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Examining Specificity of Neural Correlates of Childhood Psychotic-like Experiences During an Emotional n-Back Task

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ABSTRACT

BACKGROUND: Psychotic-like experiences (PLEs) during childhood are associated with greater risk of developing a psychotic disorder in adulthood, highlighting the importance of identifying neural correlates of childhood PLEs. Furthermore, impairment of cognitive functions, such as working memory and emotion regulation, has also been linked to psychosis risk as well as to disruptions in several brain regions. However, impairments in these domains have also been linked to other disorders, including depression. Therefore, the aim of the current study was to examine whether neural impairments in regions associated with working memory and implicit emotion regulation impairments are specific to PLEs versus depression.

METHODS: The current study used an emotional n-back task to examine the relationship between childhood PLEs and neural activation of regions involved in both working memory and implicit emotion regulation using data from 8805 9- to 11-year-olds in the Adolescent Brain Cognitive Development (ABCD) Study 2.0 release. To examine specificity, we also analyzed associations with depressive symptoms.

RESULTS: Our results indicated that increased PLEs during middle childhood were associated with decreased activation of the dorsolateral prefrontal cortex, striatum, and pallidum during trials requiring working memory. In contrast, increased activation of the parahippocampus, caudate, nucleus accumbens, and rostral anterior cingulate during face-viewing trials was associated with increased depressive symptoms.

CONCLUSIONS: These results support the dimensional view of psychosis across the lifespan, providing evidence that neural correlates of PLEs, such as decreased activation during working memory, are present during middle childhood. Furthermore, these correlates are specific to psychotic-like symptoms as compared with depressive symptoms.

Keywords: Depression, Emotional n-back, Implicit emotion regulation, Neuroimaging, Psychotic-like experiences, Working memory

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Psychotic-like experiences (PLEs), such as subclinical delusional ideation and perceptual distortions, are experienced by approximately 5% to 8% of the general population (1). Research shows that PLEs are even more common (13%–15%) among children and adolescents (2,3). Furthermore, persisting PLEs are associated with an increased risk for developing a psychotic disorder (4), as well as other psychological disorders (5), later in life. Importantly, individuals with PLEs share multiple risk factors and correlates of clinical psychosis, such as cognitive impairments (6–8), particularly in working memory (9,10) and emotion regulation (11), as well as increased internalizing symptoms (12,13). Therefore, it has been suggested that significant PLEs may indicate a premorbid stage of psychosis risk (14).

Previous studies have demonstrated that both children (15,16) and adolescents (9,10,17,18) at risk for psychosis show poorer performance on working memory tasks. In longitudinal studies, working memory deficits have been linked to higher delusional ideation at follow-up (19) as well as progression to psychosis (20,21). Furthermore, psychosis risk is also associated with abnormal activation of several brain regions during working memory tasks (22), particularly the dorsolateral prefrontal cortex (DLPFC) (23–26). However, the pattern of DLPFC activation has been inconsistent in both adolescent and adult psychosis risk populations, with some studies reporting increased activation compared with control subjects (25–27) and others reporting decreased activation (23,24). It has been suggested that increased DLPFC activation is due to inefficient processing during working memory in psychosis risk (27) or may be compensatory for deficits in other regions (21,28,29). Increased parahippocampal activity has also been found in both schizophrenia (30,31) and familial risk for psychosis (32) during memory tasks.

Despite some variability in results, abnormalities in neural activation during working memory are often present in psychosis risk, thereby constituting a potential marker for

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psychosis spectrum symptoms. However, there is not strong evidence that these impairments are specific to psychosis risk rather than general psychopathology. Research suggests that working memory deficits also occur in other psychiatric disorders, such as depression (33–35). Similar to psychosis risk, research examining depressive symptoms finds abnormal activation in lateral prefrontal regions (36,37), as well as the anterior cingulate cortex (ACC) (38), during working memory. Furthermore, depression has been associated decreased functional connectivity between cortical regions of the default mode network and subcortical regions, such as the hippocampus, during working memory (39). This, along with the high rate of comorbidity between psychosis and depressive disorders (40,41), makes it difficult to characterize risk factors specific to psychosis. Thus, the current study aimed to examine whether working memory impairments show evidence of specificity to PLEs.

Psychosis risk is also often associated with impairments in emotion regulation and reactivity (11,42–44). Similar to working memory impairments, emotion regulation impairments have been shown to occur in depressive disorders as well (45–47), although differences are evident between psychosis risk and depression. For example, psychosis risk is associated with deficits in recognizing negative emotions such as fear and sadness (48), while depressive symptoms are associated with deficits in happy face recognition (49). Regardless, research indicates that psychotic and depressive disorders are associated with similar emotion regulation strategies, and these strategies are significantly more dysfunctional than those in nonpatient control subjects (11). These impairments are typically associated with abnormal function of cortical regions, such as the DLPFC and ACC (50,51), as well as subcortical regions associated with emotion and salience processing [i.e., hippocampus, amygdala, striatum, and pallidum (50,52,53)]. It has been suggested that overactivation of subcortical regions linked to emotion processing may lead to disruptions in cortical circuits that control the cognitive regulation of emotion, particularly in regard to depression (54). While there is a lack of literature examining these deficits in 9- and 10-year-old children, Wolf *et al.* (55) did use separate n-back and emotion regulation tasks to examine neural activation in adolescents (11–22 years of age) exhibiting psychosis spectrum symptoms, providing evidence that younger at-risk individuals exhibited the same functional abnormalities (i.e., reduced activation of executive control circuitry during working memory and increased activation of subcortical regions during emotion recognition) that are found in schizophrenia (28). Given the gaps in the literature regarding younger populations, the current study also examined whether PLEs during middle childhood were related to implicit emotional regulation impairments and whether such impairments were specifically related to PLEs versus depressive symptoms.

In the current study, we examined the relationship between childhood PLEs and neural activation during an emotional n-back (EN-back) task using data from 9- to 11-year-olds in the Adolescent Brain Cognitive Development (ABCD) Study. The EN-back task (56) is a variant of the original Human Connectome Project n-back task (57) that taps into implicit emotion regulation and reactivity processes, as well as working memory, and has been shown to activate a number of regions previously implicated in both psychosis risk and depression. Specifically, just like the traditional n-back task, the memory component of the EN-back task activates core brain regions relevant for working memory, including the DLPFC, ACC, hippocampus, and parahippocampus (57–59). However, unlike the traditional n-back task, the stimuli include sets of happy, fearful, and neutral faces. The processing of these stimuli reliably activates regions involved in implicit emotion regulation and reactivity [i.e., DLPFC, amygdala, and striatum (60,61)], with the hypothesis that this reflects the need to prevent emotional reactivity to the emotional content of faces from interfering with working memory. We tested the hypothesis that altered activation of a priori brain regions (i.e., DLPFC, hippocampus, parahippocampus, amygdala, striatum, pallidum, and ACC) would be associated with increased PLEs during middle childhood. Furthermore, given evidence that both PLEs and depressive symptoms are associated with impairments in implicit emotion regulation and working memory, we also analyzed relations with depressive symptoms to examine specificity.

METHODS AND MATERIALS

Participants

A sample of 8805 children who completed the in-scanner EN-back task was obtained from ABCD Study data release 2.0 (see Acknowledgments and Disclosures), a large-scale study tracking 11,874 children aged 9 to 11 years from 21 different research sites across the United States. The study was approved by a central institutional review board at the University of California, San Diego. All study participants provided written informed consent prior to participating. Participants were removed from analyses for having task data that did not pass quality assurance criteria (i.e., did not have at least one run that was complete, passed protocol compliance, and was preceded by field maps within the last two scans; n = 531) or owing to missing data (n = 205). Participants were also removed from analyses for having poor overall accuracy (≤.60; n = 569). Following recent guidance from the ABCD Study, all participants scanned using a Philips scanner were removed from analyses (n = 979). The final sample size was 6521 individuals (see Table 1 for demographic characteristics; see Supplement for study-wide exclusion criteria).

Measures

Prodromal Questionnaire–Brief Child Version. The Prodromal Questionnaire–Brief Child Version (PQ-BC) is a 21-item self-report questionnaire that demonstrates validity as a measure of PLEs during middle childhood (16). Each item in the PQ-BC references a different PLE (e.g., "Have you felt that you are not in control of your own ideas or thoughts?"), and children responded "yes" or "no." PQ-BC total scores consisted of the summed number of "yes" responses. Owing to significant skewness (skewness = 1.99), the PQ-BC total score was logarithmically transformed [formula = LG10(X + 1)] prior to running analyses.

Depression Symptoms. A computerized version of the Kiddie-Structured Assessment for Affective Disorders and

Table 1. Demographic Characteristics for Sample (n = 6521)

Variable	Value
Age, Months	119.49 (7.54; 107 to 132)
Sex, Female[a]	3200 (49.1%)
Ethnicity	
Caucasian	3695 (56.7%)
African American	766 (11.7%)
Hispanic	1262 (19.4%)
Asian	138 (2.1%)
Other	660 (10.1%)
Financial Adversity[b]	0.4 (1.02; 0 to 7)
Average Motion, mm[c]	0.3 (0.28; 0.02 to 3.11)
Scanner Type	
Siemens	4971 (76.2%)
GE	1550 (23.8%)
PQ-BC Score[d]	2.29 (3.28; 0 to 20)
Log-transformed PQ-BC score	−0.17 (0.36; −0.52 to 0.81)
Depressive Symptoms[e]	0.23 (1.03; 0 to 13)

Values are presented as mean (SD; range) or n (%).
PQ-BC, Prodromal Questionnaire–Brief Child Version.
[a]Sex is a dichotomous variable scored as either male or female.
[b]Financial adversity is measured on a scale from 0 to 7.
[c]Average motion is calculated as average framewise displacement.
[d]PQ-BC score is on a scale from 0 to 21.
[e]Depressive symptom score is on a scale from 0 to 13.

Schizophrenia for DSM-5 (62,63) was used as a child-reported measure of depression symptoms. As has been done in previous research using the ABCD Study baseline sample (16), 13 dichotomous (0 = absent, 1 = present) depression module symptom questions (e.g., anhedonia, low mood, poor appetite) were summed to create a symptom composite score ranging from 0 to 13 and showed good internal reliability (α = .83).

EN-Back Task. The EN-back task (57) is a variant of the original Human Connectome Project n-back task (57) that measures working memory as well as implicit emotion regulation and reactivity. Participants completed 2 runs, each consisting of 8 blocks. In each run, 4 blocks were 2-back conditions and 4 blocks were 0-back conditions. For the 2-back condition, participants were instructed to respond "match" when the current stimulus was the same as the stimulus shown two trials ago. For the 0-back condition, participants responded "match" when the current stimulus was the same as the target presented at the beginning of the block. Each block consisted of 10 trials, with 160 trials total, and began with a 500-ms colored fixation to alert children of a switch in task condition, followed by a 2.5-second cue that indicated the condition (e.g., "2-back," "target =," and a photo of the target stimulus). The stimulus (i.e., positive face, negative face, neutral face, or place) was presented for 2 seconds and was then followed immediately by a 500-ms fixation cross. The average overall accuracy on the task was 0.82 (see Table 2 for accuracy by condition).

For imaging analyses, we examined 3 contrasts. The 2 memory load conditions (2-back vs. 0-back) were contrasted to measure working memory. The happy and fearful faces were contrasted with neutral faces (emotion vs. neutral) to examine responses specific to emotionally evocative stimuli as a measure of implicit emotion regulation and reactivity (61,64). In follow-up analyses, we also examined the specificity of emotions by contrasting both happy versus neutral faces and fearful versus neutral faces. While there was no a priori reason to do so, for completeness we also contrasted facial and nonfacial stimuli (face vs. place) to measure response to socially relevant versus nonsocial stimuli (65).

Imaging Procedure

A preprocessing pipeline was created using MMPS (Multi-Modal Processing Stream), a software package developed by the Center for Multimodal Imaging and Genetics (La Jolla, CA). All children were run on a 3T scanner (either Siemens [Munich, Germany] or GE Healthcare [Chicago, IL]) with a 32-channel head coil (see Supplement for additional imaging procedure details). Task-related activation strength was then calculated at the individual level using a general linear model in AFNI's 3dDeconvolve (66). The hemodynamic response function was modeled as a gamma function with temporal derivatives using AFNI. The general linear model coefficients and t statistics were then sampled onto the FreeSurfer-generated cortical surface. Processed task data were mapped to 33 cortical regions of interest (ROIs) for each hemisphere based on the Desikan-Killiany atlas (67). Subcortical structure (i.e., caudate, putamen, pallidum, hippocampus, amygdala, and nucleus accumbens) segmentations were based on FreeSurfer (automatic segmentation) subcortical parcellations (68). Based on previous research (22,25,53,55,69), ROIs focused on the DLPFC (i.e., rostral and caudal middle frontal gyrus), hippocampus, parahippocampus, amygdala, striatum (divided into the caudate, putamen, and nucleus accumbens), pallidum, and ACC (rostral and caudal). The averaged beta weights for each contrast (i.e., 2-back vs. 0-back, face vs. place, and emotion vs. neutral) for each of these ROIs were examined (the average across both trial runs).

Statistical Analyses

One-sample t tests were used to determine overall activation of ROIs for each contrast, and hierarchical linear models were used for all other analyses. Owing to the inclusion of siblings in the ABCD Study dataset, family unit was clustered as a random intercept, as were the 21 research sites. Age, sex, financial

Table 2. Task Performance (Percent Accuracy)

Task Condition	Value
Total Accuracy	0.82 (0.09; 0.61–0.99)
Working Memory Conditions	
2-Back	0.78 (0.10; 0.33–1.0)
0-Back	0.86 (0.10; 0.43–1.0)
Emotional Face Conditions	
Happy	0.83 (0.10; 0.33–1.0)
Fearful	0.83 (0.10; 0.43–1.0)
Neutral	0.84 (0.10; 0.35–1.0)
Place	0.70 (0.11; 0.30–1.0)

Values are presented as mean (SD; range).

Table 3. Model Estimates for 2-Back Versus 0-Back Contrast

	PLEs				Depression			
	β	SE	*t*	FDR-Corrected *p*	β	SE	*t*	FDR-Corrected *p*
DLPFC	−.014[a]	.012[a]	−1.156[a]	.01[a]	−.014	.012	−1.156	.54
Right	−.019[a]	.012[a]	−1.502[a]	.05[a]	−.019	.012	−1.502	.68
Left	−.009[a]	.012[a]	−0.696[a]	.02[a]	−.009	.012	−0.696	.88
Hippocampus	.016	.012	1.275	.63	.016	.012	1.275	.54
Right	.001	.012	0.089	.96	.001	.012	0.089	.97
Left	.029	.012	2.324	.30	.029	.012	2.324	.40
Parahippocampus	.016	.012	1.286	.70	.016	.012	1.286	.54
Right	.015	.012	1.205	.85	.015	.012	1.205	.68
Left	.013	.012	1.023	.95	.013	.012	1.023	.68
Caudate	−.010[a]	.012[a]	−0.823[a]	.01[a]	−.010	.012	−0.823	.67
Right	−.017[a]	.012[a]	−1.392[a]	.03[a]	−.017	.012	−1.392	.68
Left	−.002[a]	.012[a]	−0.192[a]	.02[a]	−.002	.012	−0.192	.94
Putamen	.007[a]	.012[a]	0.530[a]	.03[a]	.007	.012	0.530	.75
Right	.003	.012	0.217	.05	.003	.012	0.217	.94
Left	.005	.012	0.447	.05	.005	.012	0.447	.94
Nucleus Accumbens	.002	.012	0.138	.34	.002	.012	0.138	.92
Right	.009	.012	0.741	.96	.009	.012	0.741	.88
Left	−.006	.012	−0.502	.05	−.006	.012	−0.502	.94
Amygdala	.016	.012	1.278	.70	.016	.012	1.278	.54
Right	.014	.012	1.107	.56	.014	.012	1.107	.68
Left	.014	.012	1.168	.96	.014	.012	1.168	.68
Caudal ACC	−.014[a]	.012[a]	−1.104[a]	.03[a]	−.014	.012	−1.104	.54
Right	−.018[a]	.012[a]	−1.491[a]	.04[a]	−.018	.012	−1.491	.68
Left	−.008	.012	−0.631	.07	−.008	.012	−0.631	.88
Rostral ACC	−.001	.012	−0.107	.39	−.001	.012	−0.107	.92
Right	−.003	.012	−0.249	.32	−.003	.012	−0.249	.94
Left	.000	.012	0.034	.56	.000	.012	0.034	.97
Pallidum	.009[a]	.012[a]	0.722[a]	.03[a]	.009	.012	0.722	.67
Right	.010	.046	0.217	.05	.010	.046	0.217	.94
Left	.050[a]	.047[a]	1.066[a]	.05[a]	.050	.047	1.066	.68

ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FDR, false discovery rate; PLE, psychotic-like experience.
[a]Significant model estimate.

adversity [an assessment of material hardship or deprivation recommended as a measure of socioeconomic status (70)], average head motion, race/ethnicity, and scanner type were included as covariates (see Table 1 for details). All analyses were conducted in the R lme4 package (71). For behavioral analyses, hierarchical linear models analyzed associations between PLEs and percentage of correct responses for each condition (0-back, 2-back, positive, neutral, negative, and place). As a follow-up, we also performed a repeated-measures analysis of behavioral data, in which n-back level and stimuli type were within-subject factors, symptoms (i.e., PLEs or depressive symptoms) were dimensional factors, and accuracy was the dependent variable, to examine whether there were interactions between condition and symptom measure on accuracy. For activation analyses, hierarchical linear models analyzed associations between PLEs (or depressive symptoms) with average beta weights of each ROI for each contrast (i.e., 2-back vs. 0-back, face vs. place, and emotion vs. neutral). All analyses were false discovery rate corrected for multiple comparisons. ROI analyses were conducted as an average of both hemispheres as well as separately for each hemisphere. To examine specificity, models separately examined associations with PLEs and depressive symptoms (we also conducted follow-up analyses for all significant ROIs in which both symptom measures were associated with activation in the same model). In addition, we examined whether results remained significant when including twin status as a covariate as well as when excluding outliers (i.e., any observations where the standardized residual was greater than ±3 SD), with all results remaining consistent.

RESULTS

Task Performance

As expected, decreased overall accuracy was associated with both increased PLEs ($\beta = -1.27$, $p < .001$, $R^2 = .03$) and increased depressive symptoms ($\beta = -0.63$, $p < .001$, $R^2 = .01$). This remained true for all conditions (0-back, 2-back, positive, negative, neutral, and place), indicating that both symptom measures were related to working memory accuracy across n-back level and stimulus type. Follow-up repeated-measures analysis showed a main of effect of PLEs on accuracy ($\beta = -0.01$, $p < .001$), with no interaction between PLEs and n-back level ($\beta = 0.00$, $p = .06$) or between PLEs and

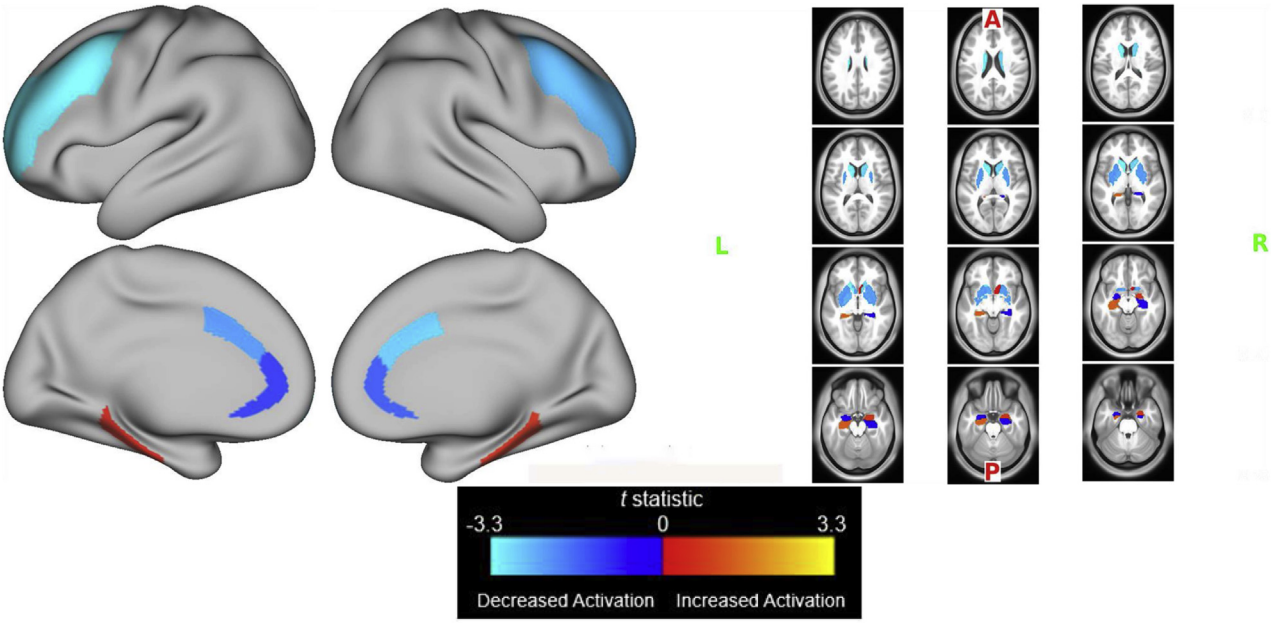

Figure 1. Association between Prodromal Questionnaire–Brief Child Version scores and activity in a priori regions of interest during 2-back vs. 0-back contrast. The image depicts *t* statistics from all models examining associations between a priori regions of interest and psychotic-like experiences whether or not they passed false discovery rate correction. The color bar depicts the *t*-statistic range. Warm colors indicate increased activation, and cool colors indicate decreased activation, relative to baseline. L, left; R, right.

stimuli type ($\beta = 0.00$, $p = .78$). Similarly, there was a main effect of depressive symptoms ($\beta = 0.00$, $p < .001$), but there was no interaction between depressive symptoms and n-back level ($\beta = 0.00$, $p = .65$) or between depressive symptoms and stimuli type ($\beta = 0.00$, $p = .36$). When both symptom measures predicted accuracy in the same model, only PLEs were significantly associated with decreased accuracy ($\beta = -0.01$, $p < .001$) (note that this was the case for overall accuracy as well as across condition and stimuli type).

Functional Brain Activation Results

2-Back Versus 0-Back Contrast. Overall, all a priori ROIs were associated with significant activation or deactivation on this contrast ($ts > |2.67|$, $ps < .01$) (see Supplemental Table S1). Decreased DLPFC activation was associated with increased PLEs on the 2-back versus 0-back contrast ($R^2 = .02$) (see Table 1, Table 3, and Figure 1). Furthermore, decreased activation of both the right DLPFC ($R^2 = .02$) and left DLPFC ($R^2 = .02$) was associated with increased PLEs. Decreased striatal activation was also associated with increased PLEs, and decreased average, right, and left caudate activation (all R^2s = .02), as well as decreased average putamen activation ($R^2 = .02$), was associated with increased PLEs. Decreased pallidum activation was also associated with increased PLEs ($R^2 = .02$). However, when examined separately for each hemisphere, only the left pallidum was significantly associated with increased PLEs ($R^2 = .02$). Activity in all ROIs described above remained significantly associated with PLEs when including 2-back accuracy in the model ($ps \leq .04$). In contrast to PLEs, there were no associations between activation and depressive symptoms for this contrast ($ps \geq .40$). Furthermore, when PLEs and depressive symptoms were included in the same model, PLEs remained significantly associated with decreased activation for these ROIs ($ps \leq .01$).

Emotion Versus Neutral Contrast. Overall, both the left and right amygdala showed significant activation for this contrast ($ts > 3.72$, $ps < .001$) (Supplemental Table S2), while the DLPFC, caudate, putamen, left nucleus accumbens, and caudal ACC showed significant deactivation ($ts < -2.85$, $ps < .03$). Contrary to our hypothesis, there was no association between activation and either PLEs or depressive symptoms while viewing emotional versus neutral faces (Table 4). These results remained consistent when examining happy versus neutral contrasts and fearful versus neutral contrasts.

Face Versus Place Contrast. Overall, the caudate, putamen, nucleus accumbens, amygdala, right rostral ACC, and left pallidum showed significant activation for this contrast ($ts > 4.99$, $ps \leq .01$) (Supplemental Table S3), while the DLPFC, hippocampus, parahippocampus, and caudal ACC showed significant deactivation ($ts < -2.71$, $ps < .02$). PLEs were not significantly associated with face versus place activation (see Table 5). In terms of depressive symptoms, and in contrast to PLEs, increased average ($R^2 = .02$) and left ($R^2 = .02$) parahippocampal activation was significantly associated with increased depressive symptoms for this contrast (Figure 2). Increased average caudate activation was associated with increased depressive symptoms ($R^2 = .02$), as was average ($R^2 = .01$) and right ($R^2 = .01$) nucleus accumbens activation for face versus place. Finally, increased average ($R^2 = .01$) and left ($R^2 = .01$) rostral ACC was also associated with increased depressive symptoms on this contrast. Activity in all ROIs described above remained significantly associated with

Table 4. Model Estimates for Emotion Versus Neutral Contrast

	PLEs				Depression			
	β	SE	*t*	FDR-Corrected *p*	β	SE	*t*	FDR-Corrected *p*
DLPFC	.003	.004	0.809	.81	−.017	.012	−1.350	.46
Right	.005	.004	1.087	.88	−.015	.012	−1.248	.63
Left	.002	.004	0.439	.88	−.017	.012	−1.353	.63
Hippocampus	−.005	.004	−1.189	.81	−.002	.012	−0.137	.89
Right	−.002	.004	−0.500	.88	−.001	.012	−0.091	.93
Left	−.007	.004	−1.706	.88	−.002	.012	−0.159	.92
Parahippocampus	−.001	.004	−0.235	.81	.011	.012	0.897	.46
Right	.002	.004	0.442	.88	.012	.012	0.949	.68
Left	−.004	.004	−0.861	.88	.007	.012	0.580	.77
Caudate	.002	.004	0.437	.81	−.005	.012	−0.427	.74
Right	.002	.004	0.426	.88	−.004	.012	−0.320	.83
Left	.002	.004	0.416	.88	−.006	.012	−0.506	.77
Putamen	−.001	.004	−0.280	.81	−.012	.012	−0.968	.46
Right	−.001	.004	−0.318	.88	−.010	.012	−0.793	.71
Left	−.001	.004	−0.217	.92	−.013	.012	−1.069	.63
Nucleus Accumbens	−.005	.004	−1.098	.81	−.020	.012	−1.592	.46
Right	−.006	.004	−1.494	.88	−.028	.012	−2.261	.48
Left	−.002	.004	−0.436	.88	−.007	.012	−0.534	.77
Amygdala	−.002	.004	−0.435	.81	.013	.012	1.063	.46
Right	−.001	.004	−0.131	.88	.015	.012	1.235	.63
Left	−.003	.004	−0.653	.88	.007	.012	0.577	.77
Caudal ACC	.004	.004	0.945	.81	−.012	.012	−0.995	.46
Right	.005	.004	1.071	.88	−.010	.012	−0.812	.71
Left	.003	.004	0.752	.88	−.014	.012	−1.100	.63
Rostral ACC	.001	.004	0.317	.81	−.018	.012	−1.481	.46
Right	.003	.004	0.589	.88	−.013	.012	−1.085	.63
Left	.000	.004	0.026	.92	−.022	.012	−1.769	.58
Pallidum	.003	.004	0.698	.81	−.015	.012	−1.199	.46
Right	.004	.004	0.874	.88	−.005	.012	−0.411	.80
Left	.002	.004	0.349	.88	−.021	.012	−1.714	.58

ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FDR, false discovery rate; PLE, psychotic-like experience.

depressive symptoms when including face accuracy in the model (*p*s ≤ .02). Furthermore, when PLEs and depressive symptoms were included in the same model, depressive symptoms remained significantly associated with increased activation for these ROIs (*p*s ≤ .02).

DISCUSSION

The current study is the first to examine the relationship between PLEs and neural activation during working memory and implicit emotion regulation during middle childhood. Our results indicate that early manifestations of psychosis risk may already show evidence of functional differences analogous to what is seen in individuals with psychotic disorders. We found evidence that reduced activation in multiple brain regions, such as the DLPFC, striatal regions, and pallidum, during working memory was associated with increased childhood PLEs. Not only were the same relationships not found with depressive symptoms, but when both symptom measures examined activation in the same model, PLEs were still significantly associated with activation in these regions, possibly indicating that these functional brain activation differences are specifically related to PLEs. Interestingly, increased activation in multiple regions, such as the parahippocampus, nucleus accumbens, rostral ACC, and pallidum, was associated with increased depressive symptoms when viewing faces versus nonfacial stimuli. In contrast, there were no significant associations with PLEs for this contrast, perhaps indicating a level of specificity to depression. While we had no a priori hypothesis regarding this contrast, it raises the possibility of distinct neural correlates specific to psychosis risk versus depression.

The results also indicated that decreased overall accuracy on the task was related to both increased PLEs and increased depressive symptoms. These relationships were expected given the current literature suggesting that working memory and emotion regulation impairments are risk factors for both psychosis and depression (9,11,35). However, when both symptom measures examined accuracy in the same model, only PLEs were associated with lower accuracy regardless of condition or stimuli type. These results align with previous research findings that individuals with emerging psychotic symptoms showed poorer working memory performance than

Table 5. Model Estimates for Face Versus Place Contrast

	PLEs				Depression			
	β	SE	*t*	FDR-Corrected *p*	β	SE	*t*	FDR-Corrected *p*
DLPFC	−.001	.004	−0.240	.95	.016	.012	1.334	.23
Right	.001	.004	0.124	.97	.011	.012	0.910	.45
Left	−.003	.004	−0.601	.97	.021	.012	1.689	.14
Hippocampus	.000	.004	0.085	.95	.013	.012	1.058	.32
Right	.001	.004	0.195	.97	.002	.012	0.195	.87
Left	.000	.004	−0.044	.97	−.002	.012	−0.159	.87
Parahippocampus	.002	.004	0.389	.95	.038[a]	.013[a]	3.012[a]	.02[a]
Right	.000	.004	0.039	.97	.027	.013	2.132	.07
Left	.003	.004	0.675	.97	.041[a]	.013[a]	3.256[a]	.02[a]
Caudate	.000	.004	0.068	.95	.030[a]	.012[a]	2.470[a]	.04[a]
Right	.000	.004	−0.059	.97	.032	.012	2.590	.05
Left	.001	.004	0.194	.97	.027	.012	2.209	.07
Putamen	.001	.004	0.319	.95	.022	.012	1.759	.11
Right	.001	.004	0.309	.97	.016	.012	1.275	.27
Left	.001	.004	0.303	.97	.026	.012	2.115	.07
Nucleus Accumbens	−.002	.004	−0.471	.95	.036[a]	.012[a]	2.918[a]	.02[a]
Right	−.001	.004	−0.132	.97	.038[a]	.012[a]	3.091[a]	.02[a]
Left	−.003	.004	−0.746	.97	.025	.012	2.035	.08
Amygdala	.002	.004	0.544	.95	.000	.012	−0.025	.98
Right	.003	.004	0.701	.97	.004	.012	0.328	.83
Left	.001	.004	0.189	.97	−.005	.012	−0.432	.78
Caudal ACC	−.002	.004	−0.537	.95	.025	.012	2.068	.07
Right	.000	.004	0.070	.97	.019	.012	1.538	.18
Left	−.005	.004	−1.106	.97	.030	.012	2.438	.06
Rostral ACC	.001	.004	0.148	.95	.028[a]	.012[a]	2.297[a]	.04[a]
Right	.001	.004	0.129	.97	.022	.012	1.772	.13
Left	.001	.004	0.156	.97	.032	.012	2.629	.05
Pallidum	.005	.004	1.201	.95	.022	.012	1.787	.13
Right	.007	.004	1.643	.97	.027	.012	2.225	.07
Left	.001	.004	0.303	.97	.026	.012	2.126	.07

ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FDR, false discovery rate; PLE, psychotic-like experience.
[a]Significant model estimate.

individuals with depressive symptoms (72), indicating that early impairments in working memory may be more strongly associated with psychosis spectrum symptoms than depression. This finding is also consistent with our imaging results, in which decreased activation of multiple regions during working memory was associated with increased PLEs but not depressive symptoms.

As predicted, decreased activation of the DLPFC during working memory was associated with increased PLEs. These results were expected given the DLPFC's role in working memory processes (73), and they align with previous research linking both structural (74–76) and functional (23–26) DLPFC abnormalities with psychosis risk. Importantly, the same relationship was not found with depressive symptoms, and this aligns with the aforementioned n-back accuracy findings. While the pattern of DLPFC activation has been inconsistent in populations at risk for psychosis [with some studies reporting increased activation compared with control subjects (25–27) and others reporting decreased activation (23,24)], this study is the first to examine the association between activation and PLEs during middle childhood and, therefore, reports the earliest finding of such an association. This indicates that early impairments in key regions, such as the DLPFC, may already be detectable at this stage of development. Thus, we provide novel evidence that reduced activation of the DLPFC during middle childhood may constitute a potential neural correlate of early psychosis spectrum symptoms.

We also found that reduced activation of striatal regions (i.e., caudate and putamen) during working memory was associated with increased PLEs. The striatum is the primary input region of the basal ganglia (77), and it is heavily connected with prefrontal regions, as well as other subcortical regions, such as the pallidum, forming a corticobasal ganglia circuit (78). This circuitry is thought to control entry of new information into long-term memory (79) and has been consistently implicated in psychosis (53,80,81). Importantly, the results also revealed that decreased pallidum activation during working memory was associated with increased PLEs. Not only has previous research implicated functional abnormalities of both the

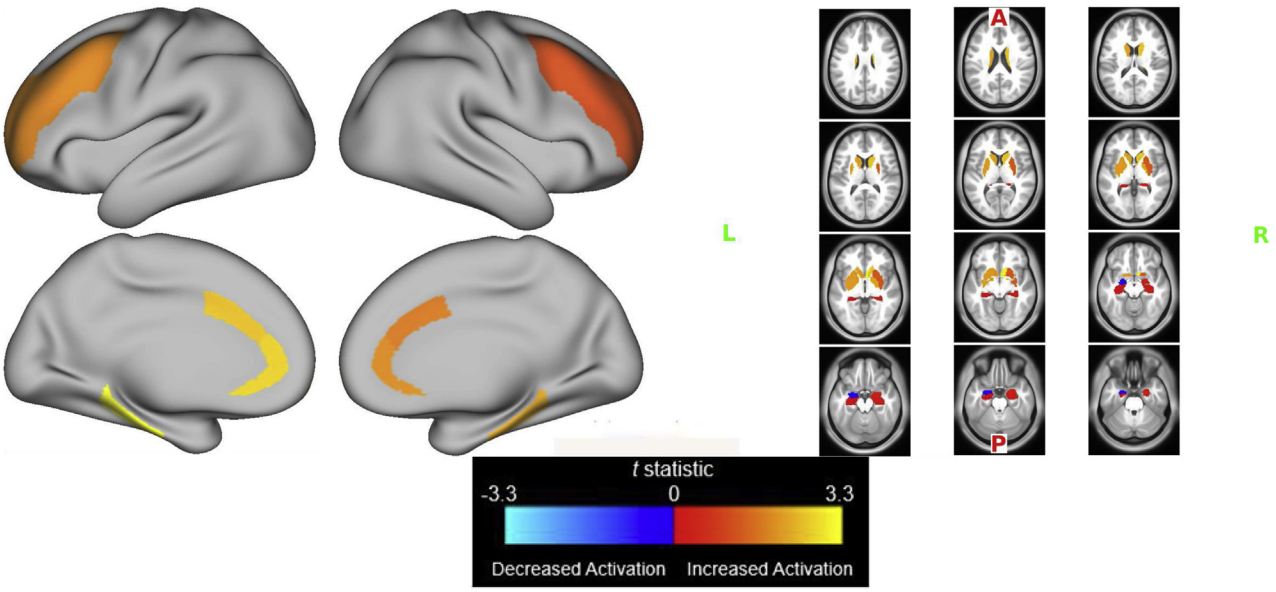

Figure 2. Association between depression scores and activity in a priori regions of interest during face vs. place contrast. The image depicts *t* statistics from all models examining associations between a priori regions of interest and depressive symptoms whether or not they passed false discovery rate correction. The color bar depicts the *t*-statistic range. Warm colors indicate increased activation, and cool colors indicate decreased activation, relative to baseline. L, left; R, right.

striatum (53) and the pallidum (53) in psychosis risk, but our results also indicate that multiple regions involved in this circuit show reduced activation during working memory. Furthermore, research has shown that decreased striatal (82) and pallidal (83,84) functional connectivity is associated with impaired cognitive function in psychosis risk as well as first-episode schizophrenia. Here we provide novel evidence that reduced activation of both the striatum and the pallidum during working memory is associated with childhood PLEs.

We also found that when simply viewing faces (as opposed to nonsocial place stimuli), symptoms of depression were associated with increased activation of several regions such as the parahippocampus, caudate, nucleus accumbens, and rostral ACC. In contrast, increased PLEs were not significantly associated with activation during face processing. Furthermore, when both symptom measures examined activation in the same model, depression was still significantly associated with each region. Nonetheless, a caveat must be noted in that we did not have an a priori hypothesis regarding this contrast. In addition, while the literature has previously shown that abnormal activation in these regions (i.e., parahippocampus, striatum, and ACC) is associated with viewing emotional faces in depression (85), there is limited research regarding the specificity of such relationships to activity in response to faces as opposed to nonfacial stimuli. However, these results are consistent with emotion recognition deficits that are commonly seen in depression (86) and, therefore, should continue to be examined in future research.

The study has several limitations. First, the study data were collected using different magnetic resonance imaging scanners and motion detection protocols (e.g., FIRMM motion correction software) across the different ABCD Study sites. We attempted to account for this by including scanner type as a covariate and ABCD Study site as a nested factor in the statistical analyses. In addition, the sample consisted of a nonclinical sample of 9- to 11-year-old children and, therefore, the PLEs reported were typically mild in severity. While PLEs during middle childhood may encompass some developmentally appropriate transient experiences (16), there is evidence that some individuals experiencing PLEs during middle childhood will go on to develop psychosis spectrum disorders (1,4). Another limitation is that the emotional faces in the current task consist of only happy and fearful expressions. It would be beneficial to replicate the study using a wider range of emotional faces (e.g., angry, sad). In addition, the current study used predefined ROIs for a priori brain regions in our hypotheses. While whole-brain or voxelwise analyses would provide much more comprehensive results, owing to computational challenges of such analyses in datasets of this size, the current ABCD Study data do not allow for such an approach. However, future ABCD Study releases may include voxelwise results and, therefore, should be used in future research. Importantly, both working memory and implicit emotion regulation impairments are present across a wide range of childhood disorders, and future research should examine other aspects of psychopathology as well. Lastly, the current study's data are cross-sectional. It is important that future research examine longitudinal data in order to better characterize the relationship between neural correlates of PLEs and progression to psychosis.

The current study helps characterize the relationship between neural activation and PLEs during middle childhood. The results demonstrate that PLEs during middle childhood are associated with decreased activation in multiple brain regions during working memory that has

previously been implicated in psychosis spectrum symptoms. The current study provides novel evidence not only that neural correlates of working memory, including decreased DLPFC, striatum, and pallidum activation, during an EN-back task are associated with PLEs, but also that these correlates may be specific PLEs as compared with depression. However, we also found that increased activation in several other regions, such as the parahippocampus, nucleus accumbens, and rostral ACC, while viewing faces was specific to depressive symptoms rather than PLEs. While the effect sizes of these relationships are small ($\beta s \leq |0.04|$), this is to be expected for nonclinical symptoms assessed before the onset of significant functional impairment in a large population sample. Thus, although our findings indicate that abnormal activation during working memory may be detectable in nonclinical PLEs, the results should be reviewed in the context of small effect sizes. Further research is needed to determine whether early alterations in working memory–related brain activation are early manifestations of psychosis risk. If they are, these findings would align with a neurodevelopmental model of psychosis in which developmental abnormalities during critical periods are possibly contributing mechanisms or markers for psychotic disorders.

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REFERENCES

1. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L (2009): A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychol Med 39:179–195.
2. Laurens K, Hodgins S, Maughan B, Murray R, Rutter M, Taylor E (2007): Community screening for psychotic-like experiences and other putative antecedents of schizophrenia in children aged 9–12 years. Schizophr Res 90:130–146.
3. Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H (2000): Children's self-reported psychotic symptoms and adult schizophreniform disorder: A 15-year longitudinal study. Arch Gen Psychiatry 57:1053–1058.
4. Kelleher I, Harley M, Murtagh A, Cannon M (2011): Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. Schizophr Bull 37:362–369.
5. Varghese D, Scott J, Welham J, Bor W, Najman J, O'Callaghan M, *et al.* (2011): Psychotic-like experiences in major depression and anxiety disorders: A population-based survey in young adults. Schizophr Bull 37:389–393.
6. Blanchard MM, Jacobson S, Clarke MC, Connor D, Kelleher I, Garavan H, *et al.* (2010): Language, motor and speed of processing deficits in adolescents with subclinical psychotic symptoms. Schizophr Res 123:71–76.
7. Kelleher I, Murtagh A, Clarke MC, Murphy J, Rawdon C, Cannon M (2013): Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: Support for the processing speed hypothesis. Cogn Neuropsychiatry 18:9–25.
8. Mollon J, Reichenberg A (2018): Cognitive development prior to onset of psychosis. Psychol Med 48:392–403.
9. Hemager N, Plessen KJ, Thorup A, Christiani C, Ellersgaard D, Spang KS, *et al.* (2018): Assessment of neurocognitive functions in 7-year-old children at familial high risk for schizophrenia or bipolar disorder: The Danish High Risk and Resilience Study–VIA 7. JAMA Psychiatry 75:844–852.
10. Rossi R, Zammit S, Button KS, Munafò MR, Lewis G, David AS (2016): Psychotic experiences and working memory: A population-based study using signal-detection analysis. PLoS One 11:e153148.
11. Livingstone K, Harper S, Gillanders D (2009): An exploration of emotion regulation in psychosis. Clin Psychol Psychother 16:418–430.
12. Laurens KR, Hobbs MJ, Sunderland M, Green MJ, Mould GL (2012): Psychotic-like experiences in a community sample of 8000 children aged 9 to 11 years: An item response theory analysis. Psychol Med 42:1495–1506.
13. Yamasaki S, Usami S, Sasaki R, Koike S, Ando S, Kitagawa Y, *et al.* (2018): The association between changes in depression/anxiety and trajectories of psychotic-like experiences over a year in adolescence. Schizophr Res 195:149–153.
14. Gur RC, Calkins ME, Satterthwaite TD, Ruparel K, Bilker WB, Moore TM, *et al.* (2014): Neurocognitive growth charting in psychosis spectrum youths. JAMA Psychiatry 71:366–374.
15. Dickson H, Cullen AE, Jones R, Reichenberg A, Roberts RE, Hodgins S, *et al.* (2018): Trajectories of cognitive development during adolescence among youth at-risk for schizophrenia. J Child Psychol Psychiatry 59:1215–1224.
16. Karcher NR, Barch DM, Avenevoli S, Savill M, Huber RS, Simon TJ, *et al.* (2018): Assessment of the Prodromal Questionnaire–Brief Child Version for measurement of self-reported sychoticlike experiences in childhood. JAMA Psychiatry 75:853–861.
17. Pflueger MO, Calabrese P, Studerus E, Zimmermann R, Gschwandtner U, Borgwardt S, *et al.* (2018): The neuropsychology of emerging psychosis and the role of working memory in episodic memory encoding. Psychol Res Behav Manag 11:157–168.
18. Zheng W, Zhang Q-E, Cai D-B, Ng CH, Ungvari GS, Ning Y-P, Xiang Y-T (2018): Neurocognitive dysfunction in subjects at clinical high risk for psychosis: A meta-analysis. J Psychiatr Res 103:38–45.
19. Broome MR, Day F, Valli I, Valmaggia L, Johns LC, Howes O, *et al.* (2012): Delusional ideation, manic symptomatology and working

memory in a cohort at clinical high-risk for psychosis: A longitudinal study. Eur Psychiatry 27:258–263.
20. Keefe RSE, Perkins DO, Gu H, Zipursky RB, Christensen BK, Lieberman JA (2006): A longitudinal study of neurocognitive function in individuals at-risk for psychosis. Schizophr Res 88:26–35.
21. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, *et al.* (2016): Association of neurocognition with transition to psychosis. JAMA Psychiatry 73:1239–1248.
22. Dutt A, Tseng H-H, Fonville L, Drakesmith M, Su L, Evans J, *et al.* (2015): Exploring neural dysfunction in "clinical high risk" for psychosis: A quantitative review of fMRI studies. J Psychiatr Res 61:122–134.
23. Choi J-S, Park J-Y, Jung MH, Jang JH, Kang D-H, Jung WH, *et al.* (2012): Phase-specific brain change of spatial working memory processing in genetic and ultra-high risk groups of schizophrenia. Schizophr Bull 38:1189–1199.
24. Schmidt A, Smieskova R, Simon A, Allen P, Fusar-Poli P, McGuire PK, *et al.* (2014): Abnormal effective connectivity and psychopathological symptoms in the psychosis high-risk state. J Psychiatry Neurosci 39:239–248.
25. Thermenos HW, Juelich RJ, DiChiara SR, Mesholam-Gately RI, Woodberry KA, Wojcik J, *et al.* (2016): Hyperactivity of caudate, parahippocampal, and prefrontal regions during working memory in never-medicated persons at clinical high-risk for psychosis. Schizophr Res 173:1–12.
26. Yaakub SN, Dorairaj K, Poh JS, Asplund CL, Krishnan R, Lee J, *et al.* (2013): Preserved working memory and altered brain activation in persons at risk for psychosis. Am J Psychiatry 170:1297–1307.
27. Seidman L, Thermenos H, Poldrack R, Peace N, Koch J, Faraone S, Tsuang M (2006): Altered brain activation in dorsolateral prefrontal cortex in adolescents and young adults at genetic risk for schizophrenia: An fMRI study of working memory. Schizophr Res 85:58–72.
28. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC (2009): Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry 66:811–822.
29. Vu M-AT, Thermenos HW, Terry DP, Wolfe DJ, Voglmaier MM, Niznikiewicz MA, *et al.* (2013): Working memory in schizotypal personality disorder: fMRI activation and deactivation differences. Schizophr Res 151:113–123.
30. Ragland JD, Gur RC, Raz J, Schroeder L, Kohler CG, Smith RJ, *et al.* (2001): Effect of schizophrenia on frontotemporal activity during word encoding and recognition: A PET cerebral blood flow study. Am J Psychiatry 158:1114–1125.
31. Achim AM, Lepage M (2005): Episodic memory-related activation in schizophrenia: Meta-analysis. Br J Psychiatry 187:500–509.
32. Di Giorgio A, Gelao B, Caforio G, Romano R, Andriola I, D'Ambrosio E, *et al.* (2013): Evidence that hippocampal-parahippocampal dysfunction is related to genetic risk for schizophrenia. Psychol Med 43:1661–1671.
33. Channon S, Baker JE, Robertson MM (1993): Working memory in clinical depression: An experimental study. Psychol Med 23:87–91.
34. Christopher G, MacDonald J (2005): The impact of clinical depression on working memory. Cogn Neuropsychiatry 10:379–399.
35. Rose EJ, Ebmeier KP (2006): Pattern of impaired working memory during major depression. J Affect Disord 90:149–161.
36. Harvey P-O, Fossati P, Pochon J-B, Levy R, LeBastard G, Lehéricy S, *et al.* (2005): Cognitive control and brain resources in major depression: An fMRI study using the n-back task. NeuroImage 26:860–869.
37. Walsh ND, Williams SCR, Brammer MJ, Bullmore ET, Kim J, Suckling J, *et al.* (2007): A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. Biol Psychiatry 62:1236–1243.
38. Schöning S, Zwitserlood P, Engelien A, Behnken A, Kugel H, Schiffbauer H, *et al.* (2009): Working-memory fMRI reveals cingulate hyperactivation in euthymic major depression. Hum Brain Mapp 30:2746–2756.
39. Figueroa CA, Mocking RJT, Van Wingen G, Martens S, Ruhé HG, Schene AH (2017): Aberrant default-mode network-hippocampus connectivity after sad memory-recall in remitted-depression. Soc Cogn Affect Neurosci 12:1803–1813.
40. Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK (2014): Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: Impact on psychopathology and transition to psychosis. Schizophr Bull 40:120–131.
41. Salokangas RKR, Ruhrmann S, von Reventlow HG, Heinimaa M, Svirskis T, From T, *et al.* (2012): Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: Prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophr Res 138:192–197.
42. Horan WP, Hajcak G, Wynn JK, Green MF (2013): Impaired emotion regulation in schizophrenia: Evidence from event-related potentials. Psychol Med 43:2377–2391.
43. van der Meer L, Swart M, van der Velde J, Pijnenborg G, Wiersma D, Bruggeman R, Aleman A (2014): Neural correlates of emotion regulation in patients with schizophrenia and non-affected siblings. PLoS One 9:e99667.
44. Dickson H, Calkins ME, Kohler CG, Hodgins S, Laurens KR (2014): Misperceptions of facial emotions among youth aged 9-14 years who present multiple antecedents of schizophrenia. Schizophr Bull 40:460–468.
45. Rive MM, van Rooijen G, Veltman DJ, Phillips ML, Schene AH, Ruhé HG (2013): Neural correlates of dysfunctional emotion regulation in major depressive disorder: A systematic review of neuroimaging studies. Neurosci Biobehav Rev 37:2529–2553.
46. Berking M, Wirtz CM, Svaldi J, Hofmann SG (2014): Emotion regulation predicts symptoms of depression over five years. Behav Res Ther 57:13–20.
47. Joormann J, Vanderlind WM (2014): Emotion regulation in depression. Clin Psychol Sci 2:402–421.
48. Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Schlögelhofer M, Mossaheb N, *et al.* (2012): Emotion recognition in individuals at clinical high-risk for schizophrenia. Schizophr Bull 38:1030–1039.
49. Rappaport LM, Carney DM, Verhulst B, Neale MC, Blair J, Brotman MA, *et al.* (2018): A developmental twin study of emotion recognition and its negative affective clinical correlates. J Am Acad Child Adolesc Psychiatry 57:925–933.e3.
50. Diekhof EK, Geier K, Falkai P, Gruber O (2011): Fear is only as deep as the mind allows: A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. NeuroImage 58:275–285.
51. Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, *et al.* (2014): Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. Cereb Cortex 24:2981–2990.
52. Larabi DI, van der Meer L, Pijnenborg GHM, Ćurčić-Blake B, Aleman A (2018): Insight and emotion regulation in schizophrenia: A brain activation and functional connectivity study. NeuroImage Clin 20:762–771.
53. Winton-Brown T, Schmidt A, Roiser JP, Howes OD, Egerton A, Fusar-Poli P, *et al.* (2017): Altered activation and connectivity in a hippocampal-basal ganglia-midbrain circuit during salience processing in subjects at ultra high risk for psychosis. Transl Psychiatry 7:e1245.
54. Drevets WC, Price JL, Furey ML (2008): Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. Brain Struct Funct 213:93–118.
55. Wolf DH, Satterthwaite TD, Calkins ME, Ruparel K, Elliott MA, Hopson RD, *et al.* (2015): Functional neuroimaging abnormalities in psychosis spectrum youth. JAMA Psychiatry 72:456–465.
56. Cohen AO, Breiner K, Steinberg L, Bonnie RJ, Scott ES, Taylor-Thompson K, *et al.* (2016): When is an adolescent an adult? Assessing cognitive control in emotional and nonemotional contexts. Psychol Sci 27:549–562.
57. Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, *et al.* (2013): Function in the human connectome: Task-fMRI and individual differences in behavior. NeuroImage 80:169–189.
58. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, *et al.* (2018): The Adolescent Brain Cognitive Development (ABCD) Study: Imaging acquisition across 21 sites. Dev Cogn Neurosci 32:43–54.
59. Owen AM, McMillan KM, Laird AR, Bullmore E (2005): N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25:46–59.

60. Gee DG, Humphreys KL, Flannery J, Goff B, Telzer EH, Shapiro M, *et al.* (2013): A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. J Neurosci 33:4584–4593.
61. Hare TA, Tottenham N, Galvan A, Voss HU, Glover GH, Casey BJ (2008): Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. Biol Psychiatry 63:927–934.
62. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, *et al.* (1997): Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988.
63. Kaufman J, Townsend LD, Kobak K (2017): The Computerized Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS): Development and administration guidelines. J Am Acad Child Adolesc Psychiatry 56:S357.
64. Dreyfuss M, Caudle K, Drysdale AT, Johnston NE, Cohen AO, Somerville LH, *et al.* (2014): Teens impulsively react rather than retreat from threat. Dev Neurosci 36:220–227.
65. Peelen MV, Downing PE (2005): Within-subject reproducibility of category-specific visual activation with functional MRI. Hum Brain Mapp 25:402–408.
66. Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173.
67. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31:968–980.
68. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, *et al.* (2002): Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355.
69. Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O, *et al.* (2012): Cognitive functioning in prodromal psychosis: A meta-analysis. Arch Gen Psychiatry 69:562–571.
70. Diemer MA, Mistry RS, Wadsworth ME, López I, Reimers F, Benner D, *et al.* (2012): Best practices in conceptualizing and measuring social class in psychological research. Anal Soc Issues Public Policy 13:77–113.
71. Bates D, Mächler M, Bolker B, Walker S (2014): Fitting linear mixed-effects models using lme4. Available at: http://arxiv.org/abs/1406.5823. Accessed July 10, 2019.
72. Grossman M, Best MW, Harrison AG, Bowie CR (2019): Comparison of the neurocognitive profiles of individuals with elevated psychotic or depressive symptoms. Early Interv Psychiatry 13:928–934.
73. Luna B, Padmanabhan A, O'Hearn K (2010): What has fMRI told us about the development of cognitive control through adolescence? Brain Cogn 72:101–113.
74. Mechelli A, Riecher-Rössler A, Meisenzahl EM, Tognin S, Wood SJ, Borgwardt SJ, *et al.* (2011): Neuroanatomical abnormalities that predate the onset of psychosis: A multicenter study. Arch Gen Psychiatry 68:489–495.
75. Giedd JN, Rapoport JL (2010): Structural MRI of pediatric brain development: What have we learned and where are we going? Neuron 67:728–734.
76. Rosso IM, Makris N, Thermenos HW, Hodge SM, Brown A, Kennedy D, *et al.* (2010): Regional prefrontal cortex gray matter volumes in youth at familial risk for schizophrenia from the Harvard Adolescent High Risk Study. Schizophr Res 123:15–21.
77. Haber SN (2014): The place of dopamine in the cortico-basal ganglia circuit. Neuroscience 282:248–257.
78. Haber SN (2016): Corticostriatal circuitry. Dialogues Clin Neurosci 18:7–21.
79. Lisman JE, Grace AA (2005): The hippocampal-VTA loop: Controlling the entry of information into long-term memory. Neuron 46:703–713.
80. Lodge DJ, Grace AA (2011): Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. Trends Pharmacol Sci 32:507–513.
81. Sabaroedin K, Tiego J, Parkes L, Sforazzini F, Finlay A, Johnson B, *et al.* (2019): Functional connectivity of corticostriatal circuitry and psychosis-like experiences in the general community. Biol Psychiatry 86:16–24.
82. Hubl D, Schultze-Lutter F, Hauf M, Dierks T, Federspiel A, Kaess M, *et al.* (2018): Striatal cerebral blood flow, executive functioning, and fronto-striatal functional connectivity in clinical high risk for psychosis. Schizophr Res 201:231–236.
83. Mwansisya TE, Wang Z, Tao H, Zhang H, Hu A, Guo S, Liu Z (2013): The diminished interhemispheric connectivity correlates with negative symptoms and cognitive impairment in first-episode schizophrenia. Schizophr Res 150:144–150.
84. Rodriguez M, Zaytseva Y, Cvrčková A, Dvořaček B, Dorazilová A, Jonáš J, *et al.* (2019): Cognitive profiles and functional connectivity in first-episode schizophrenia spectrum disorders—Linking behavioral and neuronal data. Front Psychol 10:689.
85. Stuhrmann A, Suslow T, Dannlowski U (2011): Facial emotion processing in major depression: A systematic review of neuroimaging findings. Biol Mood Anxiety Disord 1:10.
86. Demenescu LR, Kortekaas R, den Boer JA, Aleman A (2010): Impaired attribution of emotion to facial expressions in anxiety and major depression. PLoS One 5:e15058.