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Characteristics of youth with reported family history of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort

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ABSTRACT

Little is known about the impact of family history of psychosis on youth from community samples. To fill this gap, we compared youth with a first-degree relative with psychosis spectrum symptoms (i.e. family history of psychosis spectrum symptoms, FHPS) to youth without FHPS in a cross-sectional analysis of the Philadelphia Neurodevelopmental Cohort (PNC). The PNC is a racially diverse community sample of 9498 youth ages 8–21 years old, of whom 8928 completed the Family Interview for Genetic Studies to determine FHPS status. Polygenic risk score for schizophrenia (PRS—S) was available for a subsample of 4433 European Americans. FHPS youth (n = 489) constituted 5.5% of the analytic sample. After adjusting for environmental risk factors (sociodemographic variables and traumatic stressful events), FHPS youth had lower functioning on the Children's Global Assessment Scale and elevated psychosis spectrum, mood, externalizing, and fear symptoms compared to non-FHPS youth (all $p < .001$). In the European-American subsample, FHPS status was associated with poorer functioning and greater symptom burden in all four psychopathology domains (all $p < .001$), even after covarying for PRS—S. Thus, ascertaining FHPS is important because it is uniquely associated with symptoms and functional impairment in community youth beyond PRS-S and the environmental risk factors we investigated. Future research identifying environmental causes of FHPS-associated impairment could inform the development of interventions for the broad array of symptoms observed in FHPS youth.

1. Introduction

Youth with first-degree relatives with psychosis are at familial high risk for psychosis. Characterizing the neurodevelopment of youth at familial high risk for psychosis could inform the design of preventive intervention strategies for psychotic disorders (Charlson et al., 2018; Gabriel et al., 2017; Taylor et al., 2018). A meta-analysis found that offspring of a parent with schizophrenia had significantly higher rates of schizophrenia (12%, relative risk (RR) 7.54, $p < 0.001$) and all psychiatric disorders (47%, RR 1.45, $p = 0.001$) by age 20 compared to offspring of parents without schizophrenia (Rasic et al., 2014). Another meta-analysis found that youth with a family history of schizophrenia had deficits in several cognitive domains, including processing speed, verbal memory, visual memory, verbal working memory, and executive function (Cohen's d = 0.21–0.81) compared to youth without a family history of schizophrenia (Bora et al., 2014); these cognitive deficits are similar to deficits reported in adults with family histories of schizophrenia (Calkins et al., 2010; Gur et al., 2006, 2007; Mucci et al., 2018).

Prior family history of psychosis studies ascertained at-risk youth by identifying a person with schizophrenia and examining their offspring or siblings (Donatelli et al., 2010; Ellersgaard et al., 2018; Hameed and Lewis, 2016; Keshavan et al., 2008; de la Serna et al., 2011). By contrast, we studied a community sample of youth and administered the Family Interview for Genetic Studies (FIGS) to evaluate whether participants had a first-degree relative with psychosis spectrum (PS) symptoms (Calkins et al., 2014). PS symptoms are positive and disorganized symptoms that may occur in the absence of a psychotic disorder diagnosis or may be subthreshold/attenuated. Our methods are similar to a psychiatric interview or primary care evaluation (Green, 2007), where the index patient or caregiver reports family psychiatric history, as in clinical high risk for psychosis evaluations (Cannon et al., 2016;Georgopoulos et al., 2019; Miller et al., 2003; Woods et al., 2009, 2018) and psychopathology risk stratification studies in the community and primary care (Fusar-

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Poli, 2017; Green, 2007). The primary aim of our study is to address the gap in research on reported family history of psychosis in community samples.

Moreover, studies have not investigated polygenic risk score for schizophrenia (PRS—S) in association with family history in youth (Agerbo et al., 2015; Bigdeli et al., 2016). The PRS-S quantifies genetic risk for schizophrenia due to common genetic variants based on allelic association with schizophrenia and explains an estimated 7% of the liability to schizophrenia (Ripke et al., 2014). Prior work suggests that PRS-S is associated with PS symptoms in adults (van Os et al., 2017) and anxiety, depression, attention deficit hyperactivity disorder, and oppositional defiant disorder/conduct disorder in children and adolescents (Nivard et al., 2017). Our study aims to determine whether this quantitative measure of genetic risk for schizophrenia accounts for some of the psychopathology associated with a reported family history of PS symptoms (FHPS), if FHPS is indeed associated with youth psychopathology.

We hypothesized that FHPS would be associated with: 1. Greater psychopathology including PS, mood, externalizing, and fear symptoms and poorer overall functioning; 2. Poorer neurocognitive performance across the domains of executive control, episodic memory, complex cognition, and social cognition; 3. Higher PRS—S, and that PRS-S would be associated with PS, mood, externalizing, and fear symptoms. We therefore expected that some of the psychopathology associated with FHPS would be driven by the genetic risk captured by PRS—S.

2. Methods

2.1. Philadelphia Neurodevelopmental Cohort (PNC)

The PNC is an ethnically and racially diverse sample of 9498 youth ages 8–21 years old who were not seeking psychiatric treatment. Youth were enrolled between 2009 and 2012 and recruited from the Children's Hospital of Philadelphia (CHOP) pediatric health care network, which included over 30 pediatric clinics, in Pennsylvania, New Jersey, and Delaware. Participants were not recruited from psychiatric clinics, so the sample is not enriched for those seeking mental health services. The cohort and assessment have been previously described (Calkins et al., 2014, 2015). Inclusion required stable medical health, proficiency in English, and ability to complete cognitive testing. Youth with significant developmental delays were excluded. Participants were assessed clinically and cognitively, and peripheral blood samples were previously obtained for genotyping. The current study characterizes the 8928 youth (94%) for whom Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) data were available. Written assent and guardian consent were obtained for youth under age 18, and written consent was obtained for youth ages 18–21 years old. The University of Pennsylvania and CHOP institutional review boards approved the study.

2.2. Family Interview for Genetic Studies (FIGS)

A computerized and abbreviated version of the FIGS (Calkins et al., 2015; Maxwell, 1996) was administered to adult probands (age ≥ 18) or collateral informants (of probands < age 18) and screened for presence or absence of biological first-degree family history of psychopathology. The abbreviated version of the FIGS for psychosis is publicly available online (www.phenxtoolkit.org). Following affirmative responses to psychosis-related FIGS General Screening Questions for any first-degree relative of the proband, the FIGS Psychosis Checklist (Maxwell, 1996) was administered to assess lifetime history of PS symptoms. The FIGS probes for auditory and visual hallucinations, delusions, disorganized speech, and catatonia. We consider these PS symptoms because we did not directly assess the affected family members and could not confirm that the symptoms were in the context of a psychotic disorder. Family history status was based on FIGS and coded by consensus of doctoral level clinicians (NA, MEC, JHT) blinded to the youth's symptoms and neurocognitive testing to avoid influence of proband symptom and neurocognitive status on judgments about psychosis family history. Youth were divided into those with a family history of PS symptoms (FHPS) and without FHPS (non-FHPS) in first-degree biological relatives.

2.3. Demographic and environmental variables

Demographics included age, sex, race (European-American, African-American, Other), and ethnicity (Hispanic, non-Hispanic). As described previously (Moore et al., 2016), Census-based American Community Survey data and Philadelphia Police Department crime data were aggregated to give standardized scores (i.e. Z-scores) for socioeconomic status based on each participant's address. Socioeconomic status score included data on the percent of residents in poverty, percent of residents who were married, median family income, and rates of violent and non-violent crimes. Higher values indicate higher neighborhood socioeconomic status. Additionally, as previously described (Barzilay et al., 2018), lifetime traumatic stressful events was based on the number of participant endorsed items: experiencing a natural disaster; having a bad accident; thinking s/he or someone close to them could be killed or hurt badly; witnessing someone getting killed, badly beaten, or die; seeing a dead body; being attacked or badly beaten; being threatened with a weapon; or being sexually forced (including but not limited to rape).

2.4. Clinical assessment

Psychopathology was assessed using a computerized structured screening interview (GOASSESS), as described previously (Calkins et al., 2015). GOASSESS includes a modified and abbreviated version of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997) supplemented with Avolition; Expression of Emotion; Experience of Emotions and Self; Occupational Functioning; Trouble with Focus and Attention; and Disorganized Communication subscales of the Scale of Prodromal Symptoms (SOPS) (Calkins et al., 2015; Miller et al., 2003) and the PRIME Screen, which measures attenuated psychosis symptoms (Kline et al., 2012). Prior exploratory and confirmatory factor analyses of 112 assessment items (correlated-traits models) identified four psychopathology domains: PS, mood, externalizing (symptoms related to attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder), and fear (Shanmugan et al., 2016). Functioning was assessed using the Children's Global Assessment Scale (CGAS, scored 0–100) (Shaffer et al., 1983).

2.5. Neurocognitive assessment

Participants received a computerized neurocognitive battery (CNB) that took approximately 1 h to complete. The CNB consists of validated and reliable tests that are included in the PhenX Toolkit. Psychometric properties and details of the CNB were described previously (Gur et al., 2010, 2012). Briefly, the CNB included 14 tests, 12 of which provide efficiency scores, averaging accuracy and speed of correct responding, and can be divided into four domains based on an exploratory factor analysis (oblimin rotation) of efficiency scores. Standardized efficiency scores were calculated for each of the following domains (Moore et al., 2015):

1) Complex Cognition: Verbal Reasoning Test, Matrix Reasoning Test, Line Orientation Test
2) Episodic Memory: Word Memory Test, Face Memory Test, Visual Object Learning Test
3) Executive Control: Continuous Performance Test, Letter N-Back Test, Conditional Exclusion Test
4) Social Cognition: Emotion Identification Test, Emotion Differentiation Test, Age Differentiation Test

2.6. Polygenic risk score for schizophrenia (PRS—S)

Samples were genotyped on Illumina arrays - Human610_Quadv1, HumanHap550v, HumanHap550v3, HumanOmniExpress-12v1, or Human1M-Duov3_B, and standard procedures were used for data cleaning and imputation as detailed previously (Shafee et al., 2018). Of the 5019 European-American participants, standardized PRS-S for a subsample of genotyped unrelated European-American participants (n = 4433) were calculated as detailed previously (Shafee et al., 2018). PRS-S calculations were restricted to European-American participants because efforts to determine PRS-S for African Americans and other minorities are ongoing and beyond the scope of the present study. We used genome wide association study (GWAS) summary statistic data from the Psychiatric Genomics Consortium (PGC) (Ripke et al., 2014) (https://www.med.unc.edu/pgc/results-and-downloads). PRS-S was calculated using a GWAS significance threshold of $p < 0.05$ and adjusted based on the first 10 principal components from ancestry analyses.

2.7. Statistical analyses

We used *t*-tests and proportion tests to determine whether demographic and environmental variables (sex, age, race, ethnicity, neighborhood socioeconomic status, and traumatic stressful events) varied by FHPS status. We used multiple linear regression covarying for demographic and environmental variables to determine whether FHPS status was associated with psychopathology, functioning, and neurocognitive outcomes. In the subsample of European Americans, we determined whether FHPS status (FHPS n = 165; non-FHPS n = 4268) was associated with elevated PRS-S in regression models covarying for demographic and environmental variables (PRS-S was the dependent variable in this analysis). In the European-American subsample, we also included PRS-S and the interaction between FHPS and PRS-S in the multiple regression models to determine whether covarying for PRS-S attenuated the relationship between FHPS and outcomes (PRS-S was an independent variable in this analysis).

We had 10 outcomes of interest (4 psychopathology domains, overall functioning, 4 neurocognitive domains, PRS—S), and therefore used the conservative Bonferroni correction for multiple comparisons and set the significance threshold at two-tailed $p < 0.005$. We set the cutoff for trend level significance as two-tailed $p < 0.05$, and we report all trends to help readers interpret our findings and evaluate the potential for Type II Error (i.e. falsely negative findings). All analyses were done in R v3.5.1.

3. Results

3.1. Demographic and environmental characteristics

FHPS youth constituted 5.5% (n = 489) of the sample. Of FHPS youth, 321 (65.6%) had one parent (but no siblings) with PS symptoms, 127 (25.9%) had one sibling (but no parent) with PS symptoms, and 41 (8.4%) had more than one relative (parents and/or siblings) with PS symptoms. The mean age was 14.2 years. Table 1 shows that FHPS youth were more likely to be African-American and Hispanic, live in lower socioeconomic neighborhoods, and have greater lifetime exposure to traumatic stressful events (all $p < 0.001$). FHPS youth were also more likely to be female (57% vs. 52%, $p = 0.03$).

3.2. Symptoms

As hypothesized, FHPS youth had elevated symptoms across all four psychopathology domains relative to non-FHPS youth after covarying for demographic and environmental factors. Standardized mean differences (SMD) by psychopathology domain were: PS (SMD = 0.38, 95%CI 0.30–0.47), mood (SMD = 0.39, 95%CI 0.30–0.48), externalizing (SMD = 0.32, 95%CI 0.23–0.40), and fear (SMD = 0.32, 95%CI 0.23–0.41) (all $p < 0.001$) (Fig. 1).

Table 1
Cohort characteristics stratified by family history of psychosis symptoms.

	No family history of psychosis symptoms N = 8439	Family history of psychosis symptoms N = 489	p-Value[a]
n (%)			
Sex (female)	4346 (52%)	277 (57%)	0.03
Race			
African American	2726 (32%)	203 (42%)	<0.001
European American	4819 (57%)	200 (41%)	<0.001
Other	895 (11%)	86 (17%)	<0.001
Ethnicity (Hispanic)	540 (6%)	54 (11%)	<0.001
Mean (SD)			
Age (years)	14.23 (3.69)	14.20 (3.50)	0.83
Neighborhood SES Z score	0.02 (0.99)	-0.38 (1.02)	<0.001
Lifetime Traumatic Stressful Events	0.77 (1.14)	1.34 (1.61)	<0.001

[a] The categorical variables were compared using 2-sample z-tests of proportions, and the continuous variables were compared using *t*-tests. SD = standard deviation, SES = socioeconomic status (higher values indicate higher SES); Lifetime Traumatic Stressful Events (higher values = higher number of exposures endorsed).

Supporting a "dose response" effect, youth with multiple first-degree relatives with PS symptoms had higher levels of PS (SMD = 0.63, 95%CI 0.33–0.93, $p < 0.001$) and mood (SMD = 0.45, 95%CI 0.14–0.75, $p = 0.004$) symptoms compared to youth with only one parent with PS symptoms. There was a similar trend for more fear symptoms (SMD = 0.34, 95%CI 0.03–0.65, $p = 0.03$) in youth with multiple relatives with PS symptoms compared to youth with one parent with PS symptoms. In contrast, there were similar levels of externalizing symptoms (SMD = 0.06, 95%CI −0.24–0.36, $p = 0.69$) when comparing youth with multiple relatives with PS symptoms to youth with only one parent with PS symptoms (Fig. 2). Youth with one parent with PS symptoms had similar symptom levels to youth with one sibling with PS symptoms for all symptom domains (all $p > 0.05$, Fig. 2).

3.3. Overall functioning

As hypothesized, FHPS youth had lower overall functioning compared to non-FHPS youth (SMD = −0.43, 95%CI −0.52 to −0.34, $p < 0.001$) (Fig. 1) after covarying for demographic and environmental factors. Unadjusted mean CGAS was 72.91 (±SD 14.01) for FHPS versus

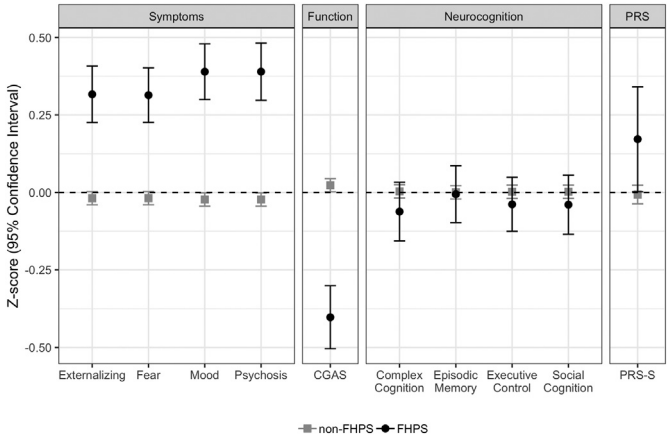

Fig. 1. Symptoms, functioning, neurocognition, and polygenic risk score for schizophrenia in FHPS and non-FHPS youth. Polygenic risk score was only calculated for the subsample of European-Americans (n = 4433). CGAS = Children's Global Assessment Scale, FHPS = family history of psychosis spectrum symptoms, PRS-S = polygenic risk score for schizophrenia.

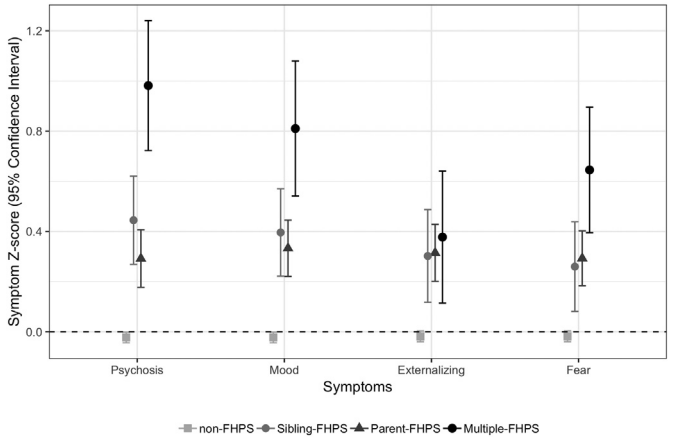

Fig. 2. How the number of family members with psychosis spectrum symptoms impacts youth symptoms. Youth with multiple relatives with psychosis spectrum symptoms had higher levels of psychosis spectrum symptoms ($p < 0.001$) and mood symptoms ($p = 0.004$), similar externalizing symptoms, and a trend for higher fear symptoms ($p = 0.03$) compared to youth with only one parent with psychosis spectrum symptoms. FHPS = family history of psychosis spectrum symptoms, Sibling-FHPS = only one sibling with FHPS, Parent-FHPS = only one parent with FHPS, Multiple-FHPS = multiple relatives (siblings and/or parents) with FHPS.

79.58 (±11.74) for non-FHPS youth ($p < 0.001$). FHPS youth had comparable overall functioning levels, whether the youth had one parent, one sibling, or multiple first-degree relatives with PS symptoms ($p > 0.05$, Online Supplemental figures).

3.4. Neurocognition

Contrary to our hypothesis, FHPS status did not predict complex cognition (SMD = 0.06, 95%CI −0.02–0.14, p = 0.15), episodic memory (SMD = −0.001, 95%CI −0.10–0.10, p = 0.97), executive control (SMD = 0.03, 95%CI −0.07–0.13, p = 0.55), or social cognition (SMD = 0.03, 95%CI −0.05–0.11, p = 0.44) efficiency outcomes (Fig. 1). When accuracy and speed scores were examined separately, there were still no significant differences between FHPS and non-FHPS youth (data not shown). Differences in neurocognitive efficiency results were not significant for FHPS youth whether the youth had one parent, one sibling, or multiple first-degree relatives with PS symptoms (Supplemental Fig. S2 available online).

3.5. Polygenic risk score for schizophrenia in the European-American subsample

PRS-S was higher in FHPS than non-FHPS youth as hypothesized in univariate analysis and after covarying for demographic and environmental factors (SMD = 0.18, 95%CI 0.02–0.34, p = 0.02) at the trend level (Fig. 1). There was a trend for higher PRS-S in youth with multiple first-degree relatives with PS symptoms (SMD = 0.80, 95%CI 0.22–1.38, p = 0.006) and one parent with PS symptoms (SMD = 0.21, 95%CI, 0.01–0.41, p = 0.04) compared to non-FHPS youth. PRS-S in FHPS youth with one sibling with PS symptoms was similar to the PRS-S in non-FHPS youth (SMD = 0.02, 95%CI −0.24–0.28, p = 0.85) (Online Supplemental Fig. S3).

We also investigated effects of FHPS on psychopathology, functioning, and neurocognitive outcomes while covarying for PRS—S, demographics, and environmental factors. FHPS remained a predictor of greater psychopathology and lower overall functioning: PS (SMD = 0.52, 95%CI 0.38–0.66), mood (SMD = 0.50, 95%CI 0.35–0.65), externalizing (SMD = 0.35, 95%CI 0.20–0.50), fear (SMD = 0.37, 95%CI 0.22–0.52), and functioning (SMD = −0.38, 95%CI 0.30–0.46) (all $p < 0.001$). Additionally, FHPS youth had reduced social cognition efficiency compared to non-FHPS youth (SMD = −0.23, 95%CI −0.39 to −0.07, p = 0.003), complex cognition efficiency was lower at the trend level in FHPS compared to non-FHPS youth (SMD = −0.19, 95% CI −0.33 to −0.05, p = 0.006); however, FHPS status was not associated with episodic memory or executive control. In summary, FHPS status was associated with a small (Cohen, 1992) social cognition deficit in European-American youth in the model covarying for PRS—S. In post-hoc analyses, we investigated whether there was a deficit in social cognition in FHPS youth in European-Americans if PRS-S was not adjusted for, and we found that when PRS-S was not included as a covariate, there was only a trend toward a social cognition deficit in FHPS (SMD = −0.18, 95%CI −0.04 to −0.32, p = 0.01). Therefore, in the European-American subsample, including PRS-S as a covariate was required to identify a small social cognition deficit in FHPS at our significance threshold of $p < 0.005$.

In models with PRS-S as the sole independent variable and multivariate models with PRS—S, FHPS, demographics, and environmental factors as covariates, PRS-S was not associated with psychopathology, functioning, or neurocognitive efficiency. In the multivariate models, the PRS-S regression coefficients for the outcomes were: PS (regression coefficient (β) = 0.01, p = 0.69), mood (β = 0.02, p = 0.27), externalizing (β =0.004, p = 0.77), fear (β = 0.005, p = 0.70), functioning (β = −0.02, p = 0.29), social cognition (β = −0.01, p = 0.37), complex cognition (β = −0.03, p = 0.05), episodic memory (β = 0.004, p = 0.76), and executive control (β = −0.01, p = 0.47). When we added a term for the interaction between PRS-S and FHPS, there was no interaction between FHPS and PRS-S for any outcome (all $p > 0.05$). That is, the null association between PRS-S and outcomes was similar for FHPS and non-FHPS youth. In univariate models, FHPS explained more variance than PRS for all outcomes, and adding PRS-S to FHPS in models did not significantly improve the amount of variance explained by the models compared to FHPS alone (see Supplementary Table S1). In multivariate models without FHPS, PRS-S was not significantly associated with any of the outcomes (see Supplementary data).

4. Discussion

We found that self- or caregiver-reported family history of PS symptoms is an important risk factor for PS, mood, externalizing, and fear symptoms and poorer functioning in community youth. We also found that FHPS youth lived in more adverse environments and had a trend toward having an increased polygenic risk score for schizophrenia, but these did not fully account for the functional impairment. Notably, FHPS youth did not have neurocognitive deficits compared to non-FHPS youth overall; however, after adjusting for PRS-S in the European-American subsample, FHPS status was associated with a small social cognition deficit.

As we hypothesized, we found reduced overall functioning and higher symptom levels across all psychopathology domains in FHPS youth compared to non-FHPS youth and an even greater increase in PS and mood symptoms when youth had multiple family members with FHPS. Our results are consistent with studies in youth (Dean et al., 2010; Donatelli et al., 2010; Ellersgaard et al., 2018; Goldstein et al., 2010; Keshavan et al., 2008; Shah et al., 2019) and adults (Dean et al., 2010; DeVylder and Lukens, 2013; Vandeleur et al., 2014), who were ascertained through recruiting offspring or siblings of patients with a psychotic disorder. Fewer studies have investigated family history in general population samples of youth using national registry data (Dean et al., 2010; Gottesman et al., 2010; Jeppesen et al., 2015) or direct interview of affected members (Ormel et al., 2005), and there is even less evidence on family history of psychosis in non-treatment seeking youth when the data is collected by asking the youth or caregivers. To our knowledge, the largest such study assessed 6356 children from the Avon Longitudinal Study of Parents and Children Cohort (ALSPAC) and found that family history of schizophrenia as reported by the parents was not associated with psychosis spectrum symptoms at age 12 years (Zammit et al., 2008). However, the study was limited in that family history information was collected using postal

questionnaires when the youth was ages 0–4 years. In contrast, our study used an in-person abbreviated version of the Family Interview of Genetic Studies to assess for family history of PS symptoms that was administered at the same time youth symptoms were assessed. Our findings expand the literature by adding evidence that asking youth and caregivers about PS symptoms in the family is important because it is associated with symptoms and functioning in community children and adolescents.

Efforts to identify youth at high risk for psychosis (Perez et al., 2015) and psychopathology more broadly (Beers et al., 2017) have the potential to increase access to early intervention services and improve long-term outcomes; however, data on how to help primary care clinicians accurately identify at-risk youth is limited (Fusar-Poli et al., 2016; Wissow et al., 2013). Our findings suggest that asking about FHPS in non-treatment seeking youth may help identify youth at risk for psychosis and psychopathology more broadly. Further research is needed to determine whether asking about FHPS adds value to traditional mental health screening in pediatric primary care (Beers et al., 2017).

A strength of our study is the large and diverse sample, which increases the generalizability of our phenotype findings and allowed us to investigate sociodemographic correlates of FHPS status. FHPS youth in the PNC were more likely to live in lower socioeconomic neighborhoods, have greater lifetime exposure to traumatic stressful events, identify as African-American and Hispanic, and be female compared to non-FHPS youth. The low socioeconomic status, high traumatic stressful event exposure, and high rate of minorities among FHPS youth in our study highlight that FHPS youth often have risk factors for adverse outcomes beyond family history (Agerbo et al., 2015; Barzilay et al., 2018; Gur et al., 2019; Laurens et al., 2015; Padmanabhan et al., 2017; Radhakrishnan et al., 2018; Thompson et al., 2009). Even after adjusting for these demographic and environmental factors, FHPS status still predicted poorer clinical and functional outcomes.

A potential explanation for the broad array of symptoms associated with FHPS is that environmental factors particularly common in FHPS households (beyond traumatic stressful events and low socioeconomic status) contribute to the wide array of symptoms in FHPS youth. This account suggests that interventions targeting disorder-specific symptoms in FHPS youth could be augmented by interventions targeting potentially modifiable environmental factors that affect a range of symptoms observed in FHPS youth. For instance, future studies could investigate whether particular family stressors and dynamics in FHPS households (Finkelhor et al., 2013; Martens and Addington, 2001; Wong et al., 2008) mediate the relationship between FHPS and poorer youth outcomes, which could inform the development of family-based preventive intervention and treatment strategies for FHPS youth. There is robust evidence for family interventions in psychosis (Onwumere et al., 2011), and it is possible that family-based interventions could be helpful for FHPS youth as well. Ideally, interventions for FHPS youth would be implemented in community settings that minimize stigma for the youth and parent (e.g., Tang et al., 2019).

Notably, while PRS-S was expectedly higher in FHPS youth at the trend level, it was surprisingly not associated with PS symptoms in non-treatment seeking youth. This lack of association is nonetheless consistent with prior research (Jones et al., 2016; Mistry et al., 2018; Sieradzka et al., 2014; Zammit et al., 2013). Moreover, PRS-S was not associated with mood, fear, or externalizing symptoms, functioning, or neurocognition in our study (Nivard et al., 2017). The literature on PRS-S and childhood psychopathology is mixed, but even studies with positive findings suggest that the variance explained by PRS-S is very small (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Germine et al., 2016; Mistry et al., 2018; Nivard et al., 2017; Shafee et al., 2018). Given the null associations between PRS-S and outcomes in our study, it is not surprising that PRS-S did not account for the psychopathology or poorer functioning associated with FHPS. Importantly, even though FHPS-associated impairment is not due to PRS—S, the impairment could be due to a wide range of genetic factors not accounted for in the PRS—S, like genes associated with PS symptoms (not just schizophrenia) or genes associated with anxiety, depression, ADHD, or other psychopathology.

In contrast to most, but not all (Georgopoulos et al., 2019), studies comparing youth with and without family histories of psychotic disorders (Bora et al., 2014; Hemager et al., 2018), we found that youth with and without family histories of PS symptoms performed similarly on neurocognitive tests. However, after adjusting for PRS-S in the European-American subsample, we did find that FHPS status was associated with a small social cognition deficit and a small complex cognition deficit (at the trend level). Thus, if there are neurocognitive deficits in FHPS youth, they are likely small. A reasonable interpretation of our findings in the context of the literature is that youth with a family history of a psychotic disorder may have larger neurocognitive deficits than youth with a reported family history of PS symptoms. This interpretation is consistent with other studies that reported larger cognitive deficits in individuals with psychotic disorders (Mesholam-Gately et al., 2009) and smaller cognitive deficits in individuals with PS symptoms (e.g. attenuated psychotic symptoms) (Bora et al., 2014; Davidson et al., 2018).

4.1. Limitations

A notable limitation is our use of self- and caregiver-report to determine FHPS status, rather than direct assessment of the youth's relative for PS symptoms. For instance, self- and caregiver-report biases could potentially increase FHPS and non-FHPS group differences if youth already at an elevated risk for psychopathology are more likely to report a family history of psychosis. Still, our study supports the use of self- and caregiver-report of FHPS for risk stratification in terms of symptom and functioning levels. The study was also limited in that we only had PRS-S for the European-American sample, so the PRS-S findings may not generalize to youth with other ancestries. An inherent limitation is that our participants were young, on average just entering the age of highest risk for schizophrenia and other psychotic disorders, so longer term follow-up will inform ultimate trajectories for FHPS youth.

4.2. Conclusions

Asking youth and their families about FHPS is important because it is uniquely associated with symptoms and functional impairment in community youth beyond PRS-S and the environmental risk factors in our analyses. Longitudinal studies of FHPS youth can identify mechanisms by which genetics and environment interact to impact outcome, and characterize both risk and resiliency factors for developing severe mental illness.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.12.021.

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