



## King's Research Portal

DOI:

[10.1176/appi.ajp.2015.14101298](https://doi.org/10.1176/appi.ajp.2015.14101298)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Stringaris, A., Vidal-Ribas Belil, P., Artiges, E., Lemaître, H., Gollier-Briant, F., Wolke, S., Vulser, H., Miranda, R., Penttilä, J., Struve, M., Fadaei, T., Kappel, V., Grimmer, Y., Goodman, R., Poustka, L., Conrod, P., Poline, J.-B., Cattrell, A., Banaschewski, T., ... Loth, E. (2015). The brain's response to reward anticipation and depression in adolescence: dimensionality, specificity and longitudinal predictions in a community-based sample. *The American Journal of Psychiatry*, 172(12), 1215-1223. <https://doi.org/10.1176/appi.ajp.2015.14101298>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

**The brain's response to reward anticipation and depression in adolescence: dimensionality, specificity and longitudinal predictions in a community-based sample**

Argyris Stringaris M.D., Ph.D., MRC. Psych. \*, Pablo Vidal-Ribas Belil M.Sc.\*, Eric Artiges M.D., Ph.D.\*, Hervé Lemaitre Ph.D., Fanny Gollier-Briant MD, PhD, Selina Wolke M.Sc., Hélène Vulser M.D., Ruben Miranda M.Psych., Jani Penttilä M.D., Ph.D., Maren Struve Ph.D., Tahmine Fadaei M.D., Viola Kappel Dipl.-Psych., Yvonne Grimmer M.D., Robert Goodman Ph.D. FRC. Psych., Luise Poustka M.D., Patricia Conrod Ph.D., Jean-Baptiste Poline Ph.D., Anna Cattrell PhD, Tobias Banaschewski M.D., Ph.D., Arun L.W. Bokde Ph.D., Uli Bromberg M.D., Christian Büchel M.D., Herta Flor Ph.D., Vincent Frouin Ph.D., Juergen Gallinat M.D., Hugh Garavan Ph.D., Penny Gowland Ph.D., Andreas Heinz M.D., Bernd Ittermann Ph.D., Frauke Nees Ph.D., Dimitri Papadopoulos Ph.D., Tomas Paus M.D., Ph.D., Michael N. Smolka M.D., Henrik Walter M.D. Ph.D., Rob Whelan Ph.D., Jean-Luc Martinot M.D., Ph.D. ‡, Gunter Schumann M.D. ‡, Marie-Laure Paillère-Martinot M.D., Ph.D. ‡, and the IMAGEN Consortium (www.imagen-europe.com)+

\*contributed equally

‡contributed equally

Authors 19-35 are listed in alphabetical order.

**Affiliations:**

From the Department of Child and Adolescent Psychiatry, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom; INSERM, UMR 1000, Research unit Imaging and Psychiatry, Service Hospitalier Frédéric Joliot, Orsay, France; University Paris-Sud 11, Orsay, France; Paris Descartes University, Sorbonne Paris Cité, Paris, France; AP-HP, Department of Adolescent Psychopathology and Medicine, Maison de Solenn, Cochin Hospital, Paris, France; Psychiatry Department 91G16, Orsay Hospital, Orsay, France; Neurospin, Commissariat à l'Energie Atomique et aux

Energies Alternatives, Paris, France; Department of Social and Health Care, Psychosocial Services Adolescent Outpatient Clinic Kauppakatu 14, Lahti, Finland; Department of Psychiatry, Université de Montréal, CHU Ste Justine Hospital, Montréal, QC, Canada; Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim / Heidelberg University, Germany; Universitaetsklinikum Hamburg Eppendorf, Hamburg, Germany; Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Charité-Universitätsmedizin, Berlin, Germany; Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim / Heidelberg University, Germany; Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland; MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, London, United Kingdom; Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitätsmedizin, Berlin, Germany; Departments of Psychiatry and Psychology, University of Vermont, USA; School of Physics and Astronomy, University of Nottingham, United Kingdom; Physikalisch-Technische Bundesanstalt (PTB), Braunschweig und Berlin, Germany; Rotman Research Institute, University of Toronto, Toronto, Canada; Department of Psychiatry and Psychotherapy, Technische Universität Dresden, Germany; and the Neuroimaging Center, Department of Psychology, Technische Universität Dresden, Germany.

**+Other Imagen Consortium members:** Pausova Z, Mann K, Barker GJ, Lawrence C, Loth E, Rietschel M, Robbins TW, Reed L, Williams S, Lourdasamy A, Costafreda S, Cattrell A, Nymberg C, Topper L, Smith L, Havatzias S, Stueber K, Mallik C, Clarke TK, Stacey D, Peng Wong C, Werts H, Williams S, Andrew C, Desrivieres S, Zewdie S, Häke I, Ivanov N, Klär A, Reuter J, Palafox C, Hohmann C, Schilling C, Lüdemann K, Romanowski A, Ströhle A, Wolff E, Rapp M, Brühl R, Ihlenfeld A, Walaszek B, Schubert F, Connolly C, Jones J, Lalor E, McCabe E, NíShiothcháin A, Spanagel R, Leonardi-Essmann F, Sommer W, Vollstaedt-Klein S, Steiner S, Buehler M, Stolzenburg E, Schmal C, Schirmbeck F, Heym N, Newman C, Huebner T, Ripke S, Mennigen E, Muller K, Ziesch V, Lueken L, Yacubian J, Finsterbusch J,

Bordas N, Bricaud Z, Galinowski A, Gourlan C, Schwartz Y, Lalanne C, Barbot A, Thyreau B, Dalley J, Mar A, Subramaniam N, Theobald D, Richmond N, de Rover M, Molander A, Jordan E, Robinson E, Hipolata L, Moreno M, Arroyo M, Stephens D, Ripley T, Crombag H, Pena Y, Lathrop M, Zelenika D, Heath S, Lanzerath D, Heinrichs B, Spranger T, Fuchs B, Speiser C, Resch F, Haffner J, Parzer P, Brunner R, Klaassen A, Klaassen I, Constant P, Mignon X, Thomsen T, Zysset S, Vestboe A, Ireland J, Rogers J.

**Previous presentation:** Preliminary results from this study were presented at the Society of Biological Psychiatry 69<sup>th</sup> Annual Meeting, New York, NY, USA, May 8-10, 2014.

**Correspondence:**

Argyris Stringaris

King's College London, Institute of Psychiatry, Psychology and Neuroscience

Department of Child and Adolescent Psychiatry

PO 85, 16 De Crespigny Park

London SE5 8AF, UK

e-mail: [argyris.stringaris@kcl.ac.uk](mailto:argyris.stringaris@kcl.ac.uk)

**Disclosures and acknowledgments:**

Robert Goodman is the owner of Youthinmind, Ltd., which provides no-cost and low-cost software and websites related to the Development and Well-Being Assessment and the Strengths and Difficulties Questionnaire. Dr. Paillère-Martinot received compensation from Janssen-Cilag company for CME activities. Pablo Vidal-Ribas gratefully acknowledges the support of the Alicia Koplowitz Foundation. Dr. Stringaris receives funding from the Wellcome Trust and the National Institute of Health Research UK and royalties from Cambridge University Press for his book The Maudsley Reader in Phenomenological Psychiatry. Dr. Gallinat has received research funding from the German Federal Ministry of Education and Research, German Science Foundation, AstraZeneca, Eli Lilly & Co, Janssen-Cilag, Bristol-Myers

Squibb and speaker fees from AstraZeneca, Janssen-Cilag, and Bristol-Myers Squibb. The other authors declare no conflict of interest.

This work was supported by the European Union-funded FP6 Integrated Project IMAGEN (Reinforcement- related behaviour in normal brain function and psychopathology) (LSHM-CT- 2007-037286), the FP7 project IMAGEMEND (IMAgining GENetics for MENtal Disorders) and the Innovative Medicine Initiative Project EU-AIMS (115300-2), the Medical Research Council Programme Grant “Developmental pathways into adolescent substance abuse” (93558), the Swedish funding agency FORMAS, the Wellcome Trust (Behavioural and Clinical Neuroscience Institute, University of Cambridge), the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London, the Department of Health UK, the Bundesministerium für Bildung und Forschung (BMBF grants 01GS08152; 01EV07111; eMED SysAlc01ZX1311A; Forschungsnetz AERIAL), the National Institutes of Health, U.S.A (RO1 MH085772-01A1), Further support was provided by the French funding agency ANR (ANR-12-SAMA-0004), an Eranet – Neuron grant (project AF12-NEUR0008-01 - WM2NA), the Assistance-Publique-Hôpitaux-de-Paris and INSERM (interface grant), Paris-Descartes-University (collaborative-project-2010), Paris-Sud-University (IDEX-2012), the Fondation de France, and the Mission Interministérielle de Lutte-contre-la-Drogue-et-la-Toxicomanie (MILDT).

This manuscript reflects only the author's views and the Community is not liable for any use that may be made of the information contained therein.

## **Abstract**

**Objective:** The authors examined whether alterations in the brain's reward network operate as a mechanism across the spectrum of risk for depression. Second, they tested whether these alterations are specific to anhedonia as compared to low mood, and predictive of depressive outcomes.

**Method:** Functional MRI was used to collect BOLD responses to anticipation of reward in the Monetary Incentive Task from 1,576 adolescents of a community-based sample. Adolescents with current and future subthreshold depression and clinical depression were compared to healthy controls in matched comparisons. In addition, BOLD responses were compared across adolescents with anhedonia, low mood, or both symptoms, cross-sectionally and longitudinally.

**Results:** Activity in the ventral striatum was reduced in subthreshold- and clinical-depression compared to healthy controls. Low ventral striatum activation predicted transition to subthreshold or clinical depression in previously healthy adolescents at two-year follow up. Brain responses during reward anticipation decreased in a graded manner between healthy adolescents, adolescents with current or future subthreshold depression and those with current or future clinical depression. Low ventral striatum activity was associated with anhedonia but not low mood; however, the combined presence of both symptoms showed the strongest reductions in ventral striatum in all analyses.

**Conclusions:** Reduced striatal activation operates as a mechanism across the risk spectrum for depression. It is associated with anhedonia in healthy adolescents, a behavioural indicator of positive valence systems, consistent with predictions based on the RDoC.

## Introduction

Alterations in the brain's reward network are evident already in adolescents with depressive disorder (1, 2) as well as in unaffected first degree relatives of patients with depression (3), and have therefore great potential as risk markers and intervention targets. However, crucial evidence for reward network alterations as a mechanism for depressive disorder is still lacking.

First, it is unclear whether reward network alterations vary across the spectrum of risk for depression. It is important to know whether adolescents with subthreshold-depression, who are at high risk of transition to clinical depression (4), have similar reward network alterations to those who fulfil criteria for a depressive disorder.

Second, the specificity of reward network alterations with depressive symptoms is unclear. Depression has been conceptualised as an imbalance in dual valence systems (5), involving reduced positive and/or high negative affect. Aetiologically, anhedonia is part of a positive valence system, whereas other depressive symptoms such as low mood are related to a negative valence system (6). Based on existing evidence, reduced frontostriatal activations during reward anticipation should be specific to anhedonia—defined as diminished motivation or desire to engage in pleasurable activities (7, 8). However, it is not clear whether reduced responses to reward in depression are exclusively associated with anhedonia, low mood or the combined effects of both symptoms. This has implications as anhedonia and low mood seem to be associated with differential treatment responses (9, 10) and developmental trajectories (11).

Finally, nearly all work on the brain's reward network has been cross-sectional (1) and it is unknown if alterations in reward system function would predict future anhedonia, low mood, or their association since they are core criteria for depression.

Here we address these outstanding questions in a large, community-based sample of adolescents using fMRI during a reward anticipation experiment, the Monetary Incentive Delay task (12) in both a cross-sectional and a longitudinal design. This task investigates reward anticipation and reward feedback

(positive and negative outcomes). Herein, we focus on reward anticipation because the anticipatory phase, rather than the feedback phase, has been most strongly linked with anhedonia (13), and we examine the feedback phase in exploratory analyses.

We first compare brain responses to reward anticipation between three carefully-matched groups: clinical depression, subthreshold-depression, and matched healthy volunteers. This allows us to investigate how such brain responses vary across the spectrum of risk for depression. We hypothesize reduced activation in frontostriatal regions during reward anticipation in the clinical and subthreshold-depression groups compared to controls, in keeping with findings from high-risk studies (3) (14). We further hypothesize that brain activity in anticipation of reward will differ in a graded manner across the risk spectrum with participants suffering from clinical depression having the lowest neural activity. We also test whether reduced activation in the reward network at baseline will predict clinical- and subthreshold-depression in previously healthy adolescents two years later.

Second, we investigate whether these reward network alterations are specific to anhedonia compared to low mood in a general population sample. So far, no studies have examined this in adolescents, though some data exist in adult samples (15). Previous studies suggest that depressed patients with anhedonia have lower dopaminergic activity in the caudate, putamen and nucleus accumbens (16) and anhedonia is associated with exerting less effort towards attaining rewards (7, 13). We hypothesize that, in cross-sectional analyses, alterations in the reward network will also be present in adolescents with anhedonia, but not those who have low mood only. Finally, we examine whether reward network alterations differentially predict who will develop anhedonia at 2-year follow up.

## **Methods and Material**

### ***Participants***

Neuroimaging and clinical data were obtained from the Imagen database established across eight sites in France, United Kingdom, Ireland, and Germany, which includes 2,223 adolescents recruited in schools



around age 14 years. Here we used data from the first and second waves of Imagen. A detailed description of recruitment and assessment procedures is found under (17). All local ethics research committees approved the study. Written consent was obtained from the parent or guardian, and verbal assent was obtained from the adolescent. After quality control for neuroimaging and behavioural tests, 1,576 adolescents were included in the study. Only a small minority ( $n=31$ ; 2%) of adolescents were medicated in this population-based sample.

### ***Measures***

***Psychiatric symptoms and diagnoses:*** Adolescent psychiatric symptoms and their impact were assessed with the Development and Well-Being Assessment (DAWBA; 18), a self-administered diagnostic questionnaire consisting of open and closed questions. The DAWBA is designed to maintain consistency across multiple cultural and language groups, as diagnoses are made by clinical raters who share a common training and participate in regular cross-language training and consensus meetings.

The DAWBA generates probabilities of having DSM-IV-TR diagnoses (19), which were used to define categorical diagnosis of depression. Further information on the DAWBA is available from <http://www.dawba.info>.

The Strengths and Difficulties Questionnaire (SDQ) was used to assess general psychopathology and functional impairment (20, 21).

All participants were coded as suffering from loss of interest/anhedonia or low mood if so rated (as ‘Yes’ or ‘No’) by self-report in the screening questions of the depression section (H) from the DAWBA. These items have good face validity (supplemental material).

Adolescents were included in a clinical depression group if they scored 4 or 5 in the depression DAWBA band (i.e., highest probability of depression). In addition, following DSM-IV-TR criteria, these

adolescents had to report at least 5 depressive symptoms including at least one core symptom (abnormally depressed/ irritable mood, and/or loss of interest) and fulfil criteria for functional impairment and duration. Twenty-two adolescents met criteria for clinical depression at baseline.

Adolescents were included in a subthreshold-depression group if in the last 4 weeks they had 3 or more depressive symptoms including at least one core symptom and 2 or more other DSM-IV depressive symptoms, without fulfilling criteria for clinical depression in terms of duration, symptom number, or significant impact on functioning (4). The same criteria were used to define a subthreshold depression group at follow-up.

Participants with any diagnosis, or any history of depression, bipolar disorder, or an AUDIT score >5 were excluded.

At baseline adolescents with clinical depression (n=22) and subthreshold depression (n=101) were compared to a group of healthy controls (n=123) matched by age, sex, handedness and imaging site. The healthy control group consisted of adolescents with less than 3 symptoms of depression and a probability of having a diagnosis of major depression of less than 0.1% according to the DAWBA (Figure S1).

Other measures were collected using Psytools software (Delosis, London, UK), an online computer platform for self-assessment, and included a pubertal status score using the computerized Pubertal Development Scale (PDS: 22).

### ***Monetary Incentive Delay Task***

The participants performed a modified version of the well-established Monetary Incentive Delay task (12) to study neural responses to reward that included three conditions: reward anticipation, as well as receipt of positive or negative outcomes. A detailed description of the task is provided in the online supplement.

### ***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, Philips, General Electric, Bruker). 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. A detailed description of the fMRI data acquisition is provided in the data supplement.

### *Statistical analyses*

We used coarsened exact matching in Stata 11 to create the matched healthy control group (n=123). After matching, no differences were found between the depressed groups (together, n=123) and the controls in sex, age, handedness and imaging site (all  $p>0.05$ ).

### ***Hypothesis 1: Dimensionality of brain response to reward anticipation in adolescents as a risk for depression***

We used one-way ANOVA to compare the clinical depression group (n=22) and subthreshold depression group (n=101) at baseline to the matched healthy control group (n=123) in SPM8 controlling for pubertal stage. Analyses were thresholded at  $p<0.001$ , uncorrected at the voxel level with clusters of activated voxels considered statistically significant at  $p<0.05$ , corrected for multiple comparisons. We used small-volume-corrected region of interest analyses across a fronto-striatal-limbic mask (see data supplement). For all comparisons, brain locations were reported as x, y, and z coordinates in Montreal Neurologic

Institute (MNI) space and Wake Forest University (WFU) PickAtlas (23) was used to identify brain regions.

For subsequent analyses, we extracted the averaged beta values from the anatomical regions with significant clusters from the clinical- and subthreshold depression-matched group analyses using MarsBaR toolbox (<http://marsbar.sourceforge.net>) (24). Whole regions from the Automated Anatomical Labeling (AAL) atlas (25) were used, with the exception of the ventral striatum which we defined according to Martinez et al. (26, 27).

We tested the dimensional hypothesis cross-sectionally, using a trend analysis (28) of the gradual activation change in the significant clusters across healthy adolescents (n=1453), adolescents with subthreshold depression (n=101) and adolescents with clinical depression (n=22).

We predicted onset of subthreshold and clinical depression in previously healthy adolescents with logistic regression models with transition to subthreshold or clinical depression as the dependent variable and brain activations as the independent variable, adjusting for baseline depressive symptoms. We performed trend analysis to examine the gradual change of activation in significant clusters in healthy adolescents across three groups: those adolescents who remained healthy (n=906), those who developed subthreshold depression (n=68) and those who developed clinical depression (n=29) at the 2-year follow up.

***Hypothesis 2: Specificity of brain response to reward anticipation in adolescents of the community-based sample***

We tested the hypothesis that reduced ventral striatum activation is related to anhedonia, but not to low mood in three ways. First, we compared brain activations between adolescents who reported anhedonia (n=254) and the rest (n=1,322), using linear regression. Second, we compared brain activations between

adolescents with (n=691) and without low mood (n=885). Third, we compared adolescents with only low mood (n=510), only anhedonia (n=72), with low mood and anhedonia (n=183), and no symptoms at all (n=536) using ANCOVA. As people with both symptoms –low mood and anhedonia- were more severely impaired ( $F[2, 762] = 26.53, p < .0001$ ), the model was adjusted for functional impairment using the SDQ impact subscale.

To examine the specificity of response to reward with depressive symptoms, we used logistic regression models with type of symptom dimensions at two-year follow-up as the outcome and brain activations as predictor of interest.

Analyses were completed in Stata 11 (29) adjusting for sex, age, handedness and puberty status. The robust cluster option was used to adjust for the effects of imaging site, thus to account for the non-independence of participants from the same site.

## **Results**

### **Sample characteristics**

Table 1 provides demographic and clinical information for the three groups at baseline and follow-up.

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

Adolescents with clinical depression showed less activation in the ventral striatum bilaterally, the right medial superior frontal gyrus and left middle superior frontal gyrus compared to controls. Similarly, adolescents with subthreshold depression, versus controls, had significantly reduced activation bilaterally in the ventral striatum (Figure 1, Table S1). Reduced activation in right medial and left superior frontal

gyrus were also present in adolescents with subthreshold depression when using a less conservative threshold ( $p < 0.005$  or  $p < 0.01$  both uncorrected).

Based on these results, we extracted averaged beta values from the left and right ventral striatum, the right medial superior frontal gyrus and the left middle superior frontal gyrus.

Sex, age and puberty status were not related to neural activations (all  $p > 0.05$ )

Trend analyses showed that brain responses to reward anticipation decreased gradually among the three groups (Figure S3 in the data supplement) for left ( $z = -3.02$ ,  $p = 0.003$ ) and right ventral striatum ( $z = -2.89$ ,  $p = 0.004$ ), and right medial superior frontal gyrus ( $z = -2.53$ ,  $p = 0.011$ ).

Decreased activation in the ventral striatum predicted transition to subthreshold depression in previously healthy adolescents. Also, decreased activation in the right ventral striatum and the left middle superior frontal gyrus predicted transition to clinical depression two years later (Table 2). Reduced ventral striatum response also predicted higher levels of depressive symptoms at follow-up using the Adolescent Depression Rating Scale (supplemental material). All these results remained significant even after accounting for depressive symptoms at baseline (Table 2). Activations in the right medial superior frontal gyrus did not predict depression (all  $p > 0.05$ ).

Trend analyses (Figure 2) among healthy adolescents followed up over a 2-year period, showed that activation in right ventral striatum ( $z = -2.02$ ,  $p = 0.043$ ), left middle superior frontal ( $z = -2.38$ ,  $p = 0.017$ ) and right medial superior frontal gyri ( $z = -2.02$ ,  $p = 0.044$ ) decreased gradually across adolescents who remained healthy, those who developed subthreshold depression and those who developed clinical depression.

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

Adolescents with anhedonia ( $n = 254$ ) showed significantly decreased activation compared to those without anhedonia ( $n = 1,322$ ) in the ventral striatum (left:  $\beta = -.20$ ,  $p < 0.001$ ; right:  $\beta = -.16$ ,  $p = 0.015$ ) but not in the left middle superior frontal ( $\beta = -.03$ ,  $p = 0.417$ ) and the right medial superior frontal gyri ( $\beta = -.05$ ,

p=0.248). No significant differences in activation in the extracted regions were found between adolescents who reported low mood (n=691) and those without low mood (n=885) (left ventral striatum:  $\beta = -.03$ , p=0.546; Right ventral striatum:  $\beta = -.00$ , p=0.937; Left middle superior frontal gyrus :  $\beta = -.05$ , p=0.377; Right medial superior frontal gyrus:  $\beta = -.05$ , p=0.375).

We next split the group of adolescents with anhedonia into those with low mood (n=182) and those without low mood (n=72). Adolescents with concurrent anhedonia and low mood symptoms had decreased activation in bilateral ventral striatum versus adolescents with only low mood and adolescents without symptoms (Figure 3). These results remained significant even when adjusting for functional impairment. Full comparisons between groups in brain activations as well as in demographic and clinical variables can be found in Tables S2 and S3, respectively.

In addition, there was significant gradual decrease across healthy adolescents without anhedonia, healthy adolescents with anhedonia, adolescents with subthreshold-depression and those with clinical-depression in all examined regions except for the left middle superior frontal gyrus (left ventral striatum:  $z = -3.51$ ,  $p < 0.001$ ; right ventral striatum:  $z = -3.16$ ,  $p = 0.002$ ; left middle superior frontal gyrus:  $\beta = -1.45$ ,  $p = 0.146$ ; right medial superior frontal gyrus:  $\beta = -2.15$ ,  $p = 0.032$ ) (Figure S4).

Based on the cross-sectional findings, we tested whether decreased reward network activations predicted anhedonia at follow-up. We found that decreased activation in the left ventral striatum predicted having concurrent anhedonia and low mood over low mood only (Odds ratio=.84, 95%CI[.73, .98],  $p = 0.030$ ). Also, decreased activation in all four significant clusters predicted having both symptoms over no symptoms at all (left ventral striatum: odds ratio=.79, 95%CI[.65, .97],  $p = 0.027$ ; right ventral striatum: odds ratio=.81, 95%CI[.69, .94],  $p = 0.007$ ; left middle superior frontal gyrus: odds ratio=.72, 95%CI[.63, .82],  $p < 0.001$ ; right medial superior frontal gyrus: odds ratio=.70, 95%CI[.58, .85],  $p < 0.001$ ).

Adjusting the analyses for medication use had no effect on the results (data available upon request).

### **Exploratory analysis: Association of depression and anhedonia with ventral striatum response to positive and negative outcomes**

Adolescents with subthreshold depression showed increased response to positive outcome compared to the matched healthy controls (left ventral striatum:  $\beta = .30$ ,  $p = 0.037$ ; right ventral striatum:  $\beta = .36$ ,  $p = 0.019$ ).

No significant differences were found for clinical depression, anhedonia or low mood (Table S4).

For negative outcome, adolescents with subthreshold depression showed enhanced neural response (right ventral striatum:  $\beta = .36$ ,  $p = 0.008$ ). The same was true for adolescents with anhedonia (left ventral striatum:  $\beta = .27$ ,  $p < 0.001$ ; right ventral striatum:  $\beta = .18$ ,  $p = 0.012$ ). No significant differences were found for adolescents with clinical depression or low mood.

### **Discussion**

Using a large community-based sample of adolescents, we found that the reduced brain response to anticipation of reward in the ventral striatum in youth varies across the risk spectrum for depression, is specific to anhedonia, and increases the risk for anhedonia and low mood, as well as depressive disorder at 2-year follow-up.

The present findings of reduced activation during reward anticipation in frontostriatal regions, both in adolescents with subthreshold- and clinical-depression, are consistent with high-risk studies of depression (3, 30). Our finding of a graded significant decrease in the brain activation across groups suggests that frontostriatal responses to reward anticipation operates as a mechanism across the spectrum of risk for depression.

Also, low ventral striatum activation was only present in those who had anhedonia, suggesting that this symptom is a behavioral marker of striatal activation. However, it should be noted that adolescents with strictly only anhedonia did not differ in ventral striatal activation from those with low mood only or those



without depressive symptoms. There were very few participants with anhedonia only and this may have underpowered our analysis.

The graded increase in the probability of depression with decreasing ventral striatum activation is akin to a dose-response relationship. Taken together with the specificity of the ventral striatum under-activation for anhedonia, it strengthens the inference that ventral-striatum-based reward processing may be a mechanism -and therefore part of the causal links- leading to depression. However, further steps, for example the alleviation of depression through intervention targeting the ventral striatum, are required for establishing its role as a causal event, as opposed to a marker, in depressive illness.

We also explored the effects of positive and negative outcomes. Consistent with previous studies (31, 32) we found little evidence for alterations during positive outcome. By contrast, we found that subjects with anhedonia, but not those with low mood, showed increased activation in the ventral striatum during negative outcome. This is in keeping with previous results showing that anhedonia might be associated with sensitivity to punishment (33). As these results were exploratory, they should be further replicated.

Depression is a heterogeneous syndrome with a variety of symptoms amongst which anhedonia and low mood appear as core features. According to the Research Domain Criteria (RDoC) framework, anhedonia is linked to the positive valence system whereas low mood is linked to the negative valence system (6).

This division is not arbitrary; anhedonia and low mood are associated with different expression of symptoms (34), developmental trajectories (11) and clinical outcomes(9, 10). Moreover, anhedonia has been associated with striatal functional connectivity involving the anterior cingulate cortex, whereas depression severity has been associated with striatal networks involving the ventro-medial prefrontal cortex (35). Interestingly, the medial prefrontal cortex that also shows reduced response to reward anticipation in our depressed group (though it was not linked to anhedonia), is essential to integrate functions leading to «affective meaning» through its subcortical connections (36, 37). Indeed, our findings about the ventral striatum and its specific link with anhedonia are consistent with the notion that regulation of positive affect is a critical feature of adolescent depression (5).

Our results showed that every point decrease in standardized ventral striatum activation increased the probability of future subthreshold-depression by 20% and clinical depression by 35%, even when accounting for depressive symptoms at baseline. Moreover, a graded decrease was found in healthy adolescents that, after a 2-year follow up, either remained healthy, developed subthreshold-depression or developed clinical depression. In addition, decreased ventral striatum activation also predicted experiencing concurrent anhedonia and low mood in a 2-year follow up. Although the contribution to the variance of depression was small, our results suggest that reward circuit alterations precede the clinical expression of depression.

Although adolescents in the depression groups were more likely to be females and showed higher puberty status scores, it is unlikely that these differences could account for the neural findings. First, our main analyses were based in a sex matched group. Second, all analyses in unmatched groups were adjusted for sex and puberty status. Third, a post-hoc analysis revealed that higher puberty status was associated to sex but not depression and there was no sex by depression-group interaction. Finally, neither sex nor pubertal status nor age were correlated with ventral striatum activations. The latter may be because 80% of our sample was between 14 and 15 years old and therefore lacked variation.

This study should be seen in the light of the following limitations. First, our experiment was based on monetary rewards rather than social rewards. Future longitudinal studies should distinguish between types of reward and depressive mechanisms. However, altered neural response to reward in depression is a remarkably consistent finding despite differences in fMRI paradigms and depression indices across studies (38). Second, symptoms of anhedonia and low mood were assessed with a single question each not allowing us to examine different degrees of severity. Third, the DAWBA only provides information about the past 4 weeks rather than lifetime depression. Fourth, our follow up data do not span the period of maximum risk for developing depression and may therefore have underestimated the extent to which neural activation may predict transition.

## References

1. Forbes EE, Dahl RE. Research Review: altered reward function in adolescent depression: what, when and how? *J Child Psychol Psychiatry*. 2012;53(1):3-15. Epub 2011/11/29.
2. Kerestes R, Davey CG, Stephanou K, Whittle S, Harrison BJ. Functional brain imaging studies of youth depression: A systematic review. *Neuroimage Clin*. 2014;4:209-31.
3. Olino TM, McMakin DL, Morgan JK, Silk JS, Birmaher B, Axelson DA, et al. Reduced reward anticipation in youth at high-risk for unipolar depression: a preliminary study. *Dev Cogn Neurosci*. 2014;8:55-64. Epub 2013/12/29.
4. Klein DN, Shankman SA, Lewinsohn PM, Seeley JR. Subthreshold depressive disorder in adolescents: predictors of escalation to full-syndrome depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2009;48(7):703-10. Epub 2009/05/26.
5. Forbes EE, Dahl RE. Neural systems of positive affect: relevance to understanding child and adolescent depression? *Dev Psychopathol*. 2005;17(03):827-50.
6. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748-51.
7. Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. *Neuron*. 2012;76(3):470-85.
8. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev*. 2011;35(3):537-55.
9. McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, et al. Anhedonia Predicts Poorer Recovery Among Youth With Selective Serotonin Reuptake Inhibitor Treatment–Resistant Depression. *J Am Acad Child Adolesc Psychiatry*. 2012;51(4):404-11.
10. Paillère-Martinot M-L, Aubin F, Martinot J-L, Colin B. A prognostic study of clinical dimensions in adolescent-onset psychoses. *Schizophr Bull*. 2000;26(4):789-99.

11. Pine DS, Cohen E, Cohen P, Brook J. Adolescent depressive symptoms as predictors of adult depression: moodiness or mood disorder? *Am J Psychiatry*. 1999;156(1):133-5.
12. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*. 2001;21(16):1-5.
13. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J Abnorm Psychol*. 2012;121(3):553.
14. Sharp C, Kim S, Herman L, Pane H, Reuter T, Strathearn L. Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *J Abnorm Psychol*. 2014;123(2):298.
15. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *Neuroimage*. 2009;46(1):327-37. Epub 2009/05/22.
16. Bragulat V, Paillère-Martinot M-L, Artiges E, Frouin V, Poline J-B, Martinot J-L. Dopaminergic function in depressed patients with affective flattening or with impulsivity: [18 F] Fluoro-l-dopa positron emission tomography study with voxel-based analysis. *Psychiatry Res*. 2007;154(2):115-24.
17. Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Büchel C, et al. The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. *Mol Psychiatry*. 2010;15(12):1128-39.
18. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: Description and Initial Validation of an Integrated Assessment of Child and Adolescent Psychopathology. *J Child Psychol Psychiatry*. 2000;41(5):645-55.
19. Goodman A, Heiervang E, Collishaw S, Goodman R. The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. *Soc Psychiatry Psychiatr Epidemiol*. 2011;46(6):521-32.

20. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry*. 2001;40(11):1337-45.
21. Stringaris A, Goodman R. The Value of Measuring Impact Alongside Symptoms in Children and Adolescents: A Longitudinal Assessment in a Community Sample. *J Abnorm Child Psychol*. 2013. Epub 2013/05/17.
22. Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: Reliability, validity, and initial norms. *J Youth Adolesc*. 1988;17(2):117-33.
23. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 2003;19(3):1233-9.
24. Nymberg C, Banaschewski T, Bokde AL, Büchel C, Conrod P, Flor H, et al. DRD2/ANKK1 Polymorphism Modulates the Effect of Ventral Striatal Activation on Working Memory Performance. *Neuropsychopharmacology*. 2014.
25. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273-89.
26. Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang D-R, Huang Y, et al. Imaging Human Mesolimbic Dopamine Transmission With Positron Emission Tomography. Part II: Amphetamine-Induced Dopamine Release in the Functional Subdivisions of the Striatum. *J Cereb Blood Flow Metab*. 2003;23(3):285-300.
27. Mehta MA, Gore-Langton E, Golembo N, Colvert E, Williams SC, Sonuga-Barke E. Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *J Cogn Neurosci*. 2010;22(10):2316-25.
28. Cuzick J. A wilcoxon-type test for trend. *Statistics in medicine*. 1985;4(4):543-7.
29. StataCorp. *Stata Statistical Software: Release 11*. College Station,TX: StataCorp LP; 2009.

30. Forbes E, Christopher May J, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, et al. Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *J Child Psychol Psychiatry*. 2006;47(10):1031-40.
31. Sherdell L, Waugh CE, Gotlib IH. Anticipatory pleasure predicts motivation for reward in major depression. *J Abnorm Psychol*. 2012;121(1):51.
32. Chentsova-Dutton Y, Hanley K. The effects of anhedonia and depression on hedonic responses. *Psychiatry Res*. 2010;179(2):176-80.
33. Padrão G, Mallorquí A, Cucurell D, Marco-Pallares J, Rodriguez-Fornells A. Neurophysiological differences in reward processing in anhedonics. *Cognitive, Affective, & Behavioral Neuroscience*. 2013;13(1):102-15.
34. Buckner JD, Joiner Jr TE, Pettit JW, Lewinsohn PM, Schmidt NB. Implications of the DSM's emphasis on sadness and anhedonia in major depressive disorder. *Psychiatry Res*. 2008;159(1):25-30.
35. Gabbay V, Ely BA, Li Q, Bangaru SD, Panzer AM, Alonso CM, et al. Striatum-based circuitry of adolescent depression and anhedonia. *J Am Acad Child Adolesc Psychiatry*. 2013;52(6):628-41. e13.
36. Roy M, Shohamy D, Wager TD. Ventromedial prefrontal-subcortical systems and the generation of affective meaning. *Trends Cogn Sci*. 2012;16(3):147-56.
37. Zald DH, Mattson DL, Pardo JV. Brain activity in ventromedial prefrontal cortex correlates with individual differences in negative affect. *Proceedings of the National Academy of Sciences*. 2002;99(4):2450-4.
38. Zhang WN, Chang SH, Guo LY, Zhang KL, Wang J. The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *J Affect Disord*. 2013;151(2):531-9. Epub 2013/07/17.

**Table 1. Descriptive statistics and comparisons between analysed groups at baseline and at follow-up in demographic and clinical variables**

<b>Baseline</b>	1. Healthy matched <sup>d</sup> (N=123)		2. Subthreshold depression (N=101)		3. Clinical depression (N=22)		1 vs 2	1 vs 3	2 vs 3
	Mean	Sd	Mean	Sd	Mean	Sd	p <sup>a</sup>		
Age (years)	14.4	0.4	14.5	0.4	14.4	0.3	0.329	0.794	0.753
Puberty status	3.7	0.6	3.8	0.6	4	0.5	0.240	0.055	0.205
General psychopathology <sup>b</sup>	8.4	3.8	13.9	4.7	16.4	4.5	<0.001	<0.001	0.025
	N	%	N	%	N	%	p <sup>a</sup>		
Sex (females)	90	73	66	65	19	86	0.205	0.187	0.053
Family history of depression <sup>c</sup>	3	3	7	8	4	24	0.095	0.001	0.067
Any conduct disorder	4	3	13	13	4	18	0.007	0.005	0.513
Any anxiety disorder	5	4	33	33	17	77	<0.001	<0.001	<0.001
<b>Two year follow up</b>	1. Remained healthy (N=902)		2. New subthreshold depression (N=68)		3. New clinical depression (N=29)		1 vs 2	1 vs 3	2 vs 3
	Mean	Sd	Mean	Sd	Mean	Sd	p <sup>a</sup>		
Age (years)	16.4	0.4	16.4	0.4	16.5	0.5	0.557	0.199	0.487
Puberty status at baseline	3.6	0.7	3.7	0.6	4.1	0.7	0.114	<0.001	0.012
General psychopathology <sup>b</sup>	8.9	4.6	11.9	5.1	16.6	5.4	<0.001	<0.001	<0.001
	N	%	N	%	N	%	p <sup>a</sup>		
Sex (females)	446	49	43	63	24	83	0.026	<0.001	0.057
Family history of depression <sup>c</sup>	59	8	7	11	3	11	0.350	0.492	0.962
Any conduct disorder	79	9	10	15	10	34	0.098	<0.001	0.028
Any anxiety disorder	107	12	16	24	16	55	0.005	<0.001	0.002

<sup>a</sup> Comparison of matched groups: T-tests for independent samples and chi-square tests were employed to examine the differences between matched groups in continuous and categorical measures, respectively.

<sup>b</sup> General psychopathology was assessed with the Strengths and Difficulties Questionnaire total score.

<sup>c</sup> Information about family history of depression was only available for 1365 individuals (87% of the sample)

<sup>d</sup> Comparisons with the unmatched healthy group (N=1453) revealed that adolescents in the subthreshold and clinical depression groups scored higher in puberty status and general psychopathology, were more females, had higher rates of anxiety disorders, and in the case of clinical depression, also higher rates of family history of depression.

Sd: Standard deviation

**Table 2. Prediction of transition to subthreshold and clinical depression at 2-year follow up in previously healthy adolescents from baseline activity in the ventral striatum and left middle superior frontal gyrus**

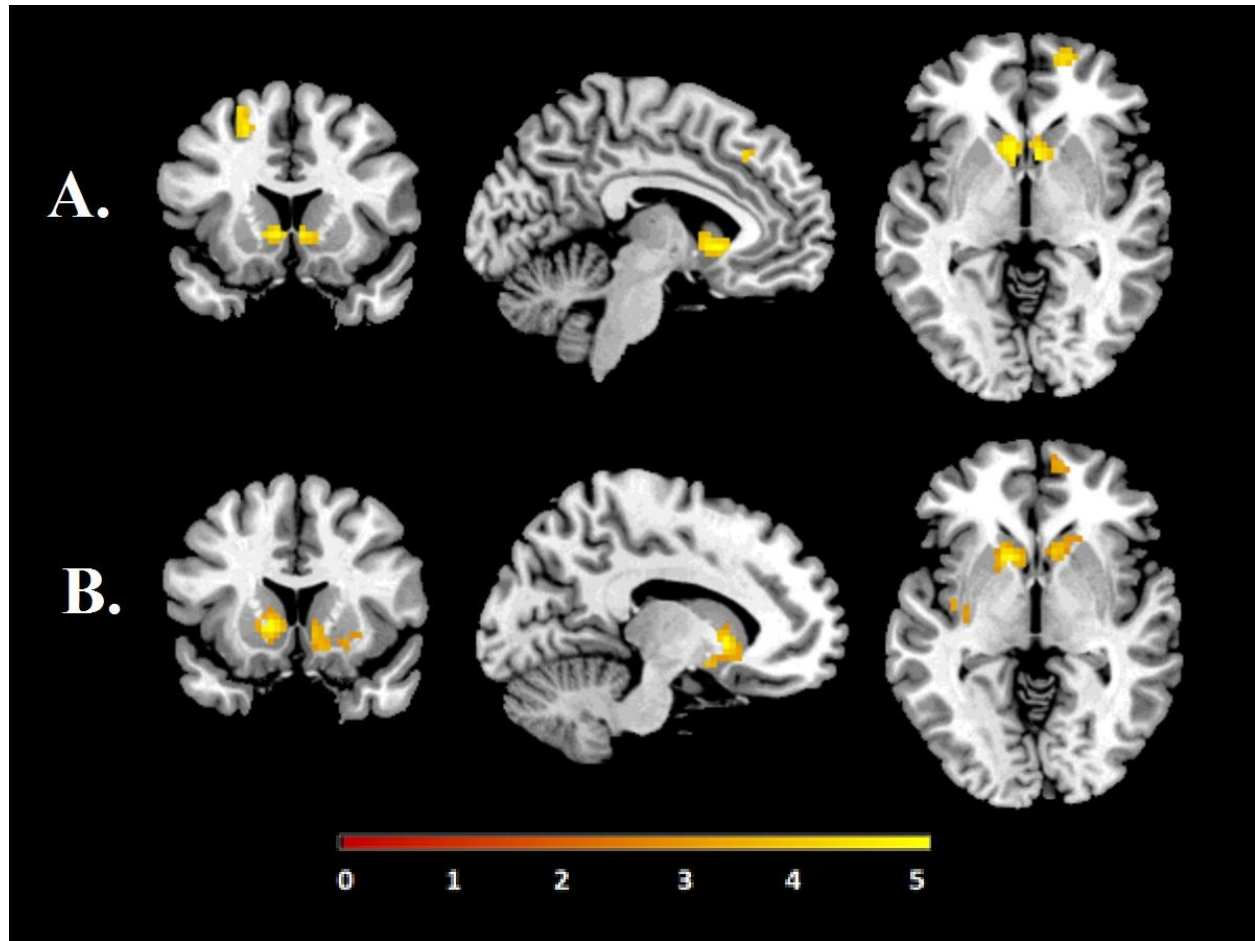
Outcome	Baseline Adjustment	Left ventral striatum			Right ventral striatum			Left middle frontal gyrus		
		Odds ratio	95%CI	p-value	Odds ratio	95%CI	p-value	Odds ratio	95%CI	p-value
Onset of subthreshold depression	Standard <sup>a</sup>	<b>.81</b>	.69, .96	0.016	<b>.82</b>	.71, .95	0.007	.87	.68, 1.12	0.284
	Symptoms at baseline	<b>.82</b>	.69, .96	0.016	<b>.82</b>	.72, .95	0.007	.88	.68, 1.12	0.297
Onset of clinical depression	Standard <sup>a</sup>	.80	.58, 1.11	0.184	<b>.66</b>	.45, .97	0.037	<b>.71</b>	.53, .96	0.027
	Symptoms at baseline	.81	.60, 1.10	0.180	<b>.68</b>	.47, .99	0.042	<b>.74</b>	.56, .98	0.035

95%CI: Confidence interval. All findings in bold are significant (p<0.05); otherwise non-significant (ns).

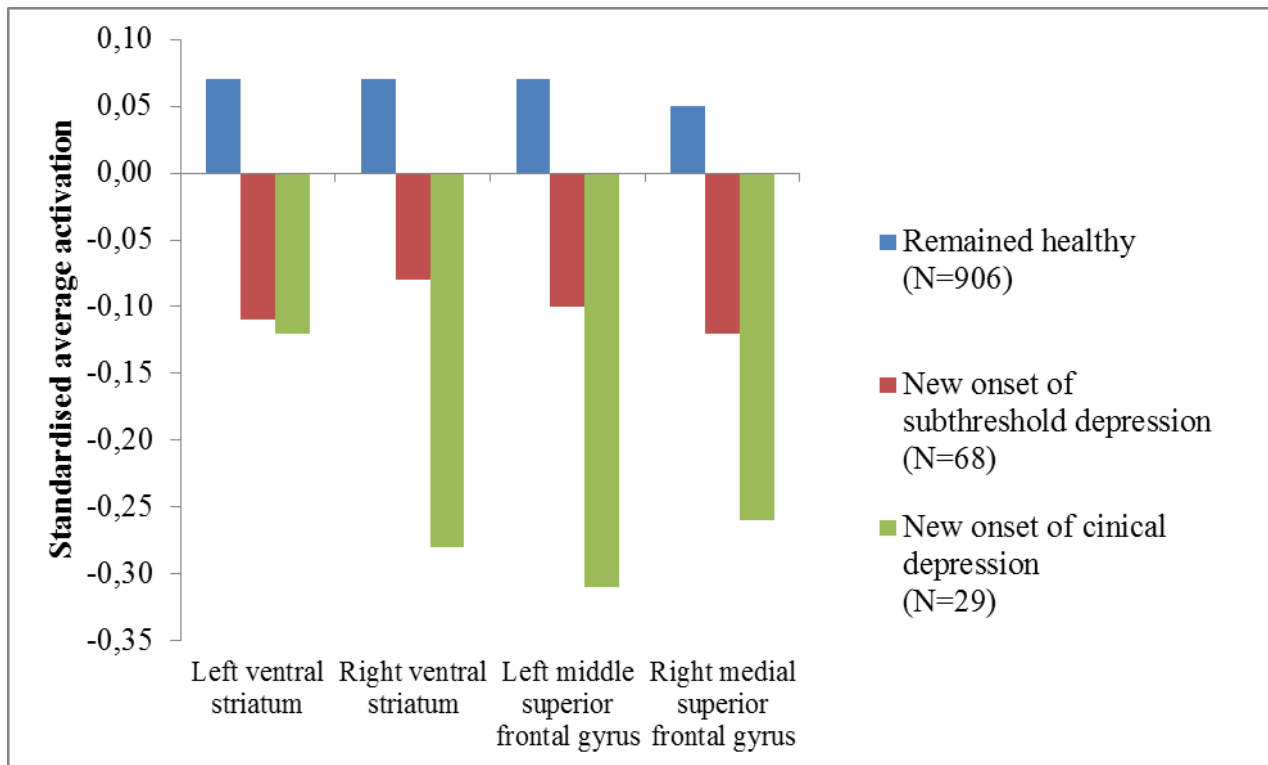
<sup>a</sup> Standard adjustment includes sex, age, handedness, and puberty status. Robust cluster option was used for site of scanning.



**Figure 1.** Decreased BOLD responses to anticipation of reward in adolescents with (A) clinical depression (n=22) and (B) subthreshold depression (n=101) compared to a matched healthy control group (n=123) overlaid on a T1-weighted structural brain image. Images are centred at: A: x=6, y=15, z=-2; B: x=-12, y=14, z=-2).



**Figure 2.** Trend analyses - Standardised BOLD response in left and right ventral striatum, left middle superior frontal gyrus, and right medial superior frontal gyrus among healthy adolescents that, after a 2-year period, remained healthy, developed subthreshold depression or developed clinical depression.



**Figure 3.** Standardised BOLD response in left and right ventral striatum among adolescents with low mood only, anhedonia only, both symptoms and adolescents without depressive symptoms from the community-based sample. *a*: (left:  $\beta = -.28$ ,  $p = 0.006$ ; right:  $\beta = -.18$ ,  $p = 0.019$ ); *b*: (left:  $\beta = -.27$ ,  $p = 0.006$ ; right:  $\beta = -.15$ ,  $p = 0.027$ ).

