Original Investigation

Functional Neuroimaging Abnormalities in Youth With Psychosis Spectrum Symptoms

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IMPORTANCE The continuum view of the psychosis spectrum (PS) implies that, in population-based samples, PS symptoms should be associated with neural abnormalities similar to those found in help-seeking clinical risk individuals and in schizophrenia. To our knowledge, functional neuroimaging has not previously been applied in large population-based PS samples and can help us understand the neural architecture of psychosis more broadly and identify brain phenotypes beyond symptoms that are associated with the extended psychosis phenotype.

OBJECTIVE To examine the categorical and dimensional relationships of PS symptoms to prefrontal hypoactivation during working memory and to amygdala hyperactivation during threat emotion processing.

DESIGN, SETTING, AND PARTICIPANTS The Philadelphia Neurodevelopmental Cohort is a genotyped, prospectively accrued, population-based sample of almost 10 000 youths who received a structured psychiatric evaluation and a computerized neurocognitive battery. The study was conducted at an academic and children's hospital health care network, between November 1, 2009, to November 30, 2011. A subsample of 1445 youths underwent neuroimaging, including functional magnetic resonance imaging tasks examined herein. Participants were youth aged 11 to 22 years old identified through structured interview as having PS features (PS group) (n = 260) and typically developing (TD) comparison youth without significant psychopathology (TD group) (n = 220).

MAIN OUTCOMES AND MEASURES Two functional magnetic resonance imaging paradigms were used: a fractal *n*-back working memory task probing executive system function and an emotion identification task probing amygdala responses to threatening faces.

RESULTS In the *n*-back task, working memory evoked lower activation in the PS group than the TD group throughout the executive control circuitry, including dorsolateral prefrontal cortex (cluster-corrected $P < .05$). Within the PS group, dorsolateral prefrontal cortex activation correlated with cognitive deficits ($r = .32$, $P < .001$), but no correlation was found with positive symptom severity. During emotion identification, PS demonstrated elevated responses to threatening facial expressions in amygdala, as well as left fusiform cortex and right middle frontal gyrus (cluster-corrected $P < .05$). The response in the amygdala correlated with positive symptom severity ($r = .16$, $P = .01$) but not with cognitive deficits.

CONCLUSIONS AND RELEVANCE The pattern of functional abnormalities observed in the PS group is similar to that previously found in schizophrenia and help-seeking risk samples. Specific circuit dysfunction during cognitive and emotion-processing tasks is present early in the development of psychopathology and herein could not be attributed to chronic illness or medication confounds. Hypoactivation in executive circuitry and limbic hyperactivation to threat could reflect partly independent risk factors for PS symptoms, with the former relating to cognitive deficits that increase the risk for developing psychotic symptoms and the latter contributing directly to positive psychotic symptoms.

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Major efforts are under way to identify neural circuit abnormalities linked to the emergence of psychosis, typically manifesting during adolescence.[1-3] Functional brain abnormalities previously identified in schizophrenia provide candidates for imaging markers associated with psychosis across the spectrum of age and clinical severity. These candidates include activation abnormalities in prefrontal cortex (PFC) during working memory[4] and in amygdala during processing of threatening facial expressions.[5-12]

Functional imaging studies examining psychosis risk have included small samples of individuals at genetic risk because of family history or help-seeking individuals at clinical risk based on attenuated psychosis spectrum (PS) symptoms. These studies have identified various abnormalities, but there are few confirmed findings.

Furthermore, prior functional magnetic resonance imaging (fMRI) studies of psychosis risk have typically examined only categorical effects, lacking adequate power to identify correlates of illness dimensions. Therefore, it remains unclear to what extent the reported abnormalities relate to positive psychotic symptoms that are used to select the samples vs negative symptoms or cognitive deficits that are likely also present.

Population-based studies have identified PS symptoms in non–help-seeking youth.[13] While rates of transition to clinically diagnosed psychosis are likely to be reduced in such samples, early subclinical psychotic symptoms are of clinical relevance even in individuals who do not transition to frank psychosis.[14,15] As noted by Kelleher and Cannon,[16] the nonclinical PS represents a valid and valuable population for investigating the early neurodevelopmental etiology of psychosis. However, application of functional neuroimaging in this context has been limited, especially at younger ages,[17-23] and it remains unknown whether PS symptoms in this population have similar neural underpinnings as those in clinical risk samples and schizophrenia as predicted by the continuum view of the extended psychosis phenotype.[16,24,25] Such population-based imaging studies are needed to understand the neural architecture of psychosis more broadly and could provide imaging markers that enhance the specificity and predictive value of early psychotic-like symptoms that may otherwise be nonspecific.

We examined executive and emotion-processing neural circuit function in a community sample of youth with PS symptoms compared with typically developing (TD) youth in the Philadelphia Neurodevelopmental Cohort (PNC). Youth with PS symptoms in this cohort exhibit significant distress as well as neurocognitive and functional impairment,[26,27] consistent with findings in other community samples[15,28] and supporting the validity of our PS identification. The large sample enables the identification of imaging features that differentiate youth with PS symptoms from TD youth as well as the examination of heterogeneity among youth with PS symptoms relating to dimensional measures of psychosis symptom severity and cognitive deficits.

We hypothesized that youth with psychosis risk would show both hypofunction of executive networks during a working memory task and hyperreactivity of amygdala in re-

sponse to threatening faces in an emotion identification task. We further hypothesized that youth with PS symptoms would perform more poorly than TD youth and that, within the PS group, executive hypofunction would correlate with cognitive deficits, while amygdala hyperreactivity would correlate with psychosis severity.

Methods

Participants

We report task-based fMRI results from youth 11 to 22 years old identified as having PS features (PS group) (n = 260) and TD comparison youth with no significant psychopathology (TD group) (n = 220) (**Table 1** and **Table 2**). The study dates were November 1, 2009, to November 30, 2011. Participants were part of the PNC, a previously genotyped, prospectively accrued community sample of almost 10 000 youths,[29] of which a subsample of 1445 underwent neuroimaging.[30] Details of the clinical and cognitive assessment have been previously reported[26,27] and are summarized in the eMethods in the Supplement. Youth with PS symptoms were identified as endorsing subthreshold symptoms (positive or negative and disorganized) on any of the following measures: (1) age-deviant PRIME Screen–Revised (PS-R) total score of at least 2 SDs above age-matched peers, at least 1 PS-R item rated as definitely agree, or at least 3 PS-R items rated as somewhat agree; (2) definite or possible hallucinations or delusions on the Kiddie Schedule for Affective Disorders and Schizophrenia psychosis screen; or (3) age-deviant total negative and disorganized Scale of Prodromal Symptoms score of at least 2 SDs above age-matched peers. The TD group lacked any significant psychopathology and any history of psychoactive medication use or inpatient psychiatric treatment. Additional exclusion criteria are summarized in the eMethods and eFigure 1 in the Supplement. All study procedures were approved by the institutional review boards of the University of Pennsylvania and The Children's Hospital of Philadelphia. All participants (and the parent or guardian for minors) provided written informed consent, and minors provided assent.

Functional Imaging

Two fMRI paradigms were used: a fractal *n*-back working memory task probing executive system function and an emotion identification task probing amygdala responses to threatening faces (**Figure 1**). The *n*-back task[31,32] used fractals and a robust block design to measure activation of the executive system across 3 levels of working memory load. To examine amygdala responses to threat, we applied a validated emotion identification paradigm,[33,34] grouping expressions into threatening (anger and fear) and nonthreatening (happy and sad) emotions for event-related analysis, as in prior work.[12,34-36] This grouping is based on prior theoretical and empirical work.[34] However, interpretations of this grouping not directly related to threat are possible (eg, negative and positive emotions), and subjective responses to particular emotional categories may vary according to individual participant characteristics, including psychiatric symptoms.

Table 1. Sex, Race, and Handedness

Variable	TD Group (n = 220)		PS Group (n = 260)		P Value[a]
	Percentage	Proportion	Percentage	Proportion	
Female sex	52.7	116F/104M	52.7	137F/123M	.99[b]
White race	61.4	135W/85 nonwhite	33.5	87W/173 nonwhite	<.001
Right handed	83.6	184 R/36 L	85.0	221 R/39 L	.71

Abbreviations: F, female; L, left; M, male; PS, psychosis spectrum; R, right; TD, typically developing; W, white.

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

[b] Two-tailed Fisher exact test was used to compare proportions for categorical variables.

Table 2. Age, Education, Parental Education, and Symptoms

Variable	Mean (SD) [Range]		P Value[a]
	TD Group (n = 220)	PS Group (n = 260)	
Age at imaging, y	16.6 (3.0) [11.2 to 22.6]	15.7 (2.7) [11.3 to 21.8]	.003[b]
Educational level, y	9.5 (2.9) [4 to 16]	8.3 (2.6) [3 to 14]	<.001
Parental educational level, y	14.6 (2.4) [7 to 20]	13.5 (2.1) [8 to 20]	<.001
Positive symptoms[c]	−0.56 (0.31) [−0.86 to 0.97]	1.16 (1.23) [−0.86 to 5.07]	<.001
Negative and disorganized symptoms[d]	−0.54 (0.36) [−0.82 to 0.95]	0.65 (1.41) [−0.82 to 6.49]	<.001
Global cognition[e]	0.21 (0.48) [−2.13 to 1.09]	−0.17 (0.60) [−2.78 to 1.08]	<.001

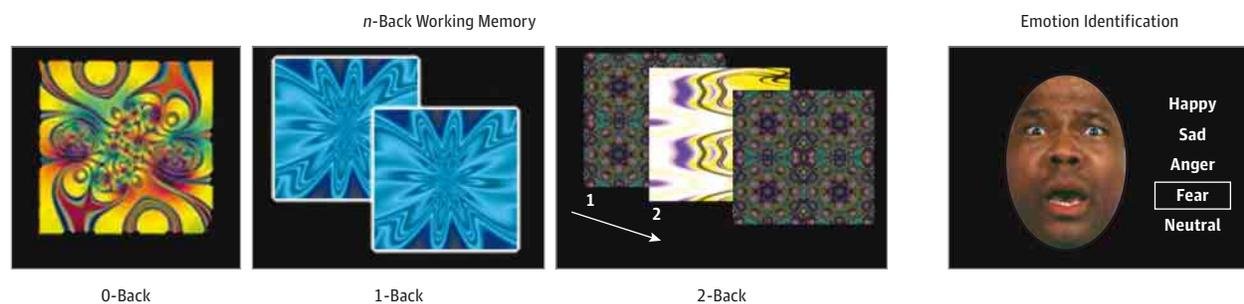[a] All P values in the table are 2-tailed, uncorrected.

[b] t Test was used for comparing group means.

[c] Age-normed total score from the PRIME Screen–Revised.

[d] Age-normed sum of negative and disorganized items from the Scale of Prodromal Symptoms.

[e] Age-normed accuracy score across Penn Computerized Neurocognitive Battery domains.

Figure 1. Functional Magnetic Resonance Imaging Paradigms

n-Back Working Memory

Emotion Identification

0-Back   1-Back   2-Back

Happy
Sad
Anger
Fear
Neutral

Two tasks were used, counterbalancing the order across participants. The fractal *n*-back task is shown on the left. Working memory was tested with complex geometric figures (fractals), with 3 levels of memory load. For the 0-back condition, participants responded with a button press to a specified target fractal. For the 1-back condition, participants responded if the current fractal was identical to the previous one. For the 2-back condition, participants responded if the current fractal was identical to the item presented 2 trials previously. Each condition consisted of a 20-trial block (60 seconds); each level was repeated over 3 blocks. The ratio of targets to foils was 1:3 in all blocks, with 45 targets and 135 foils overall. Each fractal was presented for 500 milliseconds, followed by an interstimulus interval of 2500 milliseconds. The emotion identification task is shown on the right. Faces expressing 1 of 5 emotional categories (happy, sad, anger, fear, or neutral) were displayed in a pseudorandomized event-related design; there were 12 faces in each category. Participants decided which emotion was expressed on each face. Emotional expressions were grouped into threatening (anger and fear) and nonthreatening (happy and sad) emotions for analysis. Faces were displayed for 5.5 seconds, followed by a variable interval (0.5-18.5 seconds) displaying a complex fixation crosshair matched to faces on perceptual qualities.

All imaging data were acquired on the same 3-T system (Tim Trio; Siemens) with a 32-channel headcoil using the same imaging sequences. Imaging acquisition sequences, procedures, and preprocessing methods have been previously reported[30] and are described in the eMethods in the Supplement.

Behavioral Data Analysis

For the *n*-back task, our primary behavioral measure was *d'*, which summarizes overall task performance accounting for the number of correct responses and the number of false positives.[32,37] In addition, the median response time across correct responses was calculated. For emotion identification, task performance was summarized by percentage accuracy and the median correct response time. Behavioral measures were analyzed for group differences using *t* test. *P* < .05 was the significance criterion and was 1-tailed to test the hypothesis that the PS group performed more poorly than the TD group, as was expected based on prior study of the full PNC sample.[26]

Participant-Level fMRI Analysis

Participant-level statistical analyses were performed with a canonical hemodynamic response function in FEAT (FMRI Expert Analysis Tool), part of the FMRIB Software Library (FSL).[38] For the *n*-back task, 3 condition blocks (0-back, 1-back, and 2-back) were modeled. Six motion parameters and the instruction period were included as nuisance covariates, and the rest (fixation) condition provided an unmodeled baseline. The con-

Table 3. Clusters Showing Group Differences in the Key Functional Magnetic Resonance Imaging Contrasts[a]

Voxels	Region	Maximum z Score	Cohen's d	x	y	z
2-Back > 0-Back, TD > PS						
9208	dACC/paracingulate/SMA	6.36	0.60	−4	10	54
	Frontal pole L	5.87	0.55	−34	48	14
	Anterior insula L	4.34	0.41	−28	28	−2
	Anterior insula R	4.24	0.40	34	26	−2
	Middle frontal gyrus L	4.69	0.44	−46	18	34
	Superior frontal gyrus L	6.30	0.59	−28	−6	62
	Superior frontal gyrus R	4.55	0.43	28	−2	52
	Thalamus/caudate/pallidum B	5.11	0.48	−10	−18	14
	Midbrain R	4.21	0.40	8	−14	−10
4596	Superior lateral occipital R	6.33	0.60	10	−70	62
	Superior lateral occipital L	4.86	0.46	−20	−74	60
	Precuneus	5.20	0.49	4	−68	52
	Superior parietal lobule L	4.43	0.42	−26	−56	44
	Superior parietal lobule R	4.51	0.43	28	−56	44
2361	Cerebellum L	5.32	0.50	−8	−72	−26
	Cerebellum R	4.80	0.45	32	−62	−30
1304	Frontal pole R	5.29	0.50	34	42	22
	Middle frontal gyrus R	4.00	0.38	40	28	38
209	Pons	4.44	0.42	2	−38	−40
160	Occipital pole R	3.73	0.35	24	−84	−10
116	Cerebellum L	4.08	0.38	−28	−40	−40
86	Occipital pole L	4.02	0.38	−24	−92	−2
2-Back > 0-Back, PS > TD						
129	Superior frontal gyrus	4.77	0.45	−12	36	58
Threat PS > TD						
470	Superior frontal gyrus R	4.27	0.40	26	20	64
195	Amygdala R	4.44	0.42	28	−4	−18
146	Superior frontal gyrus L	4.40	0.41	−26	22	48
58	Fusiform cortex L	3.43	0.32	−44	−70	−8
54	Middle frontal gyrus L	3.77	0.35	−34	6	62
50	Amygdala L	3.70	0.35	−24	−4	−18
Threat TD > PS						
619	Supramarginal gyrus R	5.31	0.50	64	−28	28
198	Supramarginal gyrus L	4.00	0.37	−64	−18	28
55	Insula L	4.03	0.38	−40	4	2

Abbreviations: B, bilateral; dACC, dorsal anterior cingulate; L, left; PS, psychosis spectrum; R, right; SMA, supplementary motor area; TD, typically developing.

[a] Statistical threshold z > 3.09 and cluster extent $P < .05$ (>41 voxels). Peak z score x, y, z coordinates are in Montreal Neurological Institute space. Peak Cohen's d effect size is estimated from the peak z score using the following formula: $d' = 2z$ / (square root of the sample size).

trast of interest was 2-back greater than 0-back, capturing the effect of increasing working memory load. For emotion identification, events were modeled as 5.5-second boxcar, matching the duration of face presentation. Five individual emotion regressors were included along with their temporal derivatives and 6 motion parameters. The contrast of interest was threat (anger plus fear greater than fixation). Nonthreat and neutral were also examined to assess the specificity of effects observed for threat.

Group-Level fMRI Analysis

For each participant, first-level statistical maps for contrasts of interest were entered into second-level group analyses. The PS and TD groups were compared using voxelwise whole-brain analyses, followed by region of interest (ROI) analyses. Whole-brain group analyses used voxelwise linear mixed-effects analysis using FMRIB Local Analysis of Mixed Effects (FLAME1) in FSL. Type I error was controlled by cluster correction for multiple voxelwise comparisons using voxel height z score greater than 3.09 and cluster extent significance threshold $P < .05$, calculated using Monte Carlo simulations implemented in Analysis of Functional NeuroImages (AFNI) AlphaSim. Hypothesized within-group correlations with cognition and symptom severity (using the measures in Table 2) were examined in relation to first-level regression parameters averaged across voxels within specific ROIs. These ROIs were defined functionally from clusters showing significant abnormalities in the PS group. For the n-back task, we used bilateral dorsolateral PFC (DLPFC) regions showing reduced activation in PS relative to TD in the 2-back greater than 0-back contrast (8-mm-radius spheres surrounding peak coordinates in middle frontal gyrus regions listed at the top in **Table 3**).

Figure 2. Executive System Hypofunction During the *n*-Back Task
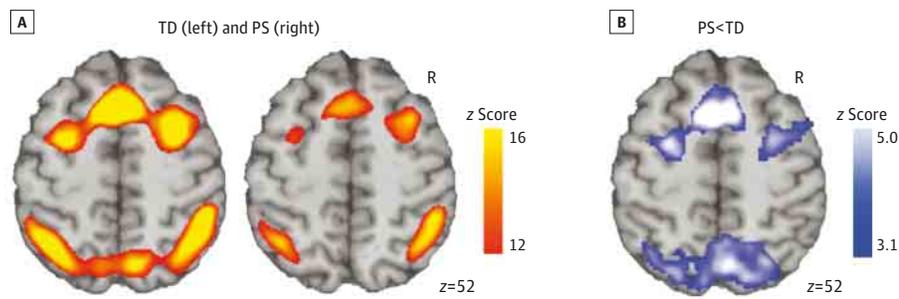
A, The contrast evaluating the effect of working memory load (2-back greater than 0-back) robustly recruited executive function regions, including dorsal anterior cingulate and bilateral dorsolateral prefrontal cortex, with a qualitatively similar regional pattern in both the psychosis spectrum (PS) and typically developing (TD) groups (thresholded z score, 12-16 for display). B, The PS group showed significantly reduced activation in these regions (significant clusters shown in blue; z > 3.09, P < .05). R indicates right.

For emotion identification, we used bilateral amygdala clusters showing greater activation in PS than TD in the threat contrast (listed at the bottom in Table 3). The key ROI results were also examined with confound and sensitivity regression analyses described in the eMethods and eResults in the Supplement. Exploratory whole-brain voxelwise correlations with cognition and positive symptom severity were also conducted with the same multiple comparison approach described above.

Results

Demographic and Clinical Variables

As expected, the PS group had significantly higher levels of PS symptoms (Table 2). Overall cognitive performance on the Computerized Neurocognitive Battery was lower in the PS group, consistent with findings in the full PNC sample.[26] In addition, the PS group was significantly younger, achieved fewer years of education (even after accounting for age), and had lower average parental education. The groups did not differ in sex ratio.

Behavioral Performance

In the *n*-back task, the PS group exhibited worse discrimination accuracy (*d'*) than the TD group ($t = 6.13$, $P < .001$). The response times did not differ ($t = 0.43$, $P = .66$). As memory load increased, the expected decrease in accuracy was seen in both groups. The group accuracy difference was strongest at the highest (2-back) level of difficulty (eTable 1 in the Supplement). In the emotion identification task (eTable 2 in the Supplement), the PS group responded more slowly ($t = 1.81$, $P = .04$) and showed a statistical trend toward lower accuracy ($t = -1.51$, $P = .07$) in identifying threat emotions, with more robust performance impairment evident for nonthreat emotions and the task overall but no significant performance difference for neutral faces.

Task Activation

Both the PS and TD groups demonstrated expected regional task activation patterns. For the *n*-back task, the primary contrast of interest captured the effect of working memory load (2-back greater than 0-back). This contrast revealed robust activation of multiple brain regions in the executive network (**Figure 2**A) as well as the task-deactivated default mode network, both of which contribute to working memory performance.[32] For the emotion identification task, the primary contrast of interest examined activation to threatening faces (anger and fear) relative to baseline. This threat contrast revealed robust activation in bilateral amygdala (**Figure 3**A), our primary ROI in this task, as well as in multiple regions previously shown to activate in facial emotion tasks, including fusiform and orbitofrontal cortex.[39]

Task- and Region-Specific Activation Abnormalities

Group differences were present in both tasks, but the direction and location of abnormalities in the PS group differed by task. In the *n*-back task, the PS group showed reduced activation in prefrontal regions as hypothesized, including DLPFC bilaterally, paracingulate and cingulate, and bilateral frontal pole (Figure 2B, Table 3, and eFigure 2 in the Supplement). Beyond the PFC, the PS group also showed reduced activation bilaterally in multiple regions previously linked to executive function and working memory. Except for a small region of right superior frontal gyrus where the PS group showed reduced load-dependent deactivation, no group differences were observed outside of task-activated and load-sensitive regions, and there were no significant regions where the PS group activated more than the TD group. Exploratory analysis of each level of working memory load showed few group differences at 0-back or 1-back levels, and these were limited to task-deactivated regions. At the 2-back level, group differences were similar to those seen in the 2-back greater than 0-back contrast, although not as strongly (eTable 3 in the Supplement). Therefore, group differences were only seen within the executive network at higher levels of working memory load.

During emotion identification, the PS group had elevated blood oxygenation level-dependent responses to threatening expressions in amygdala (Figure 3B, Table 3, and eFigure 3 in the Supplement). The PS group also showed greater activation in left fusiform cortex and right middle frontal gyrus, less deactivation in bilateral superior frontal gyrus, and re-

Figure 3. Amygdala Hyperactivation to Threat in the Emotion-Processing Task
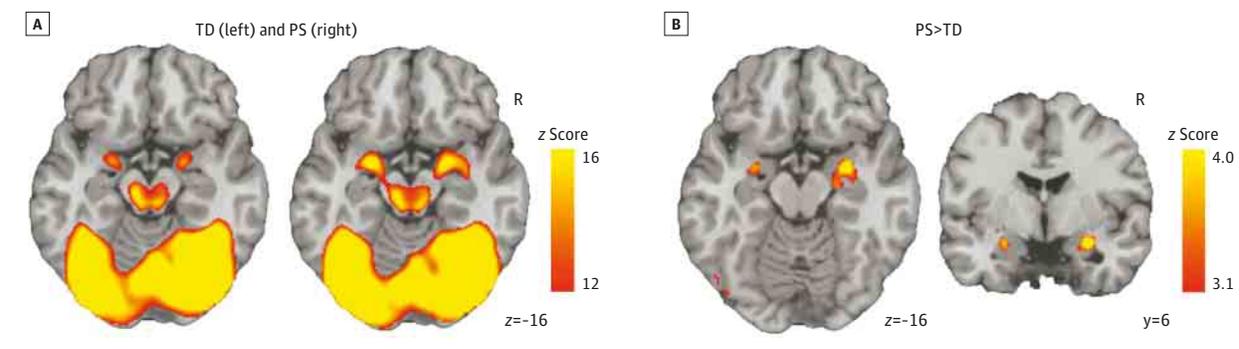
A, Facial emotion-processing activated amygdala and other regions implicated in emotion and face processing, with a qualitatively similar regional pattern in both the psychosis spectrum (PS) and typically developing (TD) groups

(thresholded z score, 12-16 for display). B, The PS group showed significantly greater activation in bilateral amygdala (significant clusters shown in red; z > 3.09, P < .05). R indicates right.

duced activation in bilateral supramarginal gyrus and left insula. We examined the nonthreat and neutral condition for comparison and found no significant group differences within amygdala (eTable 4 and eTable 5 in the Supplement).

Correlations With Cognition and Psychotic Symptoms

The PS group was heterogeneous in the severity of core clinical dimensions. We examined whether activation in the key regions showing group differences was selectively linked to cognitive deficits, positive psychotic symptoms, or negative and disorganized symptoms.

Within the PS group, there was a significant correlation between global cognitive ability and bilateral DLPFC activation in the 2-back greater than 0-back contrast ($r = 0.32$, $P < .001$) (scatterplot in eFigure 4 and exploratory whole-brain analysis in eTable 6 in the Supplement). Significant correlations were seen in the other areas of executive function circuitry as well. The n-back activation in DLPFC or other regions showing group differences did not correlate with the severity of positive symptoms or negative and disorganized symptoms ($P > .50$ for all).

A different pattern of dimensional correlations was seen for amygdala activation in the emotion identification task. Within the PS group, amygdala activation to threat did not correlate significantly with cognitive ability ($r = -0.02$, $P = .82$). However, there was a small but significant positive correlation between the dimensional severity of positive psychotic symptoms and bilateral amygdala activation to threat ($r = 0.16$, $P = .01$) (scatterplot in eFigure 5, exploratory whole-brain analysis in eTable 7, and individual PS-R item analysis in eTable 8 in the Supplement). Effects were similar in left amygdala ($r = 0.18$, $P = .005$) and right amygdala ($r = 0.15$, $P = .02$). No correlation with negative and disorganized symptoms was found ($r = -0.001$, $P = .99$). Amygdala response to threat was not associated with DLPFC working memory activation ($r = 0.10$, $P = .15$).

Confound and Sensitivity Analyses

We examined the influence of potential confound variables showing significant group differences, the effect of comorbid disorders, or a history of psychiatric treatment. The details of these analyses are summarized in the eMethods, eResults, and eTables 9, 10, 11, 12, and 13 in the Supplement. While these analyses identified relationships of these factors to the key imaging outcomes, the key group differences and correlations reported above remained significant and could not be fully attributed to these other variables. However, the group difference in DLPFC n-back activation was strongly attenuated by covarying global cognition or n-back task accuracy and was moderately attenuated by covarying demographic factors that correlated with cognitive performance. This outcome likely reflects substantial shared variance between factors related in complex causal pathways to both cognitive performance and risk for psychosis rather than indicating that the reduced DLPFC activation in the PS group is an artifact of demographic differences.[40]

Age effects are of particular interest in this developmental PNC cohort. Age showed significant relationships to fMRI activation, increasing DLPFC n-back activation, and decreasing amygdala threat activation (eTables 9, 10, 11, and 12 in the Supplement). However, age effects cannot explain our results because covarying for age only reduced group differences by 10% to 20% (eTables 9 and 11 in the Supplement), and the key group differences remained significant in subsamples matched for age (eTable 14 in the Supplement). Furthermore, we found no significant group × age interaction effects, which is in contrast to smaller studies in clinical high-risk samples that reported group × age effects in amygdala activation during emotion processing[41] and in PFC and other regions during a working memory task.[42]

Discussion

To our knowledge, we present the largest functional neuroimaging study to date of youth with PS symptoms and the first such fMRI study to apply a population-based approach to identifying youth with PS symptoms. We find that PS symptoms are associated both with executive circuit hypofunction during working memory and with amygdala hyperreactivity during processing of threatening emotional

expressions. Evaluation of these two categorical effects revealed significant within-group heterogeneity. Executive hypofunction was related to cognitive deficits but not to symptom severity, while amygdala hyperfunction showed the reverse pattern.

PS Hypofunction in Executive System Circuitry During Working Memory

Deficits in recruiting prefrontal executive control circuitry during working memory tasks are among the most consistent fMRI findings in schizophrenia.[4] The same abnormality has also been reported in clinical risk samples, including a 2012 meta-analysis.[43] Our findings in a large independent sample provide a reliable confirmation that executive system hypofunction is found in youth with PS symptoms.

The largest single clinical risk fMRI study[44] before our own, published after the meta-analysis by Fusar-Poli,[43] showed increased working memory–related activity in executive circuitry. We applied a fractal n-back paradigm in which youth with PS symptoms had impaired performance that correlated with activation deficits. In contrast, Yaakub et al[44] applied a verbal working memory task that did not elicit performance deficits in the psychosis risk group. These divergent findings may be reconciled by DLPFC inefficiency as seen in schizophrenia, in which hypoactivation is associated with impaired performance, while hyperactivation occurs when performance is equated.[45-47] In addition, the use by Yaakub et al[44] of letter stimuli may have contributed to increased DLPFC recruitment and spared performance in the risk group by facilitating a verbal rehearsal strategy, which our fractal n-back task was designed to minimize.[31]

PS Hyperactivation in Amygdala During Threat Emotion Processing

Reduced behavioral performance during emotion identification has been repeatedly found in clinical risk and spectrum samples,[48-53] including the PNC.[26] Two small fMRI studies have examined facial emotion processing in clinical risk. One study[54] reported increased right fusiform activation across emotions and increased amygdala response in the neutral greater than sad contrast. The other study[41] did not comment on group differences in amygdala activation but noted abnormal correlations between amygdala activation and age, as well as abnormal amygdala-prefrontal connectivity. In our large PS sample, we identified amygdala hyperreactivity in response to threatening emotional expressions during emotion identification. Our hypotheses focused on amygdala. However, other visual and prefrontal regions also showed increased activation in the PS group but without the threat selectivity seen in amygdala. Amygdala activation abnormalities during emotion processing are consistently reported in schizophrenia, particularly in response to potentially threatening emotions.[5-7,9-12] In schizophrenia, amygdala hypoactivation is more commonly reported than hyperactivation during emotion-processing tasks.[5,6,8] However, this hypofunction may relate to hyperactivation to neutral expressions often used as a baseline,[6,7,55] to the use of implicit paradigms,[8] and to nonspecific disease-associated factors, such as medication effects.[12] Our ap-

proach avoided these factors, which may have allowed the positive correlation between symptoms and amygdala activation to also increase the mean activation across the PS group.

Heterogeneity in Dimensional Relationships

In addition to these categorical group effects, our study is the first to date to demonstrate dissociable dimensional relationships for these two abnormalities in youth with PS symptoms. Executive system hypofunction during working memory was related to cognitive ability but not to positive psychotic symptom severity, whereas amygdala hyperreactivity during emotion processing showed the reverse pattern. The correlation we observed between cognition and n-back activation is consistent with findings in schizophrenia and in healthy control subjects.[32,46] Some studies[10,56] of amygdala activation during emotion processing in schizophrenia have identified correlations with negative symptoms, while other studies[56-58] have found a relationship to positive symptom severity, as we observed herein.

Our findings support two distinct mechanisms of psychosis risk, with one linked to executive dysfunction and the other linked to positive symptoms. Speculatively, these two abnormalities could interact to increase psychosis risk, with amygdala hyperreactivity to threat increasing the likelihood of paranoid feelings or ideas and with executive dysfunction reducing the ability to cognitively contextualize excessive fears or unusual experiences. At least within the milder spectrum of psychosis severity, our results suggest that impaired executive system function may constitute a risk factor for the development of psychosis but is not directly related to progression along the severity of positive symptoms, a path consistent with a prior study[59] using structural equation modeling. In contrast, amygdala reactivity to threat appears to relate to psychosis severity but not cognition and may therefore constitute a subclinical illness phenotype rather than a marker of trait vulnerability. Because positive symptom severity has shown the greatest predictive power for transition to frank psychosis,[3] this relationship suggests that amygdala responses to threat may be particularly useful in augmenting clinical data for predicting such transition. In contrast, cognitive deficits may appear earlier and be of greater use in efforts to screen for risk before the emergence of positive PS symptoms. Clarifying the degree to which reduced cognition and executive circuit function in youth with PS symptoms reflects baseline differences in IQ vs deterioration associated with PS pathophysiology will require longitudinal study in this population.

Implications of a Population-Based Approach

Our study is the first to date, to our knowledge, to examine imaging findings in PS identified through a population-based approach. This process facilitated the identification of a PS sample far larger than fMRI samples in prior studies of help-seeking clinical risk individuals (maximum, 60; median, <20), with greatly enhanced statistical power and control of type I and type II error. This approach yielded neuroimaging phenotypes similar to those found in help-seeking clinical risk samples and in established schizophrenia, providing strong neurobiological evidence supporting a continuum account of

PS pathophysiology.[16,24] Our sampling strategy also identified youth with PS symptoms younger than those typically studied in high-risk samples. Therefore, our findings help define patterns of neural dysfunction associated with PS at an earlier age, a critical step toward developing interventions that might bend the curve of disease trajectory[60] and permit primary prevention of schizophrenia and other adverse long-term outcomes associated with PS.

The present cross-sectional analysis does not define the extent to which observed neuroimaging abnormalities are driven by the subgroup that will transition to frank psychosis. Evidence of continuum effects in PS[16,24] makes it likely that our findings are not limited to this subgroup, and the proportion of individuals in our population-based approach who transition to schizophrenia is likely to be lower than is seen with typical clinical high-risk ascertainment strategies. With planned longitudinal follow-up, our large sample size should yield both a sizable transition cohort and a large nontransitioning group, providing statistical power to better identify transition-related abnormalities and further enhancing the value of our present findings.

The observed correlations and group differences are small in magnitude, which points to the value of a large sample in identifying small effects that may have important mechanistic implications. However, with small effect sizes, it is prudent to emphasize that the reported phenotypes by themselves cannot serve to clinically categorize individuals. Future work may identify subgroups showing larger effects, and the current phenotypes may contribute to multivariable approaches with significant predictive usefulness.

Our criteria did not require help-seeking behavior or recent progression of symptom severity and independently incorporated negative and disorganized symptoms. Therefore, our PS sample includes individuals who had been excluded by most high-risk studies. Given the importance of negative and disorganized symptoms in clinical risk,[14,61-65] we believe that this broader inclusion constitutes a strength, and our follow-up of 300 youth with PS symptoms and 200 TD youth will permit the reexamination of our results with respect to traditional high-risk criteria.

Symptoms such as depression, anxiety, irritability, and mania are elevated in PS and could potentially affect the brain phenotypes examined herein. Our supplementary analyses indicate that the reported findings in PS are not explained by comorbid conditions. However, a history of depression was associated with less *n*-back DLPFC impairment, and a history of anxiety was associated with greater amygdala threat hyperactivation. Future work with the full neuroimaging sample will include a detailed exploration of how other dimensions of psychopathology relate to working memory and emotion processing. In addition, further studies incorporating more definitively threatening situations, such as fear conditioning paradigms, will be important to further elucidate the role of amygdala responses to threat in PS.

Conclusions

Our study demonstrates that early PS symptoms in a population-based youth sample are associated with a pattern of functional abnormalities similar to that previously found in established schizophrenia. Specific circuit dysfunction during cognitive and emotional tasks emerges at an early age in association with PS symptoms and cannot be attributed to chronic illness or medication confounds. Such imaging biomarkers may reveal novel therapeutic targets and mechanisms of treatment efficacy and could help tailor interventions targeting specific populations and symptom domains. Integrating functional imaging phenotypes with neuroanatomic, genetic, and clinical data can help advance the field beyond sole reliance on symptom-based classification. Such integrated measures may yield more robust quantification of risk,[59] which can be tested in longitudinal follow-up and applied to improve diagnosis, prevention, and treatment.

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