gyrus	−24	32	24	2.71	0.0034	147
L superior frontal gyrus	−26	28	26	2.7	0.0035	147
F-S activations: friend > stranger						
L insula	−40	22	−10	3.59	0.0002	565
R superior medial frontal cortex	4	54	24	2.71	0.0034	41

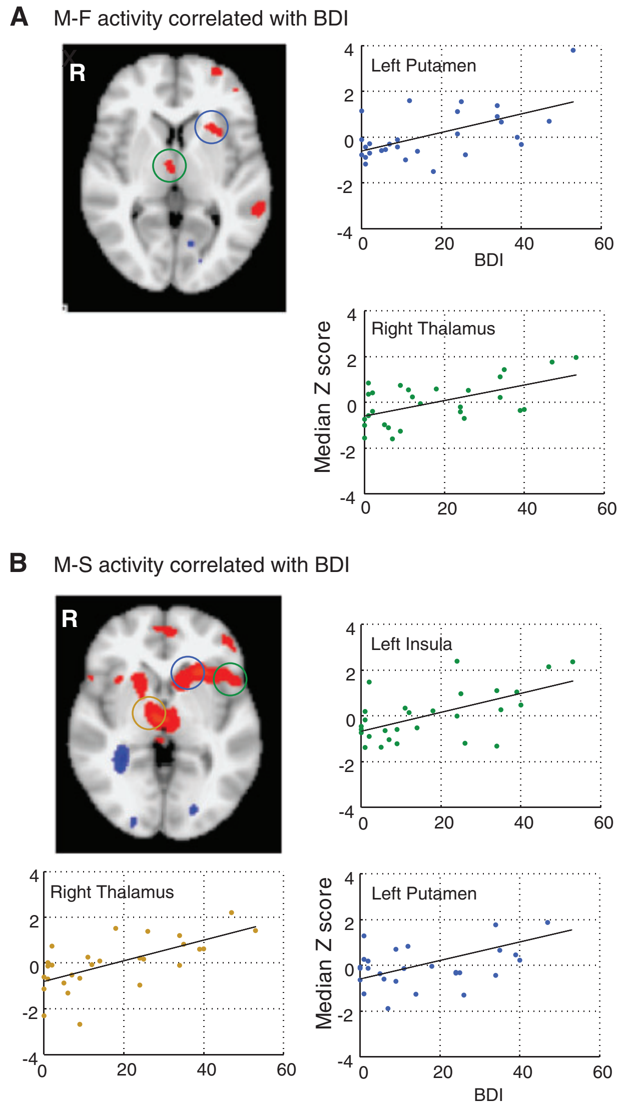

Fig. 1 The correlation between BDI scores and the median *Z*-score of BOLD signal in representative anatomical regions is illustrated. The significance of the regression is represented by R^2 (the percentage of variance that can be explained by the linear relationship) and *P*-values. To avoid an inflated correlation between behavioral data and the fMRI driven by a few voxels that had high *Z*-scores, each cluster was first extended to $Z > 1.65$. The median *Z*-score values for all the voxels that belonged to both the extended cluster and the brain-atlas defined anatomical region for each subject were determined and served as the *Y*-coordinate values in the scatter plots. (**A**) BDI and M–F contrast at right thalamus ($R^2 = 0.33$, $P = 0.001$) and left putamen ($R^2 = 0.34$, $P = 0.001$). (**B**) BDI and M–S contrast at left insula ($R^2 = 0.35$; $P = 0.001$), right thalamus ($R^2 = 0.43$, $P < 0.001$) and left putamen ($R^2 = 0.29$, $P = 0.003$).

with AAI score (Figure 2, Supplementary Table S4). The results are summarized below.

For M–F contrast, after covarying for depression, increasingly insecure attachment was associated with increased sub-cortical activity in right medial thalamus and left ventral caudate. As with the BDI, in these regions, scatter plots demonstrated strong linear relationships between relative activation and AAI scores. (These findings are illustrated in part in Figure 2A.)

In the M–S contrast, sub-cortical activation clusters were present in bilateral ventral putamen and left medial thalamus, and activation in the frontal cortex localized to the left superior medial frontal and right inferior orbitofrontal cortex, and bilateral lateral-PFC (left middle and inferior, and right superior frontal gyri). Deactivations were found in the right middle orbitofrontal cortex and bilaterally in the middle temporal gyri. (These findings are illustrated in part in Figure 2B.)

For the F–S contrast, no AAI-related activity was found in sub-cortical areas. As with M–F contrast, strong activation was present in the left superior medial frontal cortex, and additionally in the left superior frontal gyrus and insula bilaterally. As with M–S contrast, deactivations were noted in the left posterior cingulate and orbitofrontal cortex.

Table 3 Significant brain activity contrasts related to aai coherence of mind score

Brain Region	*X*	*Y*	*Z*	*Z*-score	*P*-value	Cluster size
M-F activations: mother > friend						
R thalamus	8	−6	16	2.94	0.0016	191
L caudate	−14	6	18	2.71	0.0034	58
M-S activations: mother > stranger						
L superior medial frontal cortex	0	36	38	4.39	0	2294
R middle frontal gyrus	30	22	54	2.74	0.0031	2294
L inferior orbitofrontal cortex	−42	46	0	3.88	0.0001	464
L inferior orbitofrontal cortex	−24	24	−2	3.56	0.0002	536
R inferior frontal gyrus	50	28	26	2.94	0.0016	107
L superior frontal gyrus	−30	4	58	2.76	0.0029	64
L putamen	−24	24	−2	3.56	0.0002	536
R thalamus	10	−12	4	3	0.0013	239
R thalamus	10	−8	12	2.98	0.0014	239
R putamen	16	18	0	3.12	0.0009	210
M-S deactivations: mother < stranger						
L posterior cingulate gyrus	−4	−54	28	3.58	0.0002	1624
L inferior orbitofrontal cortex	−4	68	−6	3.19	0.0007	154
R superior frontal gyrus	20	12	26	2.66	0.0039	28
F-S activations: friend > stranger						
R paracingulate gyrus	4	38	32	3.34	0.0004	1399
L superior medial frontal cortex	−2	26	46	3.23	0.0006	1399
R superior frontal gyrus	14	26	52	2.68	0.0037	1399
L insula	−40	18	−8	3.05	0.0011	272
R insula	36	22	−4	2.59	0.0048	47
F-S deactivations: friend < stranger						
L posterior cingulate gyrus	−6	−50	2	2.85	0.0022	1438
L posterior cingulate gyrus	0	−32	46	2.72	0.0033	1438
L middle orbitofrontal cortex	−8	58	−10	3.59	0.0002	320

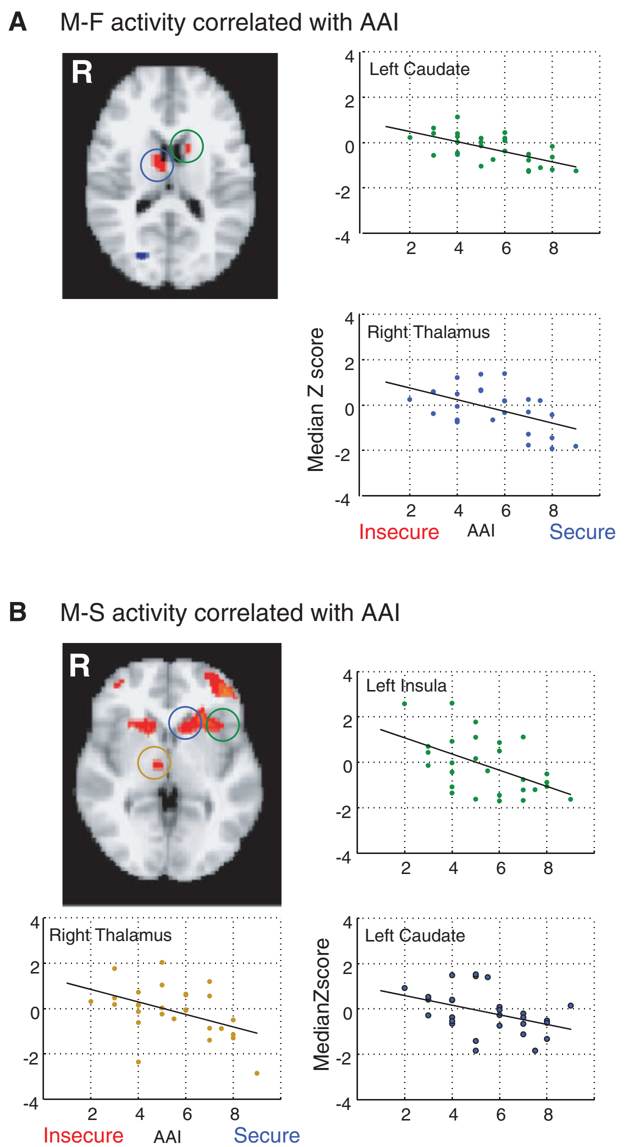

Fig. 2 The correlation between AAI scores and the median *Z* score of BOLD signal in representative anatomical regions is illustrated. The significance of the regression is represented by R^2 (the percentage of variance that can be explained by the linear relationship) and *P*-values. To avoid an inflated correlation between behavioral data and the fMRI driven by a few voxels that had high *Z*-scores, each cluster was first extended to $Z > 1.65$. The median *Z*-score values for all the voxels that belonged to both the extended cluster and the brain-atlas defined anatomical region for each subject were determined and served as the *Y*-coordinate values in the scatter plots. (**A**) AAI and M–F contrast at left caudate ($R^2 = 0.39$; $P = 0.003$) and right thalamus ($R^2 = 0.25$, $P = 0.006$). (**B**) AAI and M–S contrast at right thalamus ($R^2 = 0.21$, $P = 0.013$).

Depression-attachment interaction

For attachment figure *vs* stranger viewing, M–S contrast demonstrated both cortical and sub-cortical areas of enhancing interactions between depression and insecure attachment. Increases in activity were found in bilateral putamen (Table 4, Figure 3B), and right orbitofrontal cortex areas (Table 4, Figure 3A) (i.e. activation was greater for depressed subjects when they were insecurely attached), and decrease in activity was found in the left superior frontal gyrus (i.e. activity was greater for non-depressed subjects when they were securely attached) (Table 4, Figure 3C). F–S contrast demonstrated a cortical area of enhancing interaction with increases in left anterior paracingulate gyrus activity (i.e. activation was greater for depressed subjects when they were insecurely attached) (Table 4, Figure 3D).

DISCUSSION

In this study, we developed and tested a method that uses fMRI imaging to investigate the effects of attachment security and depressed mood on brain activity in young adult women in response to early and late attachment figures—their mothers and close female friends, respectively. To our knowledge, this is the first brain imaging study to examine the relationship between adult attachment and depression, and one of only two studies (Strathearn *et al.*, 2009) to find neural correlates of attachment insecurity as measured by the AAI.

We predicted (i) that depression and insecure attachment will be subserved by distinct but overlapping neural networks previously identified in studies of depression and mother's response to infants, (ii) that depression and

Table 4 Significant brain activity contrasts related to AAI × BDI interaction

Brain region	*X*	*Y*	*Z*	*Z*-score	*P*-value	Cluster size
M–S activations: positive enhancing interaction						
R orbitofrontal cortex	36	26	−14	2.91	0.0018	294
R putamen	20	22	−4	2.74	0.0031	294
L putamen	−20	22	−4	3	0.0013	119
R frontal pole	16	38	−10	2.63	0.0043	93
M–S deactivations: negative enhancing interaction						
L superior frontal gyrus	−20	30	32	3	0.0013	97
F–S activations: positive enhancing interaction						
L paracingulate gyrus	−6	24	32	2.85	0.0022	75

insecure attachment would demonstrate enhancing interactions, and (iii) that neural responses would differ between early and late attachment figures.

In agreement with our first hypothesis, we found that depression and insecure attachment were subserved by distinct but overlapping neural networks previously identified in studies of depression and mothers' response to infants; as hypothesized, the overlap occurred in the cortico-striato-thalamic circuitry of affect regulation (Figure 4). This finding may be related to the link observed between insecure attachment and depression and the greater treatment resistance of depression in insecurely attached individuals, as overlap in areas of correlation indicates additive effects for depression and insecure attachment.

Chiefly, the areas of attachment overlap with depression comprised orbital and medial PFC regions, anterior insula and anterolateral PFC regions, as found by Strathearn and colleagues (2009), and ventral caudate, ventral putamen and medial thalamus, in contrast to their findings. Common to depression and insecure attachment, in attachment—figure *vs* stranger (M–S and F–S) contrasts were associations with relative activation of superior medial frontal cortex and anterior insula (Figure 4A and B)—regions involved in outcome prediction and integration of internal state (Huettel *et al.*, 2005; Paulus and Stein, 2006). Elevated anterior insular activity has been linked to intolerance of uncertainty (a function of negative outcome prediction bias) in processing affectively ambiguous faces (Simmons *et al.*, 2008). This is consistent with negative outcome prediction bias in depression (Alloy and Ahrens, 1987) and negative predictions of the availability of attachment figures in insecure attachment (Shaver and Mikulincer, 2002). This finding also accords with Buchheim and colleagues' finding of greater dorsal ACG activation in response to 'monadic' pictures for subjects with unresolved attachment trauma (Buchheim *et al.*, 2008).

In several brain regions within the cortico-striato-thalamic network, however, activity was uniquely associated with either depression or attachment insecurity. For M–F contrast (Figure 4C), BDI scores alone correlated with activity in the dorsolateral prefrontal cortex (DLPFC)-thalamic circuit, which modulates the orbitomedial prefrontal cortex (OMPFC)-circuit activity subserving persistent negative mood (D'Amasio, 1994; Price and Drevets, 2010).

Notably, contrary to our specific predictions, we found clusters of OFC activity associating with both AAI and BDI. We also found no activity in perigenual ACG-amygdalar pathways, as had been described with blood flow PET and fMRI BOLD studies where increased activity in the perigenual ACG has been seen repeatedly with high negative affect-related tasks (George *et al.*, 1995; Mayberg *et al.*, 1999; Elliott *et al.*, 2000; Urry *et al.*, 2006, Wager *et al.*, 2008). Given the absence of negative affect activation in our paradigm, the absence of activity in the reciprocal perigenual ACG-amygdalar loop is not a surprising outcome. Our findings, therefore, highlight the persistence of abnormal neural function in depression even under conditions relating to attachment with low or no negative valence.

In contrast, insecure attachment alone correlated with activation in the medial thalamus and ventral caudate, which are related more specifically to reward/punishment-associated brain activity (Knutson *et al.*, 2001) and affectively motivated behavior and memory (Fu *et al.*, 2004; Hamilton and Gotlib 2008). In addition, mother-stranger and friend-stranger relative deactivations, associated with insecure attachment, were found in the temporal lobes bilaterally, and might be related to the impaired verbal organization of attachment-related memories that characterize lower scores on the AAI coherence of mind scale (Siegel, 1999).

The finding that insecure attachment is associated with enhanced brain activity in brain regions linked to affectively motivated behavior and memory (Fu *et al.*, 2004; Hamilton and Gotlib, 2008) suggests that depressed patients with insecure attachment styles could benefit from components of behavioral therapy approaches that target emotional reward motivated behaviors, as are found in Cognitive Behavioral Therapy (Fava *et al.*, 1998), and components of therapeutic approaches such as transference focused therapy that target emotional memory (Kernberg *et al.*, 2008) and emotion focused therapy, targeting attachment injury (Johnson *et al.*, 2001).

Of interest, our finding, in secondary analysis, of linear effects both for AAI and BDI scores suggests dose–response relationships between both depression and attachment security and activity in relevant brain regions. This is consistent with dimensional approaches to mood disorders proposed for DSM-V and other studies of depressed mood (Morilak and Frazer, 2004; Brown and Barlow, 2005).

In accord with our second hypothesis, we found that insecure attachment enhanced the effects of depression on brain activity in response to both pictures of mothers (M–S contrast-relative activation in putamen and inferior orbitofrontal cortex and deactivation in lateral PFC) and

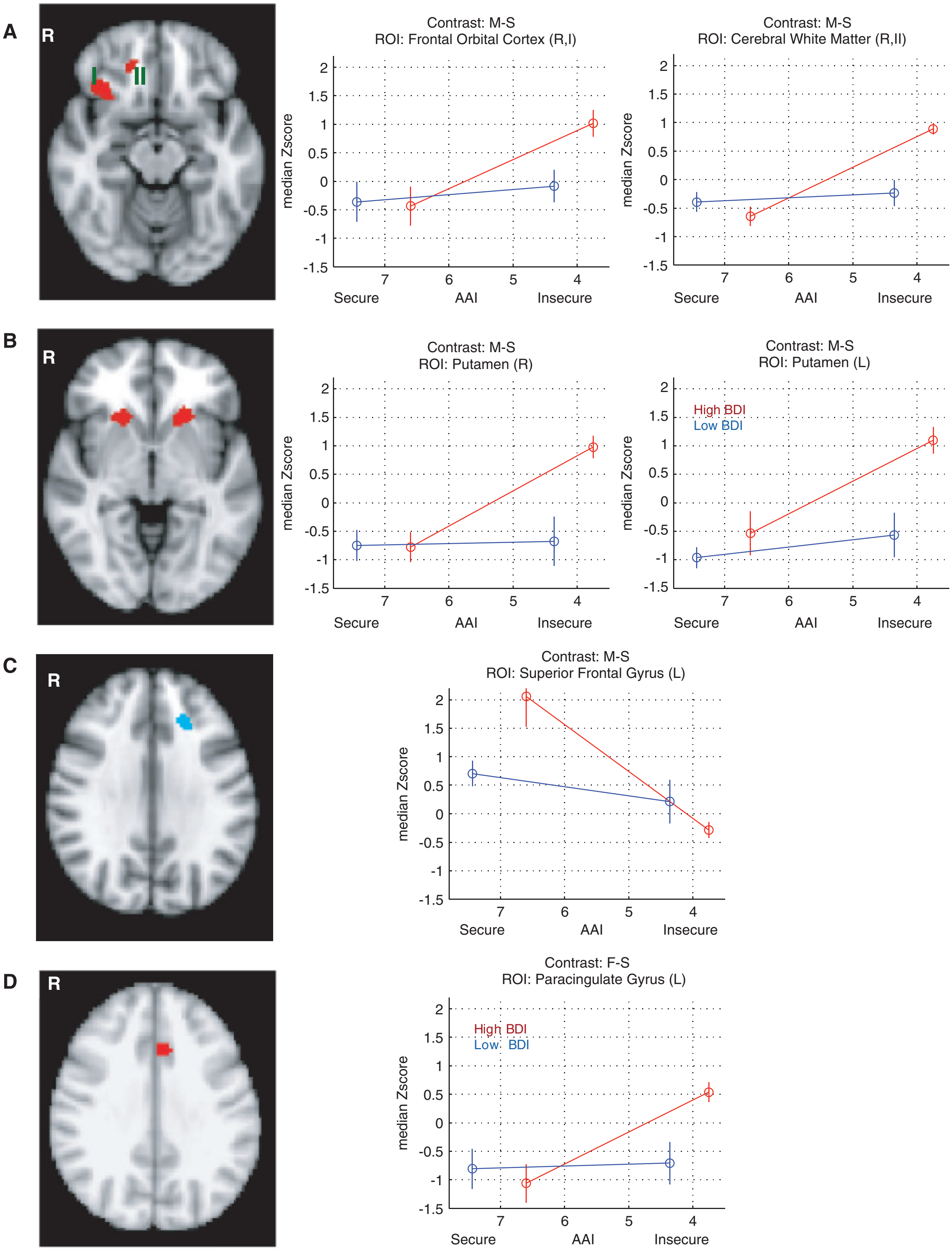

Fig. 3 The effect of interaction between BDI and AAI on the BOLD signal for (**A**) M–S contrast at right inferior orbitofrontal cortex (OFC) ($R^2 = 0.76$, $P < 0.000001$) and White Matter ($R^2 = 0.48$, $P = 0.00026$); (**B**) M–S contrast at right ($R^2 = 0.67$, $P = 0.000001$) and left putamen ($R^2 = 0.56$; $P = 0.000039$); (**C**) left superior frontal gyrus ($R^2 = 0.77$, $P < 0.000001$) and (**D**) F–S contrast at left paracingulate gyrus ($R^2 = 0.66$, $P = 0.000002$). *X*-coordinate represents group mean AAI score, *Y*-coordinate represents group median *Z*-score in the region of interest. Red lines represent the relationship between the BOLD signal for the contrast and AAI score for subjects with BDI score ≥ 14 (depressed), and blue lines for subjects with BDI score ≤ 13 (non-depressed). Error bars represent the standard error.

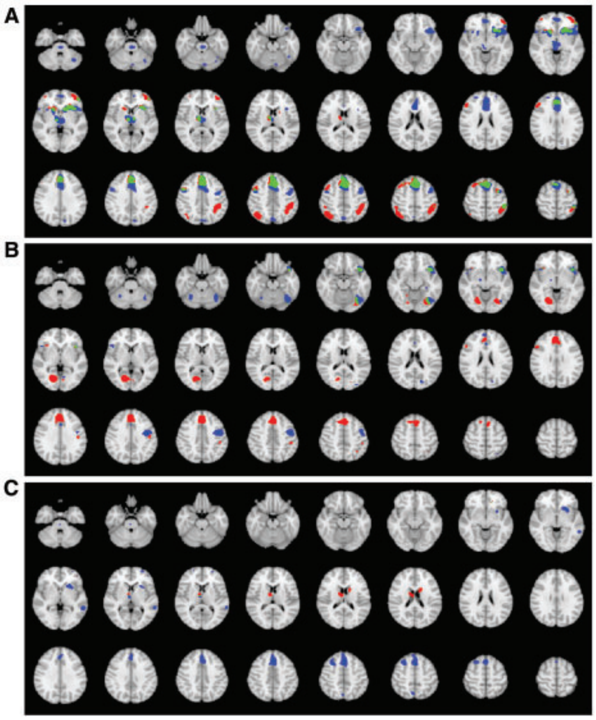

Fig. 4 Brain activity positively correlated with AAI-insecurity after covarying for BDI in red, positively correlated with BDI after covarying for AAI-insecurity in blue and areas of overlap in green. (**A**) M–S contrast, (**B**) F–S contrast and (**C**) M–F contrast. Only clusters of AAI or BDI-correlated voxels with peak voxel *Z*-score >2.32 ($P < 0.01$) are shown.

close friends (F–S contrast-activation in medial PFC). No interaction effects were found for the M–F contrast, though here too there was a trend to significance in the OFC. However, as expected, the effects of depression and insecurity of attachment were in the same direction. Thus, floor and ceiling effects on BOLD signal may have limited our sensitivity in detecting interaction effects.

Orbitofrontal activity has been linked to emotion regulation and mother–infant bonding while the caudate has been linked to emotional reward driven behavior (Nitschke *et al.*, 2004; Noriuchi *et al.*, 2008; Price and Drevets, 2010). The presence of altered activity in these emotional reward-related areas is consistent with interpretation of insecure attachment as a failure to respond positively to maternal attention (Bowlby, 1977). Indeed, the effects of early attachment disruptions on brain activity consistently implicate the OMPFC (Hanson *et al.*, 2010; Teicher *et al.*, 2010). As distress activates the attachment system, for depressed subjects, mother images, acting as early-attachment cues, may elicit activity in the striatum promoting approach behavior (Strathearn *et al.*, 2009). In insecurely attached depressed subjects, this activity may be increased simultaneously with heightened approach-regulating activity in the lateral OFC (Roelofs *et al.*, 2009), resulting in the observed pattern of enhancing interactions.

Elevated activity in the caudate and putamen has also been linked to increased accessibility of negatively valenced memories in depression (Fu *et al.*, 2004; Hamilton and Gotlib, 2008). Our finding of enhanced putaminal activity only in insecurely attached depressed subjects suggests that the interaction of depression (and the negative thinking associated with depressed mood) with insecure attachment, which is highly comorbid with depression and was not controlled for in these studies, may have contributed to this finding in those studies.

In agreement with our third hypothesis, for depression, attachment security, and their interaction effects, activation with pictures of mothers involved both cortical and sub-cortical components of cortico-striato-thalamic circuits. In contrast, neural activity in response to pictures of friends was exclusively cortical.

These results, which suggest a stronger sub-cortical component for early attachment, are in keeping with the chronology of brain development and may thus help explain the relative durability of attachment style. Furthermore, the finding of primarily cortical activity associations during friend viewing supports the hypothesis that late attachment may form in a more 'top-down' cortically dominated manner, derived from patterns determined in early attachment formations (Shaver and Mikulincer, 2002).

Dysfunction in and disruptions of relationships with attachment figures often serve as triggers for depression and subsequently as targets for repair in psychotherapeutic interventions. Our findings may support consistency between a 'top-down' theory of psychotherapeutic efficacy in the treatment of depression (Goldapple *et al.*, 2004; DeRubeis *et al.*, 2008) and the psychodynamic conception of the therapist as a corrective attachment figure (Wallin, 2007). On the other hand, it is possible that love in the transference (Fox, 1998; Novick & Novick 2000) may allow for the psychotherapeutic relationship to provide a corrective attachment experience working in a 'bottom-up' sub-cortically mediated manner (Ortigue *et al.*, 2010).

LIMITATIONS

This study has a number of limitations. First, while familiarity was controlled for in the mother–friend contrast (representing early attachment), there was no equivalent control for late attachment. Second, though the measures of attachment security and style derived from the AAI are thought to characterize adult subjects' attachment in general, adult attachment style and security are recognized to vary somewhat in relation to the particular relationship in question; thus, while the content of the AAI relates specifically to the subjects' parental relationships, we had no direct measure of attachment to the friend (Mikulincer *et al.*, 2002). Nonetheless, in terms of our behavioral data, no significant differences were found between valence or salience ratings of mother and friend (Table 1).

Third, though all subjects had to have been raised by their mothers and in contact with them, we were unable to control for the degree of contact with mothers or friends. Fourth, the administration of the AAI, which focuses on memories of early parental relations, on the morning of the scan, may have heightened affective responses toward mothers more so than toward friends. Thus, it is possible that some of the observed difference between M–S and F–S activity is attributable to a priming effect. In addition, as mother and friend were different for each subject, and photographs were obtained naturalistically, and provided by the subjects, facial affects could not be standardized across subjects or controlled for in the analysis. Furthermore, because we specifically sought to be able to observe interaction effects between AAI and BDI scores, a mixed sample approach was required and the effects of depression in the complete absence of insecure attachment, and vice-versa, could not be observed in this study. Finally, while we were able to covary for attachment security as measured by the coherence of mind scale, the number of insecure attachment-type categorizations in our sample left analysis by attachment type (e.g. preoccupied *vs* dismissing) underpowered.

CONCLUSIONS

We have developed and tested a method to assay brain function associated with depressed mood and attachment insecurity. Our results indicate that depression and attachment insecurity are subserved by distinct but overlapping components of cortico-striato-thalamic circuits related to affect regulation. In addition to additive effects indicated by areas of overlap, enhancing interactions are also present between insecure attachment and depression, supporting a contributory role for insecure attachment in depression, and potentially accounting for the greater difficulty of treating depression in patients with insecure attachment.

Further, we identified differences in neural activity related to early (mother) and late (close friend) attachment figures. Greater sub-cortical activation for early attachment and primarily cortical activation for late attachment support a 'top-down' model for adult attachment formation, which may be relevant to understanding how and when psychotherapy is able to effect therapeutic change in attachment and how such a change may work to treat depression and reduce recurrence.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

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