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Polygenic Risk of Psychosis and Ventral Striatal Activation During Reward Processing in Healthy Adolescents

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IMPORTANCE Psychotic disorders are characterized by attenuated activity in the brain's valuation system in key reward processing areas, such as the ventral striatum (VS), as measured with functional magnetic resonance imaging.

OBJECTIVE To examine whether common risk variants for psychosis are associated with individual variation in the VS.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional study of a large cohort of adolescents from the IMAGEN study (a European multicenter study of reinforcement sensitivity in adolescents) was performed from March 1, 2008, through December 31, 2011. Data analysis was conducted from October 1, 2015, to January 9, 2016. Polygenic risk profile scores (RPSs) for psychosis were generated for 1841 healthy adolescents. Sample size and characteristics varied across regression analyses, depending on mutual information available (N = 1524-1836).

MAIN OUTCOMES AND MEASURES Reward-related brain function was assessed with blood oxygen level dependency (BOLD) in the VS using the monetary incentive delay (MID) task, distinguishing reward anticipation and receipt. Behavioral impulsivity, IQ, MID task performance, and VS BOLD were regressed against psychosis RPS at 4 progressive *P* thresholds ($P < .01$, $P < .05$, $P < .10$, and $P < .50$ for RPS models 1-4, respectively).

RESULTS In a sample of 1841 healthy adolescents (mean age, 14.5 years; 906 boys and 935 girls), we replicated an association between increasing psychosis RPS and reduced IQ (matrix reasoning: corrected $P = .003$ for RPS model 2, 0.4% variance explained), supporting the validity of the psychosis RPS models. We also found a nominally significant association between increased psychosis RPS and reduced MID task performance (uncorrected $P = .03$ for RPS model 4, 0.2% variance explained). Our main finding was a positive association between psychosis RPS and VS BOLD during reward anticipation at all 4 psychosis RPS models and for 2 *P* thresholds for reward receipt (RPS models 1 and 3), correcting for the familywise error rate (0.8%-1.9% variance explained).

CONCLUSIONS AND RELEVANCE These findings support an association between psychosis RPS and VS BOLD in adolescents. Genetic risk for psychosis may shape an individual's response to rewarding stimuli.

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Psychotic disorders share considerable genetic variance[1,2] and have considerable overlap in the clinical phenotype.[3] There is thus increasing interest in biological and psychological mechanisms that may operate across these disorders. Attempts to unify mechanisms in psychosis use methods such as magnetic resonance imaging (MRI) to explore the neural circuits that are disrupted in psychosis.[4-6] Psychosis is characterized by changes in reward valuation systems and underlying frontostriatal circuitry.[7-11] A recent meta-analysis[12] suggests that psychosis is associated with alterations in ventral striatal (VS) blood oxygen level dependency (BOLD), suggesting that VS BOLD during reward processing may be a candidate mechanism by which psychosis susceptibility manifests. This hypothesis is also supported by associations between VS BOLD and negative symptoms (see the meta-analysis by Radua et al[12]). Studies have further found that reward processing is heritable[13] and altered in relatives of patients with psychosis,[14] suggesting that genetic risk may contribute to VS BOLD.

Individual genetic risk loci confer small amounts of susceptibility[1]; however, risk profile scores (RPSs) explain larger proportions of variance for psychosis and can be used to predict variance in related phenotypes.[1] We recently found that a schizophrenia RPS was associated with an attenuated VS BOLD response during a probabilistic learning task,[15] suggesting that the cumulative effect of risk single-nucleotide polymorphisms was associated with the VS BOLD alterations previously observed in patients with psychosis[16-18] and unaffected relatives.[19] However, it is currently not known whether polygenic risk of psychotic disorders is associated with reward processes, such as anticipation and receipt, as assayed using the monetary incentive delay (MID) task.[20] The MID task assays BOLD during incentive processing and is relatively independent of reward-based learning (participants learn the stimulus-reward associations before scanning)[21] compared with probabilistic learning paradigms, which assay an individual's ability to dynamically update assumptions based on choice behavior and outcomes.[15,22] The putative absence of a learning component within the MID paradigm will address whether the psychosis RPS is associated with affective salience toward reward. To answer this question, we used the IMAGEN[23] cohort (http://www.imagen-europe.com/) to probe VS BOLD for associations with the psychosis RPS. We initially assayed the psychosis RPS rather than schizophrenia and bipolar summary data sets because (1) in a sample of healthy adolescents, we replicated an association between increasing psychosis RPS and reduced IQ[12]; (2) we hypothesize that VS BOLD will be linked to the genetic risk that is shared between schizophrenia and bipolar disorder; (3) we aimed to reduce the number of RPS comparisons; and (4) recent success has linked psychosis RPS to other imaging phenotypes.[24]

On the basis of a previous meta-analysis,[12] we anticipated that the psychosis RPS would be associated with reductions in VS BOLD during reward anticipation in the MID task and to a lesser extent during reward receipt, mirroring the findings in people with manifest psychosis.[12] We also used a psychosis RPS approach to probe for putative association with (1) intelligence using the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV),[25] (2) behavioral impulsivity using a delay discounting paradigm,[26] and (3) MID task performance. We assay intelligence to ensure that the putative psychosis RPS effects on reward are independent of intelligence. The delay discounting paradigm quantifies an individual's ability to delay gratification, a phenotype that is heritable[27] and altered in psychosis.[28,29] Using a psychosis RPS approach, we sought to determine whether psychosis RPS was associated with these phenotypes. Together, we anticipate that these regressions will help elucidate how common risk for psychosis may affect reward systems in the adolescent brain.

Key Points

Question Do common genetic risk alleles for psychosis contribute to reward processing in adolescents?

Findings In a study of the IMAGEN cohort of 1528 adolescents, common genetic risk alleles for psychosis explain approximately 1% to 2% of the variance in reward processing in the ventral striatum (as measured using functional magnetic resonance imaging).

Meaning Common genetic risk for psychosis may shape an individual's response to rewarding stimuli.

Methods

Participants

We analyzed data from the IMAGEN project, a well-characterized, European, multicenter, genetic-neuroimaging study in adolescence[23] (**Table 1**). Participants were recruited from March 1, 2008, through December 31, 2011, through secondary schools at 8 sites located in England, France, Ireland, and Germany. Data analysis was conducted from October 1, 2015, to January 9, 2016. The IMAGEN project had obtained ethical approval by the local ethics committees and written informed consent from all participants and their legal guardians. Standard operating procedures for IMAGEN are available at http://www.imagen-europe.com/en/Publications_and_SOP.php. All individuals were screened for magnetic resonance contraindications and medical conditions. All participants were assessed for psychopathologic conditions as part of a scale tailored to adolescents and based on *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*), as well as *DSM-IV* (Development and Well-Being Assessment Interview). Participants were excluded based on the presence of schizophrenia or bipolar disorder, neurodevelopmental disorders (such as autism), or an IQ of less than 70 (for further exclusion criteria, see the Supplement in the article by Schumann et al[23]).

Genetic Data

To ensure high quality and sufficient quantity, we semiautomated DNA extraction.[8] The Illumina Quad 610 chip (Illumina Inc) was used for genome-wide genotyping of approximately 600 000 autosomal single-nucleotide polymorphisms.

As part of the IMAGEN project, DNA was extracted from blood samples. Genotyping methods and quality control de-

Table 1. Sample Size for Each Psychosis Risk Profile Score Regression Analysis

Variable	Sample Size, No.	Age, Mean (SD), y	Male/Female, No.	Mean (SD) Finding
IQ (WISC-IV)				
Block design	1835	14.52 (0.90)	903/932	50.51 (9.51)
Vocabulary	1833	14.52 (0.90)	902/931	49.87 (8.46)
Matrix reasoning	1835	14.52 (0.90)	903/932	26.41 (4.03)
Similarities	1836	14.52 (0.90)	903/933	30.39 (5.59)
Reward (behavior)				
Delay discounting (log *k*)	1822	14.52 (0.90)	927/895	−1.88 (0.61)
MID (No. of successful trials, maximum of 22 per reward level)	1732	14.51 (0.92)	856/876	13.76 (1.95)
MID (No. of early responses)	1737	14.51 (0.91)	857/880	0.11 (0.1)
Reward (fMRI)				
Anticipation	1528	14.56 (0.45)	740/788	NA
Receipt	1559	14.56 (0.45)	769/790	NA

Abbreviations: fMRI, functional magnetic resonance imaging; MID, monetary incentive delay; NA, not applicable; WISC-IV, Wechsler Intelligence Scale for Children–Fourth Edition.

tails can be found in the eMethods in the Supplement. After quality control, 502 160 single-nucleotide polymorphisms were considered for the psychosis RPS score calculation in 1841 individuals (for whom demographic data were also available).

Generation of RPSs

Psychosis RPSs were calculated using the method described by the International Schizophrenia Consortium.[30] Psychosis genetic risk was estimated using publicly available results data from an international genome-wide association study of 19 779 patients with psychosis and 19 423 controls.[1] For a description of the methods used to calculate the psychosis RPSs and the characteristics of the psychosis RPSs in the sample, see the eMethods and eFigure 1 in the Supplement. In a post hoc analysis, we estimated RPSs for schizophrenia and bipolar disorder separately using available summary statistics for schizophrenia and bipolar generated by the Cross-Disorder Group of the Psychiatric Genomics Consortium.[31]

Intelligence, Behavioral Impulsivity, and Psychopathology

We measured IQs using the WISC-IV.[25] We tested psychosis RPSs against 4 parameters (similarities, vocabulary, block design, matrix reasoning) and used them as covariates to control for potential confounding IQ effects in the psychosis RPS regressions on reward function (delay discounting, behavioral MID, reward anticipation, and receipt). Delay discounting was measured with the questionnaire designed by Kirby and Maraković,[26,32] using a series of 27 choices between a hypothetic smaller, sooner and a larger, later reward. We computed a subjective discount parameter (*k*) as previously described.[29] The *k* values were log transformed before the analyses to account for a skewed distribution. Because VS BOLD has been associated with other phenotypes, such as depressive symptoms[33] and smoking behavior,[34] we additionally screened for depressive symptoms (which were rated using the Development and Well-Being Assessment Interview with a computerized diagnostic algorithm that predicts the likelihood of a clinical diagnostic rating[35]) and smoking behavior (measured using the Fagerström Test for Nicotine Dependence[36]).

Monetary Incentive Delay MRI Task

Participants performed a modified version of the MID task[20,37] during scanning. Details of the paradigm are detailed in the eMethods in the Supplement.

MRI Data Acquisition and Preprocessing

Images were processed as previously described by IMAGEN consortium[23] (eMethods in the Supplement). Because of our a priori hypotheses of associations between psychosis RPS and VS BOLD, which is consistently recruitment during the MID task,[34,38] we tested our hypothesis solely in this region of interest. The VS masks were composed of 9-mm spheres centered at the x, y, and z values of −14, 8, and −8 and 14, 8, and −8, respectively (Montreal Neurological Institute coordinates), for the left and right VS as previously described.[21,38]

Power Analysis

Using the methods outlined by Dudbridge,[39] we had 80% power to detect an effect ranging from 0.044% to 0.052% explained variance (eMethods in the Supplement).

Statistical Analysis

We ran multiple regression for the 4 WISC-IV variables, delay discounting in R version 3.0.2 (https://cran.r-project.org/), where the log-transformed hyperbolic discounts (log *k*) function as the dependent variables and psychosis RPS as the independent variable at 4 progressive *P* thresholds ($P < .05$ for RPS model 1, $P < .05$ for RPS model 2, $P < .10$ for RPS model 3, and $P < .50$ for RPS model 4). These progressive *P* thresholds explain the most variance in the clinical phenotype.[1] We correct for the number of multiple comparisons across *P* thresholds using the false discovery rate. Each regression was controlled for age, sex, testing site, IQ (measured by the 4 WISC-IV variables), and the first 5 principle components (from the variance-standardized relationship matrix of the linkage disequilibrium–pruned genotypes) to account for ancestry admixture (population stratification) and potential relatedness.[40] We repeated these regressions (using the same covariates as the delay discounting regression) for the MID task performance (as measured by number of successful attempts

Table 2. Associations Between Psychosis RPS and WISC-IV Variables[a]

WISC-IV Variable and Psychosis RPS Model	R^2	β	*P* Value
Block design (n = 1835)			
RPS model 1	0.0017	−0.05	.04
RPS model 2	0.0020	−0.06	.03
RPS model 3	0.0029	−0.05	**.01**
RPS model 4	0.0019	−0.05	.03
Vocabulary (n = 1833)			
RPS model 1	−0.0005	−0.008	.75
RPS model 2	−0.0005	0.007	.90
RPS model 3	−0.0005	−0.003	.77
RPS model 4	−0.0001	0.02	.38
Matrix reasoning (n = 1835)			
RPS model 1	0.0035	−0.06	**.006**
RPS model 2	0.0042	−0.06	**.003**
RPS model 3	0.0034	−0.07	**.007**
RPS model 4	0.0024	−0.05	.02
Similarities (n = 1836)			
RPS model 1	0.0003	−0.03	.21
RPS model 2	−0.0005	0.009	.88
RPS model 3	−0.0005	0.004	.70
RPS model 4	0.0000	0.02	.30
Log K (n = 1822)			
RPS model 1	−0.0003	0.02	.46
RPS model 2	−0.0002	0.02	.40
RPS model 3	−0.0005	0.001	.96
RPS model 4	−0.0005	0.004	.86

Abbreviations: RPS, risk profile score; WISC-IV, Wechsler Intelligence Scale for Children–Fourth Edition.

[a] Associations were adjusted for age, sex, testing site, and the first 5 principal components. The log *κ* values were adjusted for the same covariates and the 4 WISC-IV variables. Associations that survive correction for multiple comparisons (false discovery rate) are in bold.

Table 3. Associations Between Psychosis RPS and Behavioral Performance in the MID Task

MID Task and Psychosis RPS Model	R^2	β	*P* Value
Success (n = 1732)			
RPS model 1	−0.00015	−0.02	.39
RPS model 2	0.00002	−0.02	.31
RPS model 3	0.00089	−0.04	.11
RPS model 4	0.00204	−0.05	.03
Early responses (n = 1737)			
RPS model 1	−0.00057	−0.003	.89
RPS model 2	0.00036	0.03	.20
RPS model 3	0.00182	0.05	.04
RPS model 4	0.00270	0.06	.02

Abbreviations: MID, monetary incentive delay; RPS, risk profile score.

to obtain reward and proportion of early responses) and in the neuroimaging data, using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), where the dependent variables were VS BOLD during reward anticipation and receipt. We controlled for multiple testing across the VS search space using familywise error correction ($P < .05$).

Results

Psychosis RPS and IQ

We found nominally significant negative associations between the psychosis RPS and WISC-IV variables (uncorrected block design and corrected matrix reasoning) across all *P* thresholds. No associations were found between psychosis RPS and delay discounting when controlling for age, sex, testing site, WISC-IV variables, and the first 5 principle components (**Table 2**).

Psychosis RPS and MID Task Performance

We found a nominally significant association between the psychosis RPS and behavioral performance in the MID task. The psychosis RPS was negatively associated with the number of successful attempts and an increased proportion of early responses, explaining 0.18% to 0.27% of the variance, after adjusting for covariates (**Table 3**).

Table 4. Significant Voxel Clusters From the Psychosis RPS Regression During Reward Anticipation and Receipt, Controlling for Covariates, Across 4 Progressive *P* Thresholds

P Threshold	κ	MNI Coordinates (x, y, z)	*z*	Familywise Error *P*	R^2	β
Reward anticipation						
RPS model 1	7	−12,2, − 8	3.91	.01	0.008	0.10
RPS model 2	11	−12,2, − 8	4.70	.001	0.019	0.14
RPS model 3	11	−18,1, − 8	4.48	.001	0.017	0.14
RPS model 4	6	−18,2, − 5	3.95	.009	0.013	0.12
Reward receipt						
RPS model 1	NA	NA	NA	NA	NA	NA
RPS model 2	1	−9,5, − 8	3.33	.05	0.010	0.10
RPS model 3	NA	NA	NA	NA	NA	NA
RPS model 4	3	−18, − 1, − 8	3.61	.02	0.009	0.10

Abbreviations: κ, number of contiguous voxels; MNI, Montreal Neurological Institute; NA, not applicable; RPS, risk profile score.

Group Effects of Reward Anticipation and Receipt

Whole group (1-sample *t* test) effects are documented in eFigure 2 and the eResults in the Supplement.

Psychosis RPS and Reward Anticipation

We found a positive association between psychosis RPS and VS BOLD at all 4 thresholds (**Table 4** and **Figure**, A). No negative associations were found between the psychosis RPS and VS BOLD after controlling for the familywise error across the VS region of interest. To explore the effects of extreme polygeneticity (comparing individuals with the highest psychosis RPS and individuals with the lowest psychosis RPS), we split the whole sample into 10 deciles (as previous described[41]) and explored the difference between decile 1 (lowest polygenic risk) and decile 10 (highest polygenic risk) for parameter estimates extracted from the significant clusters (Cohen *d* = 0.43; 95% CI, 0.203-0.658, for RPS model 1; Cohen *d* = 0.476; 95% CI, 0.248-0.703, for RPS model 2; Cohen *d* = 0.492; 95% CI, 0.264-0.72, for RPS model 3; and Cohen *d* = 0.438; 95% CI, 0.21-0.665, for RPS model 4). All effects were significant after controlling for comparisons among the 10 deciles (corrected *P* < .001 in all cases).

Psychosis RPS and Reward Receipt

We found a positive association between the psychosis RPS and VS BOLD for RPS models 1 and 3 (Table 4 and Figure, B). No negative associations were found between the psychosis RPS and VS BOLD after controlling for the familywise error across the VS region of interest. We split the whole sample into 10 deciles and looked at the differences between decile 1 (lowest polygenic risk) and decile 10 (highest polygenic risk) for parameter estimates extracted from the significant clusters (Cohen *d* = 0.395; 95% CI, 0.171-0.62, for RPS model 1; Cohen *d* = 0.227; 95% CI, 0.004-0.45, for RPS model 3); however. only the effect identified at the RPS model 1 threshold remained significant after correcting for multiple comparisons (corrected *P* = .007).

Depressive Symptoms and Smoking Behavior

A positive association was found between psychosis RPS and number of depressive symptoms ($t_{9,1817}$ = 2.965, *P* = .003, for RPS model 4). However, no associations were found between depressive symptoms and the 6 VS BOLD parameter estimates (*P* > .40 in all cases), and the association between the psychosis RPS and VS BOLD did not significantly change after controlling for depressive symptoms. No association was found with smoking behavior and (1) the psychosis RPS (*P* > .30 in all cases) and (2) the 6 VS BOLD parameter estimates (*P* > .10 in all cases).

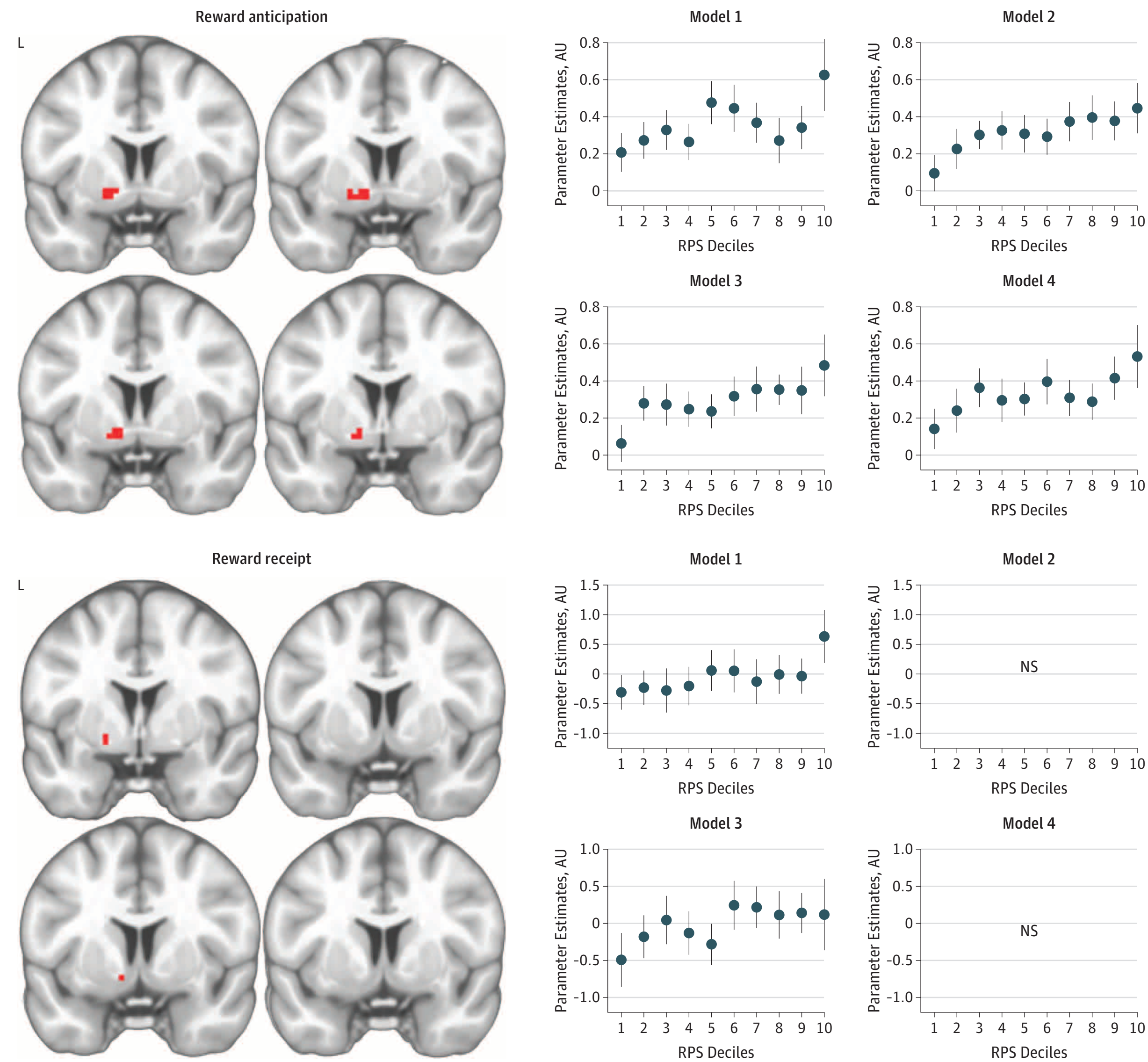
Contribution of Schizophrenia and Bipolar to Psychosis RPS Effects

The association between the psychosis RPS and WISC-IV variables (block design and matrix reasoning) was driven exclusively by the schizophrenia RPS. We did not observe a specific effect of the schizophrenia or bipolar RPS on MID task performance (success and reaction time). However, VS BOLD was influenced by schizophrenia and bipolar RPS (eResults and eTable in the Supplement).

Discussion

We observed and replicated associations between the psychosis RPS and reduced performance IQ,[42-44] supporting the validity of the psychosis RPS approach. Post hoc analysis revealed that this association was driven by the schizophrenia RPS. Additional support for the psychosis RPS model came from evidence supporting an association between the psychosis RPS and task performance during the MID task, although this association did not withstand correction for multiple comparisons, and we could not find a specific contribution from the schizophrenia or bipolar RPS. We also did not observe an association between the psychosis RPS and behavioral impulsivity, as measured using a delay discounting paradigm. Consistent with our main hypothesis, we observed an association between the psychosis RPS and VS BOLD. Consistent with our original hypothesis, the association between the psychosis RPS and VS BOLD was driven by the RPS for schizophrenia and bipolar disorder. These findings support previous associations between common psychosis risk loci (*ODZ4*, *CACNA1C*) and reward processing.[45,46] Furthermore, we build on previous

Figure. Coronal Sections at Montreal Neurological Institute Coordinate y = 5



Positive associations between the psychosis risk profile score (RPS) and blood oxygen level dependency (BOLD) in the ventral striatum (VS) during reward anticipation and reward receipt at 4 progressive *P* thresholds (*P* < .01 for RPS model 1, *P* < .05 for RPS model 2, *P* < .10 for RPS model 3, and *P* < .50 for RPS model 4), controlling for age, sex, testing site, Wechsler Intelligence Scale for Children–Fourth Edition variables, and the first 5 principal components (n = 1528 and 1559, respectively). All clusters are corrected for the familywise error across the bilateral VS (*P* < .05). Plots on the right show the mean psychosis RPSs across 10 deciles plotted against BOLD parameter estimates in the significant clusters identified in the multiple regression. Note that the 10 deciles reflect the data extracted from the clusters within the VS, which remained significant and are purely for illustration purposes. Error bars indicate 95% CI. AU indicates arbitrary units; L, left hemisphere; NS, nonsignificant.

work[15] that suggested that the schizophrenia RPS is associated with altered reward processing in healthy individuals. A previous study[12] suggests that psychosis is characterized by VS hypoactivation, which might relate to negative symptoms that underpin psychosis. However, other studies have suggested that type 2 bipolar disorder and adolescent bipolar disorder are associated with frontostriatal BOLD signal during reward anticipation[47-49] and that relatives of patients with schizophrenia have increased VS BOLD during reward receipt.[19] In line with the meta-analysis,[12] the most prominent association between psychosis RPS and VS BOLD occurred during the reward anticipation phase, suggesting that risk for psychosis may alter disrupt incentive motivation and reward salience. The receipt phase could also be less sensitive to VS activation (because of variable success rates), which could explain the weaker association with the psychosis RPS. One key difference between our study and the studies included in the meta-analysis[12] of patients with psychosis is that our sample had a mean age of 14.5, whereas the mean age of the patients in the meta-analysis was approximately 30 years. This hypothesis is supported by recent evidence supporting an age × VS BOLD interaction in adolescents with genetic risk for schizophrenia, where younger adolescent offspring have increased VS BOLD during the MID task, but older adolescents offspring have attenuated VS BOLD.[50] Genetic risk of psychosis may have different effects on brain physiologic mechanisms across the lifespan and leads to enhanced incentive salience in adolescence, which is attenuated during later stages of neurodevelopment. This finding is supported by a recent meta-analysis[51] that found that, compared with adults, adolescents (mean age, 14.1 years) have increased VS BOLD during reward processing, which is attributed to increased motivated activity during adolescence. The different direction of altered VS BOLD may also be explained by state effects (such as medication and disease chronicity).

Although our data suggest an association between the psychosis RPS and WISC-IV variables, the variance explained was small (approximately 0.2%-0.4%) but comparable to other studies[42-44] between the psychosis RPS and IQ or cognition. Our data further suggest that approximately 0.8% to 1.9% of the variance in VS BOLD may be explained by the psychosis RPS, which is comparable to another intermediate phenotype RPS study.[52] Although the VS BOLD variance explained by the psychosis RPS across the whole sample was small, comparing VS BOLD parameters estimates between the 1st and 10th deciles of the psychosis RPS suggested a moderate effect size (Cohen d = 0.22-0.49). Future studies should take advantage of large genotyped population cohorts to compare intermediate phenotypes for individuals at either end of the RPS distribution.

One limitation of the study is that we did not have negative psychosis symptom measures for the behavioral or imaging genetic sample. Such measures would have proved useful in exploring whether VS BOLD mediates the association between the psychosis RPS and negative symptoms. Currently, it remains unknown whether the putative links among psychopathologic conditions, negative symptoms, and VS BOLD are mediated by common genetic risk factors. Although we found associations between the psychosis RPS and depressive symptoms, these associations were independent of the RPS effects on VS BOLD, suggesting pleiotropic effects of genetic psychosis susceptibility. Future work should explore the role of VS BOLD during reward anticipation as a candidate mechanism by which the psychosis RPS may mediate effects on negative symptoms. Another limitation is that the association between the psychosis RPS and VS BOLD was in the opposite direction of that expected, although this finding is in line with a previous study[50] of VS BOLD and genetic risk for schizophrenia across adolescent development. A previous meta-analysis[12] suggests that psychosis is associated with attenuated BOLD in the VS, which is also linked to negative symptoms. Because we observed increased VS BOLD, the link between psychosis and psychosis symptom expression is less clear. We did not observe any association between the psychosis RPS and impulsivity.[32] This observation provides no evidence of a role in common risk for psychosis in the discounting of larger, future rewards, suggesting that myopic discounting may be a state feature of psychosis. However, these findings may help to identify the precise reward mechanisms that are altered because of increased psychosis risk. We also acknowledge that substance abuse and dependence may be confounders in the study of VS BOLD.

Conclusions

We observed negative associations between performance IQ and the psychosis RPS but not behavioral impulsivity. Consistent with our experimental hypothesis, we found associations between the psychosis RPS and VS BOLD, primarily during reward anticipation. We suggest that psychosis RPS may play a role in shaping the reward response in the adolescent brain, particularly during periods of reward sensitivity and increased incentive motivation. Future follow-up studies will be needed to assess how common genetic risk relates to (1) VS BOLD in the adult brain, (2) whether psychosis RPS affects the effect of VS BOLD on negative symptoms in adulthood, and (3) whether environmental exposure (ie, cannabis use,[53,54] early life stressors[55]) attenuate these effects. Large neuroimaging studies across multiple sites are well powered to determine such effects and determine case-control differences in subcortical volumes[56-58] and facilitate novel gene discovery.[59] These studies will aid in understanding the genetic and environmental neurobiological mechanisms of negative symptoms, which are currently refractory to antipsychotic medication.[60] Future analysis of specific genetic risk pathways will help to elucidate the neurobiological mechanisms that contribute to alterations of reward processing across the psychosis spectrum and across the lifespan.

ARTICLE INFORMATION

Correction: This article was corrected on August 22, 2016, to clarify an author's full surname in the byline.

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