Elevated Reward Region Responsivity Predicts Future Substance Use Onset but not Overweight/Obesity Onset

Supplemental Information

Supplemental Methods

The sample (*n* = 162) was recruited as to be in a healthy body mass index (BMI) range (kg/m^2; 18.0-24.0; mean BMI = 20.8 ± 1.90) at baseline. A brief phone screen interview with items from the Schedule for Affective Disorders and Schizophrenia for School Age Children – Epidemiologic Version (K-SADS-E; S1) identified current Axis I psychiatric disorders and other exclusion criteria. The K-SADS-E has shown high test-retest and inter-rater reliability (S2). Drug tests were done for every fifth participant and for participants who reported to occasional use of drugs in the past month. Those who reported drug use in the past month were tested again on their scan day to confirm that they were not using on the scan day (tests could detect substances used during the last 3 days).

One hundred and twenty-five participants were offspring of two obese or overweight (BMI ≥ 27) parents and 37 were offspring of two lean parents (BMI < 25). Participants with two obese or overweight parents (mean parental BMI = 30.5 ± 4.8) had a mean BMI of 21.0 ± 1.9. Participants with two lean parents (mean parental BMI = 22.9 ± 2) had a mean BMI of 20.1 ± 1.8. Adolescents and parents provided written informed consent for this Institutional Review Board-approved project.

Prior to the fMRI, female participants were tested for pregnancy if they had been sexually active. Participants were familiarized with the fMRI paradigms prior to scanning and the order of presentation of the paradigms was counterbalanced. Subjective hunger and pleasantness of the milkshake and tastelessness was assessed prior to the scan via cross-modal visual analogue scales and included as covariates of no interest for the food reward paradigm. Order of the food

reward and monetary reward paradigms was counterbalanced (as were runs within the paradigms).

fMRI Data Acquisition, Processing, and Analysis

Scanning was performed by a Siemens Allegra 3 Tesla head-only MRI scanner using a standard birdcage coil. Functional scans used a T2* weighted gradient single-shot echo planar imaging sequence (TE = 30 ms, TR = 2000 ms, flip angle = 80°) with an in plane resolution of 3.0 x 3.0 mm^2 (64 x 64 matrix; 192 x 192 mm^2 field of view). To cover the whole brain, 32 interleaved, no skip, 4 mm slices were acquired along the AC-PC transverse oblique plane, as determined by the midsagittal section. Prospective acquisition correction was used to adjust slice position and orientation, as well as to re-grid residual volume-to-volume motion in real-time during data acquisition for the purpose of reducing motion-induced effects (S3). All participants met the movement inclusion criteria, which were that within-run movement before correction did not exceed 2 mm in translational movement and 2^0 in rotational movement. Anatomical scans were acquired using a high-resolution inversion recovery T1 weighted sequence (MP-RAGE; FOV = 256 x 256 mm^2, 256 x 256 matrix, thickness = 1.0 mm, slice number ≈ 160).

Anatomical and functional images were manually reoriented to the AC-PC line and skull stripped using the BET function in FSL (S4). Data were then preprocessed and analyzed using SPM8 (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London) in MATLAB (The Mathworks, Inc., Natick, MA). Functional images were realigned to the mean and both the anatomical and functional images were normalized to the standard Montreal Neurological Institute T1 template brain (ICBM152). Normalization resulted in a voxel size of 3 mm^3 for functional images and a voxel size of 1 mm^3 for high-resolution anatomical images. Functional images were smoothed with a 6 mm full-width half-maximum isotropic Gaussian kernel. Anatomical images were segmented into

gray and white matter using DARTEL (S5); a mean of the resulting gray matter was used as a base for an inclusive gray matter mask.

Supplemental Results

One hundred and forty-eight participants of the 162 participants (91%) provided 1-year body fat percentage follow-up data and 153 (96%) provided 1-year follow-up data. Participants with (*n* = 148/153) versus without (*n* = 14/9) follow-up data did not differ significantly on demographic factors or any of the study variables. Change in BMI over 1-yr follow-up was mean = -0.68 ± 1.26; range = -4.30 – 3.11, which is typical of this developmental period (S6,S7). Mean change in body fat percentage over 1-yr follow-up in the full sample was mean = 0.02 ± 3.91; range = -9.77 – 10.31. There were no differences between sexes observed on pre-scan hunger level, baseline BMI, or change in body fat percentage over 1-yr follow-up. Those that were considered overweight at baseline (*n* = 13) showed a decrease in percent body fat at 1-year (mean = -3.41 ± 3.2). Females (mean = 23.94 ± 5.34) compared to males (mean = 12.80 ± 5.34) had a higher body fat percentage at baseline ($F_{(1,160)}$ = 176, $p < 0.001$). Females (mean = -0.46 ± 1.18) compared to males (mean = -.94 ± 1.29) showed a greater increase in BMI ($F_{(1,151)}$ = 5.97, p = 0.02).

There were no significant differences between the baseline substance use, baseline no substance use, substance use onset, and no substance use onset groups on sex, parental education, or on ratings of hunger and pleasantness of the milkshake and tasteless solution. Participants reporting substance use at baseline were slightly older than those reporting no substance use at baseline, $F_{(1,159)}$ = 6.63, p = 0.01.

Because visual inspection of the activation showing less activation in the caudate in participants reporting substance use at baseline vs. those reporting no substance use at baseline may place the peak in white matter, we thought it important to show that this peak was

located in gray matter based on activation in a gray matter mask that was created for the sample (Figure S1).

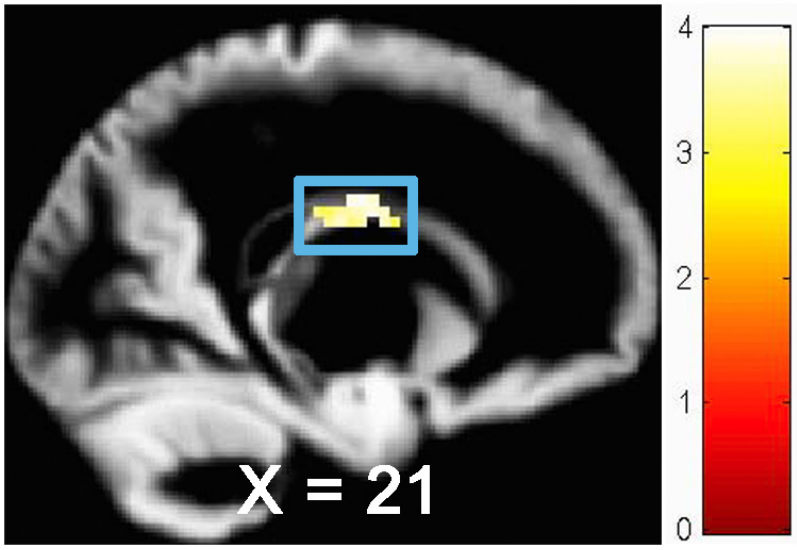

Figure S1. Participants reporting substance use at baseline showed less activation in the caudate in a gray matter mask (Montreal Neurological Institute coordinates: 21, -10, 31, Z = -3.98, k = 35) in response to receipt of monetary reward compared to participants reporting abstinence at baseline.

Supplemental References

S1. Orvaschel H (1994): Psychiatric interviews suitable for use in research with children and adolescents. In Mezzich JE, Jorge MR, Salloum IM, editors. *Psychiatric epidemiology: Assessment concepts and methods* Baltimore, MD US: Johns Hopkins. University Press, pp 509-522.

S2. Lewinsohn PM, Rohde P, Seeley JR, Klein DN, Gotlib LH (2000): Natural course of adolescent major depressive disorder in a community sample: Predictors of recurrence in young adults. *Am J Psychiatry* 157: 1584-1591.

S3. Thesen S, Heid O, Mueller E, Schad LR (2000): Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. *Magn Reson Med* 44: 457-465.

S4. Smith SM (2002): Fast robust automated brain extraction. *Hum Brain Mapp* 17: 143-155.

S5. Ashburner J (2007): A fast diffeomorphic image registration algorithm. *Neuroimage* 38: 95-113.

S6. Huh D, Stice E, Shaw H, Boutelle K (2012): Female overweight and obesity in adolescence: Developmental trends and ethnic differences in prevalence, incidence, and remission. *J Youth Adolesc* 41: 76-85.

S7. Terrell DF (2002): Overweight and obesity prevalence rates among youth in the Carolinas. *N C Med J* 63: 281-286.