Schizophrenia Bulletin vol. 51 no. S2 pp. S85–S94, 2025
https://doi.org/10.1093/schbul/sbae161

SUPPLEMENT ARTICLE

Schizotypy, Psychosis Proneness, and the Polygenic Risk for Schizophrenia and Resilience

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***Background and Hypothesis*: Schizotypy is a well-established phenotype for psychosis proneness and risk. Yet, its genetic underpinnings and relations to genetic bases of the schizophrenia spectrum are not well understood owing to conflicting findings. In a deep phenotyping approach, we hypothesized that genetic markers of risk for and to schizophrenia are differentially associated with (trait-level) dimensions of schizotypy and (state-level) prodromal symptoms. *Study Design*: In 367 (130 male, 237 female) psychiatrically healthy young adults, we assessed multiple schizotypy instruments (OLIFE, SPQ-B, Multidimensional Schizotypy Scales), aggregated into composite scores, and a measure of prodromal symptoms (PQ-16). Those were tested for direct and interactive associations with the polygenic risk score (PRS) for schizophrenia and a novel PRS for resilience to schizophrenia. *Study Results*: Both prodromal symptom number (*rho* = 0.16, p_{corr} = .018) and distress (*rho* = 0.14, p_{corr} = .027) were positively related to the schizophrenia PRS. Positive schizotypy showed a similar association but did not remain significant after correction (*rho* = 0.11, p_{corr} = .082). Schizophrenia PRS and disorganized schizotypy had a negative interactive effect on prodromal symptom distress (*b* = −0.10, p_{corr} = .048). The resilience score did not show any significant associations with any of the measures. *Conclusions*: These results further support the idea of a (partially) shared genetic basis of schizophrenia and nonclinical, predominantly positive expressions of the psychosis spectrum but also indicate relevant distinctions between the 2, possibly related to other modulating factors or general (transdiagnostic) psychopathological risk. In line with previous findings, effects seem to be more robust for state- than trait-level markers, but these may also be influencing each other.**

Key words: deep phenotyping/distress/genetics/polygenic risk score (PRS)/prodromal symptoms/schizophrenia/schizotypy/resilience

Introduction

Schizotypy as a personality trait has been proposed as a phenotypic indicator of psychosis proneness.[1–4] As such, it has established itself as a widely used dimensional marker of psychosis risk.[5] Its dimensional structure lends itself to approaches to define and investigate psychosis on a spectrum or continuum,[6,7] with an ongoing debate on how this continuum should be conceptualized.[8,9] The commonly used self-report inventories for schizotypy usually follow a 3-factor approach (positive, negative, and disorganized schizotypy), which parallels the 3-factor structure of schizophrenia as well as psychotic-like experiences (PLE), a commonly used phenotype in high-risk and early intervention research on psychosis.[10–13] In addition, findings relating schizotypy to cognitive

performance and brain imaging parameters have lent further support for its use as a dimensional marker across the schizophrenia spectrum.[14–17]

The genetics of schizotypy have, in recent years, become a more intensive topic of research.[18] Following some initial studies showing an overlap of schizophrenia and schizotypy at the level of single risk variants and genes (eg,[19,20]), subsequent studies have attempted to understand the overlap with the polygenic architecture of schizophrenia. In particular, several studies have correlated polygenic risk scores (PRS), ie, aggregates of multiple single nucleotide polymorphisms across the genome, with subclinical phenotypes. Several studies of PRS for schizophrenia and PLEs (across adult, adolescent, and childhood cohorts) have produced negative findings for such correlations (eg,[21–24]), although there are also some positive findings (eg,[25–29]).

As for schizotypy, there is some evidence for an overlap with polygenic risk for schizophrenia, but findings have not been entirely consistent. An initial large general population study by Docherty and colleagues found an association of the Schizophrenia Personality Questionnaire (brief version, SPQ-B) scores with schizophrenia PRS, in particular in males, where schizophrenia PRS was associated with negative schizotypy traits.[30] Similarly, van Os et al. reported a correlation of interview-based schizotypy scores with schizophrenia PRS, which was significant for the total score as well as positive and negative schizotypy subscales, but also for PLE scores derived from CAPE.[31] Ahangari et al. showed an association of schizophrenia PRS with interview-rated schizotypy/negative symptom dimensions, both in cohorts with prior psychosis as well as healthy subjects.[32] In contrast, a large recent association analysis of our group analyzing schizotypy and its facets (based on SPQ-B scores) in relation to schizophrenia PRS did not identify associations across 2 large cohorts.[33] Two most recent studies have re-addressed the issue to add novel insights into the problem: Tiego and colleagues used multiple schizotypy inventories for deep phenotyping and showed significant positive correlations of schizophrenia PRS with delusional experiences and reduced social interest but not the main schizotypy facets from standard schizotypy questionnaires.[34] Mas-Bermejo and colleagues did not detect a significant association between either schizotypy (assessed with the Wisconsin Schizotypy Scales (WSS)) or PLEs (CAPE) in healthy nonclinical subjects, but only for a motor subscale of a clinical high-risk status interview.[35]

In the present study, we sought to use deep phenotyping with multiple schizotypy instruments augmented by self-report assessment of prodromal symptoms in a nonclinical young adult cohort to test the hypothesis of an association with polygenic risk for schizophrenia. This approach combines the deep phenotyping approach of Tiego and colleagues[34] with an additional state-related prodromal symptom phenotype. Second, we evaluate the differential association of positive, negative, and disorganized schizotypy from 3 schizotypy inventories to identify variations in association strengths (or lack thereof). Third, in addition to testing our phenotypes against polygenic risk for schizophrenia, we also test them against a recently developed polygenic score for resilience to schizophrenia[36]: this novel molecular genetics approach focuses on genomic markers related to modifying penetrance of risk loci and mechanisms of relevance to resilience, thus providing complementary genetic information. While schizotypy is often referred to as a phenotypic expression of schizophrenia risk, in nonclinical individuals, it also constitutes a healthy variation in cognition, emotion, and behavior and might also include compensatory or protective qualities that prevent exacerbation.[1,37] Genetic underpinnings of such qualities might be reflected in variance in markers constituting the resilience PRS.

Finally, we also tested sex and IQ as possible moderators, as well as interaction terms of schizotypy facets, based on recent brain imaging studies[38] showing that the interaction of schizotypy facets might explain disproportionately large effects on neural intermediaries of genotype–phenotype links. More importantly, however, we also use this to address the conundrum of potential protection provided by particular schizotypy facets being combined with the absence or low expression of others – in particular, high positive schizotypy with low negative/disorganized schizotypy, a profile sometimes termed "benign schizotypy"[37] (or individuals described as "happy or "healthy schizotypes,"[39,40] based on their relatively low levels of psychopathology / subjective distress[37,41] and potentially higher resilience to stress.[37,42]

Methods

Study Cohort

We included a total of $n = 367$ psychiatrically healthy subjects (130 male, 237 female; mean age 23.85 years, SD 3.79) in this study. Participants consisted mostly of university students (80%) but also included salaried employees (11%), individuals in school or apprenticeship (7%) and other forms of occupation (2%).

All study participants gave written informed consent to study protocols approved by the Ethics Committee of the Medical School of the Philipps-Universität Marburg (protocols 61/18, 79/18) in accordance with the current version of the Declaration of Helsinki. The cohort overlaps mostly with a study sample we analyzed for psychometric aspects of schizotypy and related traits.[12,43] Inclusion criteria for this study were age 18-40, ability to provide informed consent, as well as Central European descent; exclusion criteria were current or past psychiatric disorders, current or past substance dependence, current or past psychiatric treatments, psychotropic drug use, central nervous neurological disorders, uncontrolled medical illness (eg, untreated hypertension or diabetes),

or learning disability (conceptualized as IQ below 80). We screened subjects for the absence of psychiatric history using the German SCID-I screening inventory.[44] Ratings on the German MWT-B[41] test were used to estimate IQ in order to exclude learning disability[45,46] and to test IQ as a possible moderator (mean IQ = 116.46, *SD* = 14.12, range = 92-142). All subjects were native German speakers.

Phenotyping

Subject phenotyping was accomplished using an online platform (SoSci Survey[47];), to which participants received individualized access and where responses to self-report questionnaires were recorded digitally.

We used 3 different complementary self-report inventories to characterize each individual for their schizotypy traits, as detailed in our previous study[12]: the Schizotypal Personality Questionnaire-Brief version (SPQ-B),[48,49] the Oxford-Liverpool Inventory of Feelings and Experiences (OLIFE),[50,51] and the Multidimensional Schizotypy Scales (MSS).[52,53] Based on the standardized values of each instrument's subscores, we additionally calculated "meta-level" composite scores for the positive, negative, and disorganized schizotypy domains, as well as a total schizotypy score.

For assessment of prodromal symptoms, we applied the Prodromal Questionnaire (PQ-16) with 16 items characterizing both occurrence and associated distress of PLE.[54]

DNA Extraction, Genome-Wide Genotyping and Imputation

DNA was extracted from whole blood samples using standard procedures. Genome-wide genotyping was conducted using Illumina's Infinium Global Screening Array-24 BeadChip (GSA, customized to include additional markers with relevance to psychiatric disorders; San Diego, CA, USA). Standard quality control procedures (eg, sample call rate > 0.98; variant call rate > 0.98; Minor Allele Frequency (MAF) > 0.01; removal of variants deviating from Hardy-Weinberg equilibrium ($P < 1e\text{-}06$); checking for sex mismatches and heterozygosity outlier) were carried out using the PLINK software package.[55] Genotypes of the samples were phased using Eagle (v. 2.4.1) and imputed using Minimac (v. 4) with 1000 Genomes Project Phase 3 data as a reference panel.[56–58] Variants that showed a low imputation accuracy ($R^2 < 0.6$) were excluded from the calculation of PRS.

Calculation of PRS and Outlier Detection

PRS was computed by using summary statistics from the respective genome-wide association studies (GWAS) of the Psychiatric Genomics Consortium[59] and Hess et al.[36,60] (see previous work for more details[61]), as the sum of the risk alleles (common variants with MAF > 1%) weighed by their effect estimates. For the schizophrenia PRS we used the genome-wide significant *P*-value threshold ($P = 5 \times 10^{-8}$). As for the schizophrenia resilience PRS, no genome-wide significant variants were identified, we chose the threshold that best discriminated between cases and controls in the original GWAS ($P = .3$). In an initial sample of 371 participants, we identified 2 pairs of cryptic relatives with pi-hat ≥ 0.125 and randomly excluded 1 person of each pair. Further, to control for genetic heterogeneity due to population structure, the first 8 multidimensional scaling (MDS) components based on pairwise identity-by-state distance matrix were computed in PLINK v1.90b6.24 and included as covariates in all analyses. Based on this, 2 participants were identified as genetic outliers with a distance from the mean of > 6 SD in the ancestry components and excluded from the analyses, resulting in a final study sample of $n = 367$ participants.

Statistical Analysis

Statistical analyses were performed in R[62] (version 4.2.0), RStudio[63] (version 2023.09.0 + 463), and jamovi[64] (version 2.3.21.0). To analyze (partial) bivariate associations between polygenic risk and resilience scores and schizotypy and PLE measures, we ran partial nonlinear (Spearman's rho) correlation analyses. To test for interaction effects (between schizotypy facets, between PRS and schizotypy facets and between PRS and sex and IQ), we specified and tested linear regression models, including the 2 main effects and the interaction term. In all analyses, sex and the first 8 ancestry components were included as covariates. For interaction analyses, continuous variables have been mean-centered and standardized. As schizotypy and PLE facets within one instrument as well as across instruments are typically correlated, we applied false discovery rate (FDR) correction for multiple comparisons, as it is an established method for the correction of multiple comparisons but less conservative than family-wise-error-correction. We have applied FDR correction using the R function *p.adjust*, which was implemented in the stats package.

Results

Association Analyses

Composite scores (see figure 1): We found a significant positive association between PQ-16 Total and PQ-16 Distress Total and the PRS for schizophrenia. We also found a nominally significant positive association between the Positive Schizotypy Composite score and the schizophrenia PRS, which was, however, reduced to a trend after FDR correction. There was no significant association between the resilience PRS and any of the scores.

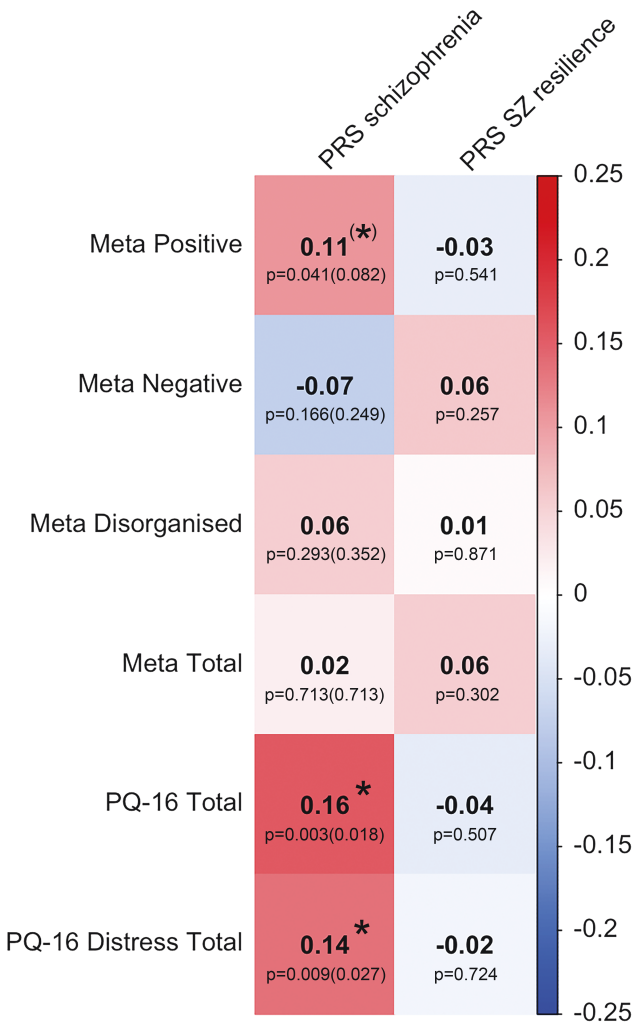

Fig. 1. Correlations (Spearman's rho) of schizotypy meta-scores (derived from combining MSS, SPQ-B, and OLIFE measures) and prodromal symptoms (PQ-16) with PRS for schizophrenia and resilience to schizophrenia, respectively. All correlations are partialized for sex and MDS components c1–c8 and FDR-corrected (in brackets) for the respective number of comparisons (*)Nominally significant, *Significant after FDR correction.

Single scores (see table 1): We found a nominally significant negative association between the OLIFE Introvertive Anhedonia score (negative schizotypy) and the PRS for schizophrenia, which was, however, reduced to a trend finding after FDR correction. There were no significant findings between the schizophrenia PRS and any of the other scores or between the resilience PRS and any of the scores.

Analysis of Interaction Effects Between Schizotypy Facets

We tested whether interactions of schizotypy facet composites were associated with polygenic risk and resilience scores. None of the interaction terms (Positive × Negative, Positive × Disorganized, Negative × Disorganized) showed any significant association with any of the PRS.

Analysis of Interaction Effects of Schizotypy Facets × PRS on PLE

We further tested if the association between the PRS for schizophrenia and state-level PLE occurrence and distress was dependent on trait-level schizotypy composite scores. We found one significant negative interaction effect between PRS for schizophrenia and the disorganized composite score, predicting PLE distress ($F(12,354) = 18.22$, $P < .001$; $R^2 = 0.39$; interaction effect estimate $b = -0.102$, $P = .004$ ($p_{corr} = .048$)). Specifically, this shows an inverse relationship between PRS for schizophrenia and PLE distress, dependent on the level of disorganized schizotypy: a positive association in below-average disorganized schizotypy, yet a negative association in above-average disorganized schizotypy (see figure 2).

Analysis of Interaction Effects of PRS Schizophrenia × PRS SZ Resilience

To test the potential influence of PRS SZ resilience on the association between the PRS SZ and schizotypy and PLE expressions, we also ran exploratory interaction analyses between the 2 PRS, set up as the previous interaction models. While we find no effect on PLE occurrence ($F(12,354) = 1.07$, $P = .387$; $R^2 = 0.03$) or distress ($F(12,354) = 1.22$, $P = .365$; $R^2 = 0.04$), the interaction effect is significant for the composite negative scale ($F(12,354) = 2.38$, $P = .006$; $R^2 = 0.07$; interaction effect estimate $b = 0.32$, $P = .027$), but not for the positive ($F(12,354) = 1.16$, $P = .313$; $R^2 = 0.04$) or disorganized ($F(12,354) = 1.22$, $P = .270$; $R^2 = 0.04$) composite scores. The same pattern also shows when testing the singular instrument scores with a significant effect for OLIFE Introvertive Anhedonia ($F(12,354) = 2.41$, $P = .005$; $R^2 = 0.08$; interaction effect estimate $b = 0.11$, $P = .048$), and trends for MSS negative ($F(12,354) = 2.79$, $P = .001$; $R^2 = 0.09$; interaction effect estimate $b = 0.10$, $P = .070$) and SPQ-B Interpersonal ($F(12,354) = 1.85$, $P = .039$; $R^2 = 0.06$; interaction effect estimate $b = 0.11$, $P = .058$). In all models, post hoc analyses reveal that there is a stronger negative association between PRS schizophrenia and negative schizotypy under the lowest PRS SZ resilience scores (see figure 3).

Analysis of Interaction Effects of Sex × PRS

Sex was not a significant moderator between schizophrenia risk or resilience PRS and the composite schizotypy or PLE facets in any of the tested models.

Analysis of Interaction Effects of IQ × PRS

In none of the models did we find IQ to be a significant moderator between schizophrenia risk or resilience

Table 1. Correlations of Schizotypy Scores (MSS, SPQ-B, and OLIFE Sum/Overall Scores and Subscores) With PRS for Schizophrenia and Resilience to Schizophrenia

Schizotypy Measure		PRS Schizophrenia	PRS SZ Resilience
MSS Positive	rho	0.064	0.005
	P	.230	.929
MSS Negative	rho	−0.040	0.075
	P	.448	.157
MSS Disorganized	Rho	0.071	−0.029
	P	.179	.580
MSS Sum	Rho	0.018	0.054
	P	.741	.306
OLIFE Unusual Experiences	Rho	0.092	0.024
	P	.082	.656
OLIFE Introvertive Anhedonia	Rho	**−0.147**	0.026
	P (p_{corr})	**.005 (.065)**	.629
OLIFE Cognitive Disorganization	rho	0.088	−0.036
	P	.098	.501
OLIFE Impulsive Nonconformity	rho	0.093	0.029
	P	.079	.590
OLIFE Total	rho	0.034	−0.003
	P	.518	.962
SPQ-B Cognitive Perceptual	rho	0.079	−0.057
	P	.134	.279
SPQ-B Interpersonal	rho	−0.000	0.086
	P	.997	.106
SPQ-B Disorganized	rho	−0.005	0.079
	P	.917	.135
SPQ-B Total	rho	0.013	0.078
	P	.799	.142

All correlations are partialized for sex and MDS components c1–c8; rho = Spearman's rho; p_{corr} = *P*-value, FDR-corrected for the respective number of comparisons.
Abbreviation: SZ, schizophrenia.

PRS and the composite schizotypy or PLE occurrence or distress.

Discussion

Our study set out to analyze the relation of (trait) schizotypy as well as (state) prodromal symptoms with either polygenic risk for schizophrenia or polygenic resilience to schizophrenia in a cohort of psychiatrically healthy young adults. The 3 major findings of our study relate to the questions of (a) differential associations of schizotypy facets with polygenic schizophrenia risk, (b) the relation of schizotypy as a trait-type marker vs. more state-like markers (captured with the PQ-16) and their differential association to genetic risk, and finally (c) the hypothesis that polygenic risk vs. resilience might differentially link to schizotypy dimensions. Our study delivers novel insights into these 3 aspects and might help to advance our understanding of how a (multi)dimensional phenotype characterizing a spectrum relates to genetic disease risk.

A main finding of our study is that polygenic schizophrenia risk is mainly associated with state-like and (to a lesser degree) trait-like markers (nominally significant in our sample, but not significant following FDR correction) capturing experiences within the positive dimension, but not negative, disorganized, or overall schizotypy.

This result partially contrasts earlier negative findings in 2 nonclinical cohorts using the SPQ-B[33] and a study[35] using the CAPE and WSS, resp., but is in line with a more recent study showing associations of a "delusional experiences" dimension (derived from multiple inventories addressing schizotypy/psychosis proneness).[34] Considering the methodological heterogeneity across these studies, we would argue that subtle yet significant differences in phenotypes, as shown in a recent study of ours,[12] might account for these differences and actually advance our understanding of how the wider psychosis spectrum relates to genetic schizophrenia risk. First, we note that both our study and the study of Tiego and colleagues[34] show an association with positive dimension phenotypes, in both cases based on composite scores derived from multiple inventories rather than a single questionnaire or subscale. In fact, our follow-up analysis on single schizotypy inventories failed to demonstrate direct associations with single positive subscales from applied questionnaires. This may indicate the degree specificity of single instruments, reflecting their respective conceptualization of the construct of schizotypy and supporting the previously

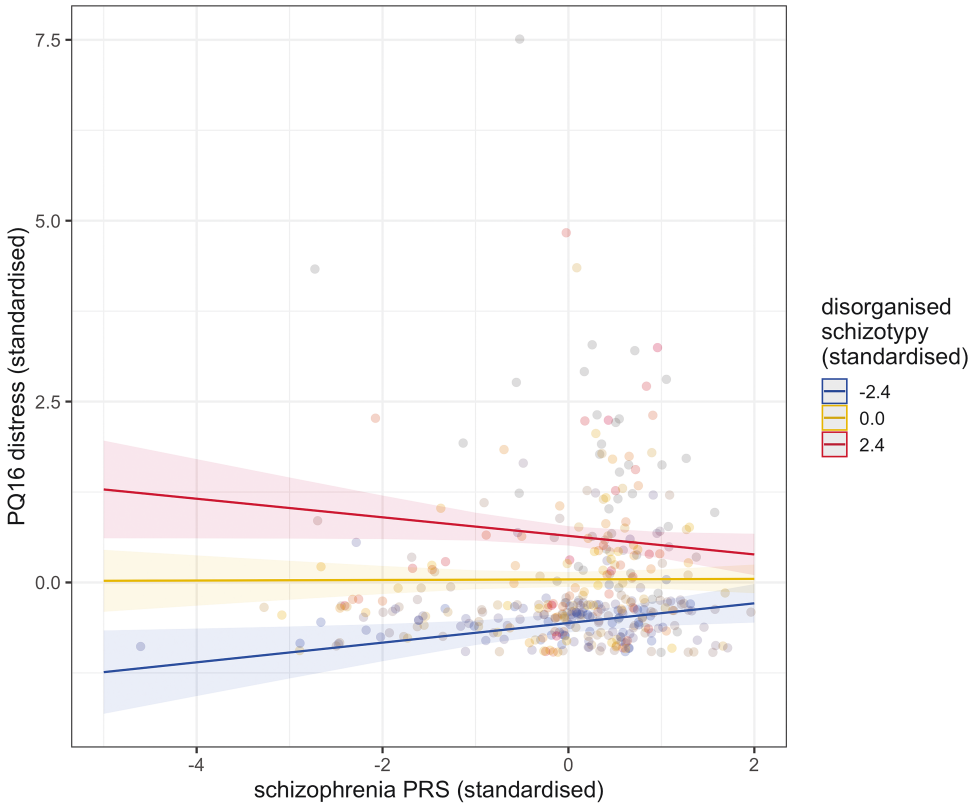

Fig. 2. Interaction effect of schizophrenia PRS and composite disorganized schizotypy on PLE distress. Line and point colors represent (from top to bottom) mean +1 standard deviation/above average, mean, and mean −1 standard deviation/below average levels of disorganized schizotypy.

discussed need for a refinement of schizophrenia spectrum phenotypes and a revision of the self-report measures in use.[3,12,65] Further studies, including and comparing the correlates of multiple instruments, might help dissect sources of variance that can be linked to genetic risk.

Second, the association of schizophrenia risk with prodromal symptoms, mainly represented as positive dimension items,[37] and (yet only nominally significant) with positive (rather than negative, disorganized or overall) schizotypy is echoed in positive associations identified in studies linking psychosis-like experiences to schizophrenia PRS.[25,26,29] This also raises the question of whether positive dimension characteristics, including and maybe even especially state-like symptoms and symptom-like manifestations of psychosis risk, might actually be more closely associated with the transition into manifest disease. We further show that the expression of genetic schizophrenia risk into state-like symptoms may also be dependent on underlying trait-level (disorganized) schizotypy but seems to be independent of IQ and sex.

And third, we find evidence for an interactive effect between risk and resilience polygenic variance for the expression of schizotypy expressions. Interestingly, other than the direct associations, this effect is specific to the negative dimension, both in our aggregated composite score and the single instruments, hinting at a robust pattern.

Early on, both Raine[66] and Meehl[67] have argued for different trajectories of schizotypy with different genetic underpinnings. In fact, Raine's earlier observations on studies in the clinical schizophrenia spectrum[66] and the findings of both our and 2 recent schizotypy genetics studies in nonclinical cohorts[34,35] also need to be considered in the broader context on which aspects of the psychosis spectrum they might be related to in particular. The GWAS on which the schizophrenia PRS is based[59] has shown that—as is to be expected for a complex disorder—a multitude of genes and different pathways contribute to the overall case–control differences. Yet, it is unclear how much specificity they bear for a static schizotypy trait phenotype and how well overall risk variants identified through case–control studies are able to reflect dimensional variance.

Also, it has been stressed previously that variation in schizotypy might not only be related to features directly relating to the schizophrenia spectrum but also to factors like resilience or susceptibility to environmental factors,[1,2] and our results also indicate that interaction of risk and resilience genes can modulate schizotypy levels. In other words, schizotypy and psychosis proneness phenotypes, as used today, might contain elements that are closely related to the schizophrenia spectrum but also those related (less specifically) to proneness to mental illness

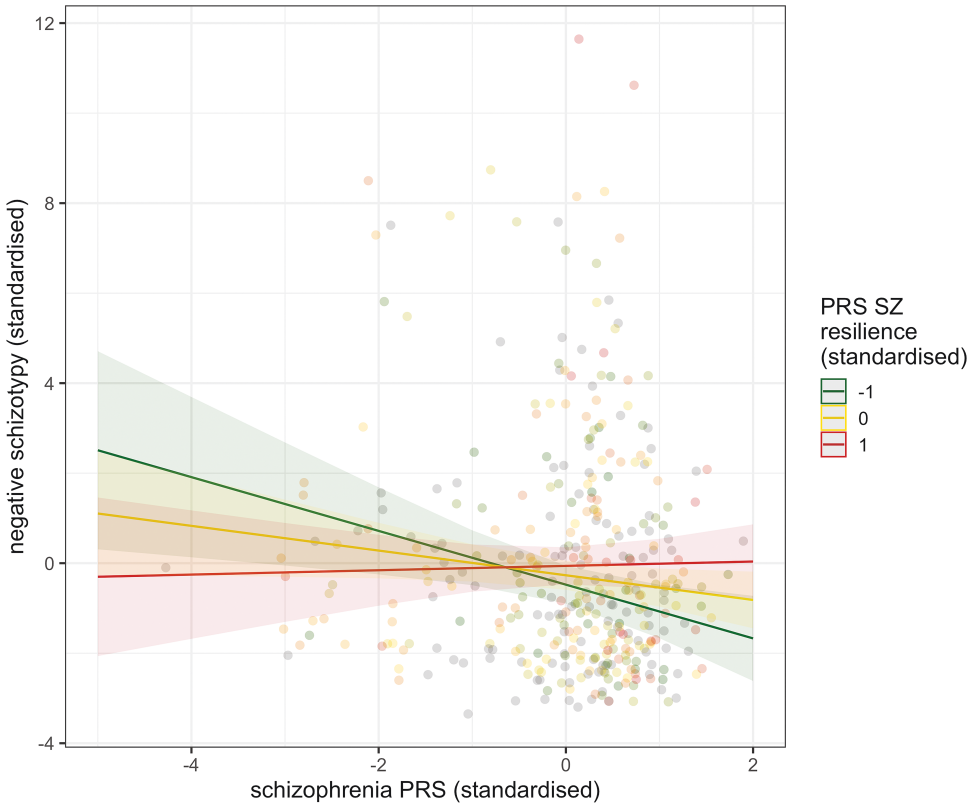

Fig. 3. Interaction effect of schizophrenia PRS and SZ resilience PRS on composite negative schizotypy. Line and point colors represent (from top to bottom) mean −1 standard deviation/below average, mean, and mean +1 standard deviation/above average levels of SZ resilience PRS.

more generally.[1] This line of argument is supported, for example, by twin studies demonstrating the overlap of schizotypy and general personality features like neuroticism,[68] as well as the mediating role of neuroticism for the impact of positive schizotypy on psychosocial functioning.[69] Conversely, the schizophrenia PRS is not only linked to schizophrenia but also symptoms across diagnostic boundaries,[70] indicative of the overlap with other disease spectra.

Our study, as well as the other recent cross-sectional studies on schizotypy genetics, show, however, some significant limitations. Even when assuming schizotypy to be a trait-level marker, these studies fail to incorporate dynamic factors leading to the emergence of psychopathology, either subclinical or clinical. Social stress, for example, has been shown to predict the emergence of psychotic-like features (states) from both positive and negative schizotypy.[71] In addition, there is a developmental perspective.[72] Schizotypy in adolescence or childhood, even if assessed reliably, might indicate less temporally stable state-type (rather than trait) characteristics and is differentially associated with later outcomes.[73,74]

Finally, we need to consider the lack of direct associations of phenotype measures with the novel PRS for resilience to schizophrenia.[36] This PRS has been constructed on the basis of genetic mechanisms or pathways that modulate the penetrance of genetic and other effects. The significant interaction between the risk and resilience PRS in our results reflects this as well: The effect of the PRS for schizophrenia is dependent on the level of PRS resilience to schizophrenia—albeit in an unintuitive pattern, as we find a negative association between schizophrenia PRS and negative schizotypy under low resilience PRS. Both the risk and resilience PRS, to a certain degree, reflect the diagnosis of schizophrenia, for which the prevalence of positive symptoms is prevailing. While through growing GWAS, many candidate genes for the (overall) schizophrenia risk could be identified, genetic underpinnings of symptom dimensions or patterns are still largely unknown and might be needed to better disentangle such associations.

Considering our above discussion on the predictive value of static trait-like schizotypal features as opposed to more state-like/fluid characteristics, one might also assume that the resilience PRS could be more related to biological processes further downstream, ie, those with importance to either transition of risk states into manifest disease or the transition of emerging first-episode symptoms into a more chronic disease course. This might also explain the lack of direct association with trait-level features.

Limitations of our study include the sample size, which is an intermediary to the 2 recent deep phenotyping

studies,[34,35] but considerably smaller than the community or population-based studies limited to using abbreviated characterizations of risk traits or states (eg,[21,25,33]). Also, our focus on a psychiatrically healthy community sample does not allow inference on subjects with prior or concurrent clinical psychopathology, which needs to be considered given previous reports of diverging associations of PRS with subclinical psychosis phenotypes present in relatives of patients but not controls.[23]

In conclusion, our study provides evidence linking prodromal symptoms, which include positive schizotypal features,[12] to polygenic risk for schizophrenia, with additional nominally significant association of positive schizotypy. This lends further support to the notion of an overlap of schizotypy and schizophrenia on a genetic level, while there seems to be a large proportion of variance unshared between the 2 constructs, possibly those related to general psychopathology, transdiagnostic risk, resilience to mental disorder, and biological factors (eg, inflammation/immunity) that is relevant to the transition, onset, or chronification of disease.

Funding

This study was supported in part by research grants of the University Hospital Giessen and Marburg (UKGM): grant 11/2017 MR (to I.N.) and grant 05/2018 MR (to Sarah Grezellschak and I.N.), as well as partially through Forschungscampus Mittelhessen (FCMH) FlexiFunds grants 2017_2_1_5 (to I.N. and Philipp Grant) and 2018_2_1_1 (to I.N.). I.N. received support from the Deutsche Forschungsgemeinschaft (DFG, grants NE2254/1-2, NE2254/2-1, NE2254/3-1, and NE2254/4-1, NE2254/6-1). I.N. is a PI of and supported by the DYNAMIC center, which is funded by the LOEWE program of the Hessian Ministry of Science and Arts (Grant Number: LOEWE1/16/519/03/09.001(0009)/98).

Conflicts of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Barrantes-Vidal N, Grant P, Kwapil TR. The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophr Bull.* 2015;41:S408–S416.
2. Debbane M, Eliez S, Badoud D, Conus P, Fluckiger R, Schultze-Lutter F. Developing psychosis and its risk states through the lens of schizotypy. *Schizophr Bull.* 2015;41:S396–S407.
3. Grant P, Green MJ, Mason OJ. Models of schizotypy: the importance of conceptual clarity. *Schizophr Bull.* 2018;44:S556–S563.
4. Kwapil TR, Barrantes-Vidal N. Schizotypy: looking back and moving forward. *Schizophr Bull.* 2015;41:S366–S373.
5. Taylor JH, Calkins ME, Gur RE. Markers of psychosis risk in the general population. *Biol Psychiatry.* 2020;88:337–348.
6. Nelson MT, Seal ML, Pantelis C, Phillips LJ. Evidence of a dimensional relationship between schizotypy and schizophrenia: a systematic review. *Neurosci Biobehav Rev.* 2013;37:317–327.
7. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med.* 2009;39:179–195.
8. Haslam N, McGrath MJ, Viechtbauer W, Kuppens P. Dimensions over categories: a meta-analysis of taxometric research. *Psychol Med.* 2020;50:1418–1432.
9. Lenzenweger MF. Schizotypy, schizotypic psychopathology, and schizophrenia: hearing echoes, leveraging prior advances, and probing new angles. *Schizophr Bull.* 2018;44:S564–S569.
10. Fonseca Pedrero E, Debbane M. Schizotypal traits and psychotic-like experiences during adolescence: an update. *Psicothema.* 2017;29:5–17.
11. Mark W, Toulopoulou T. Psychometric properties of "community assessment of psychic experiences": review and meta-analyses. *Schizophr Bull.* 2016;42:34–44.
12. Pfarr JK, Meller T, Evermann U, Sahakyan L, Kwapil TR, Nenadic I. Trait schizotypy and the psychosis prodrome: current standard assessment of extended psychosis spectrum phenotypes. *Schizophr Res.* 2023;254:208–217.
13. Cicero DC, Jonas KG, Li K, Perlman G, Kotov R. Common taxonomy of traits and symptoms: linking schizophrenia symptoms, schizotypy, and normal personality. *Schizophr Bull.* 2019;45:1336–1348.
14. Ettinger U, Mohr C, Gooding DC, et al. Cognition and brain function in schizotypy: a selective review. *Schizophr Bull.* 2015;41:S417–S426.
15. Zouraraki C, Karamaouna P, Giakoumaki SG. Cognitive processes and resting-state functional neuroimaging findings in high schizotypal individuals and schizotypal personality disorder patients: a systematic review. *Brain Sci.* 2023;13:615.
16. Zouraraki C, Karamaouna P, Karagiannopoulou L, Giakoumaki SG. Schizotypy-independent and schizotypy-modulated cognitive impairments in unaffected first-degree relatives of schizophrenia-spectrum patients. *Arch Clin Neuropsychol.* 2017;32:1010–1025.
17. Siddi S, Petretto DR, Preti A. Neuropsychological correlates of schizotypy: a systematic review and meta-analysis of cross-sectional studies. *Cogn Neuropsychiatry* 2017;22:186–212.
18. Walter EE, Fernandez F, Snelling M, Barkus E. Genetic consideration of schizotypal traits: a review. *Front Psychol.* 2016;7:1769.
19. Meller T, Schmitt S, Stein F, et al. Associations of schizophrenia risk genes ZNF804A and CACNA1C with schizotypy and modulation of attention in healthy subjects. *Schizophr Res.* 2019;208:67–75.
20. Roussos P, Bitsios P, Giakoumaki SG, et al. CACNA1C as a risk factor for schizotypal personality disorder and schizotypy in healthy individuals. *Psychiatry Res.* 2013;206:122–123.
21. Jones HJ, Stergiakouli E, Tansey KE, et al. Phenotypic manifestation of genetic risk for schizophrenia during adolescence in the general population. *JAMA Psychiatry* 2016;73:221–228.
22. Sieradzka D, Power RA, Freeman D, et al. Are genetic risk factors for psychosis also associated with dimension-specific

psychotic experiences in adolescence? *PLoS One.* 2014;9:e94398.
23. van Os J, Pries LK, Delespaul P, et al; Genetic Risk and Outcome Investigators (GROUP). Replicated evidence that endophenotypic expression of schizophrenia polygenic risk is greater in healthy siblings of patients compared to controls, suggesting gene-environment interaction. The EUGEI study. *Psychol Med.* 2020;50:1884–1897.
24. Zammit S, Hamshere M, Dwyer S, et al. A population-based study of genetic variation and psychotic experiences in adolescents. *Schizophr Bull.* 2014;40:1254–1262.
25. Legge SE, Jones HJ, Kendall KM, et al. Association of genetic liability to psychotic experiences with neuropsychotic disorders and traits. *JAMA Psychiatry* 2019;76:1256.
26. Pain O, Dudbridge F, Cardno AG, et al. Genome-wide analysis of adolescent psychotic-like experiences shows genetic overlap with psychiatric disorders. *Am J Med Genet B Neuropsychiatr Genet.* 2018;177:416–425.
27. Velthorst E, Froudist-Walsh S, Stahl E, et al; iPSYCH-Broad ASD Group, the IMAGEN consortium. Genetic risk for schizophrenia and autism, social impairment and developmental pathways to psychosis. *Transl Psychiatry.* 2018;8:204.
28. Jones HJ, Heron J, Hammerton G, et al; 23 and Me Research Team. Investigating the genetic architecture of general and specific psychopathology in adolescence. *Transl Psychiatry.* 2018;8:145.
29. Karcher NR, Paul SE, Johnson EC, et al. Psychotic-like experiences and polygenic liability in the adolescent brain cognitive development study. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2022;7:45–55.
30. Docherty AR, Shabalin AA, Adkins DE, et al. Molecular genetic risk for psychosis is associated with psychosis risk symptoms in a population-based UK cohort: findings from generation Scotland. *Schizophr Bull.* 2020;46:1045–1052.
31. van Os J, van der Steen Y, Islam MA, et al. Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. *Psychol Med.* 2017;47:2421–2437.
32. Ahangari M, Bustamante D, Kirkpatrick R, et al. Relationship between polygenic risk scores and symptom dimensions of schizophrenia and schizotypy in multiplex families with schizophrenia. *Br J Psychiatry.* 2023;223:301–308.
33. Nenadic I, Meller T, Schmitt S, et al. Polygenic risk for schizophrenia and schizotypal traits in non-clinical subjects. *Psychol Med.* 2022;52:1069–1079.
34. Tiego J, Thompson K, Arnatkeviciute A, et al. Dissecting schizotypy and its association with cognition and polygenic risk for schizophrenia in a nonclinical sample. *Schizophr Bull.* 2023;49:1217–1228.
35. Mas-Bermejo P, Papiol S, Via M, et al. Schizophrenia polygenic risk score in psychosis proneness. *Eur Arch Psychiatry Clin Neurosci.* 2023;273:1665–1675.
36. Hess JL, Tylee DS, Mattheisen M, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium. A polygenic resilience score moderates the genetic risk for schizophrenia. *Mol Psychiatry.* 2021;26:800–815.
37. Grant P, Hennig J. Schizotypy, social stress and the emergence of psychotic-like states – a case for benign schizotypy? *Schizophr Res.* 2020;216:435–442.
38. Sahakyan L, Meller T, Evermann U, et al. Anterior vs posterior hippocampal subfields in an extended psychosis phenotype of multidimensional schizotypy in a nonclinical sample. *Schizophr Bull.* 2021;47:207–218.
39. McCreery C, Claridge G. A study of hallucination in normal subjects—I. Self-report data. *Pers Individ Differ.* 1996;21:739–747.
40. McCreery C, Claridge G. Healthy schizotypy: the case of out-of-the-body experiences. *Pers Individ Differ.* 2002;32:141–154.
41. Dagnall N, Denovan A, Drinkwater KG. Longitudinal assessment of the temporal stability and predictive validity of the revised paranormal belief scale. *Front Psychol.* 2022;13:1094701.
42. Kline E, Wilson C, Ereshefsky S, et al. Schizotypy, psychotic-like experiences and distress: an interaction model. *Psychiatry Res.* 2012;200:647–651.
43. Nenadic I, Meller T, Evermann U, et al. Subclinical schizotypal vs. autistic traits show overlapping and diametrically opposed facets in a non-clinical population. *Schizophr Res.* 2021;231:32–41.
44. Wittchen H-U, Wunderlich U, Gruschwitz S, Zaudig M. *SKID-I. Strukturiertes Klinisches Interview für DSM-IV*. Hogrefe; 1997.
45. Lehrl S. *Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B*. 5th ed. Testzentrale; 2005.
46. Lehrl S, Triebig G, Fischer B. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand.* 1995;91:335–345.
47. Leiner D. *SoSci Survey (Version 3.2.01-i) [Computer software]*. https://www.soscisurvey.de
48. Fonseca-Pedrero E, Ortuno-Sierra J, Lucas-Molina B, et al. Brief assessment of schizotypal traits: a multinational study. *Schizophr Res.* 2017;197:182–191.
49. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophr Bull.* 1991;17:555–564.
50. Mason O, Claridge G. The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): further description and extended norms. *Schizophr Res.* 2006;82:203–211.
51. Mason O, Claridge G, Jackson M. New scales for the assessment of schizotypy. *Pers Individ Differ.* 1995;18:7–13.
52. Kwapil TR, Gross GM, Burgin CJ, Raulin ML, Silvia PJ, Barrantes-Vidal N. Validity of the multidimensional schizotypy scale: associations with schizotypal traits and normal personality. *Personal Disord.* 2018;9:458–466.
53. Kwapil TR, Gross GM, Silvia PJ, Raulin ML, Barrantes-Vidal N. Development and psychometric properties of the multidimensional schizotypy scale: a new measure for assessing positive, negative, and disorganized schizotypy. *Schizophr Res.* 2018;193:209–217.
54. Loewy RL, Bearden CE, Johnson JK, Raine A, Cannon TD. The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. *Schizophr Res.* 2005;79:117–125.
55. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet.* 2007;81:559–575.
56. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. *Bioinformatics.* 2010;26:2867–2873.
57. Das S, Forer L, Schonherr S, et al. Next-generation genotype imputation service and methods. *Nat Genet.* 2016;48:1284–1287.
58. Auton A, Brooks LD, Durbin RM, et al; 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature.* 2015;526:68–74.

59. Trubetskoy V, Pardinas AF, Qi T, et al; Indonesia Schizophrenia Consortium. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature.* 2022;604:502–508.
60. Hess JL, Mattheisen M, Greenwood TA, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium. A polygenic resilience score moderates the genetic risk for schizophrenia: replication in 18,090 cases and 28,114 controls from the Psychiatric Genomics Consortium. *Am J Med Genet B Neuropsychiatr Genet.* 2023;195:e32957.
61. Koutsouleris N, Dwyer DB, Degenhardt F, et al; PRONIA Consortium. Multimodal machine learning workflows for prediction of psychosis in patients with clinical high-risk syndromes and recent-onset depression. *JAMA Psychiatry* 2021;78:195–209.
62. R Core Team. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing; 2018.
63. Posit team RStudio. *Integrated development environment for R*. Posit Software, PBC, http://www.posit.co/
64. The jamovi project. *jamovi (Version 2.3) [Computer Software]*. https://www.jamovi.org
65. Tiego J, Martin EA, DeYoung CG, et al; HiTOP Neurobiological Foundations Work Group. Precision behavioral phenotyping as a strategy for uncovering the biological correlates of psychopathology. *Nat Ment Health.* 2023;1:304–315.
66. Raine A. Schizotypal personality: neurodevelopmental and psychosocial trajectories. *Annu Rev Clin Psychol.* 2006;2:291–326.
67. Meehl PE. Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *J Personal Disord.* 1990;4:1–99.
68. Macare C, Bates TC, Heath AC, Martin NG, Ettinger U. Substantial genetic overlap between schizotypy and neuroticism: a twin study. *Behav Genet.* 2012;42:732–742.
69. Barrantes-Vidal N, Ros-Morente A, Kwapil TR. An examination of neuroticism as a moderating factor in the association of positive and negative schizotypy with psychopathology in a nonclinical sample. *Schizophr Res.* 2009;115:303–309.
70. Smigielski L, Papiol S, Theodoridou A, et al. Polygenic risk scores across the extended psychosis spectrum. *Transl Psychiatry.* 2021;11:600.
71. Barrantes-Vidal N, Chun CA, Myin-Germeys I, Kwapil TR. Psychometric schizotypy predicts psychotic-like, paranoid, and negative symptoms in daily life. *J Abnorm Psychol.* 2013;122:1077–1087.
72. Debbane M, Barrantes-Vidal N. Schizotypy from a developmental perspective. *Schizophr Bull.* 2015;41:S386–S395.
73. Green MJ, O'Hare K, Laurens KR, et al. Developmental profiles of schizotypy in the general population: a record linkage study of Australian children aged 11-12 years. *Br J Clin Psychol.* 2022;61:836–858.
74. O'Hare K, Watkeys O, Dean K, et al. Childhood schizotypy and adolescent mental disorder. *Schizophr Bull.* 2024;50:69–77.