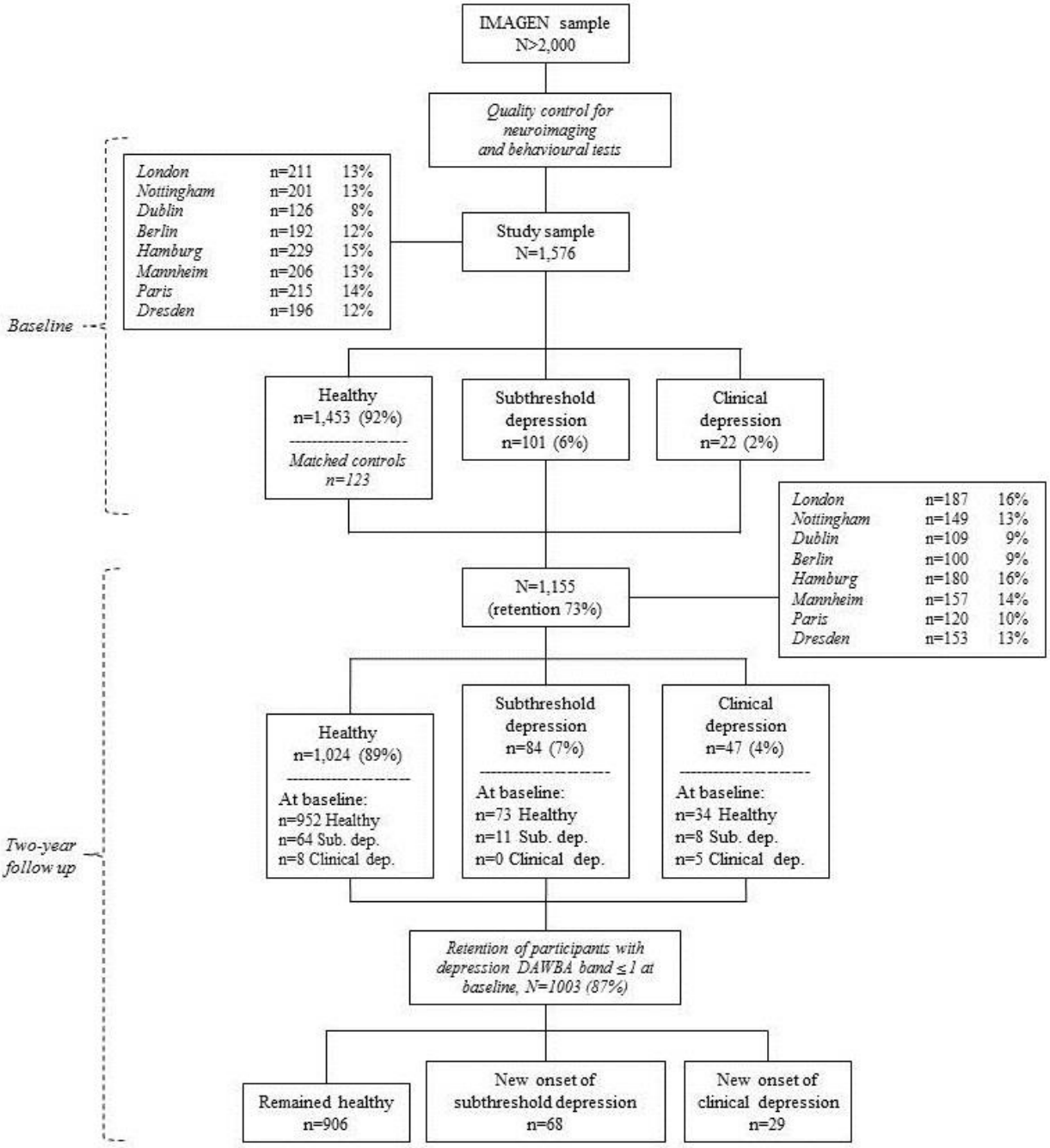
Data Supplement for Stringaris et al., The Brain's Response to Reward Anticipation and Depression in Adolescence: Dimensionality, Specificity, and Longitudinal Predictions in a Community-Based Sample. Am J Psychiatry (doi: 10.1176/appi.ajp.2015.14101298)

## Supplemental Methods

**FIGURE S1.** CONSORT Diagram of depression groups



***Validation of the anhedonia item of the DAWBA***

All participants were coded as suffering from loss of interest/anhedonia (*'In the last 4 weeks, have there been times when you have lost interest in everything, or nearly everything, that you normally enjoy doing?'*) or low mood (*'In the last 4 weeks, have there been times when you have been very sad, miserable, unhappy or tearful?'*) if so rated (as *'Yes'* or *'No'*) by self-report in the screening questions of the depression section (H) from the DAWBA.

We carried out a validation of the anhedonia and low mood items using the Adolescent Depression Rating Scale (ADRS) (1). The ADRS is a 10-item scale that measures depressive symptoms and was introduced in the second wave of data collection in the IMAGEN study.

Using a subsample of adolescents with ADRS scores (N=839) we employed a logistic regression model with the anhedonia item as a dependent variable and all the ADRS items as predictors of interest. We then repeated these analyses with the low mood item as outcome.

For anhedonia, only the following items were significantly associated: "Nothing really interests or entertains me" (Odds ratio=2.82; 95%CI: 1.25-6.38, p=0.012), "School/work doesn't interest me just now, I can't cope" (Odds ratio=2.24; 95%CI: 1.25-4.00, p=0.007), and "I sleep badly" (Odds ratio=1.69; 95%CI: 1.09-2.64, p=0.020).

For low mood, only the following items were significantly associated: "I feel overwhelmed by sadness and listlessness" (Odds ratio=2.20; 95%CI: 1.22-4.00, p=0.008) "I have no energy for work/school" (Odds ratio=1.61; 95%CI: 1.02-2.52, p=0.040), "I sleep badly" (Odds ratio=1.58; 95%CI: 1.06-2.34, p=0.023), and "Nothing really interests or entertains me" (Odds ratio=0.32; 95%CI: 0.13-0.80, p=0.014). It should be noted that the last item, which related positively to anhedonia, is negatively related to low mood.

***Monetary Incentive Delay Task***

The Monetary Incentive Delay task used in the present study was an adaptation of the task from, for example, Knutson et al (2). This event-related task consisted of 66 10-second trials. In each particular trial, participants were presented with one of three cue shapes (cue, 250 ms) denoting whether a target (a 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 particular trial (Figure S1). After a variable delay (4,000-4,500 ms) of fixation on a white crosshair, participants were instructed to respond by pressing a button with their left or right index finger 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 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 (for ~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. Functional magnetic resonance imaging (MRI), blood oxygen-level dependent (BOLD)-responses were measured during reward anticipation and reward feedback. This study is focused on the contrast "anticipation of large win versus anticipation of no win". Task presentation and recording of the behavioural responses were performed using Visual Basic 2005 with .NET Framework Version 2.0, and the visual and response grip system from Nordic Neuro Lab (NordicNeuroLab AS, Bergen, Norway).

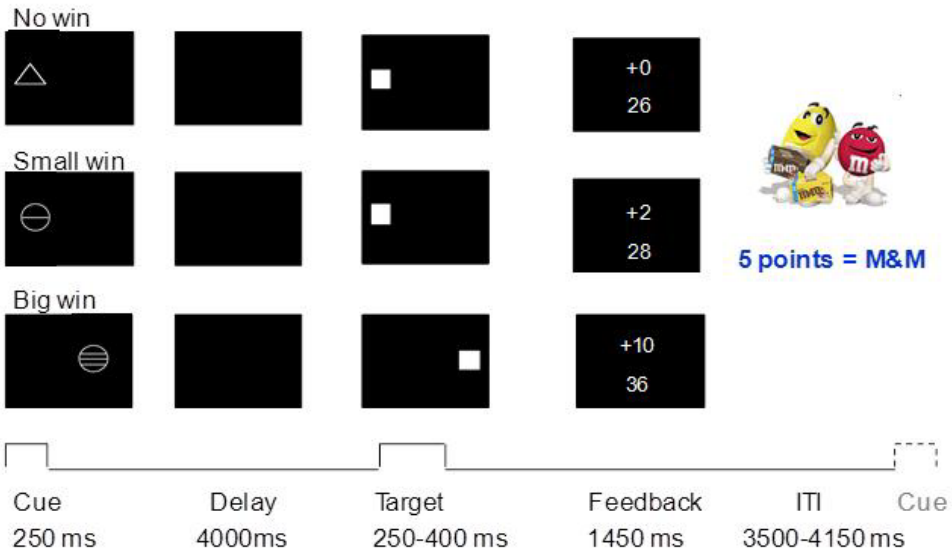



**FIGURE S2.** Outline of the stages of the Monetary Incentive Delay task.

***Magnetic Resonance Imaging Data Acquisition***

Structural and functional magnetic resonance imaging (fMRI) data were acquired at eight IMAGEN assessment sites with 3T MRI scanners of different manufacturers (Siemens, Munich, Germany; Philips, Best, The Netherlands; General Electric, Chalfont St Giles, UK; Bruker, Ettlingen, Germany). A key challenge for the ability to pool data acquired on MR scanners of different manufacturers relates to their variation in availability and implementation of particular image-acquisition techniques. To address this problem, for each technique, a set of parameters compatible with all scanners, particularly those directly affecting image contrast or signal-to-noise, was devised and held constant across sites. Where manufacturer-specific choices had to be made (for example the design of head coil), the best manufacturer-specific option was used at all sites with the same scanner type. Two quality control procedures are regularly implemented at each site: (1) The American College of Radiology phantom is scanned to provide information about geometric distortions and signal uniformity related to hardware differences in radiofrequency coils and gradient systems, image contrast and temporal stability, and a custom phantom58 is scanned for diffusion-related parameters. (2) Several healthy volunteers are

regularly scanned at each site to assess factors that cannot be measured using phantoms alone and at multiple sites to determine inter-site variability in structural and functional measures (for example, tissue contrast in raw MRI signal, tissue relaxation properties). More information about quality information can be found in Schumann et al. 2010 (3).

The scanning variables were specifically chosen to be compatible with all scanners. The same scanning protocol was used at all sites. In brief, high-resolution T1-weighted three-dimensional structural images were acquired for anatomical localization and co-registration with the functional time series. Functional MRI BOLD images were acquired with a gradient-echo, echo-planar imaging sequence. For the Monetary Incentive Delay task, 300 volumes were acquired for each subject. Each volume consisted of 40 slices aligned to the anterior commissure- posterior commissure line (2.4mm slice thickness, 1mm gap) acquired in a descending order. The echo time was optimized (echo time = 30 msec, repetition time = 2200 msec) to provide reliable imaging of subcortical areas.

Functional MRI data were pre-processed and analysed with SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). Time series data were slice-time corrected using the first slice as the reference for interpolation, and then corrected for movement (spatial realignment) to the first volume. Time series data were then non-linearly warped on the MNI space, using a custom EPI template and smoothed with a Gaussian kernel of 5mm Full-Width Half Maximum (FWHM).

At the first level of analysis, the model contained the onset of each cue and each feedback presentation. This enables separate analyses of reward anticipation and reward feedback conditions. Each trial (eg. reward anticipation high win) was convolved using the SPM default Hemodynamic Response Function (HRF). Estimated movement parameters were added to the design matrix in the form of 18 additional columns (3 translations, 3 rotations, 3 quadratic and 3 cubic translations, and each 3 translations with a

shift of ±1 TR). For the current analyses, we were interested in the contrast "anticipation of large win versus anticipation of no win" (2).

**Statistical Analysis – Fronto-striatal-limbic mask**

The fronto-striatal-limbic mask used in the analyses with full and subthreshold depression was made with the Wake Forest University (WFU) PickAtlas (4) and included the following regions bilaterally from the Automated Anatomical Labeling (AAL) atlas (5): *caudate, putamen, rectus, insula, olfactory, amygdala, hippocampus, cingulum anterior, frontal middle, frontal superior medial, frontal superior, frontal superior orbital, frontal medial orbital, frontal middle orbital and frontal inferior orbital.*

**Results**

**Dimensionality of brain response to reward anticipation in adolescents**

**TABLE S1. Regions of reduced activation for the contrast "anticipated large win versus no win" in adolescents with clinical depression (n=22) and subthreshold-depression (n=101) compared to matched healthy controls (n=123).**

| Anatomical regions | Cluster size (voxels) | MNI Coordinates | | | T-test | Cluster p (Familywise error) |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| **Full Depression** | | | | | | |
| Right Caudate Head | 26 | 6 | 11 | -2 | 4.40 | 0.048 |
| Right Caudate | | 12 | 20 | -8 | 3.73 | |
| Left Caudate | 40 | -6 | 17 | -2 | 4.36 | 0.010 |
| Right Medial Frontal Gyrus | 49 | 15 | 65 | 7 | 4.23 | 0.004 |
| Right Superior Frontal Gyrus | | 21 | 59 | -5 | 4.22 | |
| Left Superior Frontal Gyrus | 29 | -21 | 14 | 49 | 4.16 | 0.034 |
| Left Middle Frontal Gyrus | | -24 | 14 | 58 | 3.84 | |
| **Subthreshold depression** | | | | | | |
| Left Caudate Head | 83 | -12 | 14 | -2 | 5.54 | <0.001 |
| Left Putamen | | -18 | 8 | -8 | 5.25 | |
| Rigth Caudate Head | 54 | 12 | 20 | -5 | 4.48 | 0.003 |
| Right Caudate | | 12 | 11 | -11 | 4.44 | |

Statistical significance set at $p<0.001$, unc.; extent threshold=5 voxels; Voxel size= $27mm^3$

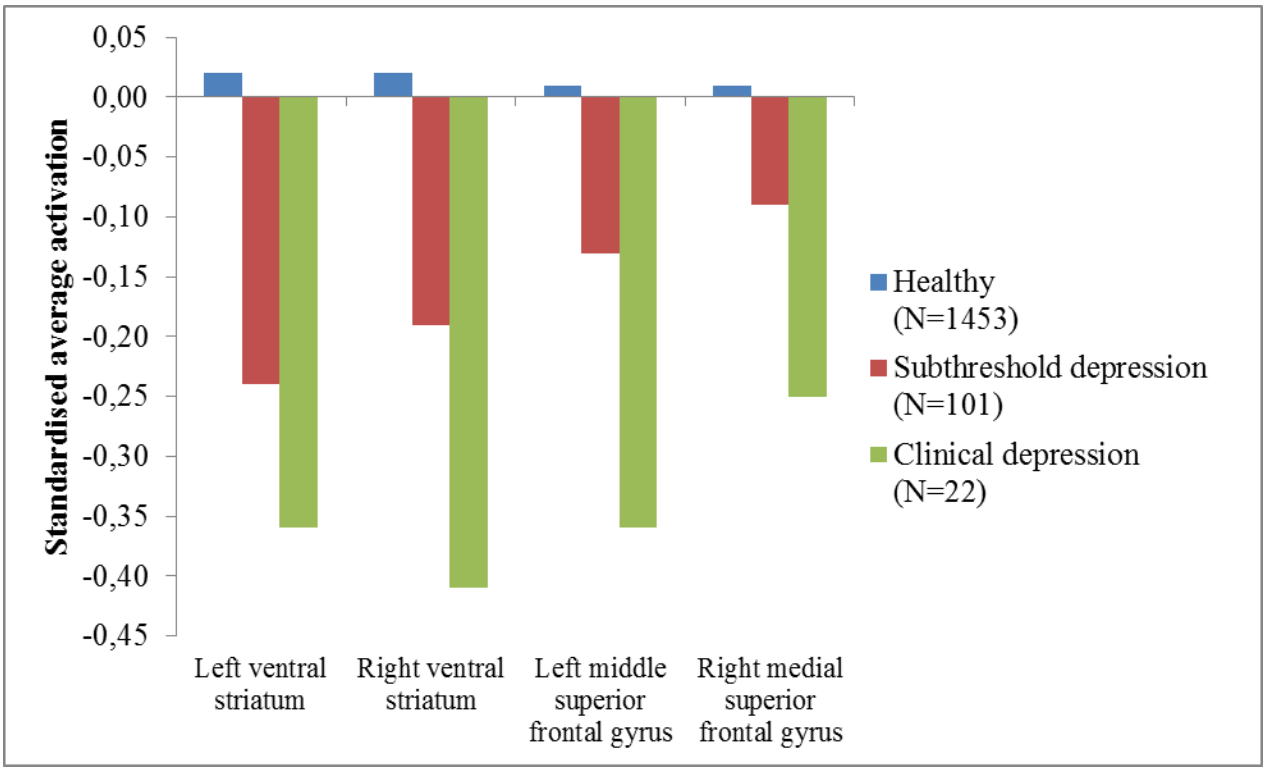



**FIGURE S3.** Trend analyses - Standardised BOLD response in left and right ventral striatum, right medial superior frontal gyrus and left middle superior frontal gyrus among healthy adolescents, adolescents with subthreshold depression and adolescents with full depression.

**The Adolescent Depression Rating Scale (ADRS)** was employed to assess depressive symptoms at follow up. The ADRS is a 10-item measure with good psychometric properties (1). Longitudinal analyses showed that reduced ventral striatum response to anticipation of reward at baseline predicted higher ADRS scores two-year later, even when controlling for functional impairment at baseline, gender, age, handedness, puberty status, and scanning site (Left ventral striatum: $\beta$= -.05, p=0.023; Right ventral striatum: $\beta$= -.05, p=0.039).

**Specificity of brain response to reward anticipation in adolescents of the community-based sample**

***Relation between ventral striatum BOLD response to anticipation of reward and other psychiatric outcomes***

We analysed whether ventral striatum activity was related to other psychiatric outcomes
Ventral striatum activation was not related to ADHD symptoms using the SDQ hyperactivity subscale (Left ventral striatum: β= -.00, p=0.815; Right ventral striatum: β= -.01, p=0.564). The same was true when considering the inattention items only (Left ventral striatum: β= .03, p=0.572; Right ventral striatum: β= .04, p=0.349).

There were very few cases with family history of bipolar disorder (n=41, 2.6%). However, this was not associated with ventral striatum activity (Left ventral striatum: β= .19, p=0.511; Right ventral striatum: β= .36, p=0.194). The very broad screening question for manic symptoms was not associated with VS either (Left ventral striatum: β= .06, p=0.142; Right ventral striatum: β= .03, p=0.564).

The presence of any anxiety disorder was not associated with ventral striatum response to reward anticipation of reward (Left ventral striatum: β= .19, p=0.511; Right ventral striatum: β= .36, p=0.194). The same was true for conduct disorders (Left ventral striatum: β= .19, p=0.511; Right ventral striatum: β= .36, p=0.194).

**Table S2. Differences in BOLD response to the anticipation of reward in adolescents with low mood only, anhedonia only or both, low mood and anhedonia**

| ROI cluster | Low mood only vs No Symptoms | | Anhedonia only vs No Symptoms | | Both vs No Symptoms | | Anhedonia only vs Low mood only | | Both vs Low mood only | | Both vs Anhedonia only | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β (95%CI) | *p*-value | β (95%CI) | *p*-value | β (95%CI) | *p*-value | β (95%CI) | *p*-value | β (95%CI) | *p*-value | β (95%CI) | *p*-value |
| Left ventral striatum | .01 (-.17, .18) | 0.939 | -.09 (-.38,.20) | 0.472 | **-.27** (-.48, -.11) | 0.006 | -.10 (-.33, .14) | 0.354 | **-.28** (-.44, -.11) | 0.006 | -.18 (-.53, .17) | 0.271 |
| Right ventral striatum | .03 (-.19, .24) | 0.765 | -.14 (-.43, .16) | 0.303 | **-.15** (-.28, -.02) | 0.027 | -.17 (-.44, .10) | 0.190 | **-.18** (-.32, -.04) | 0.019 | -.01 (-.27, .25) | 0.924 |
| Left middle superior frontal gryrus | .00 (-.15, .15) | 0.967 | .12 (-.13, .37) | 0.282 | -.09 (-.25, .08) | 0.253 | .12 (-.09, .33) | 0.217 | -.09 (-.24, .06) | 0.201 | -.21 (-.46, .04) | 0.089 |
| Right medial superior frontal gyrus | -.00 (-.16, .15) | 0.984 | .06 (-.18, .30) | 0.588 | -.08 (-.24, .08) | 0.267 | .06 (-.14, .26) | 0.508 | -.08 (-.22, .05) | 0.195 | -.14 (-.39, .11) | 0.219 |

HC: Healthy control: adolescents with no depressive symptoms (n=535); Low mood only (n=509); Anhedonia only (n=72); Both (n=182); β: Standardised coefficients; 95%CI: Confidence interval. All models are adjusted for gender, age, handedness, puberty status, and SDQ Impact. Robust cluster option was used for site of scanning. All findings in bold are significant (p<0.05); otherwise non-significant (ns).

**Table S3. Comparison between morbid groups in demographic and clinical variables**

| | 1. No symptoms (N=535) | | 2. Low mood only (N=509) | | 3. Anhedonia only (N=72) | | 4. Anhedonia & Low mood (N=182) | | 1 vs 2 | 1 vs 3 | 1 vs 4 | 2 vs 3 | 2 vs 4 | 3 vs 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD | M | SD | p-value [a] | | | | | |
| Age (years) | 14.4 | 0.4 | 14.5 | 0.4 | 14.4 | 0.4 | 14.4 | 0.4 | 0.006 | 0.339 | 0.251 | 0.672 | 0.371 | 0.856 |
| Puberty status | 3.5 | 0.7 | 3.7 | 0.7 | 3.5 | 0.7 | 3.8 | 0.7 | <0.001 | 0.563 | <0.001 | 0.005 | 0.429 | 0.003 |
| General psychopathology | 8.7 | 4.2 | 11.2 | 4.6 | 10.8 | 4.2 | 14 | 4.8 | <0.001 | <0.001 | <0.001 | 0.491 | <0.001 | <0.001 |
| | N | % | N | % | N | % | N | % | p-value [a] | | | | | |
| Gender (females) | 213 | 40 | 350 | 69 | 27 | 38 | 120 | 66 | <0.001 | 0.706 | <0.001 | <0.001 | 0.483 | <0.001 |
| Family history of depression | 20 | 4 | 47 | 11 | 6 | 10 | 22 | 14 | <0.001 | 0.058 | <0.001 | 0.868 | 0.290 | 0.448 |
| Any conduct disorder | 36 | 7 | 60 | 12 | 9 | 13 | 31 | 17 | 0.005 | 0.079 | <0.001 | 0.861 | 0.073 | 0.371 |
| Any anxiety disorder | 20 | 4 | 73 | 14 | 11 | 15 | 68 | 37 | <0.001 | <0.001 | <0.001 | 0.833 | <0.001 | 0.001 |

[a] Comparison of groups: T-tests for independent samples and chi-square tests were employed to examine the differences between groups in continuous and categorical measures, respectively.
General psychopathology was assessed with the Strengths and Difficulties Questionnaire total score.
Information about family history of depression was only available for 1365 individuals (87% of the sample)

Table S3 shows that adolescents with anhedonia and low mood, as well as adolescents with only low mood, were more mature and more likely to be females than adolescents with only anhedonia or no symptoms. They also were more likely to have family history of depression and suffer from any conduct disorder than adolescents without symptoms. Also, adolescents with any depressive symptom had more anxiety disorders and general psychopathology than adolescents without symptoms. This was also true for adolescent with both symptoms as compared to adolescents with only low mood or only anhedonia.

We then tested whether any of these differences could account for differences in brain response to—they did not as any of these variables were correlated with VS activity (all $p>0.05$).

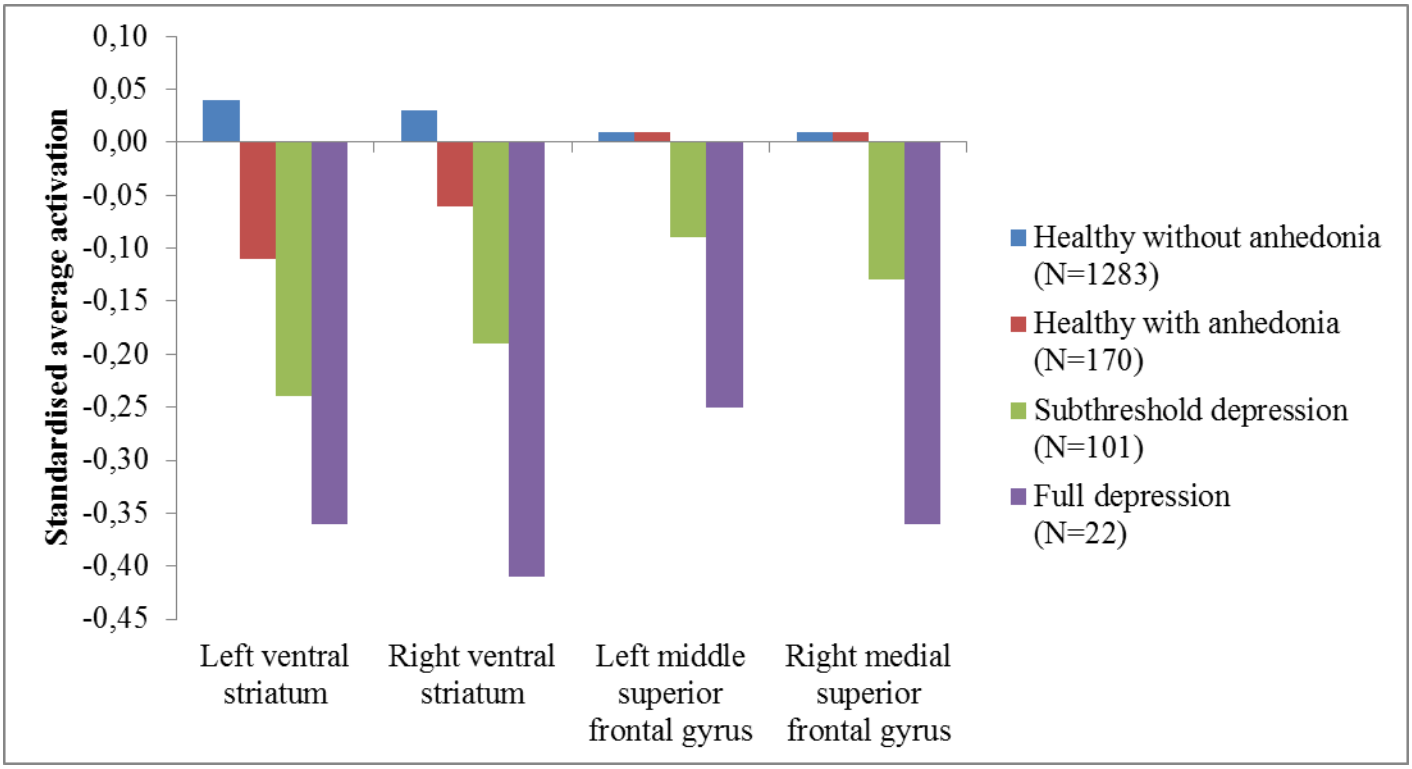



**FIGURE S4.** Standardised BOLD response in left and right ventral striatum, left middle frontal gyrus and right medial frontal gyrus among healthy adolescents without anhedonia, healthy adolescents with anhedonia, adolescents with subthreshold depression and adolescents with full depression.

## Association of depression and anhedonia with neural response to positive and negative reinforcement

**Table S4. Summary of ventral striatum BOLD response to different phases of reward processing in the Monetary Incentive Delay task in adolescents with subthreshold depression, full clinical depression, anhedonia and low mood.**

| Reward contrast | | Subthreshold dep. (N=94)[a] | | | Full clinical dep. (N=19) [a] | | | Anhedonia (N=225) [b] | | | Low mood (N=631) [c] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | β | 95%CI | p-value | β | 95%CI | p-value | β | 95%CI | p-value | β | 95%CI | p-value |
| Anticipation | Left ventral striatum | **-.58** | -84, -.33 | <0.001 | **-.69** | -1.13, -.26 | 0.002 | **-.23** | -.31, -.15 | <0.001 | -.03 | -.14, .08 | 0.601 |
| | Right ventral striatum | **-.59** | -.86, -.32 | <0.001 | **-.95** | -1.44, -.46 | <0.001 | **-.20** | -.31, -.09 | 0.004 | -.00 | -.15, .14 | 0.942 |
| Positive outcome | Left ventral striatum | **.30** | .02, .58 | 0.037 | .26 | -.26, .77 | 0.325 | .06 | -.09, .20 | 0.391 | .05 | -.09, .18 | 0.442 |
| | Right ventral striatum | **.36** | .06, .66 | 0.019 | .36 | -.20, .92 | 0.200 | .04 | -.16, .25 | 0.627 | .03 | -.06, .12 | 0.502 |
| Negative outcome | Left ventral striatum | .23 | -.03, .50 | 0.081 | .13 | -.34, .61 | 0.729 | **.27** | .17, .37 | <0.001 | .08 | -.03, .18 | 0.131 |
| | Right ventral striatum | **.36** | .10, .62 | 0.008 | .07 | -.38, .51 | 0.763 | **.18** | .05, .31 | 0.012 | .09 | -.02, .21 | 0.098 |

β: standardised coefficient. CI: confidence interval. All coefficients in bold are significant; otherwise non-significant.
[a] Compared to a matched healthy control group (N=109)
[b] Compared to adolescents without anhedonia and adjusted for the presence of low mood; sample in the model is N=1420.
[c] Compared to adolescents without low mood and adjusted for the presence of anhedonia; sample in the model is N=1420.
All analyses are adjusted for gender, age, handedness, puberty status, and clustered for scan site.

## References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