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Reward Versus Nonreward Sensitivity of the Medial Versus Lateral Orbitofrontal Cortex Relates to the Severity of Depressive Symptoms

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ABSTRACT

BACKGROUND: The orbitofrontal cortex (OFC) is implicated in depression. The hypothesis investigated was whether the OFC sensitivity to reward and nonreward is related to the severity of depressive symptoms.

METHODS: Activations in the monetary incentive delay task were measured in the IMAGEN cohort at ages 14 years (n = 1877) and 19 years (n = 1140) with a longitudinal design. Clinically relevant subgroups were compared at ages 19 (high-severity group: n = 116; low-severity group: n = 206) and 14.

RESULTS: The medial OFC exhibited graded activation increases to reward, and the lateral OFC had graded activation increases to nonreward. In this general population, the medial and lateral OFC activations were associated with concurrent depressive symptoms at both ages 14 and 19 years. In a stratified high-severity depressive symptom group versus control group comparison, the lateral OFC showed greater sensitivity for the magnitudes of activations related to nonreward in the high-severity group at age 19 (p = .027), and the medial OFC showed decreased sensitivity to the reward magnitudes in the high-severity group at both ages 14 (p = .002) and 19 (p = .002). In a longitudinal design, there was greater sensitivity to nonreward of the lateral OFC at age 14 for those who exhibited high depressive symptom severity later at age 19 (p = .003).

CONCLUSIONS: Activations in the lateral OFC relate to sensitivity to not winning, were associated with high depressive symptom scores, and at age 14 predicted the depressive symptoms at ages 16 and 19. Activations in the medial OFC were related to sensitivity to winning, and reduced reward sensitivity was associated with concurrent high depressive symptom scores.

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Not receiving expected rewards (i.e., nonreward), or receiving unpleasant stimuli or events, can produce feelings of depression (1–6). This class of stimuli activates the human lateral orbitofrontal cortex (OFC), and it has been proposed that oversensitivity or overconnectivity of the lateral OFC may be involved in depression (7). Consistent with this, unmedicated patients with depression have increased functional connectivity of the lateral OFC with brain areas involved in memory and the sense of self, including the posterior cingulate cortex and the precuneus, and these functional connectivities are decreased by treatment with antidepressants (8–12). The medial orbitofrontal reward system is also implicated in depression, and indeed the medial reward versus lateral nonreward and punishment orbitofrontal systems are often reciprocally related in their activations (13,14). Furthermore, the anhedonia of depression can be related to decreased effects of pleasant rewarding stimuli in the medial OFC (15,16), a structure that has low functional connectivity in depression with medial temporal lobe memory–related areas, consistent with the hypothesis that this contributes to or reflects the fewer happy memories in depression (11).

During reward anticipation in the monetary incentive delay (MID) task, the ventral striatum (VS), pallidum, insula, thalamus, hippocampus, cingulate cortex, midbrain, motor area, and occipital areas were activated (17,18). In previous studies, including meta-analyses (19,20), decreased activations in the striatum in the MID and other reward tasks were

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found in response to reward in both patients with depression (19) and adolescents with a high depression risk (21,22) and in the VS were found in response to monetary reward anticipation in adolescents with high depression severity (23). There was little focus on the OFC even though it is a key brain region in the reinforcement learning process and projects to the VS (7,24,25). In a gambling task, OFC activation to losing money was negatively correlated with depression symptoms in adolescents at the current time and 9 months later (26). However, the effects were not separated for the medial versus lateral OFC, which is important (as shown here). Here we report that the lateral OFC is activated by nonreward (not winning) and is more activated in those with high depressive symptom scores, whereas the medial OFC is activated by reward (winning) and is less activated in those with high depressive symptom scores.

Given this background, and because the OFC is a key brain region in emotion, reward, and reward-related learning (7,24,27–29), the central aim of this study was to test whether the OFC has sensitivity to receiving rewards or not receiving rewards (i.e., nonreward) that can be related to the severity of depressive symptoms. To test this, data from a large population of adolescents in the MID task were analyzed. Regions of the OFC that responded to reward and other parts that responded to nonreward were identified, and their sensitivity to differences between a large-win, a small-win, and a no-win condition was used to measure sensitivity to reward and nonreward. The sensitivity to reward and nonreward was then related to the severity of the depressive symptoms. The design included a longitudinal analysis and a comparison of reward and nonreward sensitivity of the OFC in subgroups with high versus low severity of depressive symptom scores, as described in more detail next and in the Methods and Materials section.

The MID task used by the IMAGEN project and analyzed here presented one of three stimuli at the beginning of a trial. These stimuli informed participants whether they would receive a large win, a small win, or no win approximately 4 seconds later when they responded. This period is termed the reward anticipation period. After participants responded, the outcome (10 points, 2 points, or 0 points) was shown in what is termed the reward feedback phase. We analyzed data from the reward anticipation phase because those data provide the best estimate of the reward value (in this task, a value of large win vs. small win vs. no win), whereas in the outcome phase activations might be related to factors other than reward value such as whether the outcome value matched the expected value. The theory being tested was that neural responses to the value of reward or nonreward are relevant to understanding depression, and the hypothesis was that in depression the lateral OFC nonreward system is more sensitive to nonreward, and the medial OFC reward system is less sensitive to rewards (30). We analyzed data only on hit trials to ensure that participants were paying attention to the task and performing it well. We note that there were no losses in this MID task.

The hypotheses that we wished to test were as follows. In this MID task, is the lateral OFC sensitive to the no-win condition, and is the medial OFC sensitive to the large-win condition? If so, is the sensitivity of the lateral OFC to no win greater in participants with high depression-related scores, and is the sensitivity of the medial OFC to wins less in participants with high depressive symptom–related scores? In addition, we hypothesized that nonreward and reward sensitivity of the brain measured at age 14 years might be related to depressive symptom scores measured at age 19 years in a longitudinal analysis.

METHODS AND MATERIALS

Participants

Longitudinal data of 1877 14-year-old Caucasian adolescents (1140 of whom were available as young adults at age 19 years) (Table 1) were included in the current study from the IMAGEN project (31). Ethical permission was obtained, and informed consent was provided by all participants and a parent/guardian of each participant (31).

Measurement of Depression Symptoms and the High-Severity Versus Control Subgroups

The depression symptoms of participants at age 19 were measured by the Adolescent Depression Rating Scale (ADRS; 10 items) (Table S1) (32), and their depression symptoms at ages 14 and 16 were assessed with screening questions from the Development and Well-Being Assessment (DAWBA; 5 items) (Table S2) (33) and the Strengths and Difficulties Questionnaire (3 items) (Table S2) (34). The

Table 1. Participant Characteristics at Ages 14 and 19

	14 Years (n = 1877)			19 Years (n = 1140)		
Characteristic	Control (n = 216), Mean (SD)	High Severity (n = 220), Mean (SD)	Contrast, p	Control (n = 206), Mean (SD)	High Severity (n = 116), Mean (SD)	Contrast, p
General Psychopathology	8.45 (4.12)	13 (5.18)	<.001	7.69 (3.83)	16.48 (4.52)	<.001
AUDIT Total Score	2.98 (3.13)	3.36 (3.05)	<.001	5.04 (3.38)	6.47 (3.80)	<.001
NEO						
Agreeableness	30.37 (5.01)	25.77 (5.64)	<.001	33.00 (5.13)	28.12 (5.21)	<.001
Conscientiousness	28.61 (7.01)	25.61 (7.20)	<.001	31.34 (6.93)	25.33 (7.09)	<.001
Extraversion	31.02 (5.31)	27.98 (5.93)	<.001	30.73 (5.23)	24.61 (6.14)	<.001
Neuroticism	18.70 (6.69)	29.78 (7.58)	<.001	17.23 (6.73)	32.87 (6.86)	<.001
Openness	25.23 (5.62)	26.56 (6.36)	.10	28.66 (6.51)	29.73 (6.89)	.16

AUDIT, Alcohol Use Disorders Identification Test; NEO, NEO Five-Factor Inventory.

DAWBA/Strengths and Difficulties Questionnaire and ADRS showed a highly reliable intercorrelation across different time points in the current data (Table S3). In the clinically relevant severity subgroup analysis, at age 19, the ADRS score was also used to select individuals with high severity of depression (ADRS score $\geq$ 6; n = 116) versus control subjects (ADRS score = 0; n = 206) (Table 1), where at least 60% of these high-severity individuals were expected to be diagnosed with depression under DSM-IV (32). At age 14, the DAWBA score was used to classify individuals into the high-severity group (DAWBA score $\geq$ 5; n = 216) versus control subjects (DAWBA score = 0; n = 220) for depression (21). The two groups were matched on age, gender, handedness, and imaging site.

Functional Magnetic Resonance Imaging MID Task

A task-based functional magnetic resonance imaging (fMRI) acquisition of a modified MID task was used to investigate neural responses to reward anticipation and reward outcome (35). The task details and acquisition parameters are provided in the Supplement. Given prior research implying reliable relationships between depression symptoms and brain responses during reward anticipation (36), we used the MID task conditions during the anticipation phase, including no win, small win, and large win in the analyses. Details of the performance of participants is provided elsewhere (18,37).

fMRI Statistical Analyses

Preprocessing and first-level analyses using a generalized linear model to measure the activations in the different win conditions were performed as described in detail in the Supplement. The population analyses were performed in a hypothesis-driven way in three steps, with full details provided in the Supplement.

Reward and Nonreward Regions of Interest During Reward Anticipation. We extracted the mean brain activations in preselected regions of interest (ROIs) (bilateral medial OFC, lateral OFC, and VS) during reward anticipation at ages 14 and 19. ROIs in the medial OFC were created using a mask set where the activation was significant at an absolute t value of 5 in the contrast of large-win versus no-win conditions and in the lateral OFC in the contrast of no-win versus large-win conditions. The mask for the lateral OFC was cut at the lateral edge of the inferior frontal sulcus so as to exclude the inferior frontal cortex, and the mask for the VS was from a previous study (18).

Multiple Regression Analysis for the Whole Population. With the whole sample, we used a multiple regression model to analyze how the activations of the six reward and nonreward ROIs (i.e., bilaterally the medial OFC, lateral OFC, and VS) were related to the depression symptom score at age 19 (measured by the ADRS), with gender, handedness, and imaging sites included as control variables in this multiple regression model. Age 19 was chosen because the symptoms of depression were expected to be more established than those at age 14 and the ADRS was available at age 19 (38). Post hoc tests were performed to test which of the six ROIs were related to depression, as described in the Supplement.

Longitudinal Analysis for the Significant ROIs in the Whole Population. We investigated whether there was a longitudinal association between the activation of the significant ROIs measured at age 14 and the depression symptoms measured at ages 16 (with the DAWBA) and 19 (with the ADRS), with full details provided in the Supplement. The tests for the longitudinal analyses were one tailed because the direction of the association had been established by the multivariate regression analysis at 19 years.

Sensitivity to Reward and Nonreward in a High-Severity Depression Group Compared With a Control Group at Both Ages 19 and 14. For the high and low severity of depression symptom groups defined above, we performed analyses of the sensitivity of the activations of the ROIs to differences of reward (the trajectory from no win to small win to large win) and to differences of not winning (the trajectory from large win to small win to no win), as described in detail in the Supplement.

Full details of the participants, the assessment of the depression symptom score, the MID task, and the fMRI analyses are provided in the Supplement.

RESULTS

Sensitivity to Reward in the Medial OFC and to Nonreward in the Lateral OFC in the Full Population

Figure 1 illustrates the ROIs in the medial and lateral OFC and the VS during the reward anticipation phase of the MID task (39) for the participants at both ages 14 (1877 participants; 49.5% male) and 19 (1140 participants; 47.3% male) (Figure S1). The boundaries of these ROIs were defined by brain activations with t values > 5 in the contrast of large win versus no win, (i.e., reward-sensitive regions such as the VS and medial OFC) as well as in the contrast of no win versus large win (i.e., nonreward-sensitive regions such as the lateral OFC) (Figure S1 and Table S4). The same masks were used for all subsequent comparisons.

The medial OFC activations showed significant reward sensitivity (i.e., graded increases from no win to small win to large win) at both ages 14 and 19 (Figure 1B, C and Table S5). Activations of the VS paralleled those in the medial OFC (Figure 1B, C and Table S5). In addition, nonreward sensitivity (i.e., graded increases from large win to small win to no win) was found for the lateral OFC at both ages 14 and 19 (Figure 1B, C and Table S5). For the OFC, these trajectory patterns of the activations in the medial and lateral OFC were significantly different, as shown by the interaction term in a two-way analysis of variance (ANOVA) (Cohen's f^2 = 0.106, $F_{2,2278}$ = 121.11, $p = 1.04 \times 10^{-50}$ at age 19; Cohen's f^2 = 0.093, $F_{2,3782}$ = 174.43, $p = 3.45 \times 10^{-73}$ at age 14).

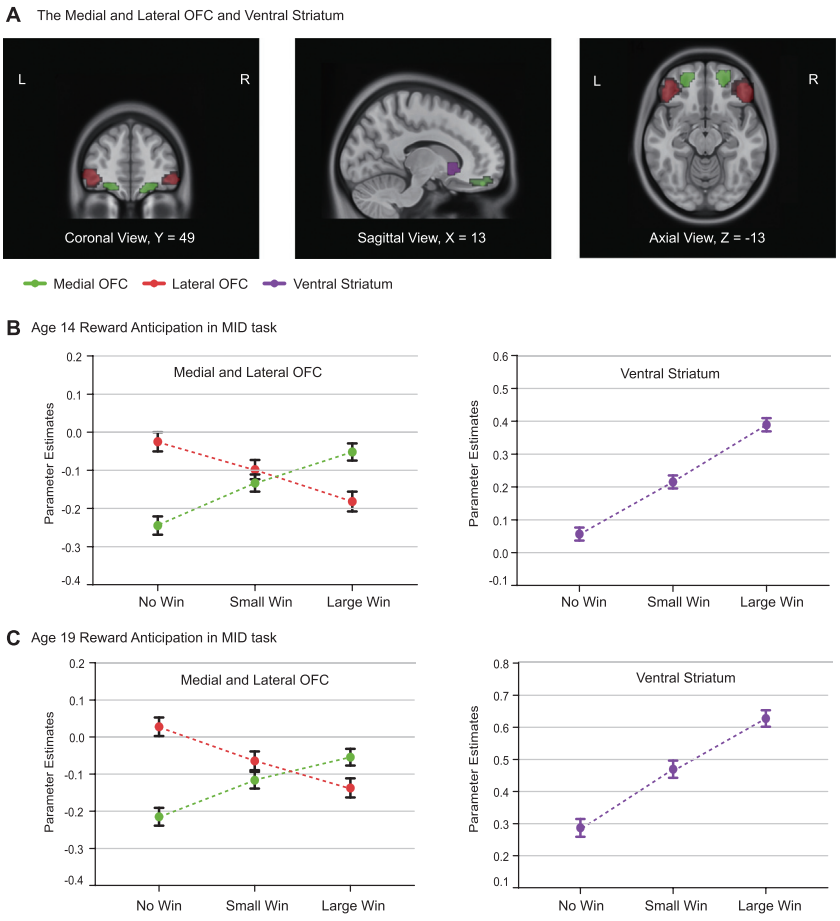

Figure 1. Medial orbitofrontal cortex (OFC), lateral OFC, and ventral striatum during reward anticipation in the monetary incentive delay (MID) task at different ages. **(A)** The masks in the current study with $t > 5$ in the contrasts of large win vs. no win and no win vs. large win at age 19. **(B, C)** Mean activations of the medial and lateral OFC and ventral striatum during reward anticipation at ages 14 **(B)** and 19 **(C)** in the whole population across the no-win, small-win, and large-win conditions. The mean and standard error are shown. The activations shown are the mean activations of the left and right hemispheres combined. L, left; R, right.

Association Analyses at Age 19 Between Reward-Related Brain Activations and the Depression Symptom Score for the Full Population

Using a multiple regression full model defined in Methods and Materials, we started with the data at age 19 and identified a significant association between the activations of ROIs for the contrasts of large win versus no win (for the bilateral medial OFC and VS) and no win versus large win (for the bilateral lateral OFC) during reward anticipation and the depression symptom score (R^2 = 1.63%, $F_{6,1133}$ = 3.14, p = 4.64 × 10^{-3}) (Table 2). The two significant regions in this full model were the left lateral OFC (Cohen's d = 0.082, t = 2.78, p = .005) (Table 2) and the right medial OFC (Cohen's d = 0.074, t = −2.16, p = .031) (Table 2). As a check for possible impacts from multicollinearity on significance levels of individual ROIs in the multiple regression model, we conducted univariate analyses to show that the above findings for the left lateral and right medial OFC were also found in separate univariate analyses and hence were not a result of multicollinearity between ROIs, and this was found to be true (left lateral OFC: r = .07, t = 2.49, n = 1140, p = .012; right medial OFC: r = −.08, t = −2.85, n = 1140, p = .004) (Figure S2A). These correlations were in the expected direction; for the medial OFC, greater depressive symptom severity was correlated with a smaller activation difference for the contrast of large win versus no win (consistent with reward insensitivity), and for the lateral OFC, greater depressive symptom severity was correlated with a larger activation difference for the contrast of no win versus large win (consistent with greater nonreward sensitivity). A follow-up model comparison further revealed that other brain regions (the bilateral VS and the left medial OFC and right lateral OFC) did not provide significant further information to what has been described for the right medial OFC and left lateral OFC, as shown in Tables S6 and S7. (In a check for gender differences, we tested whether there are significant differences between the genders for the correlations between the two OFC ROIs and the depression symptom scores. We found no statistically significant gender difference [left lateral OFC: z = −0.26, p = .795; right medial OFC: z = −0.62, p = .535].)

We further explored the depression symptom subscales of the above associations and found that the lateral OFC activations were significantly correlated with the negative feeling symptoms such as "feel overwhelmed by sadness and listlessness" and "when I feel this way I wish I were dead" (r = .083, t = 2.81, n = 1140, p = .005 and r = .086, t = 2.91, n = 1140, p = .004, respectively) (Table S8). The medial OFC activations for the same contrast were found to have a

Table 2. Multiple Regression Model Between the Activations of Bilateral Medial and Lateral OFC and VS and the Depression Symptom Score at Age 19 (MID Task)

Model	ROI	Index	Estimate	SE	t	Pr (> |t|)
Full Model	L lateral OFC	$x1$	.287	.103	2.78	5.46×10^{-3}[a]
	R lateral OFC	$x2$	−.214	.117	−1.81	.069
	L medial OFC	$x3$	.084	.130	0.64	.518
	R medial OFC	$x4$	−.341	.157	−2.16	.031[b]
	L VS	$x5$	−.003	.193	−0.02	.984
	R VS	$x6$	−.232	.195	−1.19	.234
	R^2 = 1.63%, $F_{6,1133}$ = 3.14, $p = 4.64 \times 10^{-3}$					

Generalized linear model: $Y = \beta1 \times x1 + \beta2 \times x2 + \beta3 \times x3 + \beta4 \times x4 + \beta5 \times x5 + \beta6 \times x6 +$ error, where Y is the depression symptom score. The bilateral lateral OFC activations were from the contrast of no-win vs. large-win, and the bilateral medial OFC and VS were from the contrast of large-win vs. no-win.

L, left; OFC, orbitofrontal cortex; R, right; ROI, region of interest; VS, ventral striatum.

[a]Significant at p = .01.

[b]Significant at p = .05.

nominally significant negative association with the anhedonia symptom ("nothing really interests or entertains me," $t = -2.54$, $r = -.075$, $p = .010$) (Table S8).

Longitudinal Approach for the Association Between OFC Activations and the Depression Symptom Score Using the Whole Population

At age 14, the lateral OFC activations for the contrast of no win versus large win was positively correlated with the depression symptom score across the whole population ($r = .04$, $t = 1.74$, $n = 1885$, $p_{\text{one-tailed}} = .031$). For the medial OFC, the activations for the contrast of large win versus no win at age 14 was negatively correlated with the depression symptom score at age 14 ($r = -.04$, $t = 1.75$, $n = 1885$, $p_{\text{one-tailed}} = .038$). Both results were in line with our findings at age 19.

The availability of data for the same individuals at ages 14, 16 (behavior only), and 19 enabled us to perform a longitudinal analysis, which showed that the depression symptom scores at ages 16 and 19 were related to the lateral OFC activations at age 14 just described (at 16 years, $r = .09$, $t = 3.49$, $n = 1490$, $p_{\text{one-tailed}} = 3.38 \times 10^{-4}$, measured by the DAWBA; at age 19, $r = .06$, $t = 2.14$, $n = 1273$, $p_{\text{one-tailed}} = .015$, measured by the ADRS (Figure 2 and Figure S2). In a control analysis, we showed that both longitudinal associations remained significant after regressing out the depression symptom score at age 14 (at age 16, $r = .07$, $t = 2.50$, $n = 1273$, $p_{\text{one-tailed}} = .004$; at age 19, $r = .05$, $t = 1.78$, $n = 1273$, $p_{\text{one-tailed}} = .037$). To summarize, the activation related to no win versus large win of the lateral OFC at age 14 could be an early indicator for future depression symptoms.

In a supplementary analysis to strengthen the interpretation of the finding just described, we found that it was not possible to predict the lateral OFC activations at age 19 from the depression symptom score at age 14 ($r = -.02$, $t = 0.79$, $n = 1175$, $p_{\text{one-tailed}} = .51$), suggesting that only early brain activations could predict future depression symptoms but not vice versa.

However, from the medial OFC activations at age 14, it was not possible to predict the depression symptom score at either age 16 ($r < .01$, $t = 0.08$, $n = 1490$, $p_{\text{one-tailed}} = .71$) or age 19 ($r = -.01$, $t = -0.36$, $n = 1273$, $p_{\text{one-tailed}} = .35$) (Figure 2 and Figure S2).

OFC Activations in Subgroups With High Severity of Depression Versus Control Subgroup at Age 19

The above analyses identified associations of medial and lateral OFC activations with the depression symptom score for the whole population. In the next analysis, we stratified the 1140 participants at age 19 into two clinically relevant groups: a high-severity depression group ($n = 116$) and a matched control group ($n = 206$) (see Methods and Materials for details).

Figure 3A shows that the nonreward-sensitive lateral OFC showed increased nonreward sensitivity in the high-severity depression group compared with the control group, with a significant interaction term in the two-way ANOVA (Cohen's $f^2 = 0.011$, $F_{2,640} = 3.64$, $p = .027$). This significant interaction was consistent with the multiple regression analysis conducted on the whole population (i.e., the contrast large win vs. no win), with a larger no-win to large-win activation reduction in the high-severity depression group (Cohen's $d = -0.27$, $t_{320} = -2.35$, $p = .020$). Such an increased sensitivity to nonreward in the high-severity depression group was mainly observed from no win to small win (Cohen's $d = -0.25$, $t = -2.19$, $p = .029$), but not from small win to large win (Cohen's $d = -0.03$, $t = -0.29$, $p = .77$). Furthermore, the corresponding one-way ANOVAs found a higher nonreward sensitivity effect in the high-severity group (Cohen's $f^2 = 0.116$, $F_{2,230} = 13.29$, $p_{\text{corrected}} = 6.90 \times 10^{-6}$) and a much-reduced effect size in the control group (Cohen's $f^2 = 0.016$, $F_{2,410} = 3.38$, $p_{\text{corrected}} = .070$).

Figure 3A also shows that the reward-sensitive medial OFC becomes insensitive to reward in the high-severity depression group if compared with the control group, with a significant interaction term in the two-way ANOVA (Cohen's $f^2 = 0.020$, $F_{2,640} = 6.09$, $p = .002$). This significant difference was consistent with the multiple regression analysis conducted on the whole population (i.e., the contrast large win vs. no win), with a reduced no-win to large-win activation increase in the high-severity depression group (Cohen's $d = -0.34$, $t_{320} = -2.92$, $p = .004$). Such a reduced sensitivity to reward in the high-severity depression group was mainly observed from no win to small win (Cohen's $d = -0.36$, $t = -3.10$, $p = .002$), but not from small win to large win (Cohen's $d = 0.02$, $t = 0.13$, $p = .897$). In addition, the corresponding one-way ANOVAs revealed that the control group had significant reward sensitivity (Cohen's $f^2 = 0.116$,

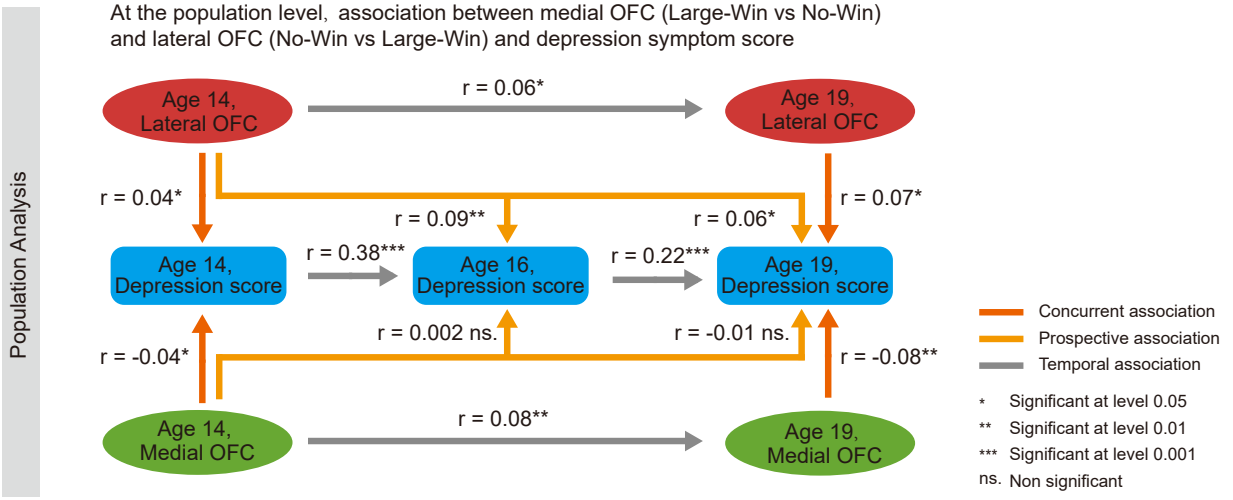

Figure 2. Associations between the lateral and medial orbitofrontal cortex (OFC) activations and the depressive symptoms scores at ages 14, 16, and 19. The concurrent and prospective associations between the lateral and medial OFC activations and the depressive symptom scores are shown. The lateral OFC measure was the activation to no win vs. large win. The medial OFC measure was the activation to large win vs. no win. The association measures are *r* values as described in the text. These results are for the whole population of participants.

$F_{2,410}$ = 23.82, $p_{corrected}$ = 3.27 × 10^{-10}), whereas the high-severity depression group had low reward sensitivity (Cohen's f^2 = 0.023, $F_{2,230}$ = 2.73, $p_{corrected}$ = .135). Thus, the depression group defined at age 19 has low reward sensitivity of the medial OFC and high sensitivity to nonreward of the lateral OFC (with this neuroimaging being performed at 19 years).

OFC Activations in Subgroups With High Severity of Depression Versus Control Subgroup at Age 14

Here we analyze how OFC activations at age 14 in the MID task related to whether the individuals are categorized into a high-severity group defined at age 14 (n = 216) and the matched control group (n = 220) (see Methods and Materials for details).

For the medial OFC, reduced sensitivity to reward was found in the high-severity group compared with the control group (Figure 3B), and this was confirmed by a significant interaction term in the two-way ANOVA (Cohen's f^2 = 0.018, $F_{2,868}$ = 6.50, p = .002). Consistent with the multiple regression analysis conducted on the whole population, we again observed a smaller no-win to large-win activation increase in the high-severity depression group (Cohen's d = −0.30, t_{434} = −3.14, p = .002). The significantly reduced sensitivity to reward in the high-severity depression group was mainly observed from small win to large win (Cohen's d = 0.21, t_{434} = 2.20, p = .028), but also with a trend from no win to small win (Cohen's d = 0.18, t_{434} = 1.84, p = .067). The further corresponding one-way ANOVAs revealed a significant reward sensitivity of the medial OFC in the control group (Cohen's f^2 = 0.0663, $F_{2,438}$ = 14.52, $p_{corrected}$ = 1.57 × 10^{-6}), but not in the depression high-severity group (Cohen's f^2 < 0.001, $F_{2,430}$ = .06, $p_{corrected}$ = 1).

For the lateral OFC, the interaction term of the two-way ANOVA was not significant for any difference in the nonreward sensitivity trajectories between the high-severity and control groups at age 14 (Cohen's f^2 < 0.001, $F_{2,868}$ = 1.13, p = .466) (Figure 3B). The one-way ANOVAs did show a significant nonreward sensitivity of the lateral OFC in both groups (high-severity group: Cohen's f^2 = 0.074, $F_{2,430}$ = 15.97, $p_{corrected}$ = 4.08 × 10^{-7}; control group: Cohen's f^2 = 0.033, $F_{2,438}$ = 7.37, $p_{corrected}$ = .001).

Thus, the depressed group defined at age 14 has low reward sensitivity of the medial OFC imaged at age 14.

Longitudinal Analysis for the Subgroup With a Future High Severity of Depression: High Nonreward Sensitivity at Age 14 Is Present in Individuals Who Have High Depression Severity at Age 19

To obtain evidence on whether OFC reward and nonreward sensitivities at age 14 are related to individuals' depressive status at age 19, we investigated whether those selected at age 19 to have high-severity depression scores (99 participants available at age 14) or no symptoms of depression (185 participants available at age 14) had different activations when imaged at age 14. (The slightly reduced sample size at age 14 was due to the imaging quality control; see Supplement for more details.)

For this analysis, at age 14, higher nonreward sensitivity of the lateral OFC was observed in participants who were in the high-severity group defined at age 19 compared with the corresponding control group at age 19 (see Figure 3C). This was confirmed by a significant interaction term (two-way ANOVA; Cohen's f^2 = 0.018, $F_{2,564}$ = 5.03, p = .003). This was consistent with the multiple regression analysis conducted on the whole population (in which a higher lateral OFC activation for the contrast no win vs. large win at age 14 was correlated with a higher depression symptom score at age 19), as follows. It was found that there was a higher lateral OFC activation for the contrast no win versus large win imaged at 14 years in the high-severity depression group defined at 19 years (Cohen's d = −0.34, t_{282} = −2.72, p = .007). Furthermore, the corresponding one-way ANOVAs revealed a significant nonreward sensitivity of the lateral OFC at age 14

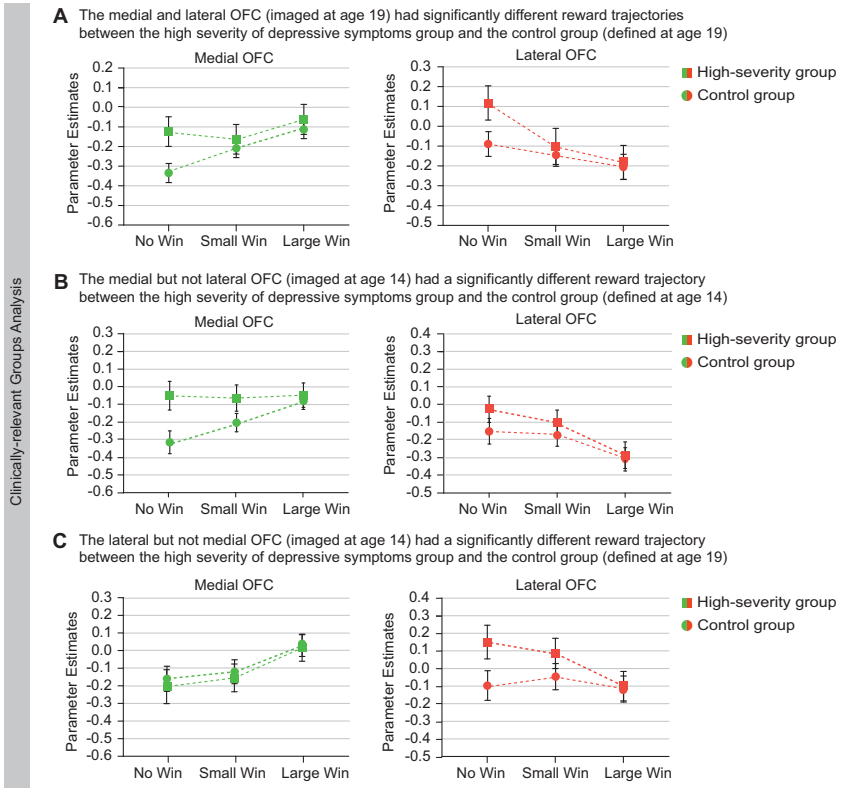

Figure 3. Activations of the medial and lateral orbitofrontal cortex (OFC) in the high-severity depressive symptoms group and the control group at ages 14 and 19. The trajectory refers to the differences among the three conditions no win, small win, and large win. **(A)** The OFC activation trajectory just defined was significant between the high depression and control groups, as shown by the interaction term in a two-way analysis of variance at age 19 for the lateral OFC (p = .027) and medial OFC (p = .002) (see Results). Post hoc tests revealed that there was a significant effect for the activation difference between no win and small win for the two groups (see OFC Activations in Subgroups With High Severity of Depression Versus Control Subgroup at Age 19 in Results). **(B)** The OFC activation trajectory (imaged at age 14) was significantly different between the high-severity depression group and the control group (defined at age 14) for the medial OFC, but not for the lateral OFC, as shown by the interaction term in a two-way analysis of variance (p = .002). Post hoc tests revealed that there was a significant effect for the activation difference between no win and small win for the two groups for the medial OFC (see OFC Activations in Subgroups With High Severity of Depressive Symptoms Versus Control Subgroup at Age 14 in Results for more details). **(C)** The OFC activation trajectory (imaged at age 14) was significantly different between the high depression and control groups (defined at age 19) for the lateral OFC (p = .003), but not for the medial OFC. Post hoc tests revealed that there was a significant effect for the activation difference between no win and large win for the two groups for the lateral OFC (see Longitudinal Analysis for the Subgroup With a Future High Severity of Depression: High Nonreward Sensitivity at Age 14 Is Present in Individuals Who Have High Depression Severity at Age 19 in Results for more details).

in participants in the high-severity group at age 19 (Cohen's f^2 = 0.085, $F_{2,196}$ = 8.37, $p_{corrected}$ = 6.50 × 10^{-4}), but not in the control group (Cohen's f^2 = 0.005, $F_{2,368}$ = 0.98, $p_{corrected}$ = .753).

Similar to the whole population result, the two-way ANOVA found no significant difference in the reward sensitivity for the medial OFC trajectories at age 14 for the two groups defined at age 19 (two-way ANOVA, Cohen's $f^2 < 0.001$, $F_{2,564}$ = 0.07, p = .466) (Figure 3C). The corresponding one-way ANOVAs showed significant reward sensitivity at age 14 for both groups defined at age 19 (high-severity group: Cohen's f^2 = 0.062, $F_{2,196}$ = 6.12, p = .001; control group: Cohen's f^2 = 0.051, $F_{2,368}$ = 9.35, p = 5.40 × 10^{-5}).

Thus, at age 14, the increased sensitivity to nonreward of the lateral OFC is associated with who will be in the high-severity depression group at age 19.

Figure 4 shows a summary of some of the findings.

Exploring the Relationship Between Depressive Symptoms and Other Candidate Brain Regions

Part of the left anterior insula had activation patterns and associations with depressive symptom severity similar to those of the right medial OFC, consistent with its inputs from the OFC (7), but differences in activations to the different reward conditions for the high-severity depressive symptom and control groups were not evident statistically (see Supplemental Results and Figure S4 for more details).

DISCUSSION

Activations of the Medial and Lateral OFC During Reward Anticipation

The first important findings in this study were that in the IMAGEN consortium (n = 1877 at age 14 and n = 1140 at age 19) there were statistically highly significant and different effects in the medial and lateral OFC during reward anticipation in the MID task (Figure 1), that is, increasing reward-related activations from no win to small win to large win in the medial OFC and graded nonreward-related increases from large win to small win to no win in the lateral OFC. This is consistent with the effects reported by O'Doherty *et al.* (13) for monetary reward and by many studies that show activation of medial OFC areas by rewards and activation of lateral OFC by punishment (unpleasant stimuli) as well as by not receiving expected rewards (7). A factor in a previous failure to detect such effects (17) may have been the low signal-to-noise ratio in the orbitofrontal region (40) (Figure S5). The current data set was sufficiently large to overcome the low signal-to-noise ratio observed for both the medial and lateral OFC (Figure S5).

Associations Between Depression and Activation Patterns of Medial and Lateral OFC

This investigation showed that groups of adolescents with high severity of depression scores versus a control group had high nonreward sensitivity for the trajectory from large win to small

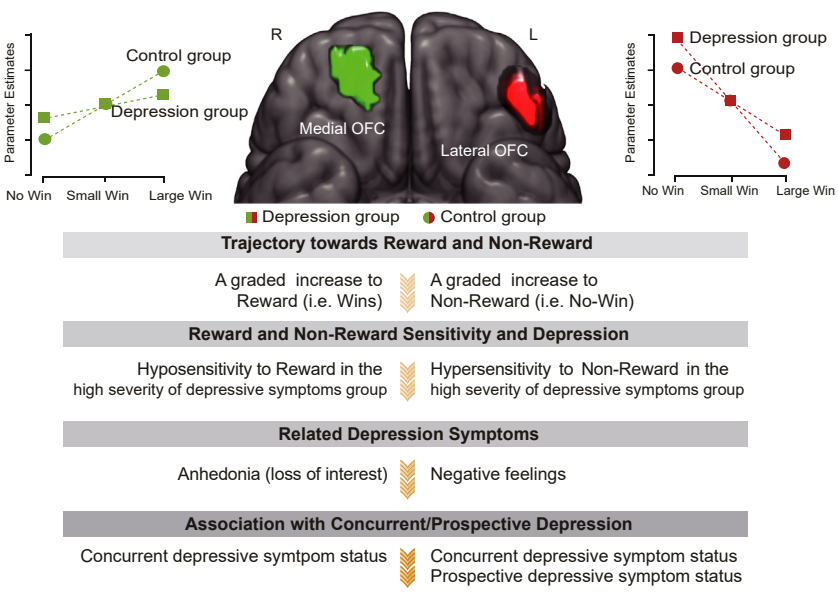

Figure 4. Summary of the main findings. The activations shown here are for the control group (circles) and high-severity depressive symptoms group (squares) for the left lateral orbitofrontal cortex (OFC) and the right medial OFC. L, left; R, right.

win to no win of the lateral OFC at age 19 (Figure 3A). In addition, the univariate analysis for the full population showed a correlation between the activation of the lateral OFC and the depressive symptom score at both ages 19 and 14 (Figure 2). Furthermore, at age 19, negative feeling symptoms (e.g., "Overwhelmed by sadness and listlessness") were associated with increased nonreward sensitivity of the lateral OFC. This is important support for the hypothesis that the negative aspects of depression can be related to increased effects of unpleasant nonrewarding and punishing stimuli in the lateral OFC (4,16,30,41).

It was also shown that the high-severity depression group had low sensitivity for the trajectory from no win to small win to large win of the medial OFC at age 19 (Figure 3A), and a similar effect was found at age 14 years (Figure 3B). This provides strong support for the hypothesis that the medial OFC reward system has blunted efficacy in depression (4,7,16). In addition, the univariate analysis for the full population showed a correlation between the activation of the medial OFC and the depressive symptom score at both ages 19 and 14 (Figure 2). In particular, at age 19 the anhedonia symptom was nominally associated with reduced reward sensitivity of the medial OFC, hence providing evidence for the hypothesis that the anhedonia of depression can be related to decreased effects of pleasant rewarding stimuli in the medial OFC during depression, effects that can be restored by antidepressants (15).

Longitudinal Evidence for the Roles of the Medial and Lateral OFC in Depression

In the longitudinal analyses, it was shown that at age 14 the increased sensitivity to nonreward of the lateral OFC is associated with who will be in the high-severity depression group at age 19 (Figure 3C). In addition, the univariate analysis for the full population showed a correlation between the activations of the lateral OFC at age 14 and the depressive symptom scores at both ages 16 and 19 (Figure S3). However, for the medial OFC, activations at age 14 were not significantly associated with the future depression symptoms or status. Therefore, these results suggest that hypersensitivity to nonreward of the lateral OFC is an indicator for both current and future depression and that hyposensitivity to reward of the medial OFC is an indicator for the current, but not future, status of depression.

Relation to Previous Evidence

In many previous studies, reduced activations to reward in depression have been described in the VS (19–23). The current study goes beyond these studies by showing that the OFC, a key brain region involved in emotion that projects to the VS (7,24,42,43), has activations in its medial OFC to reward in a very large population (of 1140 individuals at age 19) that are decreased in people with high scores for depressive symptoms. An implication is that the OFC is the key source of inputs to the VS that accounts for its reduced sensitivity to reward in depression (44). But the current study goes even further by showing that the lateral OFC is sensitive to not winning (a type of nonreward) in the same very large population and showing that this has increased sensitivity to not winning (nonreward) in people with depressive symptoms. The current results are consistent with a theory of depression that relates sensitivity to nonreward as being a key factor that can lead to depression and also reduced sensitivity to reward (30). The current findings complement the evidence from functional connectivity, which is that the lateral OFC in-reward system has increased functional connectivity in depression (45) and that the medial OFC reward system has reduced functional connectivity in depression (11,45). These differences in functional connectivity also point to increased efficacy of the lateral OFC nonreward system in depression and of decreased efficacy of the medial OFC reward system in depression. All these findings are rooted in a fundamental approach to understanding emotion in terms of brain responses to rewards and punishers/nonreward, with nonreward if no action is possible being associated with sad feelings and potentially with depression (46).

In terms of limitations and strengths, we note in analyzing data from a general population not selected to have depression that the effects related to depression might be expected to be modest, but we did find reasonable effect sizes (Cohen's *d* in the range of 0.20–0.50) when we compared win and no-win activations of the OFC in the depressive symptom and control groups. In terms of strengths, the large sample size did enable effects related to depression to be uncovered for the OFC in a general population. In addition, the results shown in Figure 1—that the medial OFC has increasing activations as the amount of reward increases, and that the lateral OFC has increasing activations as the amount of reward decreases to zero—are highly statistically significant.

Conclusions

This investigation is the first large-scale study to show that the lateral OFC is more sensitive to nonreward (the no-win condition in the current study) in individuals with a higher depression severity at both ages 19 and 14, and that the medial OFC is less sensitive to differences in reward value in those with a higher depression severity, at both ages 19 and 14. Moreover, a longitudinal approach for the first time showed that the future depression symptom scores (at ages 16 and 19) were associated with increased nonreward sensitivity of the lateral OFC (imaged at age 14) and that the current, but not future, depression symptoms were associated with the reward sensitivity of the medial OFC (at age 14 and 19). The investigation has important implications for understanding and treating depression by highlighting sensitivity to both reward and nonreward as potentially of interest for behavioral and pharmacological treatments, for the lateral and medial OFC as potential targets for drug effects (7), and also for possible treatments such as transcranial magnetic stimulation and deep brain stimulation (47,48).

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