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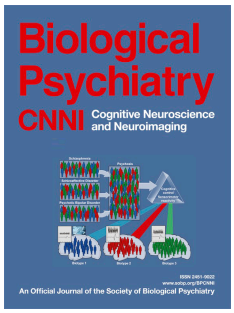

Reward vs Non-reward Sensitivity of the Medial vs Lateral Orbitofrontal Cortex Relates to the Severity of Depressive Symptoms

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Running head: The orbitofrontal cortex and 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 non-reward is related to the severity of depressive symptoms.

Methods. Activations in the monetary incentive delay task were measured in the IMAGEN cohort at age 14 (n=1877) and 19 (n=1140) with a longitudinal design. Clinically-relevant subgroups were compared at age 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 non-reward. In this general population, the medial and lateral OFC activations were associated with concurrent depressive symptoms at both age 14 and 19. In a stratified high-severity depressive symptom vs control comparison, the lateral OFC showed greater sensitivity for the magnitudes of activations related to non-reward (No-Win) in the high-severity group at age 19 (p=0.027), and the medial OFC showed decreased sensitivity to the reward magnitudes in the high-severity group at both age 14 (p=0.002) and 19 (p=0.002). In a longitudinal design, there was greater sensitivity to non-reward of the lateral OFC at age 14 for those who exhibited high depressive symptom severity later at age 19 (p=0.003).

Conclusions. Activations in the lateral orbitofrontal cortex relate to sensitivity to not winning, were associated with high depressive symptom scores, and at 14 predicted the depressive symptoms at 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.

Introduction

Not receiving expected rewards ("non-reward"), or receiving unpleasant stimuli or events, can produce feelings of depression (1-6). This class of stimuli activates the human lateral orbitofrontal cortex (lateral OFC), and it has been proposed that over-sensitivity or over-connectivity of the lateral OFC may be involved in depression (7). Consistent with this, unmedicated depressed patients 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 vs lateral non-reward and punishment orbitofrontal systems are often reciprocally related in their activations (13, 14). Further, the anhedonia of depression can be related to decreased effects of pleasant rewarding stimuli in the medial orbitofrontal cortex (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 found in response to reward in both depressed patients (19) and adolescents with a high depression risk (21, 22), and in the ventral striatum to monetary reward anticipation in adolescents with a high depression severity (23). There was little focus on the OFC, even though it is a key brain region in reinforcement learning process and projects to the ventral striatum (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 vs lateral orbitofrontal cortex which, as shown here, is important. Here we report that the lateral orbitofrontal cortex is activated by non-reward (not winning) and is more activated in those with high depressive symptom scores; whereas the medial orbitofrontal cortex is activated by reward (winning) and is less activated in those with high depressive symptom scores.

Given this background, and because the orbitofrontal cortex is a key brain region in emotion, reward, and reward-related learning (7, 24, 27-29), the central aim of this paper was to test whether the orbitofrontal cortex has sensitivity to receiving rewards or not receiving rewards ('non-reward') that can be related to the severity of depressive symptoms. To test this, data from a large population of adolescents in a monetary incentive delay (MID) task were analysed. Regions of the orbitofrontal cortex that responded to reward, and other parts to non-reward were identified, and their sensitivity to differences between a Large-Win, a Small-Win, and No-Win were used to measure sensitivity to reward and non-reward. The sensitivity to reward and non-reward was then related to the severity of the depressive symptoms. The design included a longitudinal analysis; and a comparison of reward and non-reward sensitivity of the orbitofrontal cortex in subgroups with high vs low severity of depressive symptom scores, as described in more detail next and in the Methods.

The monetary incentive delay task utilised by IMAGEN and analysed here presented one of 3 stimuli at the beginning of a trial. These informed participants whether they would receive either a Large-Win, a Small-Win, or No-Win approximately 4 s later when they responded. This period is termed the reward anticipation period. After the participant responded, the outcome (10 points, 2 points, or 0 points) was shown in what is termed the reward feedback phase. We analysed data from

the reward anticipation phase because that provides 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 other factors than reward value, such as whether the outcome value matched the expected value. The theory being tested is that neural responses to the *value* of reward or non-reward are relevant to understanding depression, and the hypothesis is that in depression the lateral orbitofrontal cortex non-reward system is more sensitive to non-reward, and the medial orbitofrontal cortex reward system is less sensitive to rewards (30). We analysed data only on hit trials to ensure that the participants were paying attention to the task, and performing it well. We note that there were no losses in this MID task.

Methods

The hypotheses that we wished to test were as follows. In this MID task is the lateral orbitofrontal cortex sensitive to the No-Win condition, and the medial orbitofrontal cortex to the High-Win condition? If so, is the sensitivity of the lateral orbitofrontal cortex to No-Win greater in participants with high depression-related scores; and is the sensitivity of the medial orbitofrontal cortex to Wins less in participants with a high depressive symptom-related score? In addition, we hypothesized that non-reward and reward sensitivity of the brain measured at 14 might be related to the depressive symptom scores measured at 19 in a longitudinal analysis.

Participants: Longitudinal data of 1877 14-year-old (1140 available at age 19, Table 1) Caucasian adolescents/young-adults were included in the present 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 vs 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 age 14 and 16 were assessed with screening questions from the Development and Well Being Assessment (DAWBA, 5 items, Table S2) (33) and Strengths and Difficulties Questionnaire (SDQ, 3 items, Table S2) (34). DAWBA/SDQ and ADRS showed a highly reliable inter-correlation across different time points in the present 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 >=6, n=116) vs control (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 utilized to classify individuals into the high-severity group (DAWBA-score >=5, n=216) at age 14 and vs control group (DAWBA-score=0, n=220) for depression (21). The two groups were matched on age, sex, handedness and imaging site.

fMRI MID task: A task-based fMRI acquisition of a modified Monetary Incentive Delay (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 Supplementary Material. 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 the participants is provided

elsewhere (18, 37).

fMRI statistical analyses:

Preprocessing and first-level analyses using a GLM to measure the activations in the different Win conditions were performed as described in detail in the Supplementary Material. The population analyses were performed in a hypothesis-driven way in three steps, with full details in the Supplementary Material.

Reward and non-reward regions of interest during reward anticipation: We extracted the mean brain activations in pre-selected regions of interest (ROIs) (bilateral medial OFC, lateral OFC and VS) during reward anticipation at age 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 vs No-Win"; and lateral OFC in the contrast of "No-Win vs Large-win". 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 analyse how the activations of the six reward and non-reward ROIs (i.e. bilaterally the medial OFC, lateral OFC and VS) were related to the depression symptom score at age 19 (measured by 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 at age 14, and the ADRS was available at 19 (38). Post-hoc tests were performed to test which of the six ROIs were related to depression, as described in the Supplementary Material.

Longitudinal analysis for the significant ROIs in the whole population: We investigated if 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 DAWBA) and 19 (with ADRS), with full details in the Supplementary Material. The tests for the longitudinal analyses were one-tailed because the direction of the association had been established by the multivariate regression analysis at age 19.

Sensitivity to reward and non-reward in a high-severity depression group compared to 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 through Small-Win to No-Win), as described in detail in the Supplementary Material.

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

Results

Sensitivity to reward in the medial OFC and to non-reward in the lateral OFC in the full population

Figure 1 illustrates the regions of interest in the medial and lateral OFC and the VS during the reward anticipation phase of the MID task (39) for the participants at both age 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-value > 5 in the contrast of "Large-Win vs No-Win", i.e.

reward sensitive regions such as the VS and medial OFC, as well as in the contrast of "No-Win vs Large-Win", i.e. non-reward 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 through Small-Win to Large-Win, at both age 14 and 19 (Figure 1B and C and Table S5). Activations of the VS paralleled those in the medial OFC (Figure 1B and C and Table S5). In addition, non-reward sensitivity, i.e. graded increases from Large-Win through Small-Win to No-Win, was found for the lateral OFC at both age 14 and 19 (Figure 1B and C and Table S5). For the OFC, these trajectory patterns of the activations in medial and lateral OFC were significantly different as shown by the interaction term in a two-way ANOVA (Cohen's f^2=0.106, $F_{(2,2278)}$=121.11, p=1.04x10^{-50} at age 19; Cohen's f^2=0.093, $F_{(2,3782)}$=174.43, p=3.45x10^{-73} at age 14).

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 the Methods, we started with the data at age 19 and identified a significant association between the activations of ROIs for the contrasts of "Large-Win vs No-Win" (for the bilateral medial OFC and VS) and "No-Win vs 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=4.64x10^{-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=0.005, Table 2) and the right medial OFC (Cohen's d=0.074, t=-2.16, p=0.031, 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 because of multicollinearity between ROIs, and this was found (left lateral OFC: r=0.07, t=*2.49,* n=1140, p=0.012; right medial OFC: r=-0.08, t=*-2.85*, n=1140, p=0.004; Figure S2A). These correlations were in the expected direction, in that for the medial OFC greater depressive symptom severity was correlated with a smaller activation difference for the contrast of "Large-Win – 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 – Large-Win" (consistent with greater non-reward 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 (z=-0.26, p=0.795 for the left lateral OFC; z=-0.62, p=0.535 for the right medial OFC).)

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=0.083, t=2.81, n=1140, p=0.005 and r=0.086, t=2.91, n=1140, p=0.004, respectively; Table S8). The medial OFC activations for the same contrast were found to have a nominally significant negative association with the anhedonia symptom ('nothing really interests or entertains me', t=-2.54, r=-0.075, p=0.010, 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 vs Large- Win" was positively correlated with the depression symptom score across the whole population (r=0.04, t=1.74, n =1885, $p_{one\text{-}tailed=}$0.031). For the medial OFC, the activations for the contrast of "Large-Win vs No-Win" at age 14 was negatively correlated with the depression symptom score at age 14 (r=-0.04, t=1.75, n=1885, $p_{one\text{-}tailed}$=0.038). Both results were in line with our findings at age 19.

The availability of data for the same individuals at ages 14, 16 (behaviour 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 age 16, r=0.09, t=3.49, n =1490, $p_{one\text{-}tailed}$=3.38x10^{-4}, measured by DAWBA; and at 19, r=0.06, t=2.14, n=1273, $p_{one\text{-}tailed}$=0.015, measured by 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 (r=0.07, t=2.50, n=1273, $p_{one\text{-}tailed=}$0.004 for age 16; r=0.05, t=1.78, n=1273, $p_{one\text{-}tailed=}$0.037 for age 19). To summarise, the activation related to "No-Win vs 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=-0.02, t=0.79, n=1175, $p_{one\text{-}tailed}$=0.51), 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 < 0.01, t=0.08, n=1490, $p_{one\text{-}tailed}$=0.71) or 19 (r=-0.01, t=-0.36, n =1273, $p_{one\text{-}tailed}$=0.35, Figure 2 and Figure S2).

OFC activations in subgroups with high severity of depression vs controls 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, i.e. a high-severity depression group (n=116) vs a matched control (n=206) group (see Methods for details).

Figure 3A shows that the non-reward sensitive lateral OFC showed increased non-reward sensitivity in the high-severity of depression group than 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=0.027). 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=-2.35, df=320, p=0.020). Such an increased sensitivity to non-reward in the high-severity depression group was mainly observed from No-Win to Small-Win (Cohen's d=-0.25, t =-2.19, p=0.029), but not from Small-Win to Large-Win (Cohen's d=-0.03, t=-0.29, p=0.77). Further, the corresponding one-way ANOVAs found a higher non-reward sensitivity effect in the high-severity group (Cohen's f^2=0.116, $F_{(2, 230)}$ =13.29, $p_{corrected}$=6.90x10^{-6}), and a much-reduced effect size in the control group (Cohen's f^2=0.016, $F_{(2, 410)}$=3.38, $p_{corrected}$=0.070).

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=0.002). 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=-2.92, df=320, p=0.004). 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*=0.002), but not from Small-Win to Large-Win (Cohen's d=0.02, *t*=0.13, *p*=0.897). In addition, the corresponding one-way ANOVAs revealed that the control group had significant reward sensitivity (Cohen's f^2=0.116, $F_{(2,410)}$=23.82, $p_{corrected}$=3.27x10^{-10}), whereas the high-severity depression group had low reward sensitivity (Cohen's f^2=0.023, $F_{(2,230)}$=2.73, $p_{corrected}$=0.135). Thus, the depressed group defined at age 19 have low reward sensitivity of the medial OFC; and high sensitivity to non-reward of the lateral OFC (with this neuroimaging performed at age 19).

OFC activations in subgroups with high severity of depression vs controls at age 14

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

For the medial OFC, reduced sensitivity to reward was found in the high-severity group compared to 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, $F_{(2,868)}$=6.5, *p*=0.002). 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=-3.14, df=434, p=0.002). 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*=2.20, df=434, *p*=0.028), but also with a trend from No-Win to Small-Win (Cohen's *d*=0.18, *t*=1.84, df=434, *p*=0.067). 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, $p_{corrected}$ =1.57x10^{-6}), but not in the depression high-severity group (Cohen's f^2 < 0.001, $F_{(2,430)}$=0.06, $p_{corrected}$=1).

For the lateral OFC, the interaction term of the two-way ANOVA was not significant for any

difference in the non-reward sensitivity trajectories between the high-severity and the control groups at age 14 (Cohen's $f^2 < 0.001$, $F_{(2,868)} = 1.13$, $p = 0.466$) (Figure 3B). The one-way ANOVAs did show a significant non-reward sensitivity of the lateral OFC in both groups (high-severity group: Cohen's $f^{2=}0.074$, $F_{(2,430)}=15.97$, $p_{corrected}=4.08\text{x}10^{-7}$; control group: Cohen's $f^{2=}0.033$, $F_{(2,438)}=7.37$, $p_{corrected}=0.001$).

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

Longitudinal analysis for the subgroup with a future high severity of depression: high non-reward sensitivity at age 14 is present in individuals who have high depression severity at age 19

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

For this analysis, at age 14, higher non-reward sensitivity of the lateral OFC was observed in the group who were in the high-severity group defined at age 19 compared to the corresponding control group at age 19 (see Figure 3C). This was confirmed by a significant interaction term (two-way ANOVA, Cohen's $f^2=0.018$, $F_{(2,564)}=5.03$, $p=0.003$). 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 vs Large-Win imaged at age 14 in the high-severity depression group defined at age 19 (Cohen's d=-0.34, t=-2.72, df=282, p=0.007). Further, the corresponding one-way ANOVAs revealed a significant non-reward sensitivity of the lateral OFC at age 14 in those in the high-severity group at age 19 (Cohen's f^2=0.085, $F_{(2, 196)}$=8.37, $p_{corrected}$=6.50x10^{-4}), but not in the control group (Cohen's f^2=0.005, $F_{(2, 368)}$=0.98, $p_{corrected}$=0.753).

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=0.466, 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=0.001; control group: Cohen's $f^{2=}$0.051, $F_{(2,368)}$=9.35, p=5.40 x10^{-5}).

Thus, at age 14, the increased sensitivity to non-reward 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 of depressive symptom and control groups were not evident statistically (see Supplementary Results for more details and Figure S4).

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), i.e. increasing reward-related activations from No-Win through Small-Win to Large-Win in the medial OFC, and graded non-reward related increases from Large-Win through 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 be the low signal noise ratio (SNR) in the orbitofrontal region (40) (Figure S5). The present data set was sufficiently large to overcome the low SNR observed for both 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 non-reward sensitivity for the trajectory from Large-Win through Small-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). Further, at age 19, negative feeling symptoms (for example "Overwhelmed by sadness and listlessness") were associated with increased non-reward 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 non-rewarding 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 through Small-Win to Large-Win of the medial OFC at age 19 (Figure 3A), and a similar effect was found at age 14 (Figure 3B), and 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). Particularly, 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 non-reward 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. These results therefore suggest that hypersensitivity to non-reward 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 ventral striatum (19-23). The present study goes beyond these studies by showing that the orbitofrontal cortex, a key brain region involved in emotion that projects to the ventral striatum (7, 24, 42, 43), has activations in its medial orbitofrontal cortex 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 orbitofrontal is the key source of inputs to the ventral striatum that accounts for its reduced sensitivity to reward in depression (44). But the present study goes even further, by showing that the lateral orbitofrontal cortex is sensitive to not winning (a type of non-reward) in the same very large population, and showing that this has increased sensitivity to not winning (non-reward) in people with depressive symptoms. The present results are consistent with a theory of depression that relates sensitivity to non-reward as being a key factor that can lead to depression, and also reduced sensitivity to reward (30). The present findings complement the evidence from functional connectivity, which is that the lateral orbitofrontal cortex in-reward system has increased functional connectivity in depression (45), and that the medial orbitofrontal cortex reward system has reduced functional connectivity in depression (11, 45). These differences in functional connectivity also point to increased efficacy of the lateral orbitofrontal cortex non-reward system in depression, and of decreased efficacy of the medial orbitofrontal cortex reward system in depression. All of these findings are rooted in a fundamental approach to understanding emotion in terms of brain responses to rewards and punishers/non-reward, with non-reward if no action is possible being associated with sad feelings and potentially with depression (46).

In terms of limitations and strengths, we note in analysing 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 0.2-0.5) when we compared Win and

No-Win activations of the OFC in the depressed and control groups. In terms of strengths, the large sample size did enable effects related to depression to be uncovered for the orbitofrontal cortex in a general population; and the results shown in Fig. 1 that the medial OFC has increasing activations as the amount of reward increases; and the lateral orbitofrontal cortex has increasing activations as the amount of reward decreases to zero, are highly statistically significant.

Conclusion

This investigation is the first large-scale study to show that the lateral OFC is more sensitive to non-reward (the No-Win condition in the present study) in those 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 score (at 16 and 19) were associated with increased non-reward sensitivity of the lateral OFC (imaged at 14); and that the current but not future depression symptoms were associated with the reward sensitivity of the medial OFC (at 14 and 19). The investigation has important implications for understanding and treating depression, by highlighting sensitivity to both reward and non-reward as potentially of interest for behavioural and pharmacological treatments, and of 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).

Disclosures

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Figure Legends

Figure 1. Medial orbitofrontal cortex (OFC), lateral OFC and ventral striatum (VS) during reward anticipation in the Monetary Incentive Delay (MID) task at different ages. A. The masks in the present 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 VS during reward anticipation at age 14 and 19 in the whole population across 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.

Abbreviations: OFC, orbitofrontal cortex; VS, ventral striatum.

Fig. 2. Associations between the lateral and medial orbitofrontal cortex activations and the depressive symptoms scores at age 14, 16 and 19. The concurrent and prospective associations between the lateral and medial OFC activations and the depressive symptoms scores are shown. The lateral OFC measure was the activation to No-Win – Large-Win. The medial OFC measure was the activation to Large-Win – No-Win. The association measures are r values as described in the text. These results are for the whole population of participants.

Abbreviations: OFC, orbitofrontal cortex.

Fig. 3. Activations of the medial and lateral OFC in the high-severity of depressive symptoms group and the control group at age 14 and 19. The trajectory refers to the difference between the three conditions, No-Win, Small-Win and High-Win. **A**. The OFC activation trajectory just defined was significantly between the high depression and control groups as shown by the interaction term in a two-way ANOVA at age 19 for the lateral OFC (p=0.027), and medial OFC (p=0.002, 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 vs controls at age 19" in the 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 ANOVA (p=0.002); 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 vs controls at age 14" in the Results for more details. **C**. The OFC activation trajectory (imaged at age 14) was significantly different between the high-depression and the control group (defined at age 19) for the lateral OFC (p=0.003), 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 non-reward sensitivity at age 14 is present in individuals who have high depression severity at age 19" under Results for more details.

Abbreviations: OFC, orbitofrontal cortex

Figure 4. A summary of the main findings. The activations shown here are for the control group (circle) and high-severity of depressive symptom (square) group for the left lateral OFC and the right medial OFC. *Abbreviations: L, left; R; right; OFC, orbitofrontal cortex*

Tables

Table 1. Participant characteristics at age 14 and 19

Characteristic	**14 y (*n*=1877)**			**19 y (n=1140)**		
	mean (sd)			***mean (sd)***		
Depression severity groups	**Control**	**High Severity**	**Contrast**	**Control**	**High severity**	**Contrast**
(defined at age 14 and 19)	**(*n*=216)**	**(*n*=220)**	**(*p*)**	**(*n*=206)**	**(*n*=116)**	**(*p*)**
General psychopathology	8.454 (4.12)	13 (5.178)	< 0.001	7.69 (3.83)	16.48 (4.52)	<0.001
AUDIT total score	2.98 (3.13)	3.36 (3.05)	< 0.001	5.04 (3.38)	6.47 (3.80)	<0.001
NEO						
Agreeableness	30.37 (5.01)	25.77 (5.64)	< 0.001	33.00 (5.13)	28.12 (5.21)	< 0.001
Conscientiousness	28.61 (7.01)	25.61 (7.20)	< 0.001	31.34 (6.93)	25.33 (7.09)	< 0.001
Extraversion	31.02 (5.31)	27.98 (5.93)	< 0.001	30.73 (5.23)	24.61 (6.14)	< 0.001
Neuroticism	18.70 (6.69)	29.78 (7.58)	< 0.001	17.23 (6.73)	32.87 (6.86)	< 0.001
Openness	25.23 (5.62)	26.56 (6.36)	0.10	28.66 (6.51)	29.73 (6.89)	0.16

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; NEO, NEO five-factor personality inventory.

Table 2. The multiple regression model between the activations of bilateral medial and lateral OFC, and VS and the depression symptom score at age 19 (MID)

Models	ROI	Index	Estimate	Std. Error	*t*	Pr (>|t|)
Full Model	L Lateral OFC	*x1*	-0.287	0.103	2.78	5.46x10-3**
	R Lateral OFC	*x2*	0.214	0.117	-1.81	0.069
	L Medial OFC	*x3*	0.084	0.130	0.64	0.518
	R Medial OFC	*x4*	-0.341	0.157	-2.16	0.031*
	L VS	*x5*	-0.003	0.193	-0.02	0.984
	R VS	*x6*	-0.232	0.195	-1.19	0.234
	R-squared: 1.63 %, $F_{(6,1133)}$=3.14, p=4.64x10^{-3}					

GLM model: Y=β1*x1 + β2*x2 + β3*x3 + β4*x4 +β5*x5 +β6*x6 + error; Y, the depression symptom scores.

Abbreviations: L left; R right; OFC, orbitofrontal cortex; VS, ventral striatum.

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"

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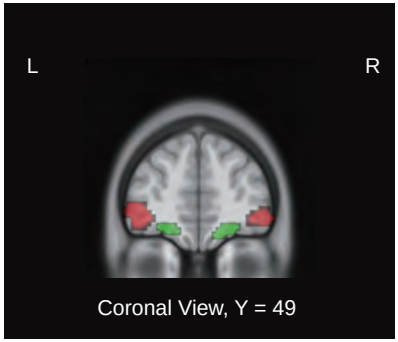
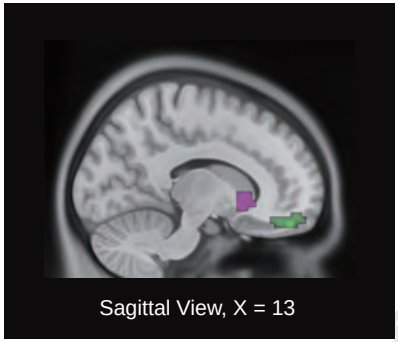
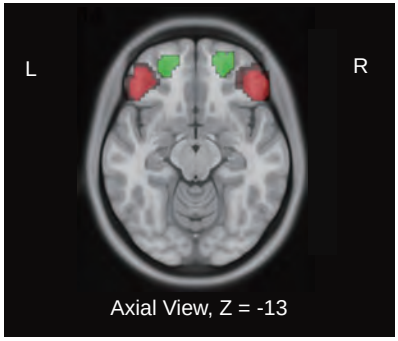
A The Medial and Lateral OFC and Ventral Striatum

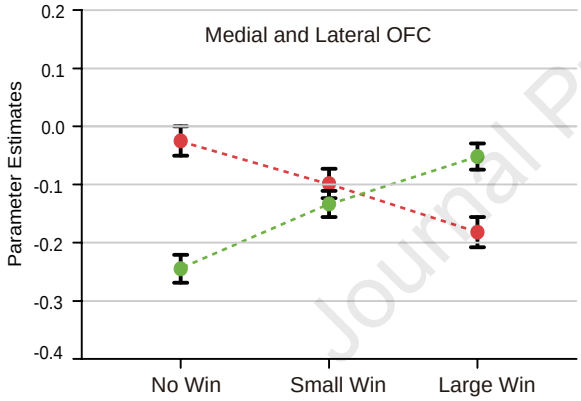


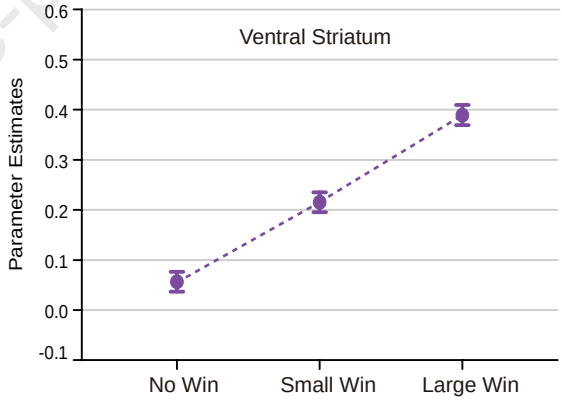




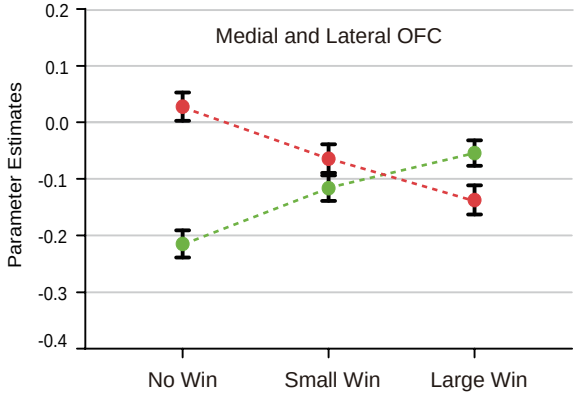
Medial OFC Lateral OFC Ventral Striatum

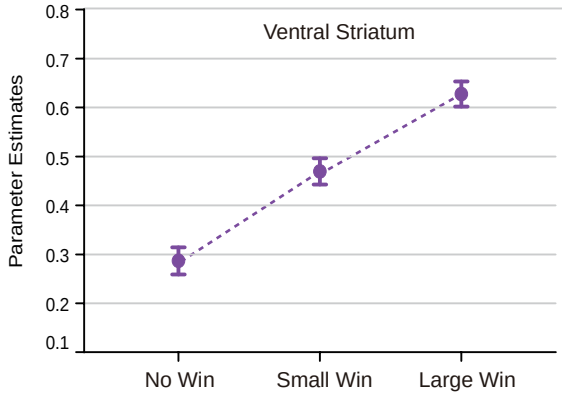
B Age 14 Reward Anticipation in MID task





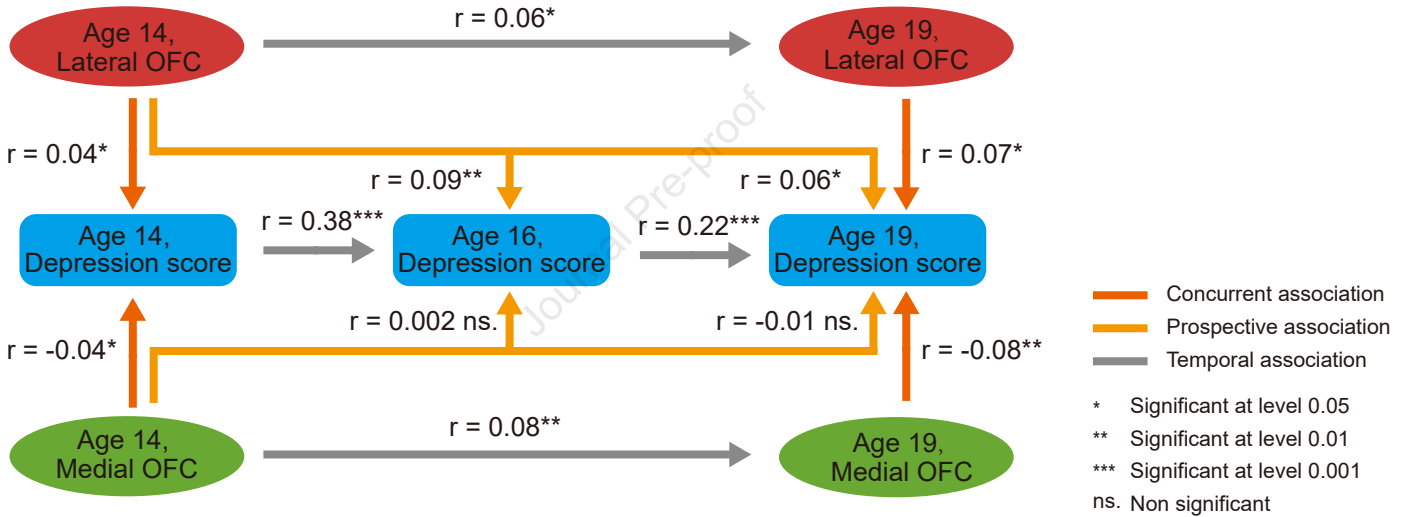
C Age 19 Reward Anticipation in MID task



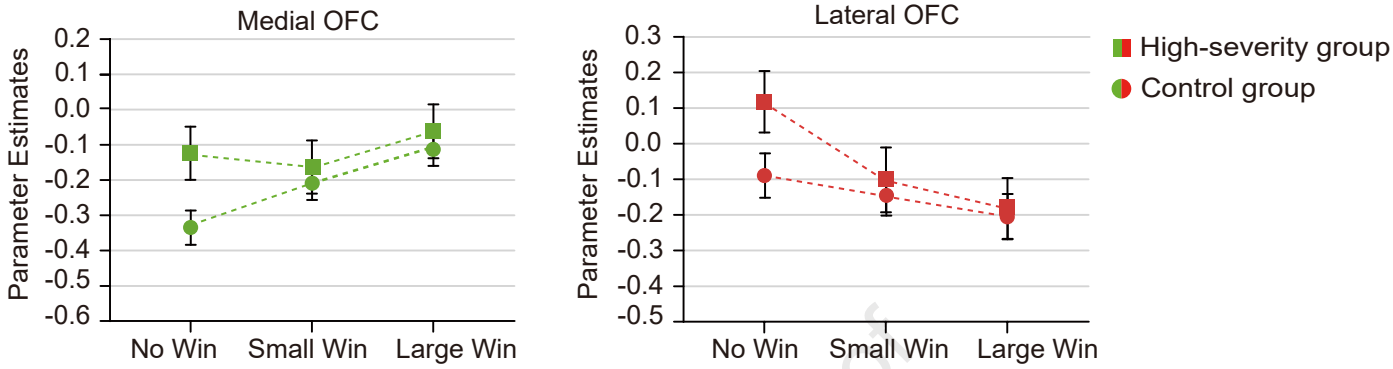


Population Analysis

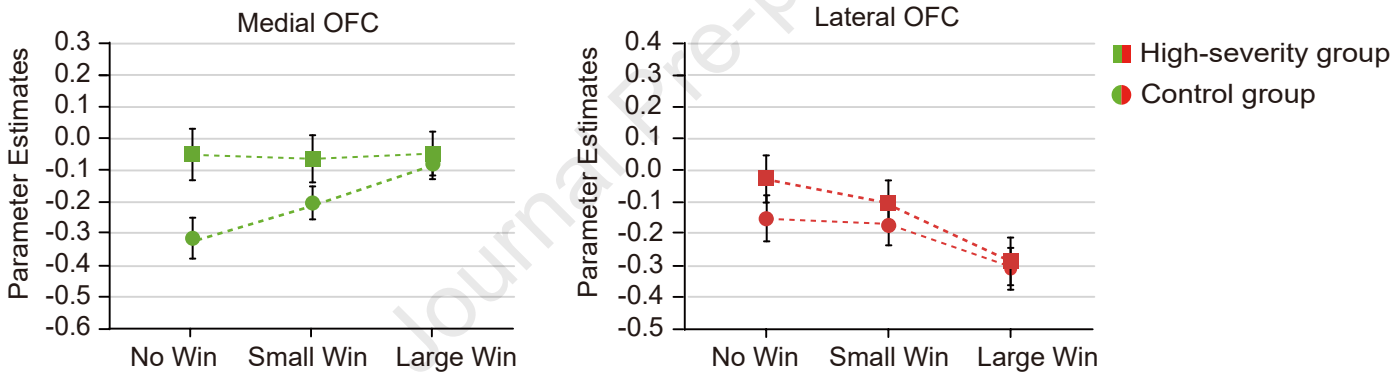
At the population level, association between medial OFC (Large-Win vs No-Win) and lateral OFC (No-Win vs Large-Win) and depression symptom score



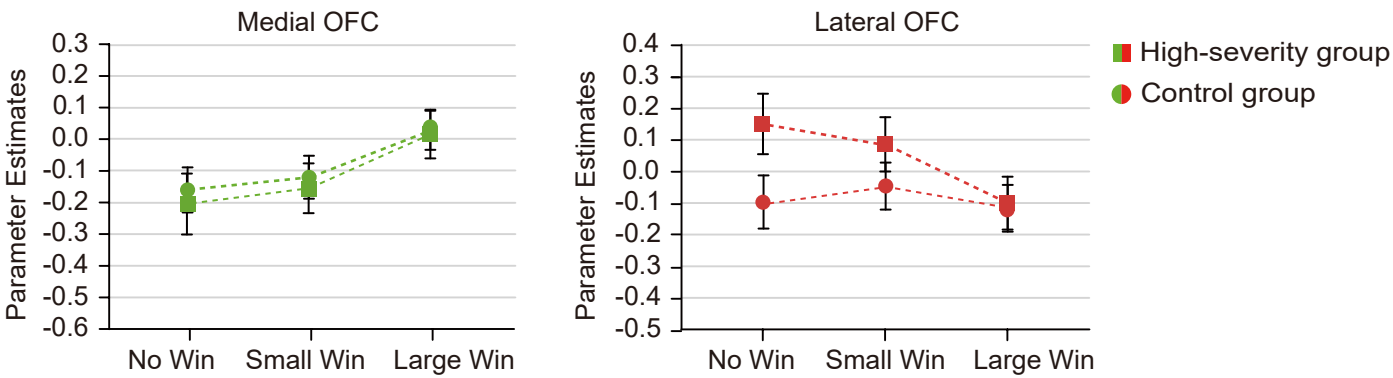
A The medial and lateral OFC (imaged at age 19) had significantly different reward trajectories between the high severity of depressive symptoms group and the control group (defined at age 19)

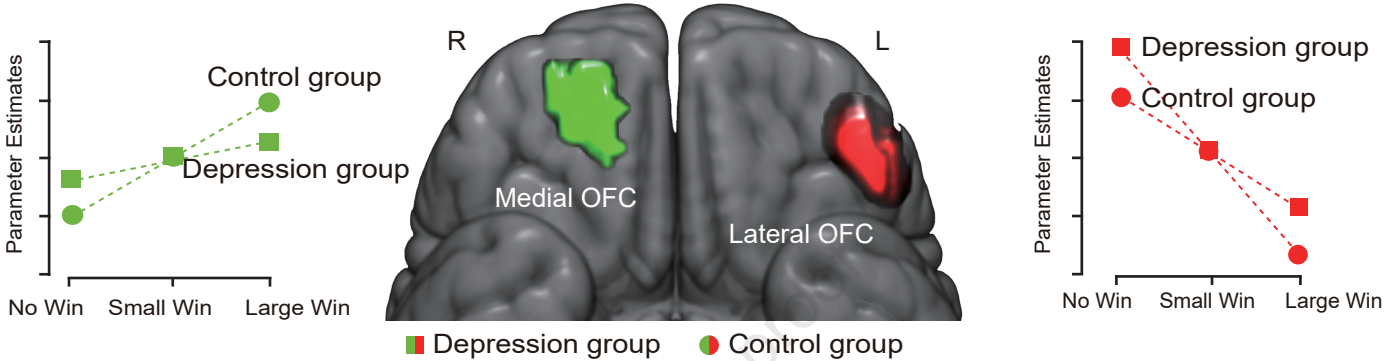


B The medial but not lateral OFC (imaged at age 14) had a significantly different reward trajectory between the high severity of depressive symptoms group and the control group (defined at age 14)



C The lateral but not medial OFC (imaged at age 14) had a significantly different reward trajectory between the high severity of depressive symptoms group and the control group (defined at age 19)





Trajectory towards Reward and Non-Reward

A graded increase to Reward (i.e. Wins) | A graded increase to Non-Reward (i.e. No-Win)

Reward and Non-Reward Sensitivity and Depression

Hyposensitivity to Reward in the high severity of depressive symptoms group | Hypersensitivity to Non-Reward in the high severity of depressive symptoms group

Related Depression Symptoms

Anhedonia (loss of interest) | Negative feelings

Association with Concurrent/Prospective Depression

Concurrent depressive symptom status | Concurrent depressive symptom status
Prospective depressive symptom status