Associations between schizophrenia polygenic risk and apathy in schizophrenia spectrum disorders and healthy controls

Lyngstad SH, Bettella F, Aminoff SR, Athanasiu L, Andreassen OA, Færden A, Melle I. Associations between schizophrenia polygenic risk and apathy in schizophrenia spectrum disorders and healthy controls.

Objective: Apathy is a central predictor of a poor functional outcome in schizophrenia. Schizophrenia polygenic risk scores (PRSs) are used to detect genetic associations to key clinical phenotypes in schizophrenia. We explored the associations between schizophrenia PRS and apathy levels in schizophrenia spectrum disorders (n = 281) and matched healthy controls (n = 298), and further how schizophrenia PRS contributed in predicting apathy when added to premorbid and clinical factors in the patient sample.

Method: Schizophrenia PRSs were computed for each participant. Apathy was assessed with the Apathy Evaluation Scale. Bivariate correlation analyses were used to investigate associations between schizophrenia PRS and apathy, and between apathy and premorbid and clinical factors. Multiple hierarchical regression analyses were employed to evaluate the contributions of clinical variables and schizophrenia PRS to apathy levels.

Results: We found no significant associations between schizophrenia PRS and apathy in patients and healthy controls. Several premorbid and clinical characteristics significantly predicted apathy in patients, but schizophrenia PRS did not.

Conclusion: Since the PRSs are based on common genetic variants, our results do not preclude associations to other types of genetic factors. The results could also indicate that environmentally based biological or psychological factors contribute to apathy levels in schizophrenia.

Significant outcomes

- There is no association between levels of apathy and the polygenic risk score for schizophrenia in patients with schizophrenia spectrum disorders and healthy controls. As opposed to clinical characteristics, polygenic risk scores do not contribute to predicting apathy levels in patients.
- Although the influence from genetic factors is not precluded, environmental factors may be important for the development of apathy.
- The schizophrenia polygenic risk score in its current form is of limited use in clinical settings.

Limitations

- Despite a moderate sample size for a clinical study, we may lack sufficient statistical power, with risks of type I as well as type II errors.
- The cross-sectional design precludes us from investigating associations to persistent negative symptoms.
- The apathy self-report measure is validated in healthy controls and first-episode psychosis patients, but not in multiple episode psychosis, and results should be interpreted with some caution.
Introduction

While the etiology of schizophrenia spectrum disorders remains largely elusive (1, 2), their heritability estimates are high (60–80%) (3, 4) and the hypothesis of an aberrant neurodevelopment as part of etio-pathogenesis is widely accepted (5–8). Improving our understanding of their underpinnings is imperative to develop new treatments and improve outcomes (1). Negative symptoms are core psychopathological phenomena in schizophrenia spectrum disorders (9). They frequently predate the onset of psychosis (10) and are associated with poor premorbid adjustment (11) and suggested to be closely related to neurodevelopmental disturbances (12–14). Due to lack of adequate treatments (15), high levels of negative symptoms predict poorer functional trajectories throughout the course of illness (16, 17).

Commonly used assessments of negative symptoms, such as the Scale for the Assessment of Negative Symptoms (18), the Clinical Assessment Interview for Negative Symptoms (19), and the Positive and Negative Syndrome Scale (20), are based on observations of behaviors, without links to biological underpinnings and thus without differentiation between primary negative symptoms and negative symptoms that are secondary to other causes, like positive symptoms or depression (i.e., secondary negative symptoms). The phenomenology of depressive symptoms may be similar to negative symptoms in schizophrenia spectrum disorders. However, telling them apart is facilitated by applying psychometric tools designed to improve this differentiation, like the Calgary Depression Scale for Schizophrenia (CDSS) (21). There is now consensus that negative symptoms comprise five symptom dimensions or negative ‘sub-symptoms’ (blunted affect, alogia, avolition/apathy, anhedonia, and asociality), clustering into two separate but related domains: the expressive and the experiential/amotivational domains (17). This differentiation is thought to reflect differences in their neurobiological substrates, and studies indicate that illness mechanisms may vary between the domains (17, 22).

Reduction of motivation and goal-directed behaviors is seen across several CNS and mental disorders. This phenomenon is called ‘apathy’ in neurology, but used interchangeably with ‘avolition’ in psychiatry. The study of apathy is facilitated by the availability of trans-diagnostic assessment scales, including self-report versions that are validated also in psychotic disorders (23), thus making larger-scale studies feasible. The mechanisms underlying avolition/apathy are not yet fully identified, but recent studies indicate complex disturbances involving the reward system (24), cognitive processes (22, 25), and defeatist attitudes (26, 27). In clinical studies of psychotic disorders, apathy appears as the strongest predictor of poor functional outcome relative to other negative sub-symptoms (28, 29).

Family studies show that negative symptoms are present in the families of individuals with schizophrenia (30–32), and the risk of other family members developing psychosis is higher if their index member with schizophrenia has severe negative symptoms (33). These findings suggest that negative symptoms are related to the genetic vulnerability for schizophrenia and thus are meaningful phenotypes in molecular genetic research (34). Positive symptoms also show familiality (30, 35), but less so than negative symptoms (31, 34). The heritability estimates of negative symptom-like traits in community samples are lower than the heritability for schizophrenia (36), but appear higher at the severe end of the negative symptom distribution and higher for negative symptoms relative to hallucinations (37). Research also suggests that the expression of negative symptoms is influenced by genetic variants (38, 39) and that the genetic variants and associated biological pathways underlying negative symptoms could be partly distinct from that of other symptom domains (40).

The genetic component of schizophrenia appears as highly polygenic (1) and mainly explained by aggregated, small effects of numerous single nucleotide polymorphisms (SNPs) scattered across the genome (41, 42). These SNPs currently map onto approximately 150 independent genetic loci (43, 44) and are often shared with several other phenotypes and across diagnostic categories (45–47). Schizophrenia polygenic risk scores (PRSs) (48) capitalize on the statistical power of the large genome-wide association studies (GWAS) from the Psychiatric Genomics Consortium (PGC) (43). Schizophrenia PRSs are computed based on the allele counts and effect sizes of SNPs associated with caseness in the PGC discovery samples and represent the en masse effects of common variants to schizophrenia risk in the individual. Studies using schizophrenia PRS have diverging findings regarding associations to the symptom dimensions of schizophrenia. Evidence supporting an association between schizophrenia PRS and positive symptoms is scarce (36, 49). Studies into negative symptoms are inconclusive, finding positive, negative as well as no statistically significant associations to schizophrenia PRS (36, 49). However, the interpretations of these studies have not taken into account the possibility of discrete biological mechanisms underlying the different negative sub-
symptoms and domains (17), which could disperse genetic signals. Linking genetic information to specific negative sub-symptoms could thus increase our ability to identify their biological substrates (39).

Aims of the study
In the present study, we investigated the association between schizophrenia polygenic risk score (PRS) and apathy in individuals with schizophrenia spectrum disorders and in healthy controls. The main research questions were as follows:

i Are schizophrenia PRSs associated with the level of apathy in patients and in healthy controls?

ii To what extent do schizophrenia PRSs predict the current level of apathy when added to pre-morbid and clinical characteristics in patients.

We hypothesized that higher levels of schizophrenia PRS would be associated with higher levels of apathy in patients and, to a lesser extent, in healthy controls. We also hypothesized that schizophrenia PRS would have an individual, but limited, explanatory effect in predicting the current level of apathy.

Methods
Participants
As part of the Thematically Organized Psychosis (TOP) Study at the Norwegian Center for Mental Disorders Research (NORMENT), 296 patients with schizophrenia spectrum disorders (schizophrenia, schizophreniform, and schizoaffective disorders, psychosis not otherwise specified) were consecutively recruited from in-patient and out-patient units of four major psychiatric clinics in Oslo. The hospitals’ catchment areas serve approximately 485 000 inhabitants and are representative of the city population’s variation in socioeconomic status. Participants were within 18–65 years of age. As allele frequencies vary widely between ethnicities (50), only participants of European ancestry origin were included.

General exclusion criteria were i) having an IQ below 70 ii) former moderate/severe head injury iii) present medical or neurological condition with associations to psychosis or apathy iv) psychosis caused by substance use. In total, 15 patients were excluded based on these criteria, leaving 281 for the analyses. Of these, 186 (66%) were first-episode psychosis (FEP) patients, while 95 (34%) had multiple psychotic episodes (MEP).

Persons randomly selected from the national population records from the same catchment areas (51) were invited by mail to participate as healthy controls (HC, n = 350). All were between 18 and 65 years old and with European ancestry. In addition to the general exclusion criteria specified above, HC were not eligible if they had a personal or family history of severe mental disorder. The mean age for HC was higher than for patients. They were matched with the patient group by randomly eliminating 52 HC with age above mean (28 women, 24 men), leaving 298 HC for the analyses. We did not match for intelligence or years of education due to the polygenic overlap between schizophrenia, cognition, and educational attainment (52, 53). Thus, matching for the intelligence quotient or educational years could introduce selection bias.

All participants gave informed, written consent according to the Declaration of Helsinki. The Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics approved the study.

Clinical assessment
Patients with schizophrenia spectrum disorders were evaluated by trained psychologists or medical doctors using comprehensive clinical interviews and neurocognitive tests. Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (54). The diagnostic inter-rater reliability was satisfactory, with a diagnostic agreement of 82% (95% confidence interval 0.60–0.94; $k = 0.77$) (55). ‘Narrow schizophrenia’ was defined as a diagnosis of schizophrenia (excluding schizoaffective and schizophreniform disorders and psychosis not otherwise specified).

Premorbid functioning was assessed with the Premorbid Adjustment Scale (PAS) (56). PAS scores were divided into age-based intervals (childhood, early adolescence, late adolescence, adulthood) and into school (PAS academic) and social functioning (PAS social). To avoid including periods with prodromal symptoms, we only applied PAS childhood scores in the analyses. Duration of untreated psychosis (DUP) (57) was defined as the duration in weeks from psychosis onset (score $\geq 4$ for $\geq 1$ week on items p1, p3, p5, p6, or g9 in the Positive and Negative Syndrome Scale (PANSS)) (20) to first adequate treatment. Age at onset (AAO) depicts the age at onset of the first psychotic episode.

Symptom dimensions were assessed with the PANSS, with 20 items divided into five symptom factors (positive, negative, disorganized, depressed,
and excited) (58). We further employed a PANSS two-factor model for negative symptoms (59) where items n1, n3, n6, g5, g7, and g13 were grouped into the expressive domain and items n2, n4, and g16 into the experiential/amotivation domain. Functioning was assessed with the function subscale of the Global Assessment of Functioning Scale, split version (GAF-F) (60).

Apathy was assessed with the Apathy Evaluation Scale self-rated version (AES-S) (61), previously applied in neuropsychiatric (62) and psychotic disorders as well as in HC (63–65). We used a 12-item abridged version of the original 18-item AES-S. In a FEP subsample of the current sample, the AES-S was highly concordant with the AES clinician-rated version (23). This is in line with recent studies describing reliable self-reports of motivational symptoms in people with schizophrenia (66) even with longer duration of illness (67, 68). The AES-S items are scored on a 1-point to 4-point Likert scale with higher sum scores representing higher levels of apathy. We defined an AES-S sum score \( \geq 27 \) (two standard deviations above mean in HC) to represent clinically significant levels of apathy, a cutoff applied also in previous studies (64, 69).

Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (21), a scale designed to enhance the differentiation between negative symptoms and depression in psychotic disorders. Alcohol and drug use were measured with the Alcohol Use Disorder Identification Test (AUDIT) and the Drug Use Disorder Identification Test (DUDIT) (70, 71) respectively. We estimated the current load of antipsychotic medication (AP) in each participant: The actual daily dose of an AP was divided by its Defined Daily Dose (DDD) (dose recommended by the WHO Collaborating Centre for Drug Statistics Method) (72). Then, if a participant used more than one AP, one ratio was computed for each and these ratios lastly summed to a ‘Sum AP’.

Genotyping
DNA (obtained from blood or saliva) was analyzed in six succeeding batches between 2014 and 2017 at deCODE Genetics, Reykjavik, Iceland, using Illumina Human OmniExpress-12 and Infinium OmniExpress-24 chips and Illumina Global screening arrays.

The genotypes were quality controlled using PLINK (version 1.9; https://www.cog-genomics.org) (73, 74). Based on the genotyping, participants were excluded if they i) were represented in duplicate (one of the duplicates was retained), ii) were mixup samples (calculated investigating ‘excess of heterozygosity’), and iii) had more than 5% missing genotype data. Variants were excluded if they deviated severely \( (P < 0.0001) \) from the Hardy–Weinberg equilibrium and had a minor allele frequency (MAF) <5% or low yield (<95% of chromosomes conferred information about the variant).

Variant imputation
Non-genotyped variants were imputed with MaCH (75) (http://www.sph.umich.edu/csg/abecasis/MACH) using the European reference samples in the Phase III release of the 1000 Genomes project. Variants not present in this reference sample or with ambiguous strand alignments were removed from the sample data set. Imputation was a three-stage process involving i) ChunkChromosome, dividing the data set into 2500 variant chunks with a 500 variant overlap; ii) MaCH, phasing each chunk (40 rounds and 400 states); and iii) Minimac, imputing each of the phased chunks to the 1000 Genomes reference panel (20 rounds and 400 states) (http://genome.sph.umich.edu/wiki/Minimac). Lastly, \( r^2 \) and MAF were estimated for all imputed variants; variants with \( r^2 < 0.2 \) or MAF < 0.05 were excluded. As part of postimputation quality control, participants were excluded if they i) were relatives (identity by descent, \( \pi \geq 0.125 \) \( n = 4 \)) or ii) had a gender differing from that determined by the X-chromosome marker homozygosity \( n = 7 \).

Population stratification analysis
To investigate the clustering of alleles due to ancestry/population stratification, we carried out a principal component analysis using PLINK (76) on a set of independent variants. This yielded 20 genetic principal components (PCs) to be used as covariates in the subsequent analyses.

Polygenic risk scores
Schizophrenia PRSs were computed using the methodology established by Purcell et al. (48). First, we performed a meta-analysis using METAL (http://csg.sph.umich.edu/abecasis/metal) (77) including all the Psychiatric Genetics Consortium’s (PGC’s) schizophrenia GWAS (PGC 2014) after removing the cohort in which the current study is based (TOP3). This meta-analysis resulted in unbiased effect sizes (ln (OR)) for all imputed variants. These variants were pruned according to their linkage disequilibrium state using PLINK’s
clump option ($r^2 < 0.25$, 500 kb window), selecting variants with the lowest $P$-values from all linkage disequilibrium blocks. The schizophrenia PRS then result from summing up the products (effect size*allele count) for all selected variants for each participant. Sixteen schizophrenia PRSs were computed including variants at $P$-value thresholds from 5 × 10$^{-8}$ to 1, at intervals of half an order of magnitude. Of these, the PRS inclusion threshold leading to most explained phenotypic variance in case–control status (Nagelkerke $R^2$) was selected for the ensuing analyses ($P$-value = 0.1).

Statistical analyses

All analyses from this point onward were performed using the IBM SPSS version 23. All variables were investigated concerning normality, outliers, collinearity, and homoscedasticity. DUP, AUDIT, and DUDIT were log10-transformed due to skewness. Independent-samples $t$-tests or chi-squared tests were used to assess differences between patients and HC, including validation of the expected PRS differences (Table 1). For all subsequent analyses, either parametric tests or their non-parametric alternatives were used as appropriate. Significance levels were pre-set to $<0.05$, two-tailed. For the first research question, associations between schizophrenia PRS and AES-S scores were explored in the complete sample and in patients and HC separately, using scatter plots and Pearson’s correlation analyses. We did three sets of follow-up analyses in the patient group. First, we repeated correlational analyses in the subgroups of FEP ($n = 186$), MEP ($n = 95$), and patients with a narrow schizophrenia diagnosis ($n = 163$). Second, we repeated correlational analyses in the full patient group ($n = 281$), substituting AES-S scores with PANSS negative symptoms as

### Table 1. Demographic and clinical variables

<table>
<thead>
<tr>
<th>Variable of interest</th>
<th>Patients $\bar{X}$ (SD)</th>
<th>$n$</th>
<th>Healthy controls $\bar{X}$ (SD)</th>
<th>$n$</th>
<th>Statistic $t$, $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29.3 (10.0)</td>
<td>281</td>
<td>30.4 (7.4)</td>
<td>298</td>
<td>$t = -1.5, P = 0.128$</td>
</tr>
<tr>
<td>Education, years completed</td>
<td>12.3 (2.7)</td>
<td>281</td>
<td>14.4 (2.2)</td>
<td>297</td>
<td>$t = -10.1, P &lt; 0.001$</td>
</tr>
<tr>
<td>Working/studying (n/%)</td>
<td>85 (30.4)</td>
<td>290</td>
<td>287 (99.0)</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>PAS acad. child (median/range)</td>
<td>1.50 (0.0–5.5)</td>
<td>255</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS soc. child (median/range)</td>
<td>1.00 (0.0–6.0)</td>
<td>255</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at psychosis onset</td>
<td>24.2 (8.3)</td>
<td>270</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUP (median/range in weeks)</td>
<td>40.0 (0–1040)</td>
<td>235</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic distribution</td>
<td>281</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Narrow schizophrenia* (n/%)</td>
<td>163 (58.0)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PNOS, sz.aff, sz.form (n/%)</td>
<td>118 (42.0)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Symptom profile/functioning</td>
<td></td>
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<tr>
<td>GAF-F</td>
<td>45.6 (12.5)</td>
<td>281</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS total‡</td>
<td>62.4 (16.7)</td>
<td>276</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS positive</td>
<td>14.9 (5.2)</td>
<td>278</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS negative</td>
<td>15.2 (6.2)</td>
<td>277</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS general</td>
<td>32.3 (8.4)</td>
<td>277</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS 2-factor§ expres.</td>
<td>11.7 (5.1)</td>
<td>278</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS 2-factor§ amotiv.</td>
<td>7.2 (3.3)</td>
<td>278</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AES-S</td>
<td>28.4 (7.4)</td>
<td>281</td>
<td>19.0 (4.8)</td>
<td>298</td>
<td>$t = 17.9, P &lt; 0.001$</td>
</tr>
<tr>
<td>AES-S sum score ≥ 27 (n/%)</td>
<td>167 (59.4)</td>
<td>281</td>
<td>26 (8.7)</td>
<td>298</td>
<td>$\chi^2 = 167.3, P &lt; 0.001$</td>
</tr>
<tr>
<td>CDSS</td>
<td>5.6 (4.8)</td>
<td>274</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUDIT (median/range)</td>
<td>5.0 (0–36)</td>
<td>290</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUDIT (median/range)</td>
<td>0.0 (0–40)</td>
<td>270</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum AP (median/range¶)</td>
<td>1.0 (0.0–6.7)</td>
<td>281</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ PRS ($F_1 = 0.1$)</td>
<td>0.017817 (0.000074)</td>
<td>281</td>
<td>0.017790 (0.000077)</td>
<td>298</td>
<td>$t = 4.2, P &lt; 0.001$</td>
</tr>
</tbody>
</table>

PAS, Premorbid Adjustment Scale; academic and social sub-scores [childhood ≤11 years]; DUP, Duration of Untreated Psychosis; PNOS, Psychosis Not Otherwise Specified; Sza, schizoaffective disorder; Szform, schizoaffective disorder; GAF-F, Global Assessment of Functioning Scale; functioning subscale; PANSS, Positive and Negative Syndrome Scale; AES-S, Apathy Evaluation Scale, self-report version; CDSS, Calgary Depression Scale for Schizophrenia; AUDIT, Alcohol Use Disorder Identification Test; DUDIT, Drug Use Disorder Identification Test; Sum AP, Sum (Actual Daily Dosage of Antipsychotic Medication/Defined Daily Dose) for a maximum of three antipsychotics used by each patient; SZ PRS, Schizophrenia Polygenic Risk Score.

Unless other is specified, values are means and standard deviations.

* Narrow schizophrenia = a diagnosis of schizophrenia (excluding schizoaffective and schizoaffective disorders and PNOS).

‡ PANSS 3-factor (Kay et al.).

§ PANSS 2-factor (Limburg et al.).

¶ $n = 61/281$ (22%) did not use any antipsychotic medication (AP). While 80% (178/220) used only one AP, the remaining 20% used two or three different APs.
one single factor (Wallwork’s model) (58) and as two factors (Liemburg’s model) (59). Third, we applied a multiple hierarchical linear regression analysis with AES-S as the dependent variable, adjusted for genotyping batch and six principal components, and entered the schizophrenia PRS at the last step. The relevant principal components were chosen based on significant bivariate correlations ($P \leq 0.1$ level) with schizophrenia PRS and/or the AES-S score. Since all these analyses were follow-up analyses of the primary, with a high degree of association between dependent variables, we did not correct for multiple testing. For the second research question, we did a series of blockwise multiple hierarchical linear regression analyses with AES-S as the dependent variable. Relevant premorbid and clinical predictors of apathy were chosen based on findings from previous research in psychotic disorders. Associations between AES-S, clinical predictors, and sources of secondary negative symptoms (depression, positive symptoms, and Sum AP) were then inspected using bivariate correlation analyses. Variables with a significant bivariate association ($P \leq 0.1$ level) to AES-S were entered into the regression model, adjusting for genotyping batch, principal components, and relevant secondary negative symptoms, then adding the schizophrenia PRS in the last block.

Results

Clinical and demographic characteristics of patients and HC are presented in Table 1. Patients had significantly fewer years of education and were less likely to be working or studying than HC. Twenty-two percent (61/281) of patients did not use any AP. Among the ones using AP, 80% (176/220) used one AP, while 20% used two or three different APs. Patients had higher mean apathy scores, and 59% had clinically significant levels of apathy, compared to 9% in HC. Schizophrenia PRSs were significantly higher in patients than in HC ($t = 4.2$, $P < 0.001$).

Associations between schizophrenia polygenic risk scores and apathy in patients and healthy controls

Scatter plots of schizophrenia PRS and AES-S scores in the complete sample, HC, and patients are shown in Fig. 1. Since patients had higher PRSs and higher apathy scores, the scatter plot of the complete sample gives an impression of an association between PRS and apathy. However, this is fully explained by the case–control status. The corresponding bivariate correlations are displayed in Table 2. We found no significant associations between schizophrenia PRS and apathy scores, neither in the patient sample ($n = 281$; $r = -0.08$, $P = 0.160$) nor in HC ($n = 298$; $r = -0.02$, $P = 0.685$). Follow-up analyses in the patient subgroups of FEP ($n = 186$, $r = -0.09$, $P = 0.214$), MEP ($n = 95$, $r = -0.02$, $P = 0.814$), and narrow schizophrenia diagnosis ($n = 163$, $r = -0.08$, $P = 0.307$) did not indicate any significant associations. Repeating correlational analyses in the full patient group ($n = 281$), applying PANSS negative symptoms as one single factor or as two factors, gave equivalent, negative results (Table 2). Multiple regression analyses, adjusting for batch and principal components, confirmed that the lack of significant associations between schizophrenia PRS and AES-S scores was not due to confounding effects (Table 3).

The contribution of schizophrenia polygenic risk scores to predicting current level of apathy when added to premorbid and clinical characteristics in patients

The bivariate correlations between AES-S, premorbid, and clinical characteristics are shown in Table 4. The variables entered in the multiple hierarchical regression analysis together explained 27% of the variance in apathy levels. There was not a statistically significant contribution from the schizophrenia PRS (Table 5).

Discussion

We found no statistically significant associations between schizophrenia PRS and levels of apathy neither in patients with schizophrenia spectrum disorders nor in healthy controls. Schizophrenia PRS did not contribute to the prediction of current levels of apathy when added to the premorbid and clinical characteristics.

To our knowledge, we are the first to investigate the relationship between schizophrenia PRS (as a measure of the polygenic contribution of common variants) and apathy (expected to be a biologically relevant negative sub-symptom). Using a broader measure of the negative symptom dimension than the AES-S could potentially have captured other aspects, associated with the PRS. However, follow-up analyses using different factor solutions for the PANSS negative symptom components produced equal results. Our findings are thus in line with the lack of associations found in several previous studies (38, 78, 79) and go against findings of negative associations (80) or positive associations in adolescents from the general population (81, 82), in FEP (83) or broader schizophrenia samples (84).
Fig. 1. Scatter plots of schizophrenia PRS and levels of apathy (AES-S) in the complete sample, healthy controls, and patients with schizophrenia spectrum disorders. [Colour figure can be viewed at wileyonlinelibrary.com]
Table 2. Bivariate correlations between schizophrenia polygenic risk scores (P = 0.1) and apathy levels in patients, healthy controls, and complete sample, and with PANSS negative symptoms as one single factor and as two factors in patients only

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Patients SZ PRS P</th>
<th>Healthy controls SZ PRS P</th>
<th>Complete sample SZ PRS P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>281</td>
<td>298</td>
<td>579</td>
</tr>
<tr>
<td>AES-S², r</td>
<td>–0.08</td>
<td>0.160</td>
<td>0.02</td>
</tr>
<tr>
<td>PANSS negative³</td>
<td>–0.06</td>
<td>0.340</td>
<td></td>
</tr>
<tr>
<td>PANSS neg. expression³</td>
<td>–0.06</td>
<td>0.294</td>
<td></td>
</tr>
<tr>
<td>PANSS neg. amotivation³</td>
<td>–0.06</td>
<td>0.286</td>
<td></td>
</tr>
</tbody>
</table>

AES-S, Apathy Evaluation Scale, self-report version; SZ PRS, Schizophrenia Polygenic Risk Score; PANSS, Positive and Negative Syndrome Scale.

Unless otherwise specified, correlations are Spearman’s rho.

¹In patients, the AES-S showed significant correlations with PANSS negative symptoms as one factor (r = 0.26, P < 0.001), with PANSS negative expressive factor (r = 0.18, P = 0.003), and with PANSS neg. amotivation factor (r = 0.42, P < 0.001).
²Negative symptoms as one single factor (Wallwork’s model).
³Negative symptoms as two factors (Liemburg’s model).

Our lack of findings could theoretically be explained by capturing an admixture of primary and secondary negative symptoms. However, bivariate correlation analyses between the AES-S and measures of substance use and antipsychotic medication load were non-significant (Table 4). Further, when we adjusted for positive symptoms and depression in the multiple regression analyses, results were not altered (Table 3 vs. Table 5). Moreover, even if cross-sectional studies may indicate a higher proportion of negative symptoms in chronic patient groups, longitudinal studies in FEP suggest that after an initial decrease, levels of apathy-like symptoms are quite stable over the first ten years of the disorder (64). The causes of secondary negative symptoms may, however, differ across FEP and MEP groups. While high levels of depressive symptoms may cause anhedonia and behavioral withdrawal in FEP, there is also a risk that treatment failures increase defeatist attitudes in MEP.

Repeating our analyses in FEP and MEP separately did not influence our findings. Lastly, the use of a broad schizophrenia diagnosis may ‘dilute’ the PRS signal. Repeating the analyses in patients with a narrow schizophrenia diagnosis did not indicate that such sample characteristics influenced our findings. There are, however, hypotheses that patients with persistent, high negative symptoms (14) or the deficit syndrome (33, 85) are a specific clinical subgroup with a specific biological basis. Since our study was cross-sectional, we could not identify this group within our sample and might miss out signals of such a specific genetic basis. Lastly, as high levels of negative symptoms may be associated with a higher heritability (33, 37), one path of investigation could have been to explore the associations between apathy and PRS in a subgroup of patients with high apathy scores. However, our sample size had insufficient statistical power for subgroup analyses.

Our findings indicate a non-existent, weak, or unstudied detectable association between the polygenic basis of schizophrenia and negative symptoms. However, the absence of significant associations may have some relevant explanations. First, common variants are estimated to explain at best 30–50% of schizophrenia’s heritability (48, 86). A fair amount of schizophrenia’s genotypic variance is thus not represented by the current schizophrenia PRS, including copy number variants (87–89), rare or de novo variants (90), and small deletions and insertions (42). Second, the current schizophrenia PRSs, based on the PGC2 discovery sample, only have the power to detect differences between cases and controls of 7.5% (PT = 0.1) in the complete TOP study. The explained variance by the schizophrenia PRS (PT = 0.1) in the current sample (n = 579) was 4.0%. In theory, the PRS threshold with the highest power to differentiate between cases and control subjects might not be the threshold with the highest association with apathy. However, to avoid

Table 3. Multiple hierarchical regression analyses exploring associations between schizophrenia polygenic risk scores and apathy levels in patients (n = 281), adjusting for genotyping batch and principal components

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>t</th>
<th>95% CI for B</th>
<th>P</th>
<th>R² change</th>
<th>Adjusted R²</th>
<th>Sig F change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.90</td>
<td></td>
<td>(–0.48, 3.27)</td>
<td>0.370</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batch</td>
<td></td>
<td>0.026</td>
<td>0.009</td>
<td>0.191</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td></td>
<td>0.039</td>
<td>0.026</td>
<td>0.099</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ PRS</td>
<td>–0.04</td>
<td>–0.66</td>
<td>(–1.16, 0.49)</td>
<td>0.512</td>
<td>0.002</td>
<td>0.024</td>
<td>0.512</td>
</tr>
</tbody>
</table>

CI, confidence interval; PC, principal component; SZ PRS, Schizophrenia Polygenic Risk Score. Explained variance for the full model (R²) = 0.066.

β, t, CI for B, and P refer to statistics from the final model. The model was adjusted for a total of six genotyping batches and six principal components; betas and 95% CIs are not reported for each batch/component for reasons of space.

The AES-S score is the dependent variable.
Table 4. Bivariate correlations between apathy levels, and premorbid and clinical characteristics in patients (n = 281)

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>AES-S</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, r</td>
<td>-0.06</td>
<td>0.326</td>
</tr>
<tr>
<td>IQ, r</td>
<td>-0.05</td>
<td>0.462</td>
</tr>
<tr>
<td>PAS acad. childhood</td>
<td>0.11</td>
<td>0.078</td>
</tr>
<tr>
<td>PAS social childhood</td>
<td>0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>Age at psychosis onset</td>
<td>-0.08</td>
<td>0.181</td>
</tr>
<tr>
<td>DUP</td>
<td>0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PANSS positive</td>
<td>0.19</td>
<td>0.002</td>
</tr>
<tr>
<td>PANSS disorg.†</td>
<td>-0.01</td>
<td>0.818</td>
</tr>
<tr>
<td>CDSS</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum AP‡</td>
<td>-0.11</td>
<td>0.071</td>
</tr>
<tr>
<td>AUDIT</td>
<td>0.05</td>
<td>0.415</td>
</tr>
<tr>
<td>DUDIT‡</td>
<td>0.04</td>
<td>0.499</td>
</tr>
</tbody>
</table>

Apathy Evaluation Scale, self-report version; IQ, intelligence quotient; PAS, Premorbid Adjustment Scale, academic and social sub-scores (childhood ≤ 11 years); DUP, Duration of Untreated Psychosis; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; Sum AP, Sum (Actual Daily Dosage of Antipsychotic Medication/Defined Daily Dosage) for a maximum of three antipsychotics used by each patient; AUDIT, Alcohol Use Disorder Identification Test; DUDIT, Drug Use Disorder Identification Test. Unless otherwise specified, correlations are Spearman’s rho.

†The variable was log10-transformed due to skewness.
‡PANSS 5-factor.

Table 5. Multiple hierarchical regression analyses exploring contributions to apathy levels† in patients from premorbid and clinical characteristics, together with schizophrenia polygenic risk scores

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>t</th>
<th>95% CI for B</th>
<th>P</th>
<th>R² change</th>
<th>Adjusted R²</th>
<th>Sig F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.90</td>
<td></td>
<td></td>
<td>0.369</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS soc. childh.</td>
<td>-0.11</td>
<td>1.79</td>
<td>(-0.60, 1.26)</td>
<td>0.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUP‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS positive</td>
<td>-0.01</td>
<td>-1.91</td>
<td>(-0.26, 0.21)</td>
<td>0.050</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDSS</td>
<td>0.40</td>
<td>6.05</td>
<td>(0.44, 0.87)</td>
<td>0.000</td>
<td>0.146</td>
<td>0.212</td>
<td>0.000</td>
</tr>
<tr>
<td>Block 3 Batch 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ PRS</td>
<td>-0.04</td>
<td>-0.71</td>
<td>(-16.586.56, 7846.59)</td>
<td>0.482</td>
<td>0.002</td>
<td>0.216</td>
<td>0.482</td>
</tr>
</tbody>
</table>

β, t, CI for B, and P refer to statistics from the final model. PAS, Premorbid Adjustment Scale, social subscale from childhood; DUP, Duration of Untreated Psychosis; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; PC, principal component; SZ PRS, Schizophrenia Polygenic Risk Score.

Explained variance for the total model (R²) = 0.271.

†The AES-S score is the dependent variable.
‡Due to skewness, DUP was log10-transformed.
§The model was adjusted for a total of six genotyping batches and six principal components; betas and 95% CIs are not reported for each batch/principal component for reasons of space.

As each common variant included in the PRS only confers small increments in risk, the sample sizes required to reveal true effects are large (91). Larger PGC discovery samples might thus detect additional common variants associated with schizophrenia, and increase the predictive power of the PRS (92, 93). The GWAS discovery samples are powered to accommodate for corrections for multiple testing, with a P-value threshold of 5 × 10⁻⁸. The sample sizes needed to investigate a low number of hypothesis-based associations are lower. The current sample size is equivalent to some of the previous studies investigating associations between PRS and clinical phenotypes (78, 83), yet larger (94) or smaller than others (36, 38, 84). Although a larger clinical sample would increase statistical power for detecting associations between clinical symptoms and the current schizophrenia PRS, the low correlation coefficients found here indicate that even though this would be theoretically interesting, the low predictive power of the current PRS would not make it a valuable tool in standard clinical settings or for personalized medicine.

Third, a potential explanation could be that apathy is not a phenomenon specific to schizophrenia. Apathy occurs in several neuropsychiatric disorders (29) and a broad spectrum of mental disorders (25). Consequently, the common genetic variants associated with apathy may not be captured by the schizophrenia PRS but rather by a cross-disorder ‘Apathy PRS’, which theoretically could be identified by pooling large cross-diagnostic discovery samples. However, considering equifinality in complex disorders, the similarity of phenotypes does not necessarily correspond to a similar genetic makeup (25, 95). Rather, equivalent phenotypes may have separate etiologies. In the case of apathy, research implies that neurological and psychiatric disorders are fairly distinct genetically (96), which could question the utility of a future cross-disorder Apathy PRS.

Fourth, apathy could be elicited by environmental factors (97) or develop through a chain of illness-related events. This includes defeatist performance beliefs (DPB) (26, 98), where cognitive impairments and associated negative experiences of goal attainment become templates for negative beliefs about own performances, reducing motivation for future goal-directed behavior (22, 99). In a recent meta-analysis, 70% of included studies found significant, positive associations between DPB and negative symptoms (100). DPB are more strongly associated with the experiential/amotivation domain than the expressive domain in some (27, 101) but not all studies (100). Negative
Expectancy Appraisals (beliefs about a reduced likelihood of success, acceptance, and pleasure in the future) (101), reduced self-efficacy (102), and stigma and stigma resistance (103) are other suggested psychological models for reduced motivation. In this line of reasoning, apathy is conceivable as a downstream psychological effect of disturbances in cognitive functioning, another key characteristic of schizophrenia spectrum disorders, and not linked to the genetic basis of the disorder itself.

In sum, we found no significant association between schizophrenia PRS and the level of apathy in schizophrenia. The ‘missing heritability’ in schizophrenia, including the large amount of variance not explained by the current schizophrenia PRS, is substantial (104) and offers one possible explanation for our results. However, the clinical utility of the current PRS has been questioned in psychiatry (105). Precision medicine aims at understanding illness etiology and pathogenesis, enabling personalized treatment of the individual. In schizophrenia, PRSs so far seem to fall short on accuracy (106) and as a prediction tool at the level of clinical phenotypes.

Acknowledgements

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Declaration of interest

Author OAA has received speaker’s honorarium from Lundbeck. All other authors declare that they have no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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