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FUNCTIONAL NEUROIMAGING PREDICTORS OF SELF-REPORTED PSYCHOTIC SYMPTOMS IN ADOLESCENTS

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ABSTRACT

OBJECTIVE: This study aimed to investigate the neural correlates of psychotic-like experiences in youth on measures of inhibitory control, reward anticipation and emotion processing. A secondary aim was to test whether these neuro-functional correlates of risk were predictive of psychotic symptoms 2 years later.

METHOD: Functional imaging response to three paradigms: the Stop-Signal, Monetary Incentive Delay, and Faces tasks was collected in youth at age 14, as part of the IMAGEN study. At baseline, youth from London and Dublin sites were assessed on psychotic-like experiences and those reporting significant experiences were compared with matched controls. Significant brain activity differences between the groups were used to predict, with cross-validation, the presence of psychotic symptoms in the context of mood fluctuation at age 16, assessed in the full sample. These prediction analyses were conducted with the London-Dublin subsample (N=246) and the full sample (N=1196).

RESULTS: Youth reporting psychotic-like experiences showed increased hippocampus/amygdala activity during neutral faces processing and reduced dorsolateral prefrontal activity during failed inhibition relative to controls. The most prominent region for classifying 16-year olds with mood fluctuation and psychotic symptoms relative to the control groups (those with mood fluctuations but no psychotic symptoms and those with no mood symptoms) included hyperactivation of the hippocampus/amygdala, when controlling for baseline psychotic-like experiences and cannabis use.

CONCLUSIONS: The results stress the importance of the limbic network's increased response to neutral facial stimuli as a marker of the extended psychosis phenotype. These findings might help to guide early intervention strategies for at-risk youth.

INTRODUCTION

There is evidence of a continuity between clinical and subclinical phenotypes of psychosis that is measurable in the general population (1) and in individuals with a psychiatric diagnosis (2). On a clinical level, individual differences in psychosis proneness are expressed across a number of psychiatric conditions besides schizophrenia, namely mood, anxiety, eating, impulse control, and substance use disorders (2). At a subclinical level this liability is characterized by "attenuated" or "brief" psychotic symptoms that might not co-exist with other diagnostic criteria (frequency and intensity) to meet full diagnosis, yet sufficient impairment is observed to motivate treatment seeking (3). This clinical high-risk state has been shown to be a robust risk factor for progression to clinically-significant psychiatric disorders (4), but does not necessarily predict to one specific disorder and instead is predictive of a number of psychopathologies that include psychotic symptoms (5).

At the far end of the extended psychosis continuum are children/adolescents from the community reporting psychotic-like experiences (i.e., perceptual abnormalities and delusional thoughts) prior to the onset of more impairing psychotic symptoms. These preclinical experiences, even though they are common in children/young adolescents (7 to 23% (6)), are associated with increased risk for psychotic or Axis I disorders over the longer term (6, 7). Studying young adolescents prone to such experiences will help to identify etiologic processes implicated in psychosis proneness, without the confounds of diverse risk factors and iatrogenic effects, such as substance misuse, medication and social impairment (8). Investigating the neural correlates of this preclinical psychosis proneness on cognitive functioning can shed light on early altered neural processes prior to significant cognitive impairments.

However, the vast majority of functional magnetic resonance imaging (fMRI) studies have focused on adults with a clinical risk to psychosis, not on young adolescents reporting psychotic-like experiences. These studies have mostly investigated the neural circuits implicated in executive functioning, social cognition and reinforcement learning. Recent fMRI studies in individuals with psychosis-spectrum symptoms have shown significant reduced activation in the dorso-lateral prefrontal cortex (dlPFC) during executive functioning (e.g., working memory, inhibitory control) relative to low-risk controls (9, 10). These results are consistent with findings of dlPFC hypoactivation in patients with clinical diagnoses of psychosis or bipolar disorder on tasks of working memory and response inhibition (11, 12), suggesting that the brain markers associated with psychosis proneness cross diagnostic boundaries.

Social cognition which encompasses emotion processing and theory of mind processes has also been identified as a domain which might differentiate individuals at clinical risk for psychosis from low-risk individuals (13). Neuroimaging studies show that the experience of high arousal negative emotions is associated, in individuals at clinical risk relative to healthy controls, with both reduced (14) and increased activation of fronto-limbic areas (9), depending on the contrast used (15), while viewing neutral material is more consistently associated with increased activation of this network (14, 16).

Another core feature of psychosis, dysfunctional reinforcement learning, was shown to be shared with distinct diagnostic categories such as major depressive and bipolar disorders (17). A recent meta-analysis of fMRI studies has demonstrated that psychosis spectrum disorders are associated with a blunted response from the ventral striatum during anticipation of reward, which might explain why patients demonstrate impaired learning of stimulus-reinforcement associations (18). Functional MRI studies with clinically at-risk individuals have shown modest

reduced activity in fronto-striatal regions during reward anticipation, relative to controls (19, 20).

Among the very few neuroimaging studies investigating the early neural correlates of preclinical psychosis proneness prior to the onset of more impairing psychotic symptoms, Modinos et al. (21, 22) found that community youth self-reporting psychotic-like experiences had reduced activation of the medial prefrontal cortex, insula and amygdala during passive viewing and reappraisal of negative pictures relative to low-risk youth. In a quite young sample of 11- to 13-year olds reporting these experiences, Jacobson et al. (23) observed reduced activity in prefrontal and temporal regions during a response inhibition task. However, the sample was small (11 in the at-risk group). Consequently, we intended to extend these findings in another community sample of young adolescents with psychotic-like experiences. Of note, considering that psychotic-like experiences are, for most individuals, transient and not persistent (1), it is crucial to understand to what extent these early neural abnormalities relate to a subsequent psychosis vulnerability in terms of clinically validated symptoms.

The primary aim of the present exploratory study was to identify brain correlates of psychotic-like experiences in youth prior to exposure to regular substance use on fMRI measures of emotion processing, inhibitory control and reward anticipation using data from the IMAGEN study, in which two sites, London and Dublin, assessed these preclinical experiences to participants when they were 14. The secondary aim was to validate whether these brain correlates predicted emergence of psychotic symptoms in the context of mood fluctuation symptoms at age 16 in the full IMAGEN sample. We hypothesized that psychotic-like experiences would be associated with reduced activity in the executive network during response inhibition, altered activity in fronto-limbic regions during processing of emotional and non-

emotional stimuli as well as modest reduced ventral striatum activity during anticipation of reward.

METHODS

Participants

2257 14-year old adolescents were recruited through high schools in the large European multicenter IMAGEN study from 8 sites across the United Kingdom, Ireland, France and Germany. Parents and adolescents gave written informed consent to the study procedures. All procedures were approved by each local institutional ethics committee. A detailed description of the study recruitment and assessment procedure, exclusion criteria, data storage and safety, as well as imaging acquisition protocol may be found elsewhere (24).

Measures

For a more detailed description of the study measures, see the online data supplement.

Psychotic-like experiences

At baseline, 14-year olds from London and Dublin completed the self-report Adolescent Psychotic-Like Symptoms Screener (25), which contains 7 items evaluating perceptual abnormalities and delusional thoughts in the past 6 months. Participants were asked to rate their responses to different statements on a 1-point scale (0=not true, 0.5=somewhat true, 1=certainly true). Based on Cannon's team (23, 25) previous studies, to identify youth with significant psychotic-like experiences, we used the following criteria: a total score ≥2 and a score ≥0.5 on the auditory hallucination (this item revealed 88% probability of predicting which

9

individuals would be classified as "at-risk", as determined by consensus ratings from the Structured Interview for Prodromal Syndromes).

Among 410 adolescents [mean (SD), 14.3 (0.4) years old; 51.7% girls] from London and Dublin sites, 300 had complete fMRI and behavioral information. Among them, 27 were classified as having significant psychotic-like experiences. None had yet started using cannabis and they reported minimal alcohol and cigarette use (<3-5 times in the previous year). Using an in-house groupwise matching script designed by the IMAGEN consortium, the group was matched (on sex, handedness, imaging site, general IQ and puberty development) to a control group 5 times larger (135 adolescents) which included those with a total score ≤ 1 and a score of 0 on the auditory hallucination question.

Psychotic symptoms at age 16

For the secondary objective of the study, psychotic symptoms were evaluated with the Self-Report Development and Well-Being Assessment interview (www.dawba.com) (26), a computer-based package of questionnaires designed to generate DSM-IV-TR psychiatric diagnoses for 5- to 16-year olds. While the schizophrenia module was not administered to participants at age 16, the bipolar module was more developmentally appropriate for this age group, and therefore all participants answered initial screening questions assessing mood dysregulation ("rapid mood changes" and "abnormally high mood"), and if positive, they were then asked three specific items assessing the presence of visual and auditory hallucinations and delusional beliefs. Among the 300 individuals from London and Dublin with complete baseline assessments, 246 (82.0%) completed the bipolar module at age 16 and were further divided into three groups: those who endorsed mood dysregulation plus hallucinatory/delusional symptoms (i.e., group with mood and psychotic symptoms, N=12), those reporting mood dysregulation without

hallucinatory/delusional symptoms (i.e., group with mood symptoms only, N=80) and those who did not endorse the mood dysregulation criteria (i.e., no mood symptoms group, N=154).

Additionally, we conducted similar analyses on the full IMAGEN sample: among the 1602 participants re-assessed at 16 years old, 1196 had complete fMRI and behavioral information and were divided into three groups: those with mood and psychotic symptoms (N=72), those with mood symptoms only (N=451), and those without any mood symptoms (N=673).

Neuroimaging tasks

We report results from three task-based fMRI paradigms: the Faces task to assess emotional processing, the Stop-Signal Task to evaluate motor inhibitory control and a modified version of the Monetary Incentive Delay Task to examine reward anticipation. The block design Faces task, known to elicit prefrontal and amygdala activations (27), uses video clips displaying a neutral expression progressively turning into angry or a second neutral expression. A control condition displays expanding/contracting circles. In the event-related adaptation of the Stop-Signal Task used to measure activation of the fronto-striatal network (28), a motor response to high frequency go signals (80% of trials) has to be inhibited when infrequently and unexpectedly (in randomised 20% of trials), a stop signal appears after the go signal. In the modified Monetary Incentive Delay task, participants had to respond to a target in order to win a previously indicated amount of points (3 trial types: no win, small win and large win). In the anticipation phase, which elicits striatal and medial prefrontal activity (29), participants were presented with cues signaling the amount of reward that could be won in a given trial.

Data analysis

fMRI

To test activity differences between the group reporting or not psychotic-like experiences on each of the contrasts of interests (Faces: angry *vs* neutral and neutral *vs* control; Stop-Signal: stop success *vs* baseline and stop failure *vs* baseline; Monetary Incentive Delay: anticipation of large reward *vs* no reward), we conducted two-sample *t* tests, using a whole-brain approach in SPM8 (Wellcome Trust Centre for Neuroimaging). Following Eklund et al. (30) recommendations for controlling type 1 error, 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 (AFNI's 3dClustSim). For our secondary objective, we used a more liberal threshold: significant voxels were required to be part of cluster of more than 10 contiguous voxels. Then, we created regions-of-interest based on the regions' coordinates and extracted the mean contrast value (betas) for each region of interest and for each subject.

Machine learning procedure

For our secondary objective, we aimed to classify youth according to 16-years old psychotic outcomes with fMRI information. We conducted cross-validated logistic regressions with elastic-net regularization to model this relationship. Cross-validation is used to evaluate how well a predictive model generalizes to out-of-sample observations. On one hand, leave-one-out cross-validations were used during classification of the groups within the smaller London-Dublin subsample; on the other hand, *k*(10)-fold cross-validations were used during classification of the groups within the full sample. Cross-validation analysis within the London-Dublin subsample allowed to test the predictive capacity of the brain markers while controlling for baseline psychotic-like experiences. Considering that the sample size of the groups was much larger in the full sample, we were able to control for more predictors such as developmental risk factors

for psychotic symptoms (i.e., cannabis, alcohol and cigarette use, as well as internalizing and externalizing behaviors (31)), gathered at age 14.

Elastic-net regularization is used to achieve better prediction performance by penalizing the regression coefficients in an attempt to minimize overfit. Elastic-net regularization is an example of a sparse regression method, which imposes a hybrid of both L1- and L2-norm penalties (i.e., penalties on the absolute (L1-norm) and squared values of the regression coefficients (L2-norm)). Model performance was evaluated using the area under the curve (AUC) of the receiver-operating characteristic (ROC), which quantifies the predicted sensitivity (true positive rate) as a function of false positive rate (1-specificity).

RESULTS

Demographic and clinical information of the groups at age 14

Reported in Table 1 are the means of the variables used as matching parameters between the 27 adolescents with and the 135 matched controls without psychotic-like experiences (no significant differences between the groups). Furthermore, the groups were not different on age, as well as alcohol, cigarette and cannabis use in the previous year.

Task activation differences between the groups

Between-group differences were present in small clusters in the three tasks (Table 2). Only two significant clusters of activity differences survived the cluster-corrected threshold of 24 contiguous voxels: a hyperactivation of the right anterior hippocampus/amygdala during passive viewing of neutral/ambiguous faces and a reduced activity in the right dlPFC during failure to inhibit a motor response in youth with psychotic-like experiences (Figure 1).

Prediction of psychotic-related symptoms at age 16

First, from the London-Dublin subsample, we classified N=12 youths reporting both mood- and psychotic-related symptoms at 16 from N=154 youths reporting no mood symptoms. The final models returned from this analysis had a mean AUC=.709 (95% CI=.706-.713, p<.01) (Figure 2A). This model included all brain regions that survived the more liberal threshold of 10 contiguous voxels (all regions reported in Table 2), and controlled for psychotic-like experiences' score at age 14 as well as demographic information (i.e., age, sex, handedness and site). All features were present in at least 9 folds (out of 10) of the final model. In addition to psychotic-like experiences, the most robust brain classifiers were cerebellum activity during processing of angry faces and the hippocampus/amygdala activity during neutral faces processing (Table 3A). The performance of each domain on its own (i.e., brain activity vs psychotic-like experiences) is displayed in Fig S1. We could not significantly classify youth with mood only symptoms (N=80) from the other two groups (i.e. mood and psychotic symptoms group, no mood symptoms group) (AUC=.532, 95% CI=.525-.539, p=.36; AUC=.453, 95% CI=.450-.456, p=.90 respectively).

In the second prediction analyses, using the full IMAGEN sample, we classified N=72 youths reporting both mood- and psychotic-related symptoms at age 16 from N=673 youths reporting no mood symptoms and from N=451 youths with mood symptoms only. The final models returned from this analysis had a mean AUC=.633 (95% CI=.630-.636, p<.0001) and AUC=.615 (95% CI=.614-.617, p=.001) respectively (Figure 2B, 2C). This model included all brain regions that survived the more liberal threshold of 10 contiguous voxels, and controlled for internalizing and externalizing behaviors, cigarette, alcohol and cannabis use, as well as demographic information (i.e. puberty development index, handedness, age, sex and site). When classifying the mood and psychotic symptoms group relative to the no mood symptoms group, only the

following features: internalizing and externalizing behaviors, cigarette and cannabis use, hippocampus/amygdala and cerebellum activity during neutral faces processing as well as cerebellum activity during angry faces processing were present in at least 9 folds of the final model (Table 3B). However, when classifying the mood and psychotic group relative to the mood only group, all features were present in at least 9 folds of the final model, with cerebellum activity during angry faces processing, fusiform activity during anticipation of reward, internalizing behaviors, cigarette and cannabis use, and hippocampus/amygdala activity during neutral face processing making the strongest contribution to group classification (Table 3C).

Finally, we classified N=451 individuals with mood symptoms only from N=673 individuals reporting no mood symptoms with a mean AUC=.553 (95% CI=.552-.553, p=.002) barely better than chance (Figure 2D). All features, except the dlPFC activity during failed response inhibition, were present in at least 9 folds of the final model. The most important classifiers were internalizing and externalizing behaviors, cannabis use, reduced activity from the cerebellum during neutral faces processing, puberty development scale, and site (Table 3D).

DISCUSSION

At age 14, across the brain networks implicated in emotion processing, response inhibition and reward anticipation, the cluster-corrected markers of psychotic-like experiences included an increased response from the hippocampus/amygdala during processing of neutral material as well as reduced activity from the dlPFC during failed inhibition. Of note, hyperactivity from the hippocampus/amygdala during the processing of neutral faces further discriminated at 2-year follow-up individuals with mood- and psychotic-related symptoms relative to the other groups in both the London-Dublin subsample and the full IMAGEN sample, even when controlling for

15

baseline psychotic-like experiences as well as cannabis and cigarette use. The cross-validation

models best discriminated the mood and psychotic group from the no mood symptoms group in

comparison to the mood only group from the no mood symptoms group.

One of the most replicated neural markers of psychosis and high-risk states is hypofunctioning

of PFC and dlPFC during executive functioning (32). Our results support findings from other

community-based studies of youth reporting psychosis-spectrum symptoms showing reduced

PFC activity during working memory and response inhibition tasks (9, 23). However, the activity

of the dlPFC during the Stop-Signal task was a weak brain classifier for adolescents reporting

both mood and psychotic symptoms relative to the other groups. A possible explanation might

be that reduced dlPFC activation is not directly related to positive or mood symptoms, but more

to disorganized symptoms or cognitive deficits (which were not assessed by our screening tools)

(9, 33). Consequently, dlPFC alterations would appear to be a promising neuro-functional

marker of the clinical risk for psychosis when, in addition to positive and negative symptoms,

significant cognitive impairments are observed; not of youth reporting psychotic-like

experiences prior to a cognitive decline. It is worth mentioning that the use of a working

memory task instead of response inhibition could have yielded more significant dlPFC results

considering that working memory paradigms, in comparison to Stroop tasks or Go-Nogos,

consistently elicit a more widespread loci of significant activation in the dLPFC and anterior

cingulate cortex in both healthy controls and schizophrenia patients (11).

The current exploratory study stresses the importance of an observed increased activity in the

limbic network in the extended psychosis phenotype. Both fMRI and perfusion studies have

highlighted increased hippocampal activity at rest and across cognitive tasks in clinically at-risk

individuals (32, 34). Interestingly, Schobel et al. (35) demonstrated that baseline

hypermetabolism of the hippocampus in clinical high-risk individuals is directly related to a subsequent volume loss (via a hyperglutamatergic state); thereby supporting the heightened hippocampus activity as a highly promising early vulnerability marker to psychotic disorders. In the context of emotion processing, a recent meta-analysis showed that the apparent deficit in amygdala activity observed in individuals with a psychotic disorder during the viewing of negative material may be explained by an elevated amygdala response to neutral material (15). These findings have led some authors to propose that abnormalities in salience attribution might be core to the extended psychosis phenotype, rather than stress reactivity, per se (36). Thus, the increased neural response to neutral information may reflect an atypical assignment of motivational salience to these stimuli (37). Results from other cognitive studies showing an impaired decoding of facial expressions in patients with psychosis and high-risk populations further suggest that the abnormal neural activity in the current study might be due to an erroneous identification of neutral faces specifically. For instance, children and adolescents reporting psychotic-like experiences over-attribute significance (i.e. negative valence) to neutral faces (38). Considering that impaired emotion recognition is linked to declining social functioning in high-risk populations (39), it represents a potential target for psychosis symptoms prevention strategies for at-risk youth, prior to subsequent impaired social functioning.

Considering that cerebellar activity significantly contributed to the classification of youth with mood- and psychotic-related symptoms relative to the other groups even in the absence of a marked alteration in individuals reporting psychotic-like experiences, its role in emotion processing in the psychosis-spectrum remains elusive but deserves to be clarified in the future.

No cluster-corrected activity difference between 14-year olds with and without psychotic-like experiences were observed during reward anticipation. Even when using a more liberal cluster

threshold, significant activity related to reward anticipation did not robustly contribute to discriminate the groups at age 16. These findings are inconsistent with recent fMRI studies showing a blunted response from the ventral striatum during reward processing in psychosis and high-risk individuals (18, 40). A possible explanation for this negative result may be explained by Radua et al.'s findings of a negative correlation between striatal activity and the severity of negative symptoms in both patients and individuals at clinical risk for psychosis (18). Here, only positive experiences/symptoms were assessed.

Limitations

The use of an extended risk phenotype (i.e. youths self-reporting psychotic-like experiences) may constitute both a strength and weakness. While it might be too liberal to predict vulnerability to specific disorders, particularly those with very low prevalence, one advantage of this approach is that it might capture a dimension of vulnerability that is implicated in a number of different psychopathological outcomes. The current study also did not investigate interactions with family, substance misuse and genetic data, which might further clarify how this extended phenotype is implicated in future psychiatric outcomes. Another potential limitation to the study is that the use of the bipolar module, at age 16, may have under-estimated the emergence of psychotic symptoms in the no mood symptoms group. However, the prevalence of psychotic symptoms is low at the end of adolescence (e.g. 5-7%) (1). Finally, the timeframe for studying outcomes was relatively brief and might predate the typical age of onset of psychotic disorders, however, this might also be considered a strength, as we were able to detect relevant brain-related abnormalities before psychotic experiences begin to cause significant functional and cognitive impairment, substance misuse and require medical intervention.

Conclusion

The results of the present study suggest that an aberrant neural response to non-salient stimuli may be an important early vulnerability marker for psychosis, at least in the context of mood fluctuations. These findings might help to guide early intervention strategies for at-risk youth. It has yet to be determined whether individual differences in emotional reactivity to non-salient stimuli can be modified in young adolescents and whether such modifications have any clinical significance for high-risk youth.

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FIGURES LEGENDS

Figure 1. Cluster-corrected activation differences between 14-year olds with (N=27) and without (N=135) psychotic-like experiences.

Abbreviations: PLEs, Psychotic-like experiences.

Only cluster-corrected activations are shown in the maps. Bar graphs refer to standard deviations (SD).

Figure 2. Receiver-operating characteristics (ROC) curves

A, ROC of age 16 classification between youth from the London-Dublin subsample with mood and psychosis symptoms and those with no mood symptoms

B, ROC of age 16 classification between youth from the full sample with mood and psychosis symptoms and those with no mood symptoms

C, ROC of age 16 classification between youth from the full sample with mood and psychosis symptoms and those with mood symptoms only

D, ROC of age 16 classification between youth from the full sample with mood symptoms only and those with no mood symptoms

Table 1. Demographic, substance use and clinical characteristics of the groups at 14 years old (baseline).

Abbreviations: SD, standard deviation; PLEs, Psychotic-like experiences.

Characteristics	PLEs group (N=27)	Control group (N=135)	P Value[a]
Demographic			
Sex: female, (%)[b]	64.3%	65.2%	.93
Age at testing, mean (SD)	14.26 (0.31)	14.35 (0.38)	.24
Imaging site: London, (%)[b]	57.1%	64.4%	.47
Right handed, (%)[b]	92.9%	91.0%	.88
Puberty status, mean (SD)	3.73 (0.72)	3.69 (0.69)	.77
Cognition			
Verbal IQ, mean (SD)	107.28 (13.64)	110.25 (13.43)	.31
Abstract reasoning IQ, mean (SD)	106.60 (16.70)	107.34 (14.04)	.82
Substance use			
Cigarette use, mean (SD)	0.43 (1.17)	0.40 (1.18)	.92
Alcohol use, mean (SD)	2.25 (1.84)	1.90 (1.84)	.37
Cannabis use, mean (SD)	0.00 (0.00)	0.08 (0.48)	.36

[a] All p-values in the table are 2-tailed, uncorrected.

[b] Unless specified by [b], t-tests were used for comparing group means. When specified by [b], Chi-squared tests were used to compare proportions for categorical variables.

Table 2. Regions showing group differences in the fMRI contrasts

Regions	Direction	T-Value	MNI coordinates			Voxels	Effect size (Cohen's d)
			x	y	z		
Faces Task, Angry > Neutral contrast							
Cerebellum L	CT > PLEs	3.58	-3	-79	-38	10	
Faces Task, Neutral > Reference							
Hippocampus/amygdala R	PLEs > CT	4.68	30	-13	-17	25*	0.987
Middle temporal gyrus R | Temporal	PLEs > CT	4.19	54	5	-20	10	
Cerebellum L	PLEs > CT	3.88	-42	-49	-32	11	
Inferior frontal gyrus, orbital part L	CT > PLEs	4.18	-30	32	-20	13	
Lingual gyrus R	CT > PLEs	4.15	21	-55	-5	12	
Fusiform gyrus L	CT > PLEs	4.14	-33	-31	-17	12	
Stop-Signal Task, Stop success > Baseline							
No significant activation difference							
Stop-Signal Task, Stop failure > Baseline							
Middle frontal gyrus R	CT > PLEs	4.65	30	38	40	37*	0.980
Caudate nucleus L	CT > PLEs	4.41	-15	8	19	10	
Monetary Incentive Delay Task, Anticipation large win > No win							
Anterior/middle cingulate gyrus R	PLEs > CT	3.77	3	29	31	13	
Fusiform gyrus L	CT > PLEs	4.40	-27	-37	-23	15	

Abbreviations: MNI, Montreal Neurological Institute space; L, left; R, right; CT, Control group reporting no significant psychotic-like experiences; PLEs, Group reporting significant psychotic-like experiences.

*Cluster presented are corrected at p<0.05 according to AFNI 3dClustSim. Other brain regions presented survived the more liberal cluster threshold of ≥ 10 contiguous voxels.

Table 3. Beta weights for prediction of age 16 outcome

A

Predictors	Mean Betas
Demographic information	
Age	0.101
Sex (male)	-0.079
Site	0.105
Handedness (right-handed)	-0.182
Symptoms	
Psychotic-like experiences at baseline	0.577
Brain ROIs	
dlPFC during failed inhibition	0.021
Caudate during failed inhibition	-0.088
Cerebellum during angry faces processing	0.276
Hippocampus/amygdala during neutral faces processing	0.253
Middle temporal during neutral faces processing	0.070
Cerebellum during neutral faces processing	-0.234
Inferior frontal during neutral faces processing	-0.126
Lingual gyrus during neutral faces processing	-0.142
Fusiform gyrus during neutral faces processing	-0.077
ACC/MCC during anticipation of reward	0.066
Fusiform gyrus during anticipation of reward	-0.216

B

Predictors	Mean Betas
Demographic and substance use information	
Cannabis use in the previous year	0.137
Lifetime cigarette use	0.150
Symptoms	
Internalizing behaviors	0.307
Externalizing behaviors	0.084
Brain ROIs	
Cerebellum during angry faces processing	0.092
Hippocampus/amygdala during neutral faces processing	0.073
Cerebellum during neutral faces processing	-0.090

C

Predictors	Mean Betas
Demographic and substance use information	
Age	0.027
Sex (male)	0.188

Site	0.023
Handedness (right-handed)	-0.020
Puberty development score	0.077
Cannabis use in the previous year	0.250
Lifetime cigarette use	0.268
Alcohol use in the previous year	-0.171
Symptoms	
Internalizing behaviors	0.297
Externalizing behaviors	0.098
Brain ROIs	
dlPFC during failed inhibition	0.100
Caudate during failed inhibition	-0.142
Cerebellum during angry faces processing	0.317
Hippocampus/amygdala during neutral faces processing	0.192
Middle temporal during neutral faces processing	0.100
Cerebellum during neutral faces processing	-0.066
Inferior frontal during neutral faces processing	-0.101
Lingual gyrus during neutral faces processing	-0.158
Fusiform gyrus during neutral faces processing	-0.135
ACC/MCC during anticipation of reward	-0.005
Fusiform gyrus during anticipation of reward	-0.306

D

Predictors	Mean Betas
Demographic information	
Age	-0.024
Sex (male)	-0.053
Site	-0.097
Handedness (right-handed)	0.041
Puberty development score	0.096
Cannabis use in the previous year	0.140
Lifetime cigarette use	-0.057
Alcohol use in the previous year	0.058
Symptoms	
Internalizing behaviors	0.154
Externalizing behaviors	0.100
Brain ROIs	
Caudate during failed inhibition	0.062
Cerebellum during angry faces processing	-0.083
Hippocampus/amygdala during neutral faces processing	-0.029
Middle temporal during neutral faces processing	-0.025
Cerebellum during neutral faces processing	-0.132
Inferior frontal during neutral faces processing	0.036
Lingual gyrus during neutral faces processing	0.071
Fusiform gyrus during neutral faces processing	0.039

ACC/MCC during anticipation of reward	0.025
Fusiform gyrus during anticipation of reward	0.088

Abbreviations: dlPFC, dorsolateral prefrontal cortex; ACC/MCC, anterior/middle cingulate

cortex.

A, Mean beta weights (averaged over 10 outer folds) of the features that were present in at

least 9 folds (out of 10) of the final model for classification of the mood and psychotic symptoms

group versus the no mood symptoms group in the London-Dublin subsample. **B,** Mean beta

weights (averaged over 10 outer folds) of the features that were present in at least 9 folds (out

of 10) of the final model for classification of the mood and psychotic symptoms group versus the

no mood symptoms group in the full IMAGEN sample. **C,** Mean beta weights (averaged over 10

outer folds) of the features that were present in at least 9 folds (out of 10) of the final model for

classification of the mood and psychotic symptoms group versus the mood symptoms only

group in the full IMAGEN sample. **D,** Mean beta weights (averaged over 10 outer folds) of the

features that were present in at least 9 folds (out of 10) of the final model for classification of

the mood symptoms only group versus the no mood symptoms group in the full IMAGEN

sample.