Reward vs Non-reward Sensitivity of the Medial Versus Lateral Orbitofrontal Cortex Relates to the Severity of Depressive Symptoms Xie, Jia, Rolls et al (2021)

Supplementary Information

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging

6: 259-269. doi: 10.1016/j.bpsc.2020.08.017.

Content

Supplementary Methods

Participants

Caucasian adolescents from the IMAGEN project were included in the present study, with data collected from eight sites across Europe (i.e. France, United Kingdom, Ireland and Germany) (1). The project was approved by all local ethics research committees, and informed consent was obtained from participants and their parents/guardians. A detailed description of the study protocol and data acquisition has been previously published (1). We investigated individuals with relevant neuroimaging data at both age 14 (baseline, N = 1877) and 19 (follow-up, N = 1140), with relevant behavior depression symptoms data at age 14 (N = 1885), 16 (N = 1490), and 19 (N = 1273).

Measurement of the depression symptom score

The Adolescent Depression Rating Scale (ADRS-10) questionnaire was used to assess depression symptoms among the adolescent population at age 19 years (2) (Table S1). In a validation study, the ADRS demonstrated good internal consistency (alpha Cronbach coefficient > 0.70) and discriminated better between adolescents with and without depression than the Hamilton Depression Rating Scale and the Beck Depression Inventory (2). In the self-rated version, ADRS-10 includes ten items and a sum score of 6 or more is typically considered as corresponding to a diagnosis of depression (3, 4), which provides “maximum sensitivity and specificity” in screening for major depressive disorder (MDD) according to the DSM-IV, and is therefore clinically relevant. Higher scores indicate an elevated presence of prodromal depression severity. At ages 14 and 16, the depression symptom scores of individuals were assessed with screening questions from the Development and Well Being Assessment (DAWBA, 5 items, Table S2) and Strengths and Difficulties Questionnaire (SDQ, 3 items, Table S2). The DAWBA/SDQ are widely used to measure psychiatric and subthreshold clinical symptoms (5). In addition, we found that DAWBA/SDQ and ADRS showed a highly reliable inter-correlation across different time points (Table S3).

At follow-up assessment (19 years old), adolescents with high depression severity (ADRS-score >= 6) were compared with a control group (ADRS-score =0) matched on age, sex, handedness and imaging site. The high-severity group was defined by ADRS scores >= 6, consisting of 116 participants (with this criterion, at least 60% of these participants would be diagnosed with depression under DSM-IV (2)), while the control group was defined by the minimum value possible for the ADRS score (i.e. 0). At baseline assesment (14 years old), adolescents with high depression severity

(DAWBA-score >= 5) were selected as a high-severity of depression group. The use of five symptoms as a criterion for depression severity follows earlier practice (6). The participants with a DAWBA -score =0 were selected as the control group. The two groups were matched on age, sex, handedness and imaging site. Furthermore, in the control group, participants with any current psychiatric diagnosis, with any history of depression or bipolar disorder, or with a score > 5 on the Alcohol Use Disorders Identification Test were excluded.

Finally, after the imaging quality correction (outliers more than 3 standard deviations away from the mean in each group), we obtained a high-severity group (N = 116) and a control group (N = 206) at age 19 and a high-severity group (N =216) and a control group (N =220) at age 14 for further analyses.

In the longitudinal analysis, those adolescents defined at age 19, with a high-severity depression score (N = 99, at age 14) were also compared with the control group (N = 185, at age 14). The reduced sample size at age 14 was due to the removal of outliers more than 3 standard deviations away from the mean in each group.

Monetary Incentive Delay task

To investigate the neural basis of reward anticipation, we analysed functional MRI activations in an adapted monetary incentive delay (MID) task that has been widely used as an assessment of reward-related performance (7). The MID task includes anticipation and feedback phases of three reward magnitudes (Large-Win, Small-Win and No-Win), and a detailed description follows.

Participants performed a modified version of the Monetary Incentive Delay (MID) task to examine neural responses to reward anticipation (8). The task consisted of 66 10-second trials. In each trial, participants were presented with one of three cue shapes (cue, 250 ms) denoting whether a target (white square) would subsequently appear on the left or right side of the screen and whether 0, 2 or 10 points could be won in that trial. After a variable delay (4,000-4,500 ms) of fixation on a white crosshair, participants were instructed to respond with left/right button-press as soon as the target appeared. Feedback on whether and how many points were won during the trial was presented for 1,450 ms after the response. Using a tracking algorithm, task difficulty (i.e. target duration which was varied between 100 and 300 ms) was individually adjusted such that each participant successfully responded on ~66% of trials. Participants had first completed a practice session outside the scanner (~5 minutes), during which they were instructed that for each 5 points won they would receive one

food snack in the form of small chocolate candies at the 14-year-old baseline session, or a small amount of cash at the 19-year-old follow-up session.

fMRI data acquisition and preprocessing

Structural and functional MRI data were acquired at eight IMAGEN assessment sites with 3T MRI scanners of different manufacturers (Siemens, Philips, General Electric, Bruker)(1). The scanning variables were specifically chosen to be compatible with all scanners. The same scanning protocol was used in all sites. In brief, high-resolution T1-weighted 3D structural images were acquired for anatomical localisation and co-registration with the functional time-series. Blood-oxygen-level-dependent (BOLD) functional images were acquired with gradient-echo, echo-planar imaging (EPI) sequence. For the MID task, 300 volumes were acquired for each participant, and each volume consisted of 40 slices aligned to the anterior commissure/posterior commissure line (2.4 mm slice thickness, 1 mm gap). The echo-time (TE) was optimised (TE=30 ms, repetition time (TR)=2,200 ms) to provide reliable imaging of subcortical areas.

Functional MRI data were analysed with SPM12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). Spatial preprocessing included: slice time correction to adjust for time differences due to multi-slice imaging acquisition, realignment to the first volume in line, non-linearly warping to the MNI space (based on a custom EPI template (53x63x46 voxels) created out of an average of the mean images of 400 adolescents), resampling at a resolution of 3x3x3mm^3 and smoothing with an isotropic Gaussian kernel of 5 mm full-width at half-maximum.

fMRI first-level analyses

At the first level analysis, changes in the BOLD response for each subject were assessed by linear combinations at the individual subject level, for each experimental condition (e.g. Target (Hit, Miss) * Phases (Anticipation, Feedback) * Reward Magnitude (No-Win, Small-Win and Large-Win), total 12 conditions). The final GLM model contained 12 task condition regressors, and 21 additional covariate regressors consisting of 12 motion regressors (3 translations, 3 rotations, 3 translations shifted 1 TR before, and 3 translations shifted 1 TR later) and 9 additional columns corresponding to the long term effects of the movement (3 nuisance variables for white matter and 6 nuisance variables for ventricles: these were built according to the method described and commonly referred to as CompCor correction (9)). The regressors modelling the experimental conditions were convolved using SPM's default HRF (Hemodynamic Response Function). In the present main analysis, we

concentrated on the reward processing phase: hit reward anticipation (termed as reward anticipation). The regression coefficients (i.e. the activation for the different Win conditions) from this first level model were used to calculate the Regions of Interest as described next and were used in the population analyses described below.

The regions of interest and analysis protocol

Regions of interest in the medial and lateral OFC were created using a mask set where the activation was significant at an absolute t value of 5 (|t| > 5) in the contrast of “Large-Win vs No-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 ventral striatum was from a previous study (7).

The activations in these ROIs were analysed for associations with the depression symptom score using a multiple regression analysis to integrate the information from these ROIs in the medial and lateral OFC and ventral striatum that are implicated in reward-related processing, with gender, handedness and imaging sites as control variables. Next, we used the model comparison to separate the key ROIs in the relationship between brain activations and depression symptoms. The model comparisons were constructed with ANOVAs using the statistical package R (10). We further checked how the depression-related reward regions relate to the development of depression symptoms at age 14, 16 and 19 (11, 12).

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 (13).

Given that the multiple regression showed a significant association between the activations of the six ROIs and the ADRS depression scores, post hoc tests were performed to investigate which of the 6 areas had significant associations, as follows. Within the full model, the regression coefficients for each ROI were tested with a t-statistic. Because these t-statistics came from a significant full multiple regression model, no further correction for multiple comparisons was needed. (The F-test effectively protects against inflated experiment-wise error rates (14).) To ensure that the ROIs from this

procedure were each significant without an impact from possible multicollinearity, we conducted univariate analyses between the depression symptom scores and each of the ROIs identified as significant by the previous procedure (with gender, handedness and imaging sites were included as control variables).

Longitudinal analysis for the significant ROIs in the whole population

We first verified whether similar effects observed at age 19 were also present at age 14, by conducting the same univariate association analyses between the activations of the significant ROIs (i.e. the left lateral OFC and the right medial OFC) and the depression scores both measured at age 14. (These tests at age 14 were one-tailed because the direction of the association had been established by the analysis at age 19.)

We then 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). (In addition, as a significant longitudinal association was observed, we checked whether the association was significant when controlling for the depression symptom score measured at age 14.)

Sensitivity to reward and non-reward in a high-severity depression group compared to a control group at both ages 19 and 14

We investigated whether each significant ROI could serve as a neural biomarker with potential clinical relevance in a contrast of the high depression severity group vs the control group. For each contrast defined at either age 14 or 19 respectively, a two-way repeated-measurement ANOVA was used to investigate the difference of the activation trajectories (i.e. from No-Win through Small-Win to Large-Win) between the high-severity and control groups (i.e. the interaction effect), where the activations for each reward condition (i.e. No-Win, Small-Win and Large-Win) were treated as repeated measurements. We were interested in the interaction term because it is analogous to our activation analyses in the whole sample where the trajectory from No-Win to Large-Win (i.e. the activation, with the Small-Win condition omitted) was associated with the depression symptoms (instead of the stratified high-severity vs control comparison here). When the interaction term was found to be significant, we checked whether the overarching No-Win to Large-Win trajectory difference between the high-severity depression group and the control group matched what was found in the whole sample analysis. When confirmed, we then investigated which sub-section of the

trajectories (i.e. from No-Win to Small-Win, and from Small-Win to Large-Win) were the driving force underlying the significantly different trajectories from No-Win to Large-Win between the high-severity and control groups. [As the two-way repeated measures ANOVA with only two repeated measurements (i.e. only considering two reward conditions) is essentially equivalent to a t-test comparing the activations (i.e. contrasting the two reward conditions of interest) between the high-severity depression group and the control group, we provide the t-statistic for all sub-sections of the trajectory analyses as this provides the direction of association, instead of the F-statistic. As above, further correction for multiple comparisons is already incorporated (14).] As a complementary analysis for the two-way repeated-measurement ANOVA, we further investigated the reward or non-reward sensitivities across the three reward conditions within the high-severity depression group, as well as within the control group, with the one-way repeated-measures ANOVA, with the p-values Bonferroni corrected for the two independent groups.

Other regions of interest and depression severity during reward anticipation in the MID task

To complement the analyses of the orbitofrontal cortex and ventral striatal regions in reward processing and their relation to the depression symptoms, other brain regions associated with reward processing and depression, e.g. the subgenual anterior cingulate cortex (sgACC) (15), anterior insula (16), and amygdala (17, 18) were also analysed, with masks from the SPM anatomy toolbox (19).

Supplementary Results

Exploring other candidate regions for depression severity and reward anticipation

The subgenual anterior cingulate cortex (sgACC) showed no significant mean activation difference between Large-Win vs No-Win (t = 0.86, p = 0.38 at age 19; t = -1.2, p = 0.22 at age 14) during reward anticipation, although a subregion could be identified with a significant association with the depression symptom score in the full sample using small-volume correction (Figure S5). Notably, the identified sgACC subregion had a higher activation during the No-Win condition in the high-severity depression group if compared to the control group at age 19 (Cohen's d = 0.14, t = -2.41, p =0.016), but not at age 14 (Figure S5).

The anterior insula was significantly activated in the MID task (i.e. Large-Win vs No-Win) at both age 14 (t = 7.24, p = 8.17×10^{-13}) and 19 (t = 5.68, p = 1.70×10^{-8}). While the mean activation showed

no significant association with depression, small-volume correction identified a sub-region in the left anterior insula/operculum with a significant association with the depression symptom score (Figure S5). The activation patterns from No-Win through Small-Win to Large-Win in this region resembled those of the right medial OFC, i.e. a blunted activation in the high depression severity group (Cohen's $f^2 < 0.001$, $F_{(2,640)} = 0.02$, $p = 0.97$) vs a graded increase in the control group (Cohen's $f^2 = 0.018$, $F_{(2,640)} = 16.66$, $p = 1.10\text{x}10^{-7}$) at age 19, between which the trajectories were significantly different (Cohen's $f^2 = 0.018$, $F_{(2,640)} = 5.79$, $p = 0.003$), while no difference could be observed at age 14 (Figure S5). The insula receives inputs from the orbitofrontal cortex and provides one route for autonomic output from the orbitofrontal cortex (20-23).

For the amygdala, while a significant activation (i.e. Large-Win vs No-Win) was observed at both ages 14 ($t = 4.02$, $p = 6.08\text{x}10^{-5}$) and 19 ($t = 6.33$, $p = 3.60\text{x}10^{-10}$), no significant association with the depression symptom score could be observed either for the mean activation or through a small-volume correction.

Supplementary Figures

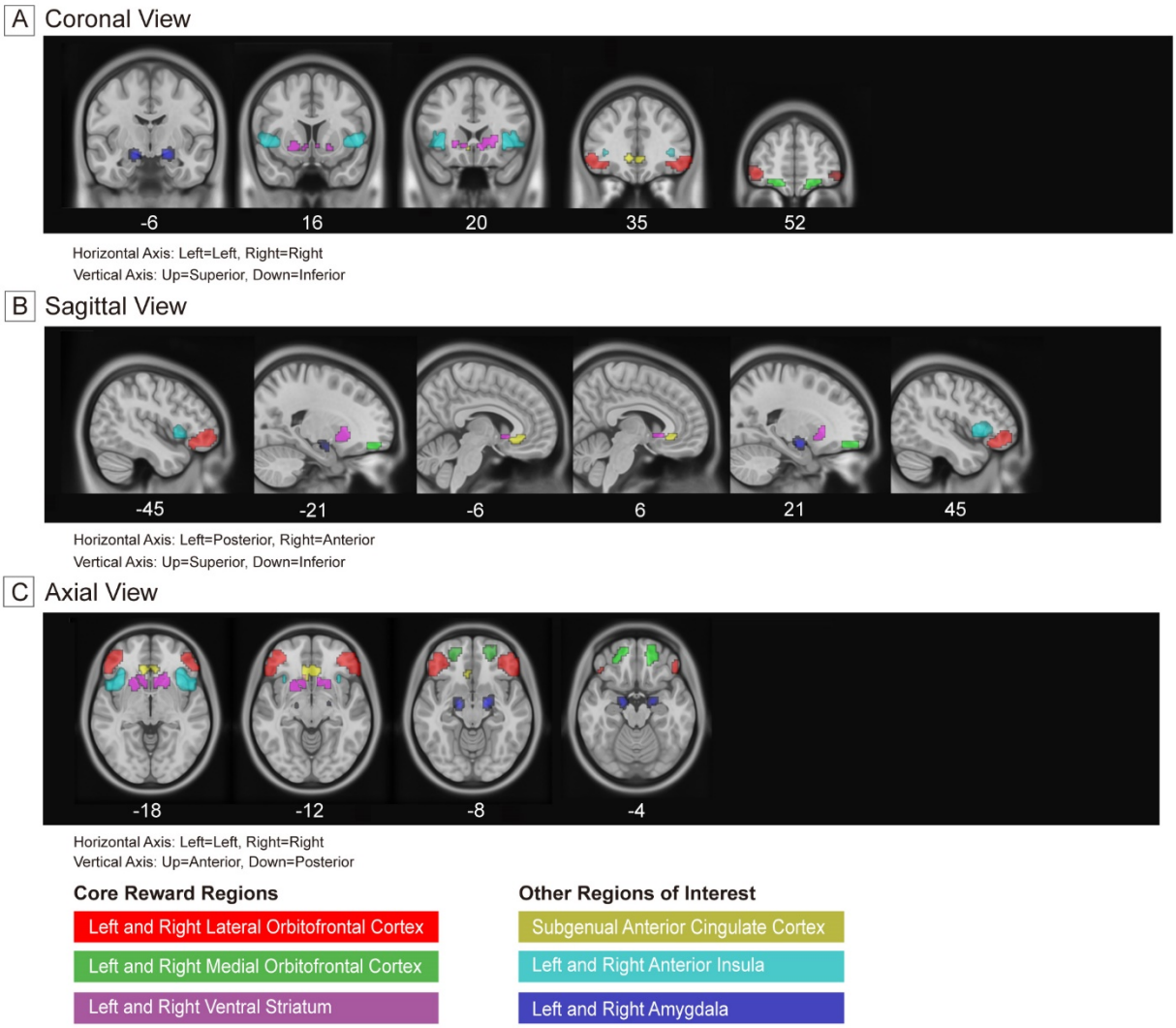

Figure S1. MID investigation, core reward regions and other regions of interest (ROI) selected for analysis (Coronal, Sagittal and Axial Views). A. A coronal view of the ROIs selected for analysis. B. A sagittal view of the ROIs selected for analysis. C. An axial view of the ROIs selected for analysis.

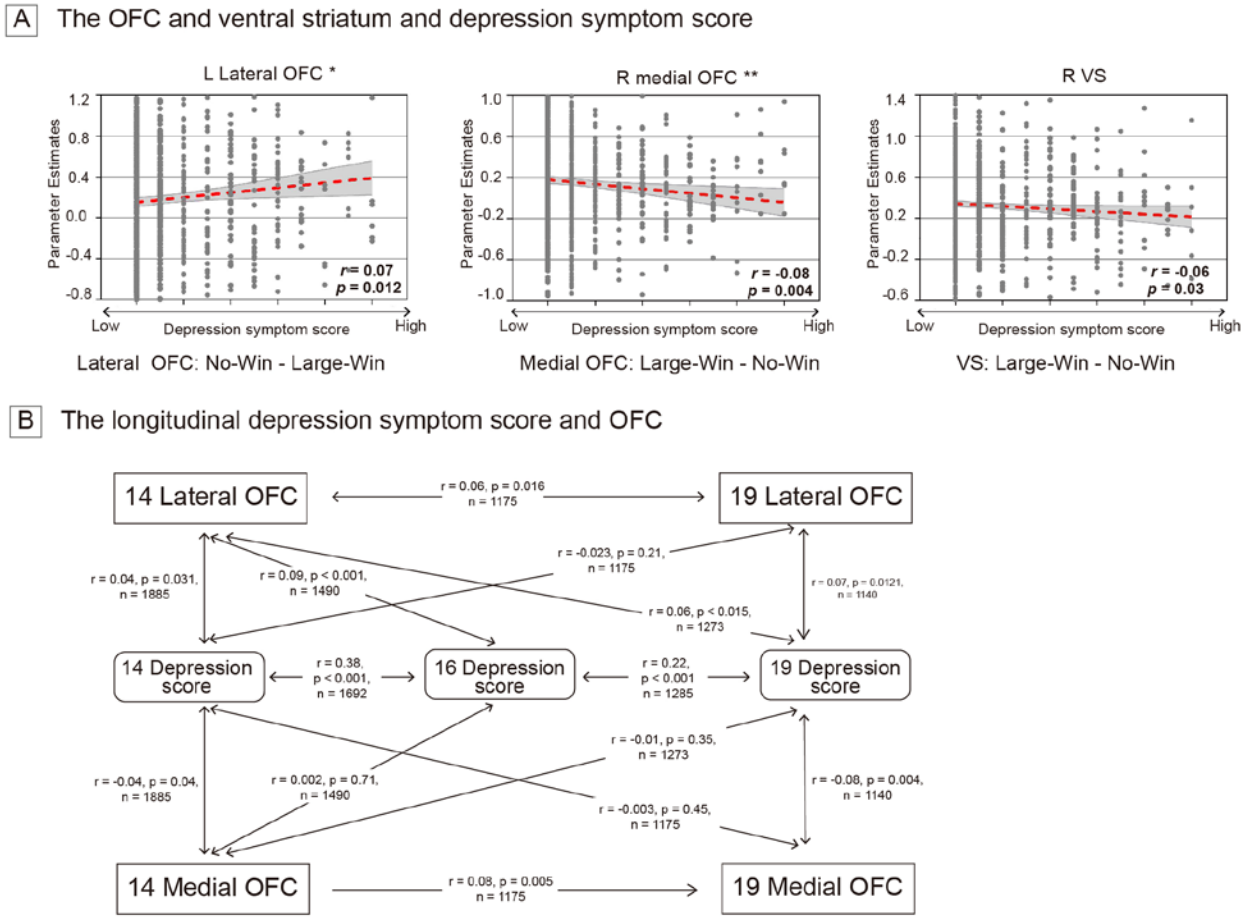

Figure S2. The associations between activations of the orbitofrontal cortex and ventral striatum and the depression symptom score. A. The univariate association between OFC and ventral striatum with depression symptom score at age 19. B. The associations within the depression symptom scores at age 14, age 16 and age 19; associations of OFC activations between age 14 and age 19; concurrent and longitudinal associations between the depression symptom scores and OFC activations at age 14, age 16 and age 19.

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

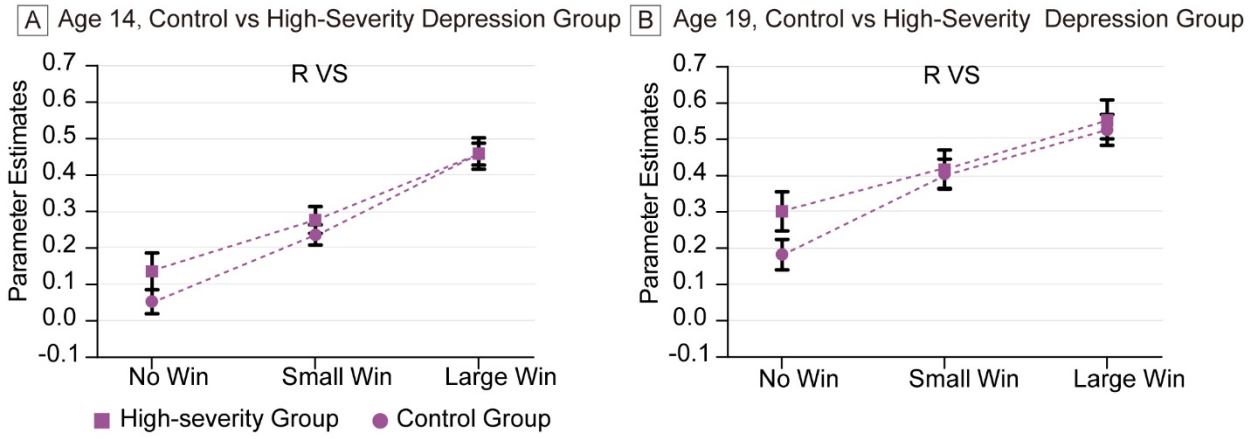

Figure S3. Activations of the ventral striatum in the control and high-severity groups for depression at age 14 and 19. A. At age 14, the ventral striatum activation trajectory in both the high-severity for depression and control groups (defined at age 14). B. At age 19, the ventral striatum activation trajectory (imaged at age 19) in both the high-severity for depression and control groups.

Abbreviations: R, right; VS, ventral striatum

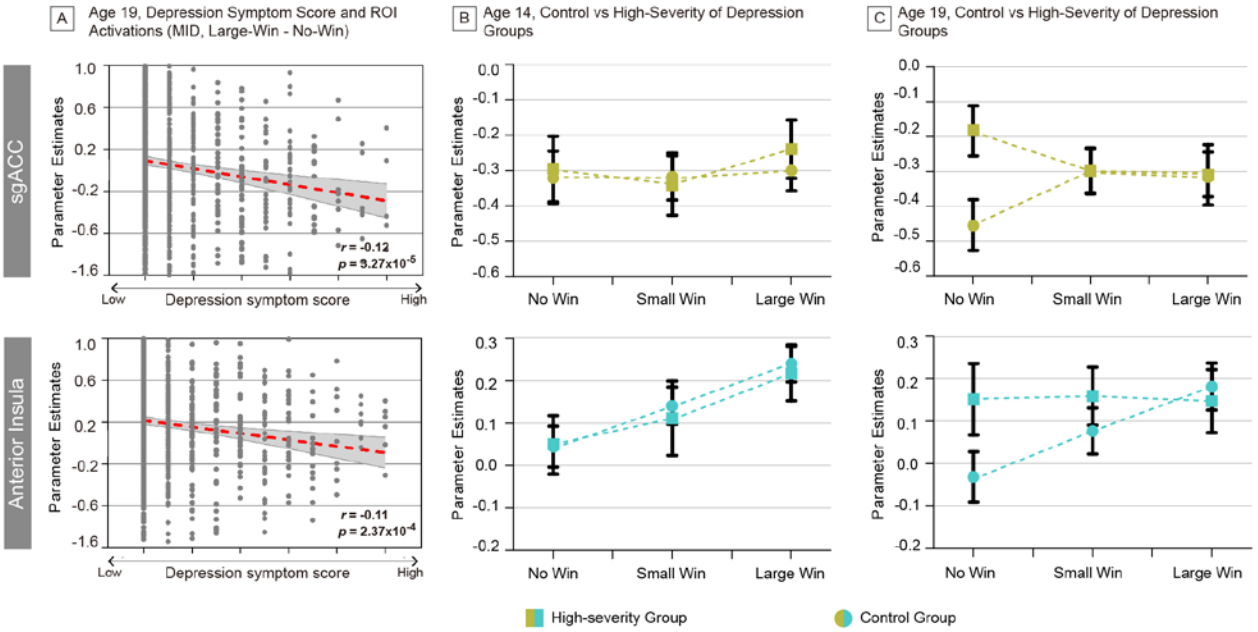

Figure S4. Activations in other regions of interest and depression severity at age 14 and 19. A. The associations between depression symptom score and brain activation (sgACC, upper; anterior insula, down). B. At age 14, the brain activation trajectory (sgACC, upper; anterior insula, down) in both high-severity depression and control groups. C. At age 19 (sgACC, upper; anterior insula, down), The ventral striatum activation trajectory in both high-severity depression and control groups.

Abbreviations: sgACC, subgenual anterior cingulate cortex.

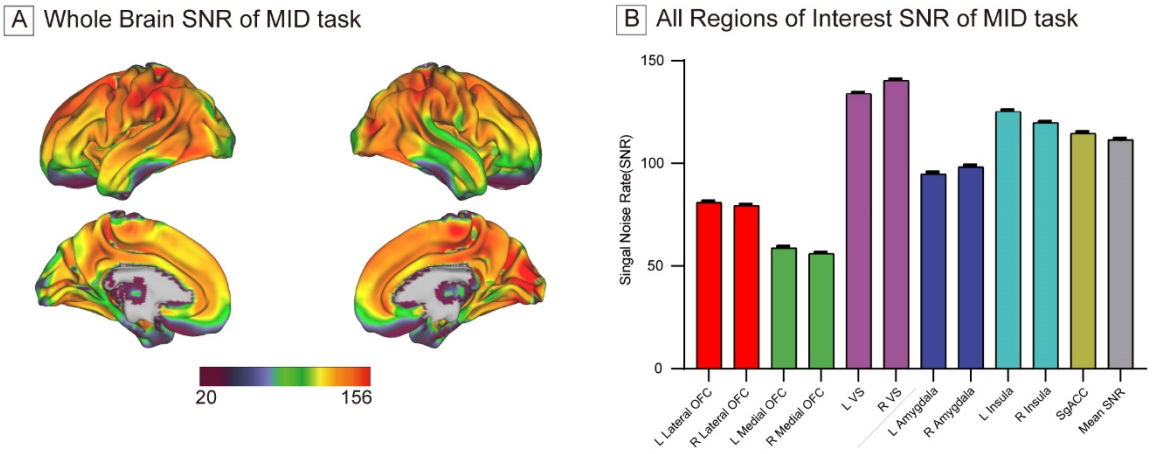

Figure S5. The signal to noise ratio (SNR) of the whole brain and regions of interest in the MID task. A. The whole brain signal to noise rate of the MID task. B. The signal to noise of the all ROIs of the MID task.
Abbreviations: SNR, signal to noise ratio. The signal to noise was measured by dividing the mean value by the standard deviation of the BOLD signal.

Supplementary Tables

Table S1. Adolescent Depression Rating Scale (ADRS)

Num.	**Items** (ADRS, 10-items self-rated version)	**Rating (0: No, 1: Yes)**	
1	I have no energy for work/school	0	1
2	I have trouble thinking	0	1
3	I feel overwhelmed by sadness and listlessness	0	1
4	Nothing really interests or entertains me	0	1
5	What I do is useless	0	1
6	When I feel this way, I wish I were dead	0	1
7	Everything annoys me	0	1
8	I feel downhearted and discouraged	0	1
9	I sleep badly	0	1
10	School/work doesn't interest me just now, I can't cope.	0	1

Table S2. The measurement of depression symptom score at age 16 and 19

Num.	**Items (1-8 DAWBA, 9-10 SDQ)**	**Rating (0: No, 1: Yes)**	
1	Depression.sad	0	1
2	Depression.irritable	0	1
3	Depression.loss.of.interest	0	1
4	Depression.recent.talk.of.dsh	0	1
5	Depression.dsh.recently	0	1
6	Depression.dsh.ever	0	1
7	Headache/stomach ach	0	1
8	Unhappy	0	1

Abbreviations: *dsh, Deliberate self-harm*

Table S3. The inter-correlation of depression symptom scores at age 14, 16 and 19

Depression symptom score	**Age 14 (DAWBA)**	**Age 16 (DAWBA)**	**Age 19 (ADRS)**
Age 14 (DAWBA/)			
Age 16 (DAWBA)	r = 0.51, n = 1692, p = 2.25e^{-111}		
Age 19 (ADRS)	r = 0.30, n = 1448, p = 5.70e^{-30}	r = 0.42, n = 1285, p = 8.69e^{-55}	

Table S4. The mean brain activations of the OFC and VS at age 14 and 19

Age	ROI	*df*	Left hemisphere			Right hemisphere		
			t	***Cohen's d***	***p***	***t***	***Cohen's d***	***p***
14	Lateral OFC	1876	12.18	-0.28	6.84~33	8.58	-0.19	1.85e-17
	Medial OFC	1876	10.66	0.24	8.71e-26	10.63	0.25	1.08e-25
	VS	1876	36.72	0.84	~0	32.83	0.76	~0
19	Lateral OFC	1139	9.17	-0.27	$2.01x10^{-19}$	8.38	-0.25	$1.58x10^{-16}$
	Medial OFC	1139	8.63	0.25	$1.90x10^{-17}$	10.52	0.30	$9.29x10^{-25}$
	VS	1139	26.10	0.77	~0	22.34	0.66	~0

Lateral OFC: No-Win – Large-Win, Medial OFC: Large-Win – No-Win

Table S5. Graded brain activation changes of OFC and VS at age 14 and 19

Age	ROI	df	No-Win to Small-Win (Small-Win – No-Win)			Small-Win to Large-Win (Large-Win – Small-Win)		
			t	***Cohen's d***	***p***	***t***	***Cohen's d***	***P***
14	Lateral OFC	1876	-6.17	0.14	7.98e-10	-8.02	0.18	1.81e-15
	Medial OFC	1876	7.02	0.16	3.17e-12	6.68	0.15	2.98e-12
	VS	1876	19.87	0.46	~0	24.68	0.57	~0
19	Lateral OFC	1139	-6.08	-0.18	$1.63 x10^{-9}$	-5.14	-0.15	$3.12 x10^{-7}$
	Medial OFC	1139	6.65	0.20	$4.38 x10^{-11}$	4.56	0.14	$5.63 x10^{-6}$
	VS	1139	15.49	0.46	~0	17.26	0.51	~0

Table S6. The regression model of the OFC activations with the depression symptom score

Model	ROI	Index	Estimate	Std. Error	*t*	Pr (>|t|)
Model 2-OFC	L Lateral OFC	*x1*	0.203	0.092	2.198	0.028 *
	R Medial OFC	*x2*	-0.307	0.119	-2.594	$9.62x10^{-3}$ **
	R-squared: 1.13 %, $F_{(2,1137)} = 6.50$, $p = 1.56x10^{-3}$					

*Abbreviations: L left, R right, GLM model: Y = β1*x1 + β2*x2 + error; Y, depression severity*

Lateral OFC: No-Win – Large-Win, Medial OFC: Large-Win – No-Win

Table S7. Results of model comparison between Model 1-Anticipation and Model 2-OFC

Model	Res. Df	RSS	Df 1	Sum of Sq	F	Pr(>F)
Model 1-Anticipation model and Model 2-OFC model	1135	4902				
	1137	4915	2	13.33	1.54	0.214

Note details of the Model 1-Anticipation and Model 2-OFC models are shown in Table 2 and Table S6.

Table S8. The association between depression symptom subscales with medial and lateral OFC activations

Num.	Items	Lateral OFC (n =1140)	Medial OFC (n=1140)
1	I have no energy for work/school	$r = 0.029,\ p_{uncorrected} = 0.321$	$r = -0.057,\ p_{uncorrected} = 0.053$
2	I have trouble thinking	$r = 0.063,\ p_{uncorrected} = 0.033$	$r = -0.072,\ p_{uncorrected} = 0.015$
3	I feel overwhelmed by sadness and listlessness	$r = 0.083,\ p_{uncorrected} = 0.005$	$r = -0.047,\ p_{uncorrected} = 0.116$
4	Nothing really interests or entertains me	$r = 0.046,\ p_{uncorrected} = 0.11$	$r = -0.075,\ p_{uncorrected} = 0.010$
5	What I do is useless	$r = 0.086,\ p_{uncorrected} = 0.004$	$r = -0.058,\ p_{uncorrected} = 0.048$
6	When I feel this way, I wish I were dead	$r = 0.064,\ p_{uncorrected} = 0.030$	$r = -0.048,\ p_{uncorrected} = 0.106$
7	Everything annoys me	$r = 0.033,\ p_{uncorrected} = 0.261$	$r = -0.050,\ p_{uncorrected} = 0.094$
8	I feel downhearted and discouraged	$r = 0.037,\ p_{uncorrected} = 0.210$	$r = -0.052,\ p_{uncorrected} = 0.079$
9	I sleep badly	$r = 0.033,\ p_{uncorrected} = 0.259$	$r = -0.046,\ p_{uncorrected} = 0.120$
10	School/work doesn't interest me just now, I can't cope.	$r = 0.016,\ p_{uncorrected} = 0.581$	$r = -0.045,\ p_{uncorrected} = 0.131$

Lateral OFC: No-Win – Large-Win, Medial OFC: Large-Win – No-Win

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