Polygenic Risk Score associated with specific symptom dimensions in first-episode psychosis

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ABSTRACT

Recent Genome-Wide Association Studies (GWAS) have provided evidence for the involvement of a number of genetic variants in schizophrenia (SCZ). The objective of the current study was to examine the association between these variants and symptom dimensions, evaluated prospectively over a period of 24 months, in a clinically well-characterized sample of individuals (n=241) with first-episode psychosis (FEP). The genetic variants were analyzed collectively as captured through a Polygenic Risk Score (PRS), calculated for each individual. At each evaluation time point (baseline, 1, 2, 6 and 24 months), correlation analysis was conducted with PRS and symptom dimension scores assessed by the Positive and Negative Syndrome Scale (PANSS). We also examined the association of PRS with global symptom rating, depression, anxiety, social and occupational functioning as measured by widely used and well validated scales. At baseline, significant positive correlation was observed between PRS and the general psychopathology dimension of the PANSS but no associations were observed with the positive or negative symptom dimensions. Anxiety, assessed using the Hamilton Anxiety Rating Scale, was also significantly correlated with the PRS. No significant correlation was observed with other symptom dimensions or with the PANSS score at the later evaluations. These results provide novel evidence of an association between general psychopathology and PRS in young people with first episode psychosis. They also demonstrate that it is important to note the dynamic changes of symptoms over time when trying to refine the relationship between genetic factors and phenotypes.

Keywords: Schizophrenia, First-episode psychosis, Polygenic Risk Score, General psychopathology, PANSS, Anxiety

1. Introduction

Schizophrenia (SCZ) spectrum psychoses are often regarded as the most serious of all mental disorders. The primary symptoms are positive (delusions, hallucinations, disorganization of thought and behavior), with to a varying degree, negative (poverty of thought and affect, apathy and social withdrawal), depressive, manic and anxiety symptoms in the acute phase; and residual symptoms and social disability in the longer term. With onset typically occurring during adolescence or early adulthood, psychotic disorders have serious long-term implications including reduced life expectancy (Chang et al., 2011), disruption of social and emotional development, education underachievement, unemployment (Switaj et al., 2012), and suicide (Hor and Taylor, 2010).

Schizophrenia spectrum disorders have a strong genetic component, and it is now well-elucidated that a large number of independent loci contribute to their etiology, each adding only a small risk. Both common and rare risk variants have been implicated. It has been estimated that a half to one-third of the genetic risk is indexed by common alleles that can be assayed in Genome-Wide Association Studies (GWAS) (International Schizophrenia Consortium et al., 2009; Ripke et al., 2013). Recently, the Schizophrenia Working Group of the Psychiatric Genomics Consortium reported results of the most recent GWAS conducted with a sample size > 150,000 (36,989 cases and 113,075 controls) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). 108 independent genetic loci were shown to be associated with SCZ, passing criteria for genome-wide significance ($P \leq 5 \times 10^{-8}$). A recent advancement in psychiatric genetics has been the use of a Polygenic Risk Score (PRS) in association analyses (International Schizophrenia Consortium et al., 2009). A PRS is essentially derived by aggregating genetic risk variants identified from GWAS into one score. The major advantage of this approach is that the power of

a large GWAS can be robustly utilized for a smaller sample, since the statistical power of a PRS is exponentially better compared to that of a single SNP (Dima and Breen, 2015).

Several recent studies have examined the association between SCZ PRS score with symptoms of the disorder. In one of the first studies of this kind, PRS score was shown to be significantly different when comparing cases versus controls (Derks et al., 2012). However, within the affected group, no association was observed between PRS and any of the 5 symptom dimensions of psychosis analyzed (depression, disorganization, mania, positive and negative symptoms). A second study reported a lack of association between SCZ PRS and "psychotic experiences" in a large non-clinical community sample of adolescents between 12 to 18 years of age (Sieradzka et al., 2014). Here the instrument used was the Specific Psychotic Experiences Questionnaire (SPEQ) which includes self-reported paranoia, hallucinations, cognitive disorganization, grandiosity, anhedonia, and parent-rated negative symptoms. This group also used the Psychotic-Like Symptoms Questionnaire (PLIKS-Q), but observed no association with SCZ PRS. In yet another study, conducted with the large non-clinical ALSPAC cohort, no association was observed between SCZ PRS and psychotic experiences (Zammit et al., 2014). Psychotic experiences were assessed, at 12 years of age, as a single categorical construct (i.e. any one of a number of different positive experiences).

In the studies described above, SCZ PRS was derived from earlier GWAS that identified 13 risk loci (Ripke et al., 2013). More recent studies have derived a SCZ polygenic risk score from the 108 loci implicated in the most recent GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In a study conducted with adolescents from the ALSPAC cohort, measures of negative symptoms, depressive and anxiety disorders were added to the PLIKS-Q described above (Jones et al., 2016). As before, no association was observed with

psychotic experiences. However, significant association was observed between SCZ PRS and negative symptoms as well as anxiety disorders. In another recent study, no association was observed with symptom severity and overall functioning as measured by the Global Assessment of Functioning (GAF) scale, nor with antipsychotic dosage (Hettige et al., 2016).

While the results of these studies are interesting, the major disadvantage is that they were most likely conducted in patients at different stages of the illness and treatment, which may obscure any relationship between symptoms and PRS. A recent study, conducted with a sample of first-episode psychosis (FEP) patients, concluded that PRS was a reliable predictor of case-control status (Vassos et al., 2016). However, no analysis was presented on the association of PRS with symptom dimensions of SCZ. The objective of the current study was to use a clinically well-characterized sample of individuals with FEP, who are engaged in a structured treatment program: (1) to refine the association between the SCZ PRS and symptom dimensions of psychotic disorder, and, (2) to examine the association of SCZ PRS with symptom dimensions over the course of the two-year treatment period. The advantages of such a sample are that the clinical manifestations of illness are not confounded by long-term exposure to medication, chronicity, and social deprivation.

2. Materials and Methods

2.1 Subjects

Individuals were recruited from among FEP patients treated at the Prevention and Early Intervention Program for Psychoses in Montreal (PEPP- Montréal) between 2003-2013. This program is a specialized, publicly-funded, early-intervention service that provides intensive medical and psychosocial management over a 24 month period (Iyer et al., 2015). PEPP- Montréal is an integrated clinical and research program that constitutes the only service for FEP patients

within a large catchment area (population of 400 000) in southwest Montréal, without alternative competing programs in its vicinity. Inclusion criteria are as follows: (1) age between 14 and 35 years; and (2) diagnoses of affective (Bipolar Disorder and Major Depressive Disorder with psychotic features) or non-affective (Schizophrenia, Schizoaffective Disorder, Schizophreniform disorder, Delusional Disorder and Psychosis Not Otherwise Specified) FEP. The clinical diagnosis is made using the Structured Clinical Interview for DSM-IV-TR (Diagnostic and Statistical Manuel for Mental Disorders, fourth edition, text revised). All diagnoses are confirmed at a consensus meeting attended by a senior research psychiatrist (RJ or AM). Only individuals with less than 30 cumulative days of treatment with antipsychotic medication are included in the program.

Of the 660 clients meeting criteria for admission to PEPP-Montreal, 573 consented to participate in the research arm of the program. These individuals were subsequently approached to participate in the genetic study, and written informed consent was obtained from those interested (n=241). This study was approved by the Ethics Review Board at the DMHUI and McGill University.

As part of the program, patients are stabilized on second-generation anti-psychotic medication following a defined protocol. The program uses standardized structured evaluations to monitor symptoms, and implement treatment plans tailored to the needs of the patient. Evaluations are conducted at regular intervals (baseline and months 1, 2, 3, 6, 12, 18 and 24) by highly trained research staff. Inter-rater reliability sessions are regularly held and any observed drift in ratings is corrected.

2.2 Instruments and assessment

Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1988; Kay et al., 1989). This scale is a standardized, validated instrument devised for the assessment of symptoms. It consists of 30 items, each rated on a 7-point scale of severity. Of the 30 items, an equal number of items are summed in the overall positive symptom score (7 items) and negative symptom score (7 items). The remaining 16 items constitute a measure of "general psychopathology". The inclusion of a scale to measure general psychopathology has been noted to be one of the key advantages over the other instruments widely used to assess symptoms: Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) (Kay et al., 1988). The general psychopathology index was intended to serve as a measure of overall severity of illness, independent of positive and negative symptoms. Symptomatic state/ outcome was assessed using the Global Assessment of Functioning (GAF) scale. Since comorbid anxiety disorders and depression are common with psychotic disorders, assessment using the Hamilton Anxiety Rating Scale (HARS) (Hamillton, 1959) and Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990) were also conducted at each evaluation. Psychosocial functioning was assessed at baseline and 24-month follow-up using the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). These scales are extensively used in treatment outcome studies.

2.3 Genetics

DNA was extracted from blood or saliva samples collected from each participant. Of the 128 initial sites showing a significant association in the SCZ GWAS, several overlapping regions were implicated (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In order to define loci conservatively so as to include only physically independent regions of the

genome, associated regions that were not separated by at least 250kb were merged to obtain 108 loci in the GWAS. From each of these merged regions, only one single nucleotide polymorphism (SNP) was selected for genotyping. A total of 10 chromosomal regions lacking a unique SNP ID (chr1_8424984_D; chr2_146436222_I; chr2_149429178_D; chr2_200825237_I; chr5_140143664_I; chr6_84280274_D; chr7_2025096_I; chr7_24747494_D; chr11_46350213_D; chr11_46350213_D) were not included in the panel for genotyping. A total of 98 SNPs were therefore selected for genotyping using Sequenom iPlex Gold Technology at the McGill Innovation Center, Montreal (Ehrich et al., 2005) - SNP rs115329265 was genotyped under the alias rs1233578 as given in dbSNP. Of these:

1) 6 failed at primer design due to repeated region (rs35518360, rs12704290, rs140505938, rs7819570, rs12845396, rs56873913);

2) 1 failed at primer design due to neighbor SNPs (rs5937157);

3) 4 failed at the stage of genotyping (rs1702294, rs11693094, rs6002655, rs11139497);

4) 3 were excluded from the final analysis since the genotyping call rate was less than 90% (rs8042374, rs75059851, rs679087);

A total of 84 SNPs were successfully genotyped with a call rate greater than 90%. Every plate included duplicates of two reference samples used to estimate genotyping error. Genotypes for these samples were read with 100% accuracy on each of the plates.

For each SNP, the "risk allele" was unambiguously assigned based on the PGC GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Each individual was assigned a score of 0, 1 or 2 depending on the presence of 0, 1, or 2 copies of the risk allele respectively. For each SNP, the score was multiplied by the Odds Ratio obtained in the GWAS. The scores for each SNP for each individual were summed to give the Polygenic Risk Score (PRS)

for each individual. Only those DNA samples having a call rate greater than 90% (n=215) were included in the final PRS analysis in order to apply strict quality control criteria.

2.4 Statistical analysis

Correlation analysis was conducted (in SPSS) between PRS and each of the symptom dimension scores at each time point. Since 5 clinical domains were tested for association with PRS (PANSS, GAF, HARS, CDSS, and SOFAS), correction for multiple testing was applied, and the threshold for significance was set at $P<0.01$ (0.05/5). A highly significant correlation was observed between the total and dimensional scores of the PANSS at each time point (Supplementary Table; S1). Correction was not applied for each of the SNPs that together form the composite polygenic risk score since these SNPs were the most validated genetic factors in the SCZ GWAS, with the objective of balancing Type I and Type II error.

3. Results

Demographic and clinical characteristics are presented for subjects participating in the genetic study (Table 1). Relative to those who did not participate in the genetic study, the group of individuals who did participate were younger and less likely to have completed high school, had lower IQ, lower age of onset of psychotic symptoms, and a significantly higher PANSS positive symptom sub-scale score. A significant correlation was observed between SCZ PRS and baseline measures: (1) general psychopathology assessed by the PANSS, (2) anxiety assessed by the HARS (Table 2a). Higher PRS score was associated with higher scores on the general psychopathology subscale, as well as greater anxiety symptoms. By month1 evaluation and lasting till the 24 month evaluation, a lack of association was noted between PRS and any of the symptom measures. It may be noted that after the first month of treatment, there is a significant decrease in

symptoms, particularly positive and general psychopathology symptoms (Table 2b). No association was observed with CDSS, SOFAS and GAF scores at any of the time points (Table 2a).

This analysis was conducted in a sample with 76.4% Caucasian ethnicity. However the SCZ GWAS data used to derive the Odds Ratio used in the PRS analysis are from European-derived and (a small proportion of) Asian samples. In order to ensure that the results are not confounded by population stratification, the analysis was repeated in a subset of the sample including only those with Caucasian ethnicity. Here again, the demographic characteristics were significantly different from those Caucasian subjects who did not give consent to participate (younger, with a lower age of onset), though the two groups did not differ with respect to their clinical dimensions (Table 3). Given that the smaller Caucasian sample likely has lower statistical power, a less stringent threshold for significance ($P<0.05$) was applied to this post hoc analysis. Once again, significant correlation was observed between SCZ PRS and baseline measures of: (1) general psychopathology and negative symptoms assessed by the PANSS, (2) anxiety assessed by the HARS (Table 4).

4. Discussion

Here we report an association between general psychopathology and SCZ PRS, noted for the first time in young people with first episode psychosis. The most important contribution of this study is the detailed and systematic assessment of symptoms conducted as treatment progresses over a two-year period. By following the course of symptom progression, it is clear that the association with psychopathology is most significant at the acute phase of the illness, when patients first enter the treatment program and while their symptoms are still actively expressed. As the

acute symptoms remit, association is no longer observed. The second interesting result noted is the association between SCZ PRS and anxiety symptoms. These results show an important internal consistency since anxiety is one of the items on the general psychopathology scale (PANSS G2-anxiety).

It is also interesting that even at the acute phase of the illness, no association is observed with positive symptoms. Several previous studies have examined SCZ PRS with positive symptoms or psychotic experiences in different populations (Derks et al., 2012; Jones et al., 2016; Sieradzka et al., 2014). However, none of these studies reported an association. In the most recent study, examining various symptom dimensions in the ALSPAC cohort, an association was observed with negative symptoms and anxiety disorder but not with psychotic experiences and depressive disorder (Jones et al., 2016), similar to our observation in youth with FEP. These results suggest that the genetic variations identified in the SCZ PRS increase the risk for psychotic disorders through a general susceptibility to mental illness. This susceptibility may find expression in manifestation of different symptoms (positive, negative, mood, etc.). Such a vulnerability model is compatible with the observation that a spectrum of severe mental illnesses share an important fraction of their genetic vulnerability. It is also possible that the lack of association with positive symptoms may be an artifact arising from the sampling methods used in the GWAS. By virtue of it being a large conglomerate of samples, it necessarily includes patients at vastly different stages of the disorder and with a diverse spectrum of symptoms. It is therefore reasonable that an association is observed with overall psychopathology related to psychosis and not with any specific symptoms.

The major limitation of our study is the relatively small sample size. Despite being one of the largest longitudinal samples of individuals with first episode psychosis, it may not be

adequately powered to identify small effects of cumulative genetic risk. However, it is important to note that using the PRS approach helps capitalize on the power of large GWAS (which have minimal phenotyping) to be used in smaller genetic studies having exquisite phenotyping. The second major limitation of the study is that some of the demographic/clinical features of clients who respond to the invitation to participate in the genetic study are different from those who do not (Table 1). However, it may be noted that all individuals are gauged on their ability to provide informed consent before being approached, and not on the basis of any genetic selection criteria. The clinical/demographic differences in the two groups should therefore not have a significant impact on a genetic association study. However it is underscored that this may present a limitation to the generalizability of findings to the entire FEP sample.

It is also noted that many polygenic studies use larger sets of SNPs with decreasingly lower significance, and find that the variance explained by PRS and the significance improves compared to PRS using only 108 SNPs. However this analysis requires genome-wide SNP data, which is not available for this sample. This may represent an important limitation of the study and may explain why associations with other symptom dimensions were not observed. Nonetheless, it is remarkable that all the results obtained in the current study are completely consistent with previous studies. In addition to earlier reports on lack of association with positive symptoms, a recent study reported a lack of association between SCZ PRS and symptom severity/ overall functioning, as assessed by the GAF (Hettige et al., 2016). This result is consistent with our findings of a lack of association with symptom severity evaluated by GAF. Perhaps combining the two important strengths of large GWAS with systematic, detailed phenotyping presents an important step forward in the field. Despite these interesting results, more molecular work needs to be done to understand how specific pathways are related to the onset of psychosis.

Disclosures

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Table 1: Demographic/clinical characteristics comparing FEP subjects who participated in the genetic study versus those who did not

	Participants (n=241)	**Non-participants (n=332)**	**Statistic and P value**
Sex (% male)	73.7	65.7	$\chi^2 = 4.15$, $df = 1$, P = 0.04
Ethnicity (% Caucasian)	76.6	73.0	$\chi^2 = 0.92$, $df = 1$, P =0.37
Age (years)	22.8 (4.1)	24.3 (4.9)	**$F_{(1,561)} = 13.3$, P < 0.001**
Age at onset (years)	22.0 (4.1)	23.2 (5.1)	**$F_{(1,532)} = 9.2$, P = 0.002**
Duration of untreated psychosis (DUP)	55.8 (129.6)	57.3 (100.8)	$F_{(1,426)} = 0.02$, P = 0.88
Socio-economic status (%middle class)	23.4	23.4	$\chi^2 = 1.65$, $df = 2$, P =0.44
Education (%less than high school)	40.8	30.6	$\chi^2 = 5.96$, $df = 1$, P =0.01
Full-scale IQ	94.4 (15.2)	99.7 (14.5)	**$F_{(1,426)} = 13.4$, P < 0.001**
Non-affective disorder (%)	74.9	67.1	$\chi^2 = 6.88$, $df = 2$, P =0.03
PANSS total	86.6 (17.6)	83.8 (17.5)	$F_{(1,504)} = 3.05$, P = 0.08
PANSS- Positive symptoms	26.9 (6.0)	25.5 (6.2)	**$F_{(1,545)} = 7.5$, P = 0.006**
PANSS- Negative symptoms	18.8 (6.8)	18.1 (6.7)	$F_{(1,519)} = 1.12$, P = 0.29
PANSS- General Psychopathology	41.0 (9.5)	40.2 (9.5)	$F_{(1,527)} = 0.87$, P = 0.35
Global Assessment of Functioning (GAF)	29.0 (7.2)	30.8 (10.7)	$F_{(1,554)} = 5.03$, P = 0.025
Calgary depression scale	4.9 (4.9)	5.1 (4.7)	$F_{(1,537)} = 0.18$, P = 0.67
Hamilton Anxiety Rating Scale	9.8 (7.3)	10.6 (7.8)	$F_{(1,506)} = 1.66$, P = 0.2
Social and Occupational Functioning Assessment Scale (SOFAS)	41.8 (13.1)	41.1 (13.4)	$F_{(1,493)} = 0.41$, P = 0.52

Values as mean (S.D.) unless otherwise specified; Results passing the threshold for statistical significance (P<0.01) have been highlighted

Table 2a: Correlation analysis between PRS and clinical parameters at specified evaluation time points

Parameter	Baseline		1 month		2 month		6 month		24month	
	Coeff.	P-value	Coeff.	P-value	Coeff.	P-value	Coeff.	P-value	Coeff.	P-value
PANSS total	**0.19**	**0.006**	0.19	0.01	0.09	0.25	0.07	0.33	-0.04	0.70
Positive symptoms	0.08	0.260	0.12	0.10	0.07	0.35	0.06	0.38	-0.13	0.10
Negative symptoms	0.16	0.023	0.16	0.03	0.01	0.90	0.01	0.85	0.03	0.74
General Psychopathology	**0.20**	**0.003**	0.16	0.03	0.14	0.07	0.10	0.15	-0.03	0.72
Global Assessment of Functioning (GAF)	-0.02	0.801	-0.02	0.76	0.07	0.32	0.07	0.36	0.09	0.26
Calgary depression scale	0.06	0.390	0.01	0.92	0.04	0.56	0.05	0.48	-0.21	0.01
Hamilton Anxiety Rating Scale	**0.24**	**<0.001**	0.07	0.34	0.11	0.16	0.09	0.22	-0.04	0.67
Social and Occupational Functioning Assessment Scale (SOFAS)	-0.09	0.225	NA	NA	NA	NA	NA	NA	0.10	0.28

Coeff.: Pearson Correlation Coefficient; NA: Not assessed**;** Results passing the threshold for statistical significance (P<0.01) have been highlighted.

Table 2b: Scores for each clinical parameter given as mean (SD) at specified evaluation time points

Parameter	Baseline	1 month	2 month	6 month	24month
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
PANSS total	86.4 (17.7)	63.7 (16.6)	57.4 (15.4)	56.1 (18.0)	52.7 (16.7)
Positive symptoms	27.0 (6.0)	16.1 (6.7)	13.1 (5.7)	12.9 (6.2)	12.3 (6.1)
Negative symptoms	18.6 (6.9)	16.0 (5.5)	15.6 (5.6)	14.8 (6.2)	14.0 (5.9)
General Psychopathology	40.9 (9.6)	32.0 (8.8)	28.8 (7.6)	28.5 (8.9)	26.1 (8.0)
Global Assessment of Functioning (GAF)	29.3 (7.1)	43.9 (15.3)	49.2 (15.4)	53.6 (17.7)	60.0 (19.3)
Calgary depression scale	5.0 (4.9)	3.1 (3.7)	2.6 (3.2)	2.4 (3.7)	1.3 (2.1)
Hamilton Anxiety Rating Scale	9.7 (7.1)	5.5 (4.8)	4.6 (5.1)	4.1 (4.9)	3.1 (4.2)
Social and Occupational Functioning Assessment Scale (SOFAS)	42.1 (13.0)	NA	NA	NA	62.5 (15.6)

NA: Not assessed.

Table 3: Demographic/clinical characteristics comparing Caucasian study participants with Caucasian FEP subjects who did not participate in the study

	Participants (n=162)	**Non-participants (n=240)**	**Statistic and P value**
Sex (% male)	75.9	67.5	$\chi^2 = 3.33$, *df* = 1, P = 0.07
Age (years)	23.0 (4.0)	24.5 (4.6)	**$F_{(1,398)} = -3.35$, P = 0.001**
Age at onset (years)	22.1 (4.1)	23.4 (4.8)	**$F_{(1,385)} = -2.7$, P = 0.006**
Duration of untreated psychosis (DUP)	58.6 (141.1)	56.4 (94.4)	$F_{(1,357)} = 0.17$, P = 0.86
Socio-economic status (%middle class)	26.3	26.0	$\chi^2 = 0.64$, *df* = 2, P =0.73
Education (%less than high school)	38.5	29.5	$\chi^2 = 3.36$, *df* = 1, P =0.07
Full-scale IQ	96.4 (15.1)	100.4 (14.4)	**$F_{(1,303)} = -2.37$, P = 0.001**
Non-affective disorder (%)	75.1	66.7	$\chi^2 = 5.3$, *df* = 2, P =0.07
PANSS total	84.2 (18.6)	84.1 (17.0)	$F_{(1,363)} = 0.03$, P = 0.98
PANSS- Positive symptoms	26.4 (6.2)	26.0 (6.1)	$F_{(1,391)} = 0.71$, P = 0.48
PANSS- Negative symptoms	17.9 (7.0)	17.8 (6.6)	$F_{(1,375)} = 0.14$, P = 0.89
PANSS- General Psychopathology	39.9 (9.9)	40.3 (9.4)	$F_{(1,379)} = -0.39$, P = 0.7
Global Assessment of Functioning (GAF)	29.6 (7.3)	30.0 (9.3)	$F_{(1,393)} = -0.54$, P = 0.6
Calgary depression scale	5.1 (5.2)	5.21 (4.8)	$F_{(1,382)} = -0.36$, P = 0.72
Hamilton Anxiety Rating Scale	9.6 (7.1)	10.7 (7.8)	$F_{(1,362)} = -1.39$, P = 0.16
Social and Occupational Functioning Assessment Scale (SOFAS)	42.4 (13.7)	41.2 (13.5)	$F_{(1,341)} = 0.85$, P = 0.39

Values as mean (S.D.) unless otherwise specified

Table 4: Correlation analysis between PRS and clinical parameters at specified evaluation time points in the Caucasian sample

Parameter	Baseline		1 month		2 month		6 month		24month	
	Coeff.	**P-value**	**Coeff.**	**P-value**	**Coeff.**	**P-value**	**Coeff.**	**P-value**	**Coeff.**	**P-value**
PANSS total	0.16	0.05	**0.22**	**0.01**	0.15	0.08	0.01	0.88	-0.03	0.72
Positive symptoms	0.005	0.95	0.13	0.14	0.11	0.22	-0.04	0.63	-0.10	0.27
Negative symptoms	**0.19**	**0.02**	**0.21**	**0.01**	0.08	0.33	0.06	0.46	0.05	0.60
General Psychopathology	**0.19**	**0.02**	**0.18**	**0.03**	**0.20**	**0.02**	0.06	0.51	-0.03	0.70
Global Assessment of Functioning (GAF)	-0.02	0.80	-0.09	0.32	0.06	0.49	-0.05	0.57	0.02	0.80
Calgary depression scale	0.12	0.13	0.02	0.79	0.09	0.29	0.04	0.62	-0.26	0.01
Hamilton Anxiety Rating Scale	**0.22**	**0.01**	0.09	0.28	0.17	0.05	-0.06	0.47	-0.04	0.71
Social and Occupational Functioning Assessment Scale (SOFAS)	-0.08	0.33	NA	NA	NA	NA	NA	NA	0.03	0.76

Coeff.: Pearson Correlation Coefficient; NA: Not assessed**;** A less stringent threshold for significance (P<0.05) was applied to this post hoc analysis. Results passing the threshold for statistical significance (P<0.05) have been highlighted.

Supplementary Table 1_Correlation matrix

Correlations

		pantotlb	panptotb	pantotb	pangtotb	pantotl1	panptot1	pantot1	pangtot1	pantotl2	panptot2	pantot2	pangtot2	pantotl6	panptot6	pantot6	pangtot6	pantot24	panpto24	pantno24	pangto24
pantotlb	Pearson Correlation	1	.596**	.782**	.917**	.517**	.240**	.541**	.458**	.385**	.112	.473**	.346**	.216**	.081	.285**	.188*	.171*	-.013	.255**	.165*
	Sig. (2-tailed)		.000	.000	.000	.000	.001	.000	.000	.000	.137	.000	.000	.004	.284	.000	.013	.033	.872	.001	.038
	N	209	209	209	209	177	181	178	178	175	176	176	175	173	178	175	175	155	162	159	157
panptotb	Pearson Correlation	.596**	1	.143*	.391**	.188*	.230**	.074	.168*	.150*	.170*	.102	.137	.032	.132	-.046	.065	.077	.090	-.026	.096
	Sig. (2-tailed)	.000		.038	.000	.011	.001	.320	.023	.043	.020	.169	.065	.673	.072	.535	.380	.331	.246	.743	.220
	N	209	218	211	213	182	188	183	184	183	185	184	184	181	187	183	184	161	169	165	164
pantotb	Pearson Correlation	.782**	.143*	1	.636**	.454**	.099	.711**	.342**	.360**	.022	.626**	.246**	.328**	.091	.513**	.240**	.200*	-.043	.405**	.140
	Sig. (2-tailed)	.000	.038		.000	.000	.184	.000	.000	.000	.771	.000	.001	.000	.225	.000	.001	.012	.582	.000	.079
	N	209	211	212	210	178	183	179	179	178	179	179	178	176	181	178	178	156	164	160	159
pangtotb	Pearson Correlation	.917**	.391**	.636**	1	.542**	.278**	.444**	.543**	.389**	.157*	.380**	.417**	.164*	.081	.197**	.180*	.139	-.041	.197*	.163*
	Sig. (2-tailed)	.000	.000	.000		.000	.000	.000	.000	.000	.035	.000	.000	.029	.275	.008	.015	.080	.598	.012	.039

	N	209	213	210	214	181	185	182	182	179	181	180	180	177	183	179	180	159	166	163	161
pantotl1	Pearson Correlation	.517**	.188*	.454**	.542**	1	.770**	.652**	.930**	.773**	.568**	.587**	.718**	.467**	.372**	.387**	.430**	.302**	.066	.380**	.276**
	Sig. (2-tailed)	.000	.011	.000	.000		.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.436	.000	.001
	N	177	182	178	181	183	183	183	183	163	165	164	164	154	160	156	157	138	143	141	139
panptotl	Pearson Correlation	.240**	.230**	.099	.278**	.770**	1	.151*	.643**	.606**	.716**	.196*	.551**	.290**	.395**	.074	.288**	.226**	.156	.190*	.180*
	Sig. (2-tailed)	.001	.001	.184	.000	.000		.041	.000	.000	.000	.011	.000	.000	.000	.348	.000	.007	.059	.022	.030
	N	181	188	183	185	183	189	184	185	168	170	169	169	159	165	161	162	142	148	145	144
pantotl	Pearson Correlation	.541**	.074	.711**	.444**	.652**	.151*	1	.502**	.497**	.082	.790**	.357**	.344**	.077	.534**	.240**	.166	-.122	.429**	.121
	Sig. (2-tailed)	.000	.320	.000	.000	.000	.041		.000	.000	.296	.000	.000	.000	.329	.000	.002	.051	.146	.000	.153
	N	178	183	179	182	183	184	184	183	164	166	165	165	155	161	157	158	139	144	142	140
pangtotl	Pearson Correlation	.458**	.168*	.342**	.543**	.930**	.643**	.502**	1	.714**	.508**	.489**	.726**	.425**	.341**	.290**	.438**	.268**	.065	.274**	.290**
	Sig. (2-tailed)	.000	.023	.000	.000	.000	.000	.000		.000	.000	.000	.000	.000	.000	.000	.000	.001	.437	.001	.001
	N	178	184	179	182	183	185	183	185	165	167	166	166	155	161	157	158	139	144	142	140
pantotl2	Pearson Correlation	.385**	.150*	.360**	.389**	.773**	.606**	.497**	.714**	1	.786**	.704**	.931**	.466**	.445**	.298**	.448**	.462**	.179*	.447**	.471**

	Sig. (2-tailed)	.000	.043	.000	.000	.000	.000	.000	.000		.000	.000	.000	.000	.000	.000	.000	.000	.033	.000	.000
	N	175	183	178	179	163	168	164	165	184	184	184	184	159	164	161	161	136	142	139	138
panptot2	Pearson Correlation	.112	.170*	.022	.157*	.568**	.716**	.082	.508**	.786**	1	.232**	.687**	.383**	.531**	.084	.415**	.392**	.233**	.317**	.387**
	Sig. (2-tailed)	.137	.020	.771	.035	.000	.000	.296	.000	.000		.001	.000	.000	.000	.285	.000	.000	.005	.000	.000
	N	176	185	179	181	165	170	166	167	184	186	185	185	160	166	162	163	138	144	141	140
pantot2	Pearson Correlation	.473**	.102	.626**	.380**	.587**	.196*	.790**	.489**	.704**	.232**	1	.521**	.348**	.186*	.466**	.261**	.288**	-.013	.446**	.272**
	Sig. (2-tailed)	.000	.169	.000	.000	.000	.011	.000	.000	.000	.001		.000	.000	.017	.000	.001	.001	.873	.000	.001
	N	176	184	179	180	164	169	165	166	184	185	185	184	160	165	162	162	137	143	140	139
pangtot2	Pearson Correlation	.346**	.137	.246**	.417**	.718**	.551**	.357**	.726**	.931**	.687**	.521**	1	.411**	.407**	.203**	.445**	.417**	.169*	.333**	.472**
	Sig. (2-tailed)	.000	.065	.001	.000	.000	.000	.000	.000	.000	.000	.000		.000	.000	.010	.000	.000	.044	.000	.000
	N	175	184	178	180	164	169	165	166	184	185	184	185	159	165	161	162	137	143	140	139
pantotl6	Pearson Correlation	.216**	.032	.328**	.164*	.467**	.290**	.344**	.425**	.466**	.383**	.348**	.411**	1	.808**	.781**	.940**	.376**	.142	.404**	.379**
	Sig. (2-tailed)	.004	.673	.000	.029	.000	.000	.000	.000	.000	.000	.000	.000		.000	.000	.000	.000	.088	.000	.000
	N	173	181	176	177	154	159	155	155	159	160	160	159	182	182	182	182	138	145	142	140

panptot6	Pearson Correlation	.081	.132	.091	.081	.372**	.395**	.077	.341**	.445**	.531**	.186*	.407**	.808**	1	.379**	.708**	.291**	.201*	.224**	.302**
	Sig. (2-tailed)	.284	.072	.225	.275	.000	.000	.329	.000	.000	.000	.017	.000	.000		.000	.000	.000	.013	.006	.000
	N	178	187	181	183	160	165	161	161	164	166	165	165	182	188	184	185	143	150	147	145
pantot6	Pearson Correlation	.285**	-.046	.513**	.197**	.387**	.074	.534**	.290**	.298**	.084	.466**	.203**	.781**	.379**	1	.631**	.308**	.042	.478**	.251**
	Sig. (2-tailed)	.000	.535	.000	.008	.000	.348	.000	.000	.000	.285	.000	.010	.000	.000		.000	.000	.617	.000	.003
	N	175	183	178	179	156	161	157	157	161	162	162	161	182	184	184	182	140	147	144	142
pangtot6	Pearson Correlation	.188*	.065	.240**	.180*	.430**	.288**	.240**	.438**	.448**	.415**	.261**	.445**	.940**	.708**	.631**	1	.330**	.119	.304**	.388**
	Sig. (2-tailed)	.013	.380	.001	.015	.000	.000	.002	.000	.000	.000	.001	.000	.000	.000	.000		.000	.150	.000	.000
	N	175	184	178	180	157	162	158	158	161	163	162	162	182	185	182	185	140	147	144	142
pantot24	Pearson Correlation	.171*	.077	.200*	.139	.302**	.226**	.166	.268**	.462**	.392**	.288**	.417**	.376**	.291**	.308**	.330**	1	.785**	.761**	.919**
	Sig. (2-tailed)	.033	.331	.012	.080	.000	.007	.051	.001	.000	.000	.001	.000	.000	.000	.000	.000		.000	.000	.000
	N	155	161	156	159	138	142	139	139	136	138	137	137	138	143	140	140	162	162	162	162
panpto24	Pearson Correlation	-.013	.090	-.043	-.041	.066	.156	-.122	.065	.179*	.233**	-.013	.169*	.142	.201*	.042	.119	.785**	1	.327**	.629**
	Sig. (2-	.872	.246	.582	.598	.436	.059	.146	.437	.033	.005	.873	.044	.088	.013	.617	.150	.000		.000	.000

	tailed)																				
	N	162	169	164	166	143	148	144	144	142	144	143	143	145	150	147	147	162	170	166	165
panto24	Pearson Correlation	.255**	-.026	.405**	.197*	.380**	.190*	.429**	.274**	.447**	.317**	.446**	.333**	.404**	.224**	.478**	.304**	.761**	.327**	1	.592**
	Sig. (2-tailed)	.001	.743	.000	.012	.000	.022	.000	.001	.000	.000	.000	.000	.000	.006	.000	.000	.000	.000		.000
	N	159	165	160	163	141	145	142	142	139	141	140	140	142	147	144	144	162	166	166	162
pangto24	Pearson Correlation	.165*	.096	.140	.163*	.276**	.180*	.121	.290**	.471**	.387**	.272**	.472**	.379**	.302**	.251**	.388**	.919**	.629**	.592**	1
	Sig. (2-tailed)	.038	.220	.079	.039	.001	.030	.153	.001	.000	.000	.001	.000	.000	.000	.003	.000	.000	.000	.000	
	N	157	164	159	161	139	144	140	140	138	140	139	139	140	145	142	142	162	165	162	165

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Variables

pantotlb	PANSS total score at baseline
panptotb	PANSS total positive symptom sub-scale score at baseline
panntotb	PANSS total negative symptom sub-scale score at baseline
pangtotb	PANSS total general psychopathology sub-scale score at baseline
pantotl1	PANSS total score at 1 month
panptot1	PANSS total positive symptom sub-scale score at 1 month
panntot1	PANSS total negative symptom sub-scale score at 1 month
pangtot1	PANSS total general psychopathology sub-scale score at 1 month
pantotl2	PANSS total score at 2 month
panptot2	PANSS total positive symptom sub-scale score at 2 month
panntot2	PANSS total negative symptom sub-scale score at 2 month

pangtot2	PANSS total general psychopathology sub-scale score at 2 month
pantotl6	PANSS total score at 6 month
panptot6	PANSS total positive symptom sub-scale score at 6 month
panntot6	PANSS total negative symptom sub-scale score at 6 month
pangtot6	PANSS total general psychopathology sub-scale score at 6 month
pantot24	PANSS total score at 24 month
panpto24	PANSS total positive symptom sub-scale score at 24 month
pannto24	PANSS total negative symptom sub-scale score at 24 month
pangto24	PANSS total general psychopathology sub-scale score at 24 month

Supplementary Table 1_Details on SNP selection

Order of priority		
1	rs115329265	Merged into rs1233578
2	rs1702294	Genotyping failed
3	rs55833108	
4	rs2007044	
5	rs4129585	
6	rs35518360	Failed at primer design due to repeated region
8	rs4391122	
9	rs2851447	
11	rs4702	
12	rs75968099	
14	rs12887734	
15	rs8042374	Genotyping call rate 31.8%
16	rs13240464	
17	rs10791097	
18	rs11693094	Genotyping failed
19	rs1378559	

20	rs7893279	
21	rs12826178	
22	rs12129573	
23	rs6704768	
24	rs55661361	
25	rs9636107	
29	rs6065094	
30	rs11682175	
31	rs950169	
32	rs72934570	
33	rs6434928	
34	rs9607782	
35	rs36068923	
36	rs17194490	
37	rs2514218	
38	rs75059851	Genotyping call rate 72.03%
39	rs2535627	
40	rs12691307	
42	rs7432375	
46	rs5937157	Failed at primer design due to neighbor SNPs
47	rs4523957	
48	rs12704290	Failed at primer design due to repeated region
49	rs12903146	
50	rs11210892	
51	rs2905426	
52	rs140505938	Failed at primer design due to repeated region
54	rs4648845	
55	rs7405404	
57	No unique SNP ID	

56	rs6466055	
58	rs4766428	
59	rs10520163	
60	rs117074560	
61	rs6002655	Genotyping failed
63	rs9420	
64	rs11027857	
65	rs1498232	
66	rs3735025	
67	rs11139497	Genotyping failed
68	rs77149735	
69	rs56205728	
70	rs2053079	
71	rs16867576	
72	rs4330281	
73	rs3849046	
74	rs2693698	
75	rs2332700	
76	rs1501357	
77	rs6984242	
79	rs79212538	
80	rs3768644	
81	rs77502336	
82	rs6704641	
83	rs59979824	
84	rs1106568	
85	rs10503253	
87	rs11685299	
88	rs7819570	Failed at primer design due to repeated region

90	rs9922678	
92	rs2068012	
93	rs832187	
94	rs8044995	
96	rs8082590	
97	rs12148337	
98	rs12325245	
102	rs73229090	
104	rs12845396	Failed at primer design due to repeated region
106	rs9841616	
108	rs1339227	
110	rs4388249	
111	rs215411	
112	rs11740474	
114	rs12421382	
115	rs211829	
116	rs679087	Genotyping call rate 42%
118	rs7801375	
120	rs6670165	
121	rs7523273	
122	rs7267348	
123	rs4240748	
124	rs2909457	
125	rs56873913	Failed at primer design due to repeated region
127	rs10860964	
Failed	rs10803138	
Failed	rs111294930	
Failed	rs2973155	
Failed	rs7907645	

Failed	rs11191419
exclude	rs76869799
exclude	rs14403
exclude	rs75575209
exclude	rs10043984
exclude	rs12522290
exclude	rs2239063
exclude	rs324017
exclude	rs190065944
exclude	rs78322266
exclude	rs715170
exclude	rs1023500