Supplementary Online Content

Supplemental Methods

Procedures

In this 2-year prospective study, all participants completed, at baseline, a home-based assessment on clinical and demographic information and were further invited to perform cognitive tasks while their brain responses were measured with fMRI. Importantly, a subsample of 410 adolescents from London and Dublin sites further completed a baseline assessment of psychotic-like experiences. Then, 1602 participants from all sites were re-assessed two years later (i.e. 16 years old) through a home-based assessment.

Information about the magnetic resonance imaging (MRI) procedure (image acquisition sequence, standardization across MRI scanner) can be found elsewhere (1). All images were acquired on 3 Tesla scanners of different manufacturers (Siemens, Philips, General Electric, Bruker).

Further description of measures

Psychotic-like experiences

The Adolescent Psychotic-Like Symptoms Screener's items begin with the following statement: 'The next items ask about thoughts or beliefs that you could have had DURING THE PAST 6 months'. The following 4 items were adapted from the Diagnostic Interview Schedule (2): (i) 'Some people believe that their thoughts can be read', (ii) 'Have you ever believed that you were being sent special messages through the TV?', (iii) 'Have you ever thought that you were being spied upon?', (iv) ' Have you ever heard voices that no-one else could hear?'. Three additional

items, validated in community samples of children and adolescents (3, 4) were included: (v) ‘Have you ever felt that you were under the control of some special power?’, (vi) ‘Do you have some special powers that other people do not have?’, (vii) ‘Have you ever seen something or someone that other people could not see?’.

Twenty-seven 14-year olds reporting significant psychotic-like experiences were matched to a group of healthy controls five times as large. The matching script’s function was to find a group of matched adolescents, among the 300 youth with complete fMRI and behavioral information, whose parameter averages did not differ more than 5% above or below the parameter averages of the 27 adolescents with these experiences.

As for the relationship between psychotic-like experiences assessed at age 14 and emerging psychotic symptoms assessed at age 16 with the bipolar module in the London-Dublin subsample, of the twenty-seven 14-year-olds reporting significant psychotic-like experiences, follow-up information was available for 23. Of these, 6 (26.1%) had both mood and psychotic related symptoms, 6 had only mood symptoms, and 11 reported no mood symptoms. Of the 135 adolescents reporting no psychotic-like experiences at 14 years old, follow-up information was available for 109. Of these, 3 (2.8%) had both mood and psychotic related symptoms, 33 had only mood symptoms, and 73 reported no mood symptoms.

Functional imaging

All participants underwent two 45-min MRI sessions. Before each session, participants familiarized themselves with the scanner and the tasks in a practice session. In the scanner, they received a brief visual and verbal reminder of the instructions before the tasks.

The faces task is derived from Grosbras and Paus (5), where dynamic angry faces are displayed. Participants passively viewed blocks of short black and white video clips (2-5s) of three conditions: neutral faces, angry faces, and control (non-biological motion). Each block includes

four to seven video clips. In both the angry and neutral conditions, the faces were always neutral at the beginning and progressively turned angry or stayed neutral. Video clips were preferred to static faces as they allow a better recruitment of cerebral regions implicated in facial processing (6). The control condition (7) consisted of contracting and expanding concentric circles with black and white contrasts matching the contrast and motion characteristics of the faces clips. Ten 18-sec blocks were presented (5 blocks of angry faces, 5 blocks of neutral faces), interleaved with nine blocks of the control condition, for a total of 6 minutes.

The fMRI adaptation (8) of the stop-signal task (9) measures activity in brain areas related to the inhibition of an already planned motor response as well as error detection. On a total of 480 trials, a motor response to high frequency go signals (arrows pointing left or right) has to be inhibited when infrequently and unexpectedly, a stop signal appears after the go signal (arrow pointing upwards). Indeed, participants were asked to try and withhold their response when an upwards arrow followed the go-stimuli, however, they were explicitly reminded to try and respond as fast as possible to the go stimuli. Stopping difficulty is manipulated across trials by varying the delay between the onset of the go arrow and the stop arrow (stop-signal delay). Therefore, the task is individually titrated to force every subject to fail on 50% of stop trials, making every subject work at the edge of their own inhibitory capacity, and therefore adjusting for differences in success levels between subjects and groups, making it ideal for developmental studies. This 16-minute task included 80 stop trials (16.7% of trials) . Between three and seven go trials separated two stop trials. Stimulus duration in go trials was 1,000 ms and varied in stop trials (0-900ms) in accordance with the tracking algorithm (initial delay = 250ms). For this task, first-level analysis included the movement realignment regressors plus 5 task-specific regressors: (i) successful inhibitions, (ii) errors of commission, (iii) incorrect responses on go trials, (iv) late responses on go trials, and (v) correct responses on go trials.

A modified version of the monetary incentive delay task was used to assess brain response to reward anticipation (10, 11), in which each trial included a reward anticipation phase, a reward response phase, and a feedback phase. Considering that the ventral striatum hypoactivation during reward anticipation is the most replicated finding in chronic and first-episode psychosis patients as well as in individuals at clinical risk for psychosis in paradigms exploring reinforcement learning (12), the current study only focused on the anticipation phase. First, participants are presented with cues (ranging from 4.0-4.5 sec) signaling the amount of reward that could be won on a given trial (large reward = 10 points, small reward = 2 points, no reward = 0 points). Then they are instructed to respond to the response cue. Participants' outcome (score) is dependent upon their performance in this simple reaction time task. The duration of the response cue is adjusted so that 66% of the trials produce a positive feedback. Specifically, the duration of the response cue presentation varies from 250 to 400 ms and is adjusted in every trial to the participant's performance by subtracting 10 milliseconds if the success rate is greater than 66% of the trials, and adding 10 ms if the success rate is inferior to 66%. Points were converted to sweet food snacks following testing (5 points per M&M). In total, participants completed 22 trials per condition. For this task, first-level analysis included the movement realignment regressors plus 6 regressors for successful trials: (i) anticipation of large reward, (ii) anticipation of small reward, (iii) anticipation of no reward, (iv) large reward feedback, (v) small reward feedback, (vi) no reward feedback, and the same 6 regressors for unsuccessful trials.

Further description of data analysis

fMRI

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, realigned to the mean volume, non-linearly warped onto MNI space using a custom EPI template, and spatially smoothed with a 3D Gaussian kernel (5 mm full-width half maximum). Estimated movement parameters (18: 3 translational, 3 rotations, 3 quadratic, 3 cubic translations, 3 translations shifted 1 TR before and 3 shifted 1 TR later) were added as nuisance variables in first-level analysis. Each fMRI time series underwent automatic spike detection and any artifactual time points were regressed out of each subject's data. Activation maps were computed using a general linear model with an auto-regressive noise model. The regressors modeling the experimental conditions were convolved using SPM's default hemodynamic response function.

To control for multiple comparisons type 1 error following recommandations by Eklund et al. (13), we performed Monte Carlo simulations computed with AFNI's 3dClustSim. Assuming a per voxel probability threshold of p=0.001, mean residual smoothing of 8.96mm, 9.04mm, and 8.21mm in x, y and z estimated with "spm_est_smoothness" function in SPM, after 10,000 simulations, significant voxels were required to be part of cluster of more than 24 contiguous voxels giving a 0.05% probability of a cluster surviving due to chance.

For our secondary objective (predicting psychotic outcome at age 16 with brain information), we created regions of interest's masks based on the regions' coordinates using the MarsBaR SPM toolbox (14), and extracted the mean contrast value (betas) for each region of interest and for each subject.

Machine learning procedure

The elastic-net has two key parameters, alpha and lambda. The alpha balances the application of the L1- and L2-norm penalties, and the lambda controls the magnitude of shrinkage applied to the regression coefficients. These parameters are tuned within a nested *k*-fold cross-validation scheme in order to maintain the independence of the final model used in evaluating the originally set-aside *k*-fold observations (or single observation during leave-one-out cross-validation).

Supplemental Results

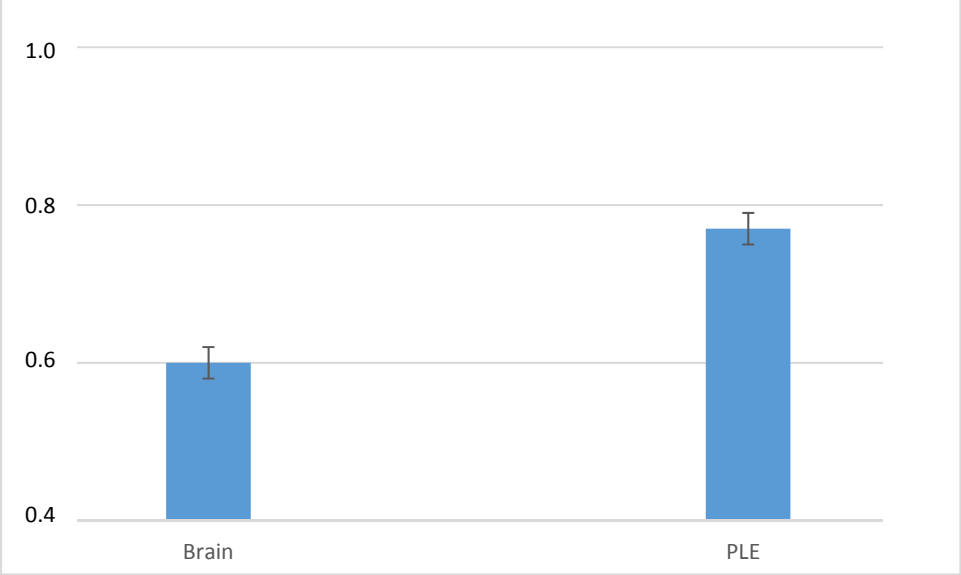
Task activation differences between groups

In the faces task, the angry relative to control contrast was also investigated to help the interpretation of the neutral relative to control contrast's findings. However, no cluster of significant activity differences in the angry relative to control contrast survived the cluster threshold of 24 contiguous voxels. Even when using a more liberal cluster threshold of 10 contiguous voxels for the prediction analyses, no significant activity differences were observed, except for an increased activity from the left cerebellum (x=-3, y=-79, z=-38 T-value=3.58 cluster=10 voxels) in healthy controls relative to those reporting psychotic-like experiences.

Prediction of psychotic-related symptoms at age 16

Following our accurate classification of youths reporting both mood- and psychotic-related symptoms at 16 (N=12) from those reporting no mood symptoms (N=154) in the London-Dublin subsample, we investigated the performance of each domain (i.e., brain activity and baseline psychotic-like experiences) on its own. Psychotic-like experiences at age 14 were more robust classifiers than brain regions, however, brain information still helped the classification (AUC > 0.6) (Figure 1S).

Figure S1. Classification accuracy for individual domains in the London-Dublin subsample.



Abbreviations: PLE, Psychotic-like experiences.

The bars represent standard deviations.

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