

# Neural Processing of Reward and Punishment in Young People at Increased Familial Risk of Depression

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**Background:** Abnormalities in the neural representation of rewarding and aversive stimuli have been well-described in patients with acute depression, and we previously found abnormal neural responses to rewarding and aversive sight and taste stimuli in recovered depressed patients. The aim of the present study was to determine whether similar abnormalities might be present in young people at increased familial risk of depression but with no personal history of mood disorder.

**Methods:** We therefore used functional magnetic resonance imaging to examine the neural responses to pleasant and aversive sights and tastes in 25 young people (16–21 years of age) with a biological parent with depression and 25 age- and gender-matched control subjects.

**Results:** We found that, relative to the control subjects, participants with a parental history of depression showed diminished responses in the orbitofrontal cortex to rewarding stimuli, whereas activations to aversive stimuli were increased in the lateral orbitofrontal cortex and insula. In anterior cingulate cortex the at-risk group showed blunted neural responses to both rewarding and aversive stimuli.

**Conclusions:** Our findings suggest that young people at increased familial risk of depression have altered neural representation of reward and punishment, particularly in cortical regions linked to the use of positive and negative feedback to guide adaptive behavior.

**Key Words:** Anterior cingulate, depression, functional magnetic resonance imaging, punishment, reward, vulnerability

Loss of interest and pleasure (anhedonia) are important symptoms in the diagnosis of acute major depression and are generally regarded as representing abnormalities in reward mechanisms. Consistent with this, functional imaging studies of depressed patients have shown abnormalities in the neural circuitry that supports reward (1–5). For example, reduced ventral striatal responses to several kinds of rewarding stimuli have been reported in acute depression, whereas Knutson *et al.* (3) found an altered pattern of responses in the anterior cingulate cortex to monetary reward. A similar neural network was identified in a study examining behavioral and neural response to feedback information during a gambling task where depressed patients showed decreased responses in the ventral striatum and anterior cingulate to feedback information of winning or losing and did not adjust their response times accordingly, unlike the control group (6).

It has been suggested that the neurobiological mechanisms underlying anhedonia could represent an endophenotype of depression that might manifest in behavioral and neural outcome changes outside acute depressive episodes (7). Although anhedonic symptoms usually remit as depression improves, it is possible that abnormalities in the neural processes underpinning reward could persist and represent vulnerability factors for future episodes of illness. In a previous study we used a paradigm involving the sight and taste of chocolate to probe reward circuitry in unmedicated recovered depressed patients (8). We found that participants recovered from depression showed decreased responses to chocolate in both ventral striatum and anterior cingulate cortex, suggesting that abnormalities in the neural basis of reward might be a trait marker of vulnerability to depression. It is also possible, however,

that changes in the neural response to reward could be a consequence of recurrent depression or its treatment.

One way to resolve this question is to study reward in people at increased risk of depression before the onset of illness. Numerous risk factors for depression have been described, but one of the most reliable is family inheritance. For example, it has been estimated that by young adulthood up to 40% of children of parents with a clinical mood disorder will have suffered a personal episode of depression (9). The present study therefore examined the neural response to sight and taste of rewarding and aversive stimuli in young people with a depressed parent but no personal history of depression (FH+) compared with matched control subjects. We hypothesized that FH+ individuals would have diminished neural responses to typical reward-related areas such as the anterior cingulate, orbitofrontal cortex, and striatum (10–13). There are also data on the neural processing of aversive tastes in healthy subjects, which have been shown to activate brain regions such as the lateral orbitofrontal cortex/insula and caudate (12). The neural processing of aversive tastes in acutely depressed patients has not been studied to our knowledge (14); however, we hypothesized that FH+ participants would have increased neural responses to the aversive condition, because we have previously shown this effect in recovered depressed patients with the same task (8).

## Methods and Materials

### Participants

We recruited 25 young people (age range 16–21 years) who had never personally suffered from major depression but who reported a biological parent with a history of major depression (FH+) (Table 1). Potential participants were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders Schedule (15) to exclude a personal current or previous history of major depression or any other Axis I disorder. The presence of major depression in a parent was assessed by the family history method with the participant as an informant (16). Parents were then approached directly with a standardized questionnaire. We included participants where a diagnosis of clinical depression had been made by a general practitioner and/or psychiatrist and the symptoms described met criteria for major depression, together with the prescription of specific treatment, either psychotherapy or medication (all but one of the

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**Table 1.** Group Demographic and Psychosocial Measures

Measure	Family History ( <i>n</i> = 25)	Control Subjects ( <i>n</i> = 25)
	Mean (SD)	Mean (SD)
Age, Years	18.6 (1.6)	19.2 (1.2)
Gender	F = 16 M = 9	F = 16 M = 9
BDI	3.6 (3.4)	2.5 (2.5)
FCPS	134 (15)	134 (12)
SHAPS	21.8 (4.17)	20.6 (4.26)
BMI	22 (2.4)	22 (2)
Chocolate Craving	6.5 (1.8)	6.3 (2)
Chocolate Liking	7.5 (1.5)	8.3 (1)
Frequency of Eating Chocolate	2 (1)	2.2 (1)

One-way analysis of variance, all  $p > .09$ .

BDI, Beck Depression Inventory; BMI, body mass index; F, female; FCPS, Fawcett Clarke Pleasure Scale; M, male; SHAPS, Snaith-Hamilton Pleasure Scale.

parents had received antidepressant medication at some stage of their illness). A history of bipolar disorder in a parent was an exclusion criterion. We did not attempt to assess the possible presence of other Axis I or II disorders in parents. We also recruited 25 control subjects (age range 16–21 years) who were determined by the same instruments to have no current or past history of major depression and no history of depression in a biological parent or other first-degree relative (HC). All participants were right-handed, according to the Edinburgh Handedness Inventory (17), and had normal or corrected to normal vision. Participants with any contraindications for magnetic resonance imaging examination or neurological disorders were excluded. Ethical approval was obtained from the Oxford Research Ethics Committee B, and after complete description of the study to the subjects, written informed consent was obtained.

None of the participants took current medication apart from the contraceptive pill. Baseline ratings of mood and anhedonia were collected with the Beck Depression Inventory (BDI) (18), the Fawcett-Clarke Pleasure Scale (19), and the Snaith-Hamilton Pleasure Scale (20). The participants also completed a “chocolate questionnaire” to measure liking, craving, and frequency of eating chocolate (13). Body mass index was also calculated for each volunteer.

### Experimental Design

We compared brain responses to rewarding and aversive stimuli across the two participant groups. Each of the following conditions were applied nine times in a randomized order (Table S1 in Supplement 1): chocolate in the mouth, chocolate picture, chocolate in the mouth with chocolate picture, medicinal-flavored strawberry in the mouth, unpleasant strawberry picture (strawberries with mold on them), and strawberry in the mouth with strawberry picture. Subjective effects of the stimuli were measured on a four-point scale rating of “pleasantness,” “intensity,” and “wanting” made on every trial by the subjects during the functional magnetic resonance imaging acquisition. The participants were instructed not to eat chocolate for 24 hours before the scan and to eat only a small breakfast on the day of scanning. Scanning took place between 9:00 AM and 12:00 noon. Mood state was recorded on the study day with the BDI.

### Rewarding and Aversive Stimuli

Stimuli were delivered to the mouth of the subject through three Teflon tubes (one for the tasteless rinse control described in the following text, one for chocolate taste, and one for strawberry taste; World Precision Instruments, Sarasota, Florida); the tubes were held between the lips. Each tube was connected to a separate

reservoir via a syringe and a one-way syringe-activated check valve (Model 14044-5; World Precision Instruments, Sarasota, Florida), which allowed .5 mL of any stimulus to be delivered manually at the time indicated by the computer. The chocolate was formulated to be liquid at room temperature, with a list of the 6 stimulus conditions described in Table S1 (Supplement 1). The aversive stimulus was a medicinal-flavored strawberry flavored placebo solution (Rosemount Pharmaceuticals, Leeds, United Kingdom), which was rated equal in intensity to the chocolate but unpleasant in valence (8). A control tasteless solution .5 mL of a saliva-like rinse solution ( $25 \times 10^{-3}$  mol/L potassium chloride and  $2.5 \times 10^{-3}$  mol/L sodium bicarbonate in distilled water) was used after every trial that had a taste component (tl in Table S1 in Supplement 1), and a control gray image was used after every trial that had a sight-only component. After trials with both sight and taste combined, both the control tasteless solution and the gray image were delivered. This allowed the subtraction on every trial of the appropriate control condition. This allows the taste, texture, and olfactory areas to be shown independently of any somatosensory effects produced by introducing a fluid into the mouth (12,21,22). Both the liquid chocolate and strawberry had approximately the same texture, which enabled them to pass freely through the Teflon delivery tubes.

### Experimental Procedure

At the beginning of each trial, one of the six stimuli chosen by random permutation was presented. If the trial involved an oral stimulus, this was delivered in a .5-mL aliquot to the mouth of the subject. At the same time a visual stimulus was presented, which was the picture of chocolate, moldy strawberries, or a gray control image of approximately the same intensity. The image was turned off after 7 sec at which time a small green cross seemed on a visual display to indicate to the subject to swallow what was in the mouth. After a delay of 2 sec, the subject was asked to rate each of the stimuli for “pleasantness” on that trial (with +2 being very pleasant and –2 very unpleasant), for “intensity” on that trial (0 to +4), and for “wanting” (+2 for wanting very much, 0 for neutral, and –2 for very much not wanting). The ratings were made with a visual analogue scale in which the subject moved the bar to the appropriate point on the scale with a button box. After the last rating the gray visual stimulus indicated the delivery of the tasteless control solution, which was also used as a rinse between stimuli; this was administered in exactly the same way as a test stimulus, and the subject was cued to swallow after 7 sec by the green cross. The tasteless control was always accompanied by the gray visual stimulus. On trials in which only the picture of chocolate or picture of strawberries was shown, there was no rinse, but the gray visual stimulus was shown to allow an appropriate contrast as previously described.

### Functional Magnetic Resonance Imaging Data Acquisition

The experimental protocol consisted of an event-related interleaved design using in random permuted sequence, the six stimuli described in Table S1 in Supplement 1. Images were acquired with a 3.0-T Varian/Siemens (Varian, Palo Alto, California) whole-body scanner at the Oxford Centre for Clinical Magnetic Resonance Imaging, where T2\* weighted echo-planar imaging slices were acquired every 2 sec (repetition time = 2). Imaging parameters were selected to minimize susceptibility and distortion artifact in the orbitofrontal cortex (23). Coronal slices with in-plane resolution of  $3 \times 3$  mm and between plane spacing of 4 mm were obtained. The matrix size was  $64 \times 64$ , and the field of view was  $192 \times 192$  mm. Acquisition was carried out during the task performance, yielding

972 volumes in total. A whole brain T2\* weighted echo-planar imaging volume of the aforementioned dimensions and an anatomical T1 volume with coronal plane slice thickness 3 mm and in-plane resolution of  $1.0 \times 1.0$  mm were also acquired.

### Data Analysis

The imaging data were analyzed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). Preprocessing of the data used realignment, reslicing with sinc interpolation, normalization to the Montreal Neurological Institute coordinate system and spatial smoothing with a 6 mm full width at half maximum isotropic Gaussian kernel. Time series nonsphericity at each voxel was estimated and corrected for (24), and a high-pass filter with a cutoff period of 128 sec was applied. In the single event design, a general linear model was then applied to the time course of activation where stimulus onsets were modeled as single impulse response functions and then convolved with the canonical hemodynamic response function (25). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation, linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding *t* statistic, which was then transformed into the unit normal distribution (SPM *Z*). Second-level, random effects analyses accounted for both scan-to-scan and subject-to-subject variability. The SPM converts the *t* statistics to *Z* scores (Table 2). We found a similar pattern of activation across the pleasant chocolate conditions, and so to minimize the number of comparisons and to increase statistical power we combined the pleasant chocolate conditions into one contrast and the unpleasant strawberry conditions into another.

We examined simple main effects of condition with one-sample *t* tests, in the healthy control group only. These results are thresholded at  $p < .05$  family-wise error (FWE) for multiple comparisons across the entire brain (Table S2 in Supplement 1). Between group analyses report small volume corrections for brain regions in which we had an a priori hypothesis on the basis of our previous studies in young people at increased familial risk and healthy control subjects and recovered depressed patients with the current task, as follows (8,10–13,26–28): ventral striatum (–4, 16, –12), cingulate cortex

(–6, 2, 46) (–8, 38, 14) (2, 26, 18) (4, 30, 8), orbitofrontal cortex (–34, 24, 0), lateral orbitofrontal cortex (44, 14, –2), and caudate (10, 14, 0). Peaks within 15 mm of these and that had a *p* value of  $< .05$  uncorrected in the whole-brain analysis and with a cluster threshold of at least 30 contiguous voxels ( $k = 30$ ) had applied small volume (FWE) corrections for multiple comparisons. Plots of contrast estimates are extracted with the plots tool in SPM8. Coordinates of the activations are listed in the stereotactic space of the ICBM152 brain of The Montreal Neurological Institute (Table 2; Table S3 in Supplement 1).

## Results

### Demographic Data and Ratings

There were no significant differences between the FH+ and control participants as determined by a one-way analysis of variance (ANOVA) for age, gender, body mass index, chocolate craving, liking, or frequency of eating chocolate (Table 1). There were no significant differences between the two groups as determined by one-way ANOVAs for measures of anhedonia (Snaith-Hamilton Pleasure Scale, Fawcett-Clarke Pleasure Scale) or mood (BDI) all  $p > .09$  (Table 1).

Ratings of pleasantness, intensity, and wanting for the stimuli were obtained during the scanning on each trial for every condition. All subjects rated the strawberry picture and taste as unpleasant and the chocolate stimuli as pleasant. With repeated measures ANOVA with “ratings” as a first factor with three levels and pleasantness, intensity and wanting, and “condition” as a second factor with six levels (Table S1 in Supplement 1 for six condition levels), there was no significant effect of group [ $F(1,48) = .002, p = .96$ ] or group  $\times$  condition  $\times$  ratings interaction [ $F(1,48) = .0, p = .98$ ] (Figure S1 in Supplement 1).

### Main Effects of Stimuli on Blood Oxygen Level-Dependent Responses

Table S2 (Supplement 1) provides a summary of the main effects of one-sample *t* tests for the rewarding chocolate stimuli versus the control stimuli and the aversive strawberry stimuli versus the control stimuli. As expected, the pleasant chocolate stimuli activated reward-relevant circuitry, including the ventral striatum, the anterior insula, and parts of the anterior cingulate cortex. The unpleasant strawberry stimuli activated areas involved in aversive processing, including the posterior insula cortex, the caudate, the lateral orbitofrontal cortex, and anterior cingulate cortex but not the ventral striatum (Table S2 in Supplement 1).

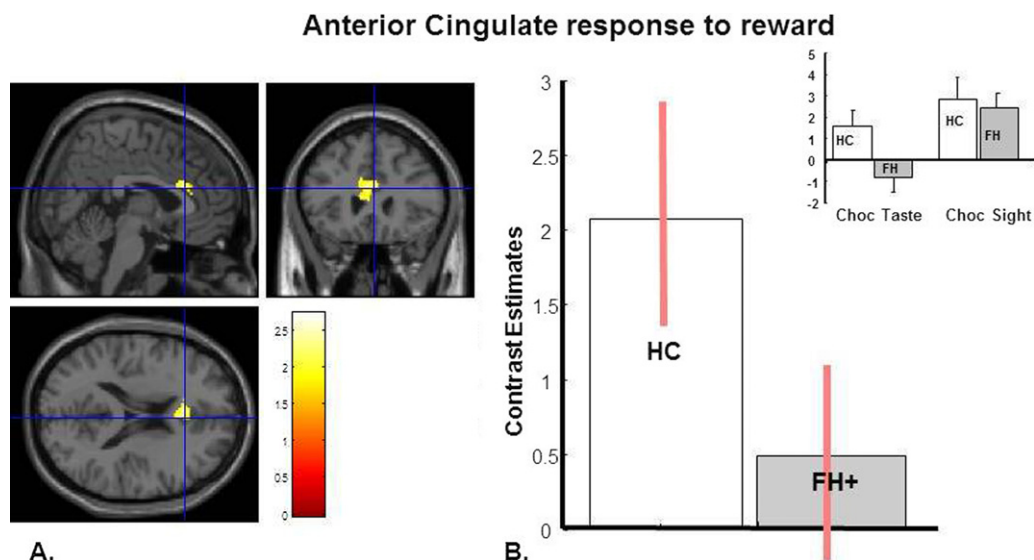
### Effect of Family History on Blood Oxygen Level-Dependent Responses

Table 2 provides a summary of the results of the interaction with group. The FH+ group, compared with the control group, showed less blood oxygen level-dependent (BOLD) activation to the chocolate stimuli combined (vs. control taste and sight) in rostral and dorsal anterior cingulate and orbitofrontal cortex (Figures 1 and 2; contributions of primary and secondary rewards shown as inset). Relative to control subjects the FH+ group also exhibited lower BOLD activation to the aversive strawberry stimuli combined (vs. control taste and sight) in the rostral and dorsal anterior cingulate cortex; however, FH+ participants showed increased BOLD activation to the strawberry stimuli in lateral orbitofrontal cortex/insula (Figure 3; contributions of primary and secondary aversive stimuli shown as inset) (Table 2).

**Table 2.** Regions Showing Significant Effect of Family History on Each Condition Relative to Control Subjects

Brain Region (Brodmann area)	MNI Coordinates			Z Score (cluster size)	<i>p</i>
	X	Y	Z		
<b>All Chocolate Stimuli</b>					
HC > FH+					
dACC	8	4	32	2.92 (72)	.01
dACC	–2	26	20	2.4 (76)	.05
rACC	10	40	22	2.7 (81)	.02
OFC	–30	34	4	2.94 (74)	.01
<b>All Strawberry Stimuli</b>					
HC > FH+					
dACC	6	2	32	3.12 (75)	.009
rACC	8	42	24	2.58 (63)	.03
FH+ > HC					
LOFC/insula	44	20	–16	3.29 (37)	.005
OFC	–24	44	–2	3.06 (78)	.01

*p* values voxel level ( $p < .05$  family-wise error) small volume corrected. dACC, dorsal anterior cingulate; FH+, family history of depression; HC, healthy control subjects; LOFC, lateral orbitofrontal cortex; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; rACC, rostral anterior cingulate.



**Figure 1. (A)** All chocolate stimuli (healthy control subject [HC] vs. people with a depressed parent but no personal history of depression [FH+]): axial, sagittal, and coronal image of decreased anterior cingulate in the FH+ group compared with the control group, small volume corrected ( $p < .05$  family-wise error for multiple comparisons). **(B)** Contrast estimates for anterior cingulate centered at  $-2, 26, 20$  for HC and FH+ groups.

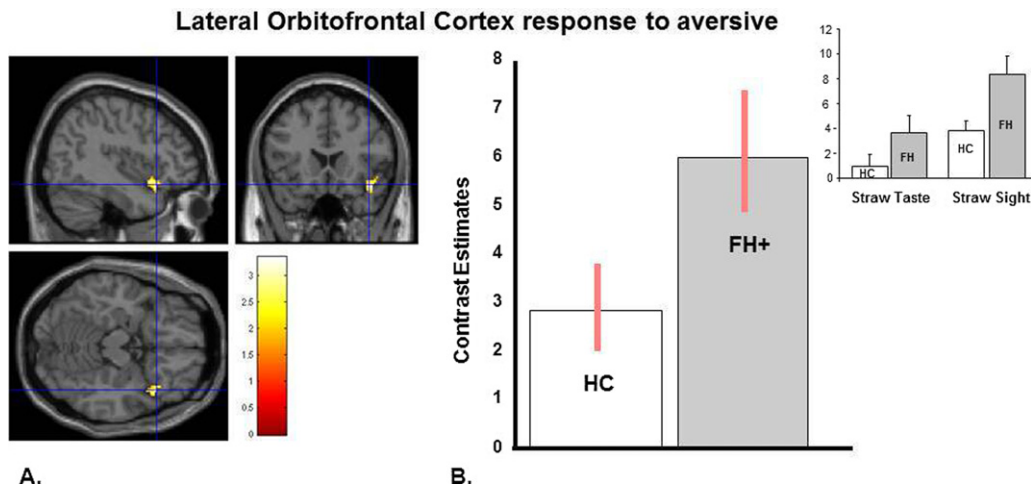
## Discussion

The aim of the current study was to examine the neural response to primary and secondary rewarding and aversive stimuli in young people at increased familial risk of depression who had never experienced depression themselves. Our findings support the hypothesis that young at-risk individuals show abnormalities in the neural representation of reward and punishment, notably in the cortical areas relevant to this processing, particularly anterior cingulate (both dorsal and rostral) but also orbitofrontal cortex and insula. However, we found no differences in ventral striatal responses to reward between the control and at-risk groups, which seems to distinguish the latter from recovered depressed patients (8). Our model permits examination of neural responses to both primary reward/aversion (taste) and secondary reward/aversion (sight) stimuli. We find that these stimuli produce rather similar, over-

lapping areas of activation; therefore, our current practice is to combine them for purposes of analysis. The present study shows that generally similar changes between FH+ and control subjects were seen with both sets of stimuli, although the differences in reward responses seemed stronger with the primary taste stimuli (Figures 1–3).

There have been relatively few studies of rewarding and aversive processing in high-risk individuals before the onset of depression. Gotlib *et al.* (29) studied girls 10–14 years of age, whose mothers suffered from recurrent depression, in a monetary incentive task. They found that, compared with control subjects, the high-risk group showed lower activation in ventral striatum to the anticipation and receipt of reward. Activity in the left insula to reward anticipation was also lowered, whereas that in right insula was increased, consistent with a role for the latter structure in prediction

**Figure 2. (A)** All chocolate stimuli (healthy control subject [HC] vs. people with a depressed parent but no personal history of depression [FH+]): axial, sagittal, and coronal image of decreased orbitofrontal cortex in the FH+ group compared with the control group, small volume corrected ( $p < .01$  family-wise error for multiple comparisons). **(B)** Contrast estimates for orbitofrontal cortex centered at  $-30, 34, 4$  for HC and FH+ groups.



**Figure 3.** (A) All strawberry stimuli (people with a depressed parent but no personal history of depression [FH+] vs. healthy control subject [HC]): axial, sagittal, and coronal image of increased lateral orbitofrontal cortex/insula in the FH+ group compared with the control group, small volume corrected ( $p < .005$  family-wise error for multiple comparisons). (B) Contrast estimates for lateral orbitofrontal cortex/insula centered at 44, 20, -16 for HC and FH+ groups.

error (29,30). Also studying children and adolescents at increased risk of depression (mean age 14 years), Monk *et al.* (31) found increased neural response in amygdala and nucleus accumbens to fearful facial expressions, whereas the accumbal response to happy faces was blunted. Although the findings of these studies differ from our own, perhaps because of the nature of the population studied or the tasks employed, they do support the suggestion that abnormalities in the neural representation of reward might be present in at-risk individuals before the onset of depressive disorder.

Our study used more direct rewarding and aversive stimuli in a somewhat older high-risk population. We also found evidence of diminished neural response to reward in young people at increased familial risk of depression, although in cortical rather than the striatal areas identified by the previous studies. Specifically we found decreased responses to the rewarding chocolate stimuli in both orbitofrontal and anterior cingulate cortex in the FH+ group compared with healthy control subjects. The orbitofrontal cortex is an integral part of the reward network (32–34) whose function includes updating neural representations of objects to reflect their current biological value (35,36). Thus in nonhuman primates, lesions of orbitofrontal cortex diminish the ability of animals to use positive feedback in tasks involving reward reversal (35,37). Dysfunction of the orbitofrontal cortex is also commonly reported in functional imaging studies of depressed patients and has been linked to impairments in probabilistic learning (5). Whether similar learning impairments in the presence of positive feedback might be present in those at increased risk of depression remains to be established.

The anterior cingulate cortex plays a role in linking actions to negative and positive outcomes (35). For example, in monkeys, lesions of the anterior cingulate impair the use of positive feedback to maintain correct response strategies after action reversal (38), whereas in humans, neuroimaging studies show that activation in the anterior cingulate cortex correlates with learning a range of action-outcome contingencies, from motor responses to abstract decision making (39). Therefore our finding of diminished activation of anterior and rostral cingulate cortex to both rewarding and aversive stimuli in FH+ participants might indicate potential difficulties in the use of rewarding and aversive information to maintain appropriate behavioral strategies.

It is of interest that in a previous study we found that FH+ participants, in contrast to healthy control subjects, failed to demonstrate affective modulation in the same region of the rostral anterior cingulate cortex in an emotional Stroop task (26), adding to the evidence that abnormal anterior cingulate activity might be a marker of vulnerability to depression. Whether there are neuroanatomical abnormalities in anterior cingulate in young people before the onset of depression is unclear. However, Boes *et al.* (40) found lower anterior cingulate volumes in boys (7–17 years of age) with subclinical depressive symptoms and a significant negative correlation between anterior cingulate volume and depressive symptomatology was stronger in participants with a positive family history of major depression. We also found impaired activation of the rostral and dorsal anterior cingulate to chocolate reward in unmedicated recovered depressed patients (8), suggesting that this abnormality might represent a trait marker of depression throughout different phases of the illness. Unlike recovered depressed patients, the high-risk group studied here did not show impaired ventral striatal responses to chocolate (8); this might suggest that the latter abnormality develops through the course of recurrent depressive illness or its treatment. However, the findings of Gotlib *et al.* (29) suggest that impaired striatal responses to reward can be demonstrated in young at-risk individuals with reward paradigms demanding a higher level of incentive responses. Our study would have been strengthened by the addition of a group of young people experiencing current major depression.

The lateral region of orbitofrontal cortex and insula are known to be activated by aversive stimuli (e.g., the unpleasant taste and sight of strawberry in present study) as well as other punishment stimuli (e.g., monetary loss) (41,42). It is therefore of interest that we found increased activation in the FH+ participants in these brain regions to the aversive strawberry condition. Depressed patients characteristically show two general kinds of behavioral response to punishment: 1) an inability to use negative feedback to guide adaptive behavior, and 2) an increased emotional response to perceived failure (14). Our finding in FH+ participants of a blunted neural response to aversive stimuli in anterior cingulate cortex but increased responses in lateral orbitofrontal cortex intriguingly maps onto both these behavioral abnormalities. Difficulties in linking punishment information with outcomes in anterior cingulate could lead to problems in responding with appropriate actions in the

presence of negative feedback. Conversely, increased aversive coding of punishment in lateral orbitofrontal cortex and insula could enhance the value of the unpleasant stimulus and lead to a greater negative emotional response.

Judged by their ratings, the FH+ participants did not have different subjective experiences of the rewarding and aversive stimuli during the study. Furthermore, their ratings on scales of mood and anhedonia did not differ from control subjects. We suggest, however, that there are ways in which abnormalities in the neural representation of reward and punishment could predispose to clinical depression in high-risk individuals.

As outlined in the preceding text, both animal and human studies suggest that deficient processing of reward and punishment in orbitofrontal cortex and anterior cingulate could lead to difficulties in using negative and positive feedback to guide behavior appropriately (35,36). It seems plausible that impairments of this sort might increase the risk of affected individuals experiencing adverse life events, which are key triggers for early episodes of depression (43); interestingly, there is evidence that people at increased genetic risk of depression might inadvertently “select” environments in which adversity is more likely (44). It is therefore possible that impairments in reward- and punishment-based learning could contribute to difficulties in social decision-making. However, it will be important in future studies to assess whether, in young people at increased familial risk of depression, impaired neural processing of reward is indeed associated with deficits in behavioral tasks designed to tap both social and reward-based learning (45). It is also possible that the abnormalities we have described might lead to impaired neural and behavioral responses to independently occurring adverse life events, making adaptive coping more difficult. To test these hypotheses it will be necessary to follow-up high-risk individuals to ascertain whether any of the neural abnormalities identified here might predict the occurrence of life events as well as the psychological responses to them, including clinical depression.

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*Supplementary material cited in this article is available online.*

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