Psychol. Med., Page 1 of 14. © Cambridge University Press 2013
doi:10.1017/S0033291712002966

ORIGINAL ARTICLE

Differential patterns of activity and functional connectivity in emotion processing neural circuitry to angry and happy faces in adolescents with and without suicide attempt

L. A. Pan[1]*, S. Hassel[2], A. M. Segreti[1], S. A. Nau[1], D. A. Brent[1] and M. L. Phillips[1,3]

[1] *Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[2] *Department of Psychiatry and Hotchkiss Brain Institute, University of Calgary, School of Medicine, Calgary, AB, Canada*
[3] *Department of Psychological Medicine, School of Medicine, Cardiff University, Cardiff, UK*

Background. Neural substrates of emotion dysregulation in adolescent suicide attempters remain unexamined.

Method. We used functional magnetic resonance imaging to measure neural activity to neutral, mild or intense (i.e. 0%, 50% or 100% intensity) emotion face morphs in two separate emotion-processing runs (angry and happy) in three adolescent groups: (1) history of suicide attempt and depression (ATT, $n=14$); (2) history of depression alone (NAT, $n=15$); and (3) healthy controls (HC, $n=15$). *Post-hoc* analyses were conducted on interactions from 3 group × 3 condition (intensities) whole-brain analyses ($p<0.05$, corrected) for each emotion run.

Results. To 50% intensity angry faces, ATT showed significantly greater activity than NAT in anterior cingulate gyral–dorsolateral prefrontal cortical attentional control circuitry, primary sensory and temporal cortices; and significantly greater activity than HC in the primary sensory cortex, while NAT had significantly lower activity than HC in the anterior cingulate gyrus and ventromedial prefrontal cortex. To neutral faces during the angry emotion-processing run, ATT had significantly lower activity than NAT in the fusiform gyrus. ATT also showed significantly lower activity than HC to 100% intensity happy faces in the primary sensory cortex, and to neutral faces in the happy run in the anterior cingulate and left medial frontal gyri (all $p<0.006$,corrected). Psychophysiological interaction analyses revealed significantly reduced anterior cingulate gyral–insula functional connectivity to 50% intensity angry faces in ATT v. NAT or HC.

Conclusions. Elevated activity in attention control circuitry, and reduced anterior cingulate gyral–insula functional connectivity, to 50% intensity angry faces in ATT than other groups suggest that ATT may show inefficient recruitment of attentional control neural circuitry when regulating attention to mild intensity angry faces, which may represent a potential biological marker for suicide risk.

Received 21 June 2012; Revised 28 November 2012; Accepted 29 November 2012

Key words: Adolescents, anterior cingulate, depression, emotion processing, insula, suicide.

Introduction

Suicidal behavior is a leading cause of morbidity and mortality in adolescence (Lubell *et al.* 2007). Despite progress in understanding risk factors for suicidal behavior (Brent *et al.* 1999), the pathogenesis is poorly understood, including possible alterations in neural circuitry that might predispose to suicidal behavior. Prevention of early-onset suicide attempt is identified as a mission of the US National Institute of Mental Health (NIMH). Progress in the prediction and prevention of suicidal behavior would be facilitated by identification of biomarkers for suicide risk, which could increase understanding of the pathogenesis of suicidal behavior in order to target and reverse such pathogenic processes.

Post-mortem studies have demonstrated abnormalities in the prefrontal cortex in adult victims of suicide (Mann *et al.* 2000). In addition, cognitive inflexibility and impaired executive function related to these brain regions have been shown to be characteristic of suicide attempters (Keilp *et al.* 2001; Jollant *et al.* 2005). One neuroimaging study in adult suicide attempters (Oquendo *et al.* 2003*b*) reported lower glucose uptake in the prefrontal cortex and anterior

* Address for correspondence: L. A. Pan, M.D., Assistant Professor of Psychiatry, Child and Adolescent Psychiatry, Loeffler Building, 121 Meyran Avenue, Room 304, Pittsburgh, PA 15213, USA.
(Email: thomasla@upmc.edu)

cingulate gyrus in high *versus* low lethality suicide attempters. With regard to emotion processing, vulnerability to suicidal behavior has been associated with differences in response to both negative and positive emotion. Specifically, adult male suicide attempters showed greater activity in the right lateral orbitofrontal cortex [Brodmann area (BA) 47] and decreased activity in the right superior frontal gyrus (BA 6) to 100% intensity angry *versus* neutral faces relative to healthy and depressed non-attempter controls. In response to 50% intensity happy faces, attempters showed greater activity than healthy and non-attempter depressed controls in the right anterior cingulate gyrus (BA 32/10) (Jollant *et al.* 2008). Together, these findings suggest that abnormal prefrontal cortical function during emotion processing may underlie vulnerability to suicidal behavior in depressed adults.

Regarding studies in adolescence, we reported in the same group of adolescents that suicide attempt may not be associated with abnormal activity in the neural circuitry supporting response inhibition. In fact, during response inhibition, adolescents with depression but no history of suicide attempt, relative to adolescents with depression and a history of suicide attempt, demonstrated a compensatory increase in activity in the right anterior cingulate gyrus (Pan *et al.* 2011). In parallel, there is evidence of greater activity during emotional processing in depressed, relative to healthy, adolescents in bilateral amygdalae and hippocampi (Lau *et al.* 2010), and greater activity in the ventromedial prefrontal cortex and anterior cingulate when viewing fearful faces (Killgore & Yurgelun-Todd, 2006). There are, however, no studies examining neural activity during emotion processing in adolescent suicide attempters. Research is therefore needed to determine the extent to which prefrontal cortical dysfunction during emotion processing may contribute to vulnerability to suicidal behavior in adolescents.

A complementary approach to regionally specific analyses assesses functional connectivity. This may be particularly salient in adolescence given prominent developmental changes in connectivity. For example, there is evidence that adults are more able to modulate activity in the anterior cingulate in response to fear and non-emotional cues than adolescents (Monk *et al.* 2003) and that maturation of emotional processing is related to the progressive acquisition of greater functional activity within the prefrontal cortex in adolescence (Yurgelun-Todd & Killgore, 2006). Fronto-limbic circuitry is implicated in pediatric depression (Hulvershorn *et al.* 2011). Abnormal functional connectivity of the anterior cingulate gyrus (BA 32), in particular, has been demonstrated during resting-state analysis with the amygdala, superior, medial and lateral prefrontal cortical regions, temporal regions, and the insula in adolescent depression (Cullen *et al.* 2009). In adult depression, at rest and to emotional pictures, there is evidence of decreased functional connectivity between the anterior cingulate gyrus and limbic regions (Anand *et al.* 2005).

The aim of the present study was to measure neural activity during processing of emotional faces in adolescents with a history of depression and suicide attempt (ATT) *versus* age-matched adolescents with a history of depression but not suicide attempt (NAT) and age-matched healthy controls (HC), using functional magnetic resonance imaging (fMRI). We hypothesized that, like adult suicide attempters (Jollant *et al.* 2008), ATT relative to the other two groups would show differential patterns of elevated prefrontal cortical activity to both angry and happy faces. We also examined functional connectivity by applying psychophysiological interaction (PPI) analysis (Friston *et al.* 1997) to fMRI data from the emotion-processing task. Existing data in depressed adults allowed us to hypothesize that both adolescent groups with a history of depression would show reduced functional connectivity among anterior cingulate gyri, prefrontal, temporal cortices and insulae to all face emotion conditions relative to HC.

Method

Participants

A total of 44 adolescents completed the study (Table 1), including those with: (1) lifetime history of suicide attempt and major depressive disorder (MDD) (ATT; $n=14$); (2) history of MDD, but no history of suicide attempt (i.e. non-attempters; NAT; $n=15$); and (3) healthy control participants without history of psychiatry disorder or suicide attempt (HC; $n=15$).

ATT and NAT were recruited from existing studies and a clinic for depressed youth. HC were recruited from existing healthy control groups and advertisements in pediatric practices. Inclusion criteria for NAT and ATT included a lifetime history of MDD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. ATT had a history of at least one suicide attempt as defined by the Columbia Classification Algorithm of Suicide Assessment (Posner *et al.* 2007). All participants were right-handed.

Exclusion criteria included neurological disorders, head injury, Verbal Subtest of the Wechsler Intelligence Test score <80 (Wechsler, 1999), use of sedative medication, drug or alcohol disorder or positive urine drug screen, pregnancy, magnetic

Table 1. *Demographic information and clinical variables*[a]

	ATT ($n=14$)	NAT ($n=15$)	HC ($n=15$)
Gender, n[b]			
Male	4	7	8
Female	10	8	7
Age, years[c]	16.21 (0.80)	15.87 (1.55)	15.27 (1.39)
Petersen Pubertal questionnaire[d]	3.14 (0.36)	3.00 (0.38)	3.07 (0.59)
BDI[e]	15.07 (15.57)	4.40 (5.58)	1.93 (3.39)
SIQ[f]	39.50 (21.86)	23.40 (11.43)	16.13 (1.46)
SCARED (c)[g]	25.64 (13.56)	10.00 (8.32)	8.13 (7.74)
SCARED (p)[h]	21.93 (13.23)	13.67 (8.20)	5.87 (7.29)

ATT, Adolescent suicide attempters; NAT, non-attempters with a history of major depressive disorder; HC, healthy controls; BDI, Beck Depression Inventory; SIQ, Suicidal Ideation Questionnaire; SCARED (c), Screen for Childhood Anxiety Related Emotional Disorders child version; SCARED (p), Screen for Childhood Anxiety Related Emotional Disorders parent version.

Data are given as mean (standard deviation) or as number of subjects.

[a] All participants taking medication were taking an antidepressant. Two NAT had augmentation with levothyroxine. One ATT had augmentation with aripiprazole, and two ATT had augmentation with antiepileptic medications (see Table 2).

[b] ATT, NAT and HC did not differ significantly in gender ratio ($p=0.391$).

[c] ATT, NAT and HC did not differ significantly in age ($F_{2,41}=0.877$, $p=0.506$).

[d] ATT, NAT and HC did not differ significantly in Petersen Pubertal questionnaire ($\chi^2=0.712$, $p=0.701$).

[e] ATT had significantly greater BDI scores than NAT and HC ($\chi^2=13.92$, $p=0.001$).

[f] ATT had significantly greater SIQ scores than NAT and HC ($\chi^2=20.53$, $p=0.0001$).

[g] ATT had significantly greater SCARED (c) than NAT and HC ($\chi^2=14.63$, $p=0.001$).

[h] ATT had significantly greater SCARED (p) scores than NAT and HC ($\chi^2=15.90$, $p=0.0001$).

resonance imaging (MRI) ineligibility, bipolar disorder or psychosis. Any ATT with suicide attempt causing neurological damage or long-term physiological effects was excluded.

DSM-IV criteria were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Kaufman *et al.* 1997). Suicide attempt was assessed at the time of the scan using the Suicide Intent Scale (Beck *et al.* 1974) and Suicide History Form (SHF; Oquendo *et al.* 2003*a*). Depression, anxiety, suicidal ideation and pubertal status were assessed with the Beck Depression Inventory (BDI; Beck *et al.* 1961), Screen for Childhood Anxiety Related Emotional Disorders (SCARED; Birmaher *et al.* 1997), Suicidal Ideation Questionnaire (SIQ; Reynolds, 1987) and the Petersen Development Scale (Petersen *et al.* 1988), respectively. After complete description of the study to all subjects, parental written informed consent and participant written informed assent were obtained.

A total of 51 participants were assessed. Exclusions included: two with claustrophobia, one with structural abnormality, one with marijuana dependence, two for younger age (10 years), and one due to scanner malfunction. No participants had to be excluded for movement (>3 mm). Median time since last attempt was 26.1 (S.D. = 29.1) months, and mean lethality of attempt from the SHF was 2.29 (S.D. = 1.20) (injury requiring medical intervention; Table S1). ATT had significantly higher SIQ, BDI and SCARED scores than NAT. Of the participants, three ATT and one NAT had a current depressive episode (BDI >20), and nine ATT and seven NAT were taking medication for depression. Medications included selective serotonin reuptake inhibitor (SSRI) antidepressant medication and augmentation (Table 2).

Paradigm

Participants completed two previously employed (Lawrence *et al.* 2004; Hassel *et al.* 2008; Versace *et al.* 2010) 6-min event-related facial emotion-processing fMRI runs with 20 faces each of 100% intensity, 50% intensity and 0% intensity (neutral) faces totaling 60

Table 2. *Medication*

	ATT ($n=8$)	NAT ($n=7$)
Antiepileptics ($n=2$)	Lamotrigine ($n=1$)	–
	Topiramate ($n=1$)	–
Antidepressants ($n=10$)	Escitalopram ($n=1$)	Escitalopram ($n=1$), Citalopram ($n=1$)
	Bupropion ($n=1$)	Buproprion ($n=1$)
	Fluoxetine ($n=4$)	Fluoxetine ($n=3$)
	Trazodone ($n=2$)	–
	Sertraline ($n=1$)	Sertraline ($n=1$)
Antipsychotics ($n=1$)	Aripiprazole ($n=1$)	–
Other ($n=2$)	–	Levothyroxine sodium ($n=2$)

ATT, Adolescent suicide attempters; NAT, non-attempters with a history of major depressive disorder.

randomized cues in each experiment of either (1) happy or (2) angry. Images were 10 individuals from a standardized series (Young *et al.* 2002). Participants viewed each image for 2 s and determined the gender of the face with a button press (index finger for female, third finger for male). Task order was counterbalanced. The interstimulus interval included a baseline fixation cross and varied from 3 s to 8 s (mean = 4.9 s). These emotion-processing tasks have been associated with reliable activity within subcortical neural regions in healthy adults (Surguladze *et al.* 2005).

Data acquisition

Scans were acquired on a 3.0 T Siemens Allegra MRI scanner. Functional scans with full coverage of the adolescent brain of 34 contiguous 3-mm axial slices were acquired with a T2-weighted gradient echo planar imaging (EPI) sequence (repetition time: 2000 ms; echo time: 30 ms; field of view: 205 mm; matrix: 64×64; in-plane resolution: 3×3 mm). Stimuli were projected onto a screen approximately 55 cm from the subject with a rear screen projector. High-resolution T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) structural images of 240 0.8-mm slices were acquired (repetition time: 1630 ms; echo time: 2.48 ms; inversion time: 800 ms; field of view: 200 mm; flip angle: 8°; matrix: 256×256).

Task performance

Task performance data were analysed using one-way analyses of variance (ANOVAs) to examine the main effect of group upon response time and numbers of correct gender responses in SPSS v. 20 (IBM, USA).

Imaging analyses

Data were pre-processed and analysed using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/). Data for each participant were first corrected for differences in acquisition time between slices; realigned using the first slice as a reference and unwarped to correct static inhomogeneity of the magnetic field and movement by inhomogeneity interactions. They were co-registered with the subject's anatomical image, segmented, normalized to standard Montreal Neurological Institute (MNI) template, re-sampled to $3 \times 3 \times 3$ mm^3 voxels, and spatially smoothed with a Gaussian kernel of 6 mm full-width at half-maximum (FWHM).

First-level fixed-effect models were constructed with 0%, 50% and 100% intensities of angry and happy facial emotions. Movement parameters from the realignment stage were entered as covariates of no interest. Trials were modeled using the canonical hemodynamic response function. Contrast maps from first-level analyses (i.e. happy condition: 100% happy face minus fixation, 50% happy face minus fixation, neutral face minus fixation; angry condition: 100% angry face minus fixation, 50% angry face minus fixation, neutral faces minus fixation) were then entered into the second-level analyses (random-effects) using a full factorial model. Separate models were computed for happy and angry conditions.

A second-level random-effects model was used for between-group comparison. We performed two separate 3 group (ATT, NAT, HC) $\times$ 3 condition (0%, 50% and 100% intensities) analyses of covariance (ANCOVAs) for angry and happy, covarying for age, to examine the group $\times$ condition interaction upon whole-brain activity. Specifically, the 3×3 ANCOVA was utilized to identify group differences of the effect of intensity difference. A 3×3 factorial design,

examining differences between intensities, allowed for cancellation of other mental processes, such as gender identification, common to all groups. Although there was no significant difference in age between the three groups, age was added as a covariate in order to further control for potential effects of brain development (as in Ladouceur *et al.* 2011; Pan *et al.* 2011). Age effect on emotion circuitry may differ differently across groups.

We maintained a cluster-level false-positive detection rate of $p<0.05$ for this pattern of neural activity using a voxel-wise threshold of $p<0.05$ with a cluster (k) extent empirically determined by Monte Carlo simulation implemented in AlphaSim (afni.nimh.nih.gov/afni/doc/manual/AlphaSim) (Gilbert *et al.* 2005; Monk *et al.* 2008; Dickstein *et al.* 2010; Pan *et al.* 2011; Kim *et al.* 2012) to account for spatial correlations between *blood* oxygen level-dependent (BOLD) signal changes in neighboring voxels. Our main findings survived small volume correction (SVC) with AlphaSim at $p<0.05$.

Peak BOLD signal changes were extracted from regions with significant group × condition interaction in both the above 3 × 3 analyses. We utilized a standard peak voxel BOLD signal change to evaluate the peak magnitude for interpretation of the interaction. This is a more conservative approach, which has been employed previously (Hassel *et al.* 2008; Pan *et al.* 2011). We then performed *post-hoc* tests on these extracted BOLD signal values to examine the extent to which pair-wise between-group differences in differences in activity contributed to the significant group × condition interactions, in the above analyses, using independent t tests and appropriate statistical thresholds to control for multiple tests. In these *post-hoc* tests for regions showing a significant group × condition interaction in the 3 × 3 ANCOVA, a significance threshold of $p<0.05/9=p<0.006$ was employed to control for the three independent between-group pair-wise tests for each of the three conditions in each region.

Functional connectivity analyses

PPI analyses were conducted to investigate the context-dependent contributions of seed region (right anterior cingulate gyrus, BA 32) activity in all the angry and happy conditions (intensities), and functional coupling with other brain regions in relation to task demands. The anterior cingulate seed region was chosen as it was activated in all groups to all conditions. PPI correlated the anterior cingulate seed region activation to other areas as a product of each condition. Motion parameters did not differ between groups, and no participant above 3 mm of motion was included in the analysis.

The PPI physiological variable was first computed by extracting the signal time course for all voxels in the right anterior cingulate gyrus region of interest (ROI) for each individual participant. The ROI was constructed using a mask from the Wake Forest University (WFU) PickAtlas with the anterior cingulate coordinates from the original whole-brain analysis. A total of six analyses were done for each participant (for 0%, 50% and 100% intensities minus baseline for happy and angry conditions). Analyses were Bonferroni corrected for multiple comparisons, with a statistical threshold of $p=0.05/6$ ($p<0.008$) for each 3 × 1 ANOVA. The PPI interaction variable was then computed as the product of the mean corrected right anterior cingulate gyrus activity and the vector coding for the experimental effect of each condition individually subtracted from baseline (1 for condition and −1 for baseline). A design matrix consisting of three regressors [(1) physiological variable, signal time course in the right anterior cingulate gyrus ROI; (2) psychological variable, representing the experimental task (condition – baseline); and (3) interaction variable] was then used to determine the PPI for each individual participant. A main effect of group analysis was then performed to examine the differences between the PPI and each group. Brain regions that received stronger right anterior cingulate gyrus influences during the angry and happy conditions subtracted from baseline were then determined by conducting a t test. We maintained $p<0.05$ for this analysis using a voxel-wise threshold of $p<0.05$ with a cluster (k) extent empirically determined by Monte Carlo simulation implemented in AlphaSim (Gilbert *et al.* 2005; Monk *et al.* 2008; Dickstein *et al.* 2010; Pan *et al.* 2011; Kim *et al.* 2012) to account for spatial correlations between BOLD signal changes in neighboring voxels.

Exploratory analyses

In exploratory analyses, we then examined potential relationships between extracted BOLD signals from the above neural regions and PPIs and: depression severity, anxiety, suicidal ideation, pubertal status, age, gender and medication status by class at the time of scanning. We employed Pearson correlation and independent t tests as appropriate in SPSS v. 20.

Results

Behavioral data

There was no significant effect of group upon task performance accuracy: percentage of accurate responses to angry faces [ATT 99.31 (S.D. = 0.9)%,

NAT 99.04 (S.D. = 1.32) %, HC 99.25 (S.D. = 1.08) %, $F_{2,43} = 0.216$, $p = 0.806$]; percentage of accurate responses to happy faces [ATT 99.5 (S.D. = 0.69) %, NAT 99.15 (S.D. = 1.56) %, HC 99.04 (S.D. = 1.32) %, $F_{2,43} = 0.534$, $p = 0.590$]; percentage of total accurate responses [ATT 99.40 (S.D. = 0.53) %, NAT 99.09 (S.D. = 0.96) %, HC 99.15 (S.D. = 0.9) %, $F_{2,43} = 0.577$, $p = 0.567$]. There was no significant effect of group upon reaction time: average reaction time to angry faces [ATT 1.01 (S.D. = 0.11) s, NAT 1.04 (S.D. = 0.17) s, HC 1.03 (S.D. = 0.11) s, $F_{2,43} = 0.098$, $p = 0.906$]; average reaction time to happy faces [ATT 1.04 (S.D. = 0.12) s, NAT 1.02 (S.D. = 0.17) s, HC 1.02 (S.D. = 0.13) s, $F_{2,43} = 0.083$, $p = 0.921$]; average total reaction time [ATT 1.03 (S.D. = 0.11) s, NAT 1.03 (S.D. = 0.16) s, HC 1.03 (S.D. = 0.11) s, $F_{2,43} = 0.001$, $p = 0.999$].

Neuroimaging data

3 × 3 ANCOVAs

A 3 group × 3 condition ANCOVA for angry faces, covarying for age, revealed group × condition interactions in different dorsal anterior cingulate gyral, prefrontal, temporal, parietal and occipital cortical regions implicated in attention, emotion and visuospatial processing (Table 3, $p < 0.05$, corrected). A 3 × 3 ANCOVA for happy faces revealed group × condition interactions in dorsal anterior cingulate gyral, prefrontal, temporal, parietal, thalamic and occipital cortical regions (Table 4, $p < 0.05$, corrected). *Post-hoc* analyses (Tables 3 and 4, Fig. 1*a*) revealed that the following significant between-group comparisons contributed to these interactions.

Angry – ATT v. NAT. ATT showed significantly increased activity relative to NAT when viewing 50% intensity angry faces in the right anterior cingulate gyrus (BA 32, $p = 0.0047$), bilateral primary sensory cortices (BA 4, left, $p = 0.00004$, right, $p = 0.002$), the left dorsolateral prefrontal cortex (BA 9, $p = 0.0002$), and the right middle temporal gyrus (BA 21, $p = 0.001$). When viewing neutral faces presented in the angry run, ATT had significantly lower activity than NAT in the left fusiform gyrus ($p = 0.003$). (Fig. 1*a*)

Angry – ATT v. HC. ATT showed significantly greater activity than HC in the left primary sensory cortex (BA 4) to angry faces at 50% intensity ($p = 0.001$).

Angry – HC v. NAT. HC showed greater activity to angry faces at 50% intensity than NAT in the right anterior cingulate gyrus ($p = 0.002$) and right ventromedial prefrontal cortex (BA 11, $p = 0.0001$).

Happy – ATT v. HC. ATT showed significantly lower activity than HC when viewing 100% intensity happy faces ($p = 0.001$) in the left primary sensory cortex (BA 4). ATT showed less activity in the right anterior cingulate gyrus (BA 32, $p = 0.0004$) and left medial frontal gyrus (BA 10, $p = 0.002$) than HC to neutral faces presented in the happy run.

Functional connectivity analyses

PPI analyses using a right anterior cingulate seed region, selected because it was active in angry and happy conditions at all intensities in all groups, revealed a significant main effect of group in bilateral insulae during the 50% intensity angry condition (Table 5, Fig. 1*b*, *p*-corrected = 0.049). There were no significant findings in the other conditions. *Post-hoc* analyses revealed significantly reduced functional connectivity in ATT *v.* NAT (left, $p = 0.002$; right, $p = 0.0001$) and *v.* HC (left, $p = 0.0001$; right, $p = 0.008$) from a right anterior cingulate gyral seed to bilateral insulae to 50% intensity angry faces.

Exploratory analyses

Exploratory analyses (Table S2) were performed to examine relationships between developmental variables (age, pubertal status), clinical variables (BDI, SCARED parent and child versions, SIQ, medication status), gender, and activity in ATT and NAT in regions showing significant differences in activity relative to HC, and to each other that emerged from the 3 × 3 interaction. A statistical threshold of $p = 0.05/8$ ($p < 0.006$) was employed to control for eight multiple tests (one for each of the exploratory variables) in each region. These analyses revealed no relationship between anxiety, medication status, gender, age, or pubertal status and activation. There was a positive correlation between activation in the right primary sensory cortex (BA 4) and BDI score in ATT to 50% intensity angry faces ($r = 0.702$, $p = 0.005$). In addition, in NAT, SIQ scores correlated negatively with activation in the left dorsolateral prefrontal cortex to 50% angry faces ($r = -0.757$, $p = 0.001$). This was repeated for the PPI extracted values, and no relationships between any of the exploratory variables and the PPI analyses were found.

Discussion

The specific aim of the study was to examine the extent to which ATT showed abnormal activity during processing of emotional faces compared with NAT and HC. We hypothesized that, like adult suicide attempters, ATT relative to the other two groups

Table 3. *Whole-brain 3 × 3 ANCOVA group (ATT, NAT, HC) × condition (A100, A50, AN) covarying for age*

Region	Side	*k*	AlphaSim *k*	MNI coordinates x	y	z	*Post-hoc* test	Condition	*t*	df	*p*	*F*
Anterior cingulate gyrus (BA 32)	R	311	13	18	21	42	ATT > NAT	A50	3.08	28	0.0047	9.44
							HC > NAT	A50	3.50	29	0.002	12.20
							HC > ATT	AN	2.24	28	0.033	5.01
Ventromedial prefrontal cortex (BA 11)	R	110	9	36	45	−9	HC > NAT	A50	4.72	29	0.0001	22.01
							ATT > NAT	A50	2.29	28	0.030	5.23
Medial frontal gyrus (BA 10)	R	48	16	6	63	−6	HC > NAT	A50	2.48	29	0.019	6.13
Primary sensory cortex (BA 4)	R	80	12	15	−33	54	ATT > NAT	A50	3.41	28	0.002	11.56
							ATT > HC	A100	2.27	28	0.031	5.15
	L	241	12	−15	−27	63	ATT > NAT	A50	4.86	28	0.00004	23.30
							ATT > HC	A50	3.64	28	0.001	13.16
Dorsolateral prefrontal cortex (BA 9)	L	33	14	−18	27	27	ATT > NAT	A50	4.33	28	0.0002	18.51
							ATT > NAT	A100	2.31	28	0.029	5.32
							ATT > HC	A100	2.54	28	0.017	6.43
Ventrolateral prefrontal cortex (BA 47)	L	520	7	−3	15	−15	NAT > HC	A100	2.40	29	0.023	5.73
Superior parietal gyrus (BA 2)	L	117	10	−45	−24	39	ATT > NAT	A50	2.71	28	0.012	7.31
Middle temporal gyrus (BA 21)	R	83	10	39	−6	−9	ATT > NAT	A50	3.89	28	0.001	14.96
Fusiform gyrus (BA 37)	R	106	12	36	−45	−9	ATT > NAT	A50	2.37	28	0.025	5.60
							HC > NAT	A50	2.18	29	0.038	4.73
	L	36	10	−36	−54	−6	NAT > ATT	AN	3.23	28	0.003	10.38
Insula (BA 13)	R	223	18	36	−6	18	HC > ATT	A100	2.63	28	0.014	6.86
							NAT > ATT	A100	2.26	28	0.032	5.08
Occipital cortex (BA 18)	R	62	15	12	−69	3	ATT > NAT	A50	2.34	28	0.027	5.44

ANCOVA, Analysis of covariance; ATT, Adolescent suicide attempters; NAT, non-attempters with a history of major depressive disorder; HC, healthy controls; A100, Angry faces 100% intensity condition; A50, Angry faces 50% intensity condition; AN, Angry faces neutral condition; MNI, Montreal Neurological Institute; *k*, cluster; df, degrees of freedom; BA, Brodmann area; R, right; L, left.

Table 4. *Whole-brain 3 × 3 ANCOVA group (ATT, NAT, HC) × condition (H100, H50, HN) covarying for age*

Region	Side	*k*	AlphaSim *k*	MNI coordinates x	y	z	*Post-hoc* test	Condition	*t*	df	*p*	*F*
Anterior cingulate gyrus (BA 32)	R	58	13	18	48	−3	HC > ATT	HN	4.05	28	0.0004	16.25
							HC > NAT	HN	2.86	29	0.008	8.14
Posterior cingulate gyrus (BA 31)	R	48	17	21	−48	36	HC > ATT	H100	2.77	28	0.010	7.63
	L	29	16	0	−57	36	ATT > NAT	H100	2.43	28	0.022	5.87
Medial frontal gyrus(BA 10)	L	58	14	−24	48	−6	HC > ATT	HN	3.40	28	0.002	11.47
							HC > NAT	HN	2.37	29	0.025	5.61
Primary sensory cortex (BA 4)	L	60	20	−33	−18	51	HC > ATT	H100	3.76	28	0.001	14.02
							HC > ATT	H50	2.75	28	0.011	7.51
							NAT > ATT	H100	2.55	28	0.017	6.47
Supplementary motor area (BA 6)	L	25	20	−30	0	36	HC > NAT	H100	2.07	29	0.048	4.26
							HC > ATT	H50	2.21	28	0.035	4.89
							NAT > ATT	HN	2.16	28	0.040	4.66
Superior parietal gyrus (BA 3)	R	40	12	57	−15	48	HC > ATT	H50	2.70	28	0.012	7.24
							HC > ATT	H100	2.16	28	0.040	4.66
							NAT > ATT	H50	2.13	28	0.043	4.50
							NAT > ATT	H100	2.42	28	0.023	5.82
Inferior parietal gyrus (BA 40)	L	35	23	−54	−27	36	ATT > NAT	HN	2.50	28	0.019	6.20
							HC > NAT	HN	2.55	29	0.017	6.47
Superior temporal gyrus (BA 41)	L	30	10	−54	−15	15	ATT > NAT	HN	2.37	28	0.025	5.58
Occipital cortex (BA 19)	L	25	20	−33	−18	51	HC > ATT	HN	2.17	28	0.039	4.70
Thalamus	R	227	33	6	−27	21	ATT > NAT	H50	2.58	28	0.015	6.60
							HC > ATT	H100	2.20	28	0.036	4.84

ANCOVA, Analysis of covariance; ATT, Adolescent suicide attempters; NAT, non-attempters with a history of major depressive disorder; HC, healthy controls; H100, Happy faces 100% intensity condition; H50, Happy faces 50% intensity condition; HN, Happy faces neutral condition; MNI, Montreal Neurological Institute; *k*, cluster; df, degrees of freedom; BA, Brodmann area; R, right; L, left.

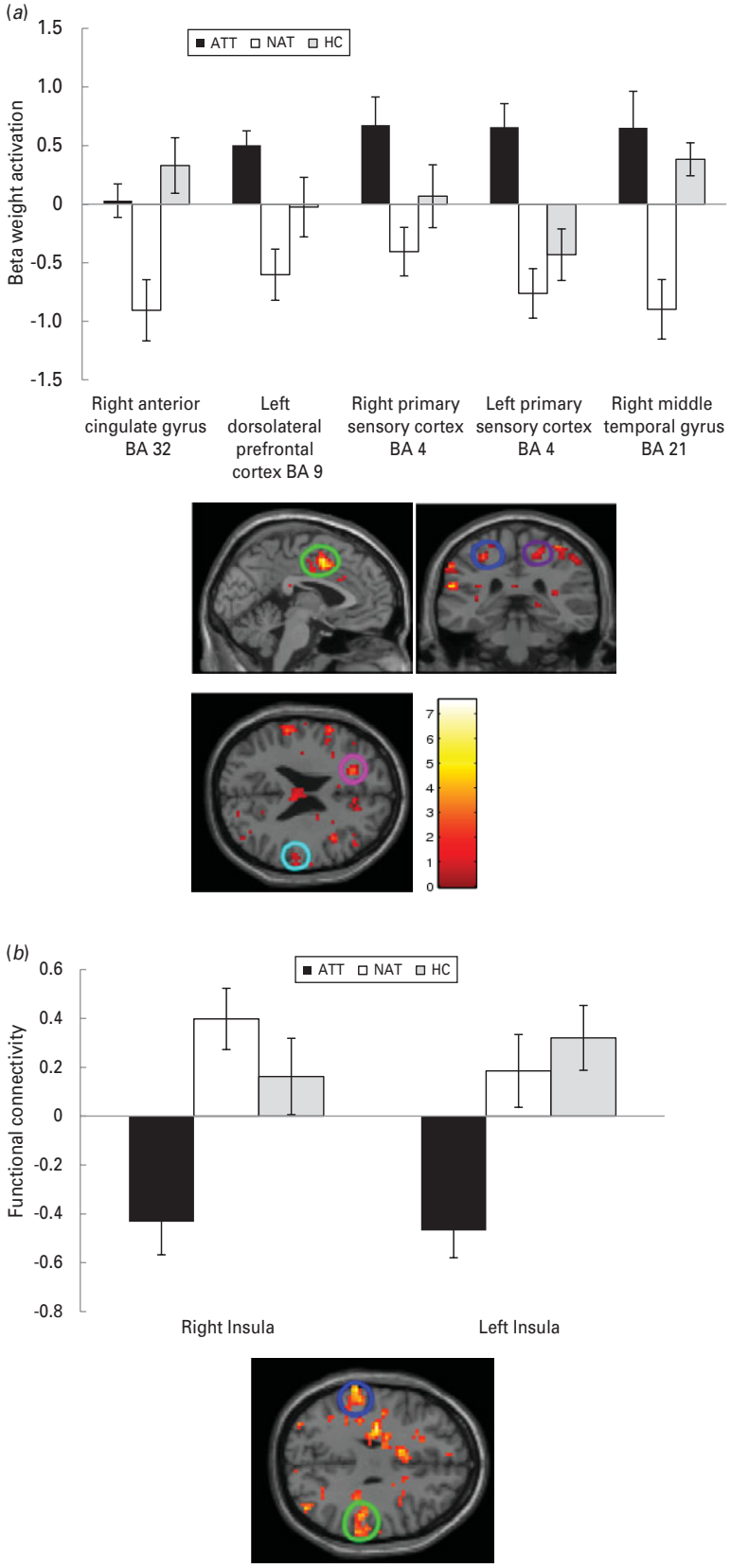

Fig. 1. (*a*) Whole-brain 3 × 3 analysis of covariance (ANCOVA) identifying differences of the effect of intensity difference when viewing 50% intensity angry faces covarying for age in all groups. Suicide attempters (ATT) > depressed non-attempters (NAT) in the right anterior cingulate gyrus [Brodmann area (BA) 32, $p = 0.0047$], bilateral primary sensory cortices (BA 4, left,

[*Legend continues on next page*

Table 5. *PPI activation with right anterior cingulate gyrus BA 32 as the seed region: 3 × 1 main effect of group (ATT, NAT, HC) × condition (A50)*

Region	Side	*k*	AlphaSim *k*	MNI coordinates x	y	z	*Post-hoc* tests	Condition	*t*	df	*p*	*F*
Insula (BA 13)	R	291	288	45	−24	27	NAT > ATT	A50	4.52	28	0.0001	20.19
							HC > ATT	A50	2.88	27	0.008	8.25
	L	458	288	−36	−39	21	NAT > ATT	A50	3.48	28	0.002	12.01
							HC > ATT	A50	4.56	27	0.0001	20.52

PPI, Psychophysiological interaction; BA, Brodmann area; ATT, Adolescent suicide attempters; NAT, non-attempters with a history of major depressive disorder; HC, healthy controls; A50, Angry faces 50% intensity condition; MNI, Montreal Neurological Institute; *k*, cluster; df, degrees of freedom; R, right; L, left.

would show differential patterns of elevated prefrontal cortical activity to angry and happy faces (Jollant *et al.* 2008). We further hypothesized that both adolescent groups with a history of depression would show reduced functional connectivity among anterior cingulate gyri, prefrontal and temporal cortices and insulae to all face emotion conditions relative to HC. Our 3 × 3 factorial design allowed for identification of group differences of the effect of intensity difference. In other words, we report on the group differences of a difference among the three intensities.

In support of our first hypothesis, when viewing 50% intensity angry faces ATT had significantly greater activity than NAT in different prefrontal cortical, anterior cingulate gyral, temporal, and sensory cortical regions, including the right dorsal anterior cingulate gyrus, bilateral primary sensory cortices, left dorsolateral prefrontal cortex, and the right middle temporal gyrus. ATT also showed significantly greater primary sensory cortical activity than HC to 50% intensity angry faces. Additionally, ATT showed reduced activity relative to the other groups in visual, sensory and prefrontal cortical regions and the anterior cingulate gyrus to intense happy faces and to neutral faces in both emotions. Largely in support of our second hypothesis, ATT, although not NAT, showed decreased functional connectivity from an anterior cingulate gyral seed region to bilateral insulae than other groups to 50% intensity angry faces.

Many of our significant findings were found in the dorsal anterior cingulate gyrus in ATT *versus* NAT and HC to 50% intensity angry faces. The dorsal anterior cingulate gyrus supports attention processing (Banich, 2009), emotion processing, salience of emotion, and generation and regulation of emotional response (Etkin *et al.* 2011). Our findings regarding this region may therefore suggest that ATT attended more to 50% intensity angry faces than NAT. Furthermore, PPIs using this anterior cingulate cortical region as a seed region revealed diminished functional connectivity from this region to bilateral posterior insulae in ATT relative to NAT and HC. The posterior insula is implicated in determining stimulus intensity, response selection (Taylor *et al.* 2009) and novelty seeking (Sugiura *et al.* 2000). Connections between the anterior cingulate and posterior insula, particularly the right posterior insula, are implicated in the anticipation of aversive experiences, especially in depressed individuals (Giesecke *et al.* 2005). Furthermore, the posterior insula has a distinct pattern of connectivity, functioning as an input region for subcortical loci such as the amygdala and striatum (Craig, 2011). In ATT, increased dorsal anterior cingulate gyral and other cortical activity, and reduced functional connectivity between this region and insulae, to 50% intensity angry faces may indicate inefficient strategies to

$p = 0.00004$, right, $p = 0.002$), left dorsolateral prefrontal cortex (BA 9, $p = 0.0002$) and the right middle temporal gyrus (BA 21, $p = 0.001$). ATT > healthy controls (HC) in the left primary sensory cortex (BA 4, $p = 0.001$). Values are means, with standard deviations represented by vertical bars. The brain image shown is the 3 × 1 contrast for 50% intensity angry faces. Sagittal image: green = right anterior temporal gyrus (BA 32). Coronal image: blue = left primary sensory cortex (BA 4); purple = right primary sensory cortex (BA 4). Horizontal image: pink = left dorsolateral prefrontal cortex (BA 9); light blue = right middle temporal gyrus (BA 21). (*b*) ATT show significantly lower functional connectivity between the right anterior cingulate gyrus and bilateral insulae when viewing 50% intensity angry faces than NAT (left, $p = 0.002$ and right, $p = 0.0001$) and HC (left, $p = 0.0001$ and right, $p = 0.008$). Values are means, with standard deviations represented by vertical bars. The left insula is shown at the top of the image (blue); the right insula is shown at the bottom (green).

regulate attention to, process the salience of, and select contextually appropriate behavioral responses to these stimuli. In contrast, the pattern of reduced anterior cingulate cortical activity in NAT relative to HC to 50% intensity angry faces may suggest abnormally diminished attention to displays of mild anger in NAT.

ATT also demonstrated greater activity than NAT to 50% intensity angry faces in: (1) the left dorsolateral prefrontal cortex, associated with motor planning and regulation of affect and action (Kaller *et al.* 2011), (2) the right middle temporal gyrus, supporting processing of familiar faces (Haxby *et al.* 2000); and (3) bilateral primary sensory cortices, that may underlie empathic responding to emotional stimuli (Nummenmaa *et al.* 2008), and greater activity than HC in the left primary sensory cortex to these faces. NAT also showed significantly less activity than HC in the right ventromedial prefrontal cortex, a region implicated in emotion valuation (Grabenhorst & Rolls, 2011) to 50% intensity angry faces. These findings may indicate greater attention to, processing of, or empathic response toward, 50% intensity angry faces in ATT than NAT and HC, and abnormally reduced attention to these faces in NAT.

Many of our findings related to 50%, rather than to 100%, intensity angry faces. Milder intensity facial expressions are more likely than 100% 'prototypical' intensity facial expressions to be representative of social displays of emotion (Calder *et al.* 1997; Surguladze *et al.* 2005). Our findings therefore suggest that ATT were distinguished from other groups by neural activity to socially relevant, rather than to prototypical, displays of anger. Greater attention to, and processing of, these pertinent social displays of disapproval may contribute to vulnerability to suicidal behavior in adolescents with a history of depression.

Additional findings indicate significantly reduced activity in anterior cingulate gyral, primary sensory, prefrontal, and visual cortical regions in ATT than NAT or HC to ambiguous neutral faces in the angry run and intense happy and neutral faces in the happy run. ATT had less activity than HC in the left primary sensory cortex to 100% intensity happy faces, less activity in the right anterior cingulate gyrus and left medial frontal gyrus than HC to neutral faces presented in the happy run, and less activity in the left fusiform gyrus than NAT to neutral faces in the angry run. This suggests that ATT may have attended less or demonstrated reduced neural response to these non-angry stimuli than other groups. The diminished regional activation in ATT compared with HC in right BA 32 and left BA 10 to neutral faces in the happy run may further indicate functional abnormalities of the anterior cingulate gyrus or its connectivity in ATT compared with HC. Furthermore, the finding of reduced primary sensory cortical activity to 100% intensity happy faces in ATT relative to HC may suggest abnormally reduced empathic response to these prototypical displays of social approval and reward in ATT (Nummenmaa *et al.* 2008).

Exploratory analyses revealed a positive correlation between activation in the right primary sensory cortex (BA 4) and BDI score in ATT to 50% intensity angry faces, indicating ATT with more depressive symptoms had more activation in this area. Given the role of the primary sensory cortex in empathic responding to sensory stimuli (Nummenmaa *et al.* 2008), this finding suggests greater empathic response to 50% intensity angry faces in ATT with greater severity depression. Surprisingly, in NAT the SIQ score correlated negatively with activation in the left dorsolateral prefrontal cortex to 50% intensity angry faces, indicating NAT with greater morbid ideation had less activity in this region. Given that ATT had greater activity in this region than NAT to 50% intensity angry faces, this finding is difficult to interpret, but suggests different strategies for processing 50% intensity angry faces in ATT compared with NAT with higher ideation.

We have previously shown that suicide attempt during adolescence may not be associated with abnormal activity in the neural circuitry supporting response inhibition, but rather that NAT, relative to ATT, demonstrated a compensatory increased recruitment of the right anterior cingulate gyrus (Pan *et al.* 2011). It is intriguing that the opposite pattern, ATT demonstrating greater activity in this area relative to NAT, was shown during 50% intensity angry face processing. Together, our findings suggest that greater recruitment of the anterior cingulate gyrus with emotion (mild angry face emotion processing), rather than functional abnormalities in this region with cognition (response inhibition), may indicate risk for suicide attempt in adolescence.

It was necessary to recruit ATT and NAT taking medication for depression. Exploratory analyses did not, however, show any significant relationships in NAT and ATT between medication status and activity to angry or happy faces in those regions showing between-group differences. Future studies should aim to recruit medicated and unmedicated ATT and NAT. Given the continued development of cingulo-frontal circuitry throughout adolescence (Monk *et al.* 2003), future longitudinal studies should also examine the developmental trajectories and functional connectivity of these regions during emotion processing.

There were other limitations to the present study. Our main findings from whole-brain analysis

survived SVC with AlphaSim at $p < 0.05$. AlphaSim is a method of correction for multiple comparisons employed in other software packages [e.g. NIMH's Analysis of Functional NeuroImages (AFNI)] and has been used in previous neuroimaging studies of pediatric populations (Gilbert *et al.* 2005; Monk *et al.* 2008; Dickstein *et al.* 2010; Pan *et al.* 2011; Kim *et al.* 2012). Future studies may focus on region of interest analyses as new data about neural circuitry underlying adolescent suicide become available. Our study only examined two emotions. Our *a priori* hypothesis involved angry and happy faces because of previous use in adults with a history of suicide attempt (Jollant *et al.* 2008). Inclusion of other emotions was limited by task duration, but should be a focus of future studies. ATT were more symptomatic than NAT, although there were few significant relationships between measures of depression, anxiety and suicidal ideation and patterns of neural activity in either ATT or NAT. It is not possible to be certain whether the differences between the groups are due to suicide attempt history or illness severity. However, NAT differed more than ATT from HC, despite ATT having greater symptomatology. This is the opposite of what would be expected if the differences were secondary to illness severity. Nonetheless, current depression severity in NAT is much closer to that of HC than ATT, and current symptoms could still be a confound.

Our study is the first to examine the functional integrity of neural circuitry in adolescents with a history of suicide attempt during emotion processing. Our findings suggest that functional abnormalities in neural circuitry implicated in emotional processing, especially in processing mild intensity angry faces, may underlie risk for suicide attempt in adolescence. A goal for future studies is thus to determine the extent to which functional abnormalities in neural circuitry supporting emotional processing and other cognitive processes relevant to suicidal behavior may yield potential biomarkers of suicide risk in adolescence.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291712002966.

Acknowledgements

All work was carried out within the Department of Psychiatry of the University of Pittsburgh. The neuroimaging data were collected at the Brain Imaging Research Center (University of Pittsburgh & Carnegie Mellon University).

We thank the participants who made this work possible.

This research was supported by the American Foundation for Suicide Prevention, the Klingenstein Third Generation Foundation Fellowship for Adolescent Depression [NIMH/National Institute of Child Health (NICHD) 1K23MH082884-01 to L.A.P.], National Institutes of Health grants (MH66775, MH65368, MH56612 and MH18951 to D.A.B.) and NIMH MH076971 (to M.L.P.).

Declaration of Interest

None.

References

Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, Mathews VP, Kalnin A, Lowe MJ (2005). Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biological Psychiatry* **57**, 1079–1088.

Banich MT (2009). Executive function: the search for an integrated account. *Current Directions in Psychological Science* **18**, 89–94.

Beck AT, Schuyler D, Herman I (1974). Development of suicidal intent scales. In *The Prediction of Suicide* (ed. A. T. Beck, H. L. P. Resnick and D. J. Lettieri), pp. 45–56. Charles Press: Bowie, MD.

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

Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, Neer SM (1997). The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry* **36**, 545–553.

Brent DA, Baugher M, Bridge J, Chen T, Chiappetta L (1999). Age- and sex-related risk factors for adolescent suicide. *Journal of the American Academy of Child and Adolescent Psychiatry* **38**, 1497–1505.

Calder AJ, Young AW, Rowland D, Perrett DI (1997). Computer-enhanced emotion in facial expressions. *Proceedings in Biological Science* **264**, 919–925.

Craig AD (2011). Significance of the insula for the evolution of human awareness of feelings from the body. *Annals of the New York Academy of Sciences* **1225**, 72–82.

Cullen KR, Gee DG, Klimes-Dougan B, Gabbay V, Hulvershorn L, Mueller BA, Camchong J, Bell CJ, Houri A, Kumra S, Lim KO, Castellanos FX, Milham MP (2009). A preliminary study of functional connectivity in co-morbid adolescent depression. *Neuroscience Letters* **460**, 227–231.

Dickstein DP, Finger EC, Skup M, Pine DS, Blair JR, Leibenluft E (2010). Altered neural function in pediatric bipolar disorder during reversal learning. *Bipolar Disorders* **12**, 707–719.

Etkin A, Egner T, Kalisch R (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Science* **15**, 85–93.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* **6**, 218–229.

Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ (2005). The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis and Rheumatism* **52**, 1577–1584.

Gilbert AR, Akkal D, Almeida JRC, Mataix-Cols D, Kalas C, Devlin B, Birmaher B, Phillips ML (2005). Neural correlates of symptom dimensions in pediatric obsessive-compulsive disorder: a functional magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry* **48**, 936–944.

Grabenhorst F, Rolls ET (2011). Value, pleasure and choice in the ventral prefrontal cortex. *Trends in Cognitive Science* **15**, 56–67.

Hassel S, Almeida JR, Kerr N, Nau S, Ladouceur CD, Fissell K, Kupfer DJ, Phillips ML (2008). Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. *Bipolar Disorders* **10**, 916–927.

Haxby JV, Hoffman EA, Gobbini MI (2000). The distributed human neural system for face perception. *Trends in Cognitive Science* **4**, 223–233.

Hulvershorn LA, Cullen K, Anand A (2011). Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. *Brain Imaging and Behavior* **5**, 307–328.

Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R, Castelnau D, Malafosse A, Courtet P (2005). Impaired decision making in suicide attempters. *American Journal of Psychiatry* **162**, 304–310.

Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, Courtet P, Phillips ML (2008). Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. *American Journal of Psychiatry* **165**, 740–748.

Kaller CP, Heinze K, Frenkel A, Läppchen CH, Unterrainer JM, Weiller C, Lange R, Rahm B (2011). Differential impact of continuous theta-burst stimulation over left and right DLPFC on planning. *Human Brain Mapping*. Published online: 14 October 2011. doi:10.1002/hbm.21423.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry* **36**, 980–988.

Keilp JG, Sackeim HA, Brodsky BS, Oquendo MA, Malone KM, Mann JJ (2001). Neuropsychological dysfunction in depressed suicide attempters. *American Journal of Psychiatry* **158**, 735–741.

Killgore WD, Yurgelun-Todd DA (2006). Ventromedial prefrontal activity correlates with depressed mood in adolescent children. *NeuroReport* **17**, 167–171.

Kim P, Thomas LA, Rosen BH, Moscicki AM, Brotman MA, Zarate CA, Blair RJ, Pine DS, Liebenluft E (2012). Differing amygdale responses to facial expressions in children and adults with bipolar disorder. *American Journal of Psychiatry* **169**, 642–649.

Ladouceur CD, Farchione T, Diwadkar V, Pruitt P, Radwan J, Axelson DA, Birmaher B, Phillips ML (2011). Differential patterns of abnormal activity and connectivity in the amygdala-prefrontal circuitry in bipolar-I and bipolar-NOS youth. *Journal of the American Academy of Child and Adolescent Psychiatry* **50**, 1275–1289.

Lau JY, Goldman D, Buzas B, Hodgkinson C, Leibenluft E, Nelson E, Sankin L, Pine DS, Ernst M (2010). BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. *NeuroImage* **53**, 952–961.

Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Frangou S, Ecker C, Phillips ML (2004). Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biological Psychiatry* **55**, 578–587.

Lubell KM, Kegler SR, Crosby AE, Karch D (2007). Suicide trends among youths and young adults aged 10–24 years – United States, 1990–2004. *MMWR Morbidity and Mortality Weekly Report* **56**, 905–908.

Mann JJ, Huang YY, Underwood MD, Kassir SA, Oppenheim S, Kelly TM, Dwork AJ, Arango V (2000). A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Archives of General Psychiatry* **57**, 729–738.

Monk CS, McClure EB, Nelson EE, Zarahn E, Bilder RM, Leibenluft E, Charney DS, Ernst M, Pine DS (2003). Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *NeuroImage* **20**, 420–428.

Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HM, Chen G, McClure-Tone EB, Ernst M, Pine DS (2008). Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of General Psychiatry* **65**, 568–576.

Nummenmaa L, Hirvonen J, Parkkola R, Hietanen JK (2008). Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. *NeuroImage* **43**, 571–580.

Oquendo MA, Halberstam B, Mann JJ (2003*a*). Risk factors for suicidal behavior: utility and limitations of research instruments. In *Standardized Evaluation in Clinical Practice* (ed. M. B. First), pp. 103–130. American Psychiatric Press: Washington, DC.

Oquendo MA, Placidi GP, Malone KM, Campbell C, Keilp J, Brodsky B, Kegeles LS, Cooper TB, Parsey RV, van Heertum RL, Mann JJ (2003*b*). Positron emission

tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. *Archives of General Psychiatry* **60**, 14–22.

Pan LA, Batezati-Alves SC, Almeida JR, Segreti A, Akkal D, Hassel S, Lakdawala S, Brent DA, Phillips ML (2011). Dissociable patterns of neural activity during response inhibition in depressed adolescents with and without suicidal behavior. *Journal of the American Academy of Child and Adolescent Psychiatry* **50**, 602–611.

Petersen AC, Crockett L, Richards M, Boxer A (1988). A self-report measure of pubertal status: reliability, validity, and initial norms. *Journal of Youth and Adolescence* **17**, 117–133.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M (2007). Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *American Journal of Psychiatry* **164**, 1035–1043.

Reynolds WM (1987). *Suicidal Ideation Questionnaire: Professional Manual*. Psychological Assessment Resources: Odessa, FL.

Sugiura M, Kawashima R, Nakagawa M, Okada K, Sato T, Goto R, Sato K, Ono S, Schormann T, Zilles K, Fukuda H (2000). Correlation between human personality and neural activity in cerebral cortex. *NeuroImage* **11**, 541–546.

Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, Williams SC, Phillips ML (2005). A differential pattern of neural response toward sad *versus* happy facial expressions in major depressive disorder. *Biological Psychiatry* **57**, 201–209.

Taylor KS, Seminowicz DA, Davis KD (2009). Two systems of resting state connectivity between the insula and cingulate cortex. *Human Brain Mapping* **30**, 2731–2745.

Versace A, Thompson WK, Zhou D, Almeida JR, Hassel S, Klein CR, Kupfer DJ, Phillips ML (2010). Abnormal left and right amygdala–orbitofrontal cortical functional connectivity to emotional faces: state *versus* trait vulnerability markers of depression in bipolar disorder. *Biological Psychiatry* **67**, 422–431.

Wechsler D (1999). *Wechsler Abbreviated Scale of Intelligence*. Harcourt Assessment: San Antonio, TX.

Young AW, Perrett D, Calder A (2002). *Facial Expressions of Emotions: Stimuli and Test* (*FEEST*). Thames Valley Test Company: Bury St Edmunds.

Yurgelun-Todd DA, Killgore WD (2006). Fear-related activity in the prefrontal cortex increases with age during adolescence: a preliminary fMRI study. *Neuroscience Letters* **406**, 194–199.