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Dimensional Traits Of Schizotypy Associated With Glycine receptor *GLRA1* Polymorphism: An Exploratory Candidate-Gene Association Study

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Abstract

Background—Schizotypy is a construct believed to capture the underlying genetic vulnerability to schizophrenia. However, few studies have investigated the genetic underpinnings of dimensional schizotypy and the closely related categorical diagnosis of schizotypal personality disorder. This is an exploratory case-control candidate gene association study examining the relationship between single nucleotide polymorphisms (SNPs) and four schizotypy dimensions in a sample enriched for dimensional schizotypy and schizotypal personality disorder (SPD).

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Contributors:

Vora performed statistical analyses using PLINK and R softwares, performed literature search, wrote the initial draft of manuscript, revised it, prepared figures and tables, and presented the work at scientific conferences. Perez-Rodriguez, McNamara, Siever, Hazlett and New were involved in data collection and curation. Perez-Rodriguez performed the revision of the manuscript, and literature search. Roussos was involved in conceptual framework of statistical design, editing of manuscript, and helped with statistical analysis. Goldman, Yuan, Zhou, and Hodgkinson developed SNP chip used in genotyping. Roussos, Vora, Hazlett and Perez-Rodriguez reviewed final draft of manuscript for submission.

Conflicts of Interest:

No conflicts declared

Methods—A sample of 137 subjects recruited from the community by the Mood and Personality Disorders Research Program at Mount Sinai (43 healthy controls [HC], 34 SPD subjects, 32 subjects with borderline personality disorder [BPD}, and 25 subjects with other personality disorders [OPD]) was assessed with the Schizotypal Personality Questionnaire (SPQ). from 130 genes Subjects were genotyped using a custom Illumina array chip (including 1,536 SNPs) developed to extract full haplotype information for 130 candidate genes involved in functional pathways deemed to be important for psychiatric disorders. Ancestry markers were used to include subjects with Caucasian heritage. Principal component analysis was used to cluster SPQ variables. Linear regression was performed to test for associations between dimensional schizotypy and candidate SNPs. Logistic regression was used to test for associations between the SNPs and the diagnosis of schizotypal personality disorder versus controls.

Results—There were significant associations between the minor alleles of three SNPs (rs2915885, rs11167557, and rs1428159) within the glycine receptor alpha 1 subunit (*GLRA1)* and dimensional schizotypy, specifically with the disorganized symptoms dimension, which remained significant after Bonferroni Correction ($p<5.682 \times 10^{-05}$). There were no significant associations between any of the SNPs and the categorical diagnosis of schizotypal personality disorder.

Conclusions—This study indicates that polymorphisms related to glycine receptor pathways may have an impact on dimensional traits of psychosis, particularly related to disorganized symptomatology.

Keywords

Psychosis; Glycine; Polymorphism; Schizotypy; Schizophrenia Spectrum; Genetics

1. Introduction

Robust evidence from family, twin, and adoption studies support an underlying genetic vulnerability to schizophrenia (Sullivan, Kendler et al. 2003). However, despite recent significant advances in the identification of relevant genetic loci associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), our knowledge of its genetic architecture remains incomplete.

One critical obstacle for elucidating the genetic underpinnings of schizophrenia is its heterogeneity across symptom dimensions, biomarkers and functional outcomes (Swerdlow et al., 2015; Ettinger et al, 2014; Kwapil & Barrantes-Vidal, 2014). This heterogeneity may suggest that there are different forms of schizophrenia, with different heritability and genetic architectures (Swerdlow, Gur et al. 2015).

One way to address the phenotypic heterogeneity in schizophrenia has been through the study of dimensional traits as opposed to focusing on the categorical diagnosis itself (Rossi & Daneluzzo, 2002). The construct of schizotypy was introduced over 50 years ago to capture the inherited liability to schizophrenia expressed as multidimensional personality traits (Barrantes-Vidal, Grant et al. 2015). Schizotypy offers a context for studying dimensional aspects of schizophrenia (Kwapil & Barrantes-Vidal, 2014). Surprisingly,

although empirical data strongly suggests that dimensional schizotypy is associated with the underlying genetic liability to develop schizophrenia (Bolinskey, James et al. 2015, Lenzenweger 2015), very few studies have explored the genetic underpinnings of schizotypy (Barrantes-Vidal, Grant et al. 2015). This is all the more surprising since, as a theoretical model of schizophrenia, the "schizotype" also represents a cleaner unit of analysis, which is free from the confounding effects of medication, global neurocognitive deficits and institutionalization (Lenzenweger 2015).

Dimensional schizotypy is closely related to the categorical diagnosis of schizotypal personality disorder (SPD), and there is high overlap between these two conditions. For example, in a recent study, high dimensional schizotypy was associated with an almost six-fold increase in the likelihood of meeting criteria for SPD (Bolinskey, James et al. 2015). In fact, the Schizotypal Personality Questionnaire (SPQ), one of the commonly used assessment instruments to assess dimensional schizotypy, is based on the DSM diagnostic criteria for SPD (Raine, 1991) - which include ideas of reference, magical thinking, unusual perceptual experiences, odd speech, suspiciousness, constricted affect, odd behavior, lack of close friends, and social anxiety (American Psychiatric Association, 2013).

Schizotypal personality disorder is a milder, non-psychotic disorder within the schizophrenia spectrum. SPD is characterized by attenuated, schizophrenia-like–but non-psychotic-traits. It shares many of the genetic, psychophysiological and neural abnormalities found in schizophrenia (Siever and Davis 2004). Indeed, there is a known genetic relationship between SPD and vulnerability to schizophrenia (Ettinger et al., 2014; Kendler et al., 2006; Kendler et al., 2014; Webb & Levinson 1993; Battaglia et al., 1999), yet few studies have investigated the genetic underpinnings of SPD.

We aimed to advance our knowledge of the architecture of the genetic liability for schizophrenia by performing an exploratory candidate gene association study in a sample enriched for high dimensional schizotypy and schizotypal personality disorder. Specifically, we examined the relationship between single nucleotide polymorphisms (SNPs) and: 1) multidimensional schizotypy traits and 2) the categorical diagnosis of schizotypal personality disorder.

2. Methods

2.1 Subjects

526 subjects (139 SPD subjects, 132 Borderline personality disorder [BPD] subjects, 155 HC, and 100 subjects with other personality disorders [OPD]) were recruited through the Mood and Personality Disorders Program at the Icahn School of Medicine at Mount Sinai using advertisement in local newspapers and internet postings, or via referral from outpatient mental health clinics at the James J. Peters VA Medical Center and the Mount Sinai Hospital. After thorough explanation of the study procedures, all participants provided written informed consent. The study was approved by the Icahn School of Medicine at Mount Sinai and James J. Peters VAMC Institutional Review Board. Exclusion criteria for all subjects included history of head trauma, neurological disease, organic mental syndrome, and mental retardation. Subjects were not taking any psychoactive prescription medications.

2.2 Structured Interview and Questionnaires

Diagnostic instruments included the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; (First, Spitzer et al. 2001)) and the Structured Interview for DSM-IV Personality Disorders (SIDP-IV; (Pfohl, Blum et al. 1997)). After SCID-I and SIDP-IV assessment, diagnosis was established via consensus meeting by a team of doctoral-level psychologists with high inter-rater reliability and expertise in evaluation of personality disorders. SPD patients met full DSM-IV criteria for SPD. Subjects who met full DSM-IV criteria for borderline personality disorder (BPD) or other personality disorders (OPD) were included as psychiatric controls. Subjects with personality disorders were excluded if they met lifetime criteria for schizophrenia, schizoaffective disorder or bipolar I disorder. Healthy control (HC) subjects had no history of any DSM-IV Axis I or II disorders.

All subjects received the Schizotypal Personality Questionnaire (SPQ, (Raine 1991)). The SPQ provides a self-reported multidimensional measure of the severity of schizotypy. It has been validated in prior work (Fonseca-Pedrero et al., 2014; Raine, 1991; Stefanis et al., 2004). The SPQ assesses self-reported symptoms including ideas of reference, magical thinking, unusual perceptual experiences, odd speech, suspiciousness, constricted affect, odd behavior, lack of close friends, and social anxiety (Raine, 1991). The SPQ has previously been divided into symptom clusters including negative symptoms, paranoid symptoms, disorganized symptoms, and cognitive/perceptual symptoms (Stefanis et al., 2004).

2.3 Genotyping

All 526 subjects were genotyped using a customized Illumina chip (Hodgkinson et al., 2008) with 1536 SNPs from 130 genes. That chip was originally designed to provide a panel of 1350 markers able to extract full haplotype information for 130 candidate genes involved in functional pathways deemed to be important for addictions, mood and anxiety disorders (Hodgkinson et al., 2008). The 130 genes that were selected for the chip are involved in neurotransmitter signaling and transduction, and have been implicated in psychiatric disease (Hodgkinson et al., 2008). A detailed description of the methods for developing the array and the genes included has been published (Hodgkinson et al., 2008). To control for population stratification, 186 ancestry markers from HapMap, minimum separation ≥ 80 kb and minimum relative frequency difference between two populations ≥ 0.7, were used. Genotyping was carried out following Illumina GoldenGate assay protocols and the arrays were imaged on an Illumina Beadstation GX500. Details of the data analysis and quality controls have been described previously (Hodgkinson et al., 2008).

Of the total sample of 526 subjects, to maximize genetic homogeneity we selected only those of European ancestry -European ancestry informative markers ≥0.50- (n=161). After excluding those subjects who had a percentage of missing genotypes greater than 20%, the final sample included 137 individuals of European ancestry (43 healthy controls, 34 SPD subjects, 32 BPD subjects and 28 OPD subjects). For demographic and diagnostic description of the final sample, see Table 1.

Of the 137 subjects assessed with the SPQ, 108 (20 HC, 31 SPD subjects, 32 BPD subjects, and 25 OPD subjects) had semi-structured diagnostic interviews performed using SCID-I

and SIDP-IV as described above. The remaining 29 subjects (3 SPD, 3 OPD, 23 HC) were diagnosed based on a diagnostic screening interview and review of medical records.

Data were cleaned using a quality control (QC) procedure for case-control association studies (Anderson et al., 2011), prior to statistical analysis. Markers were excluded if Hardy-Weinberg equilibrium was $p \leq 0.0001$. SNPs were only included if minor allele frequency was ≥ 0.05. Finally, SNPs were excluded in they had a missing genotype rate of ≥ 0.05.

2.4 Statistical Analyses

2.4.1 Principal Component Analysis of Dimensional Schizotypy Symptoms Measured with *the SPQ*—In order to characterize symptom types and reduce dimensionality, principal component analysis with orthogonal varimax rotation was performed on the full sample of subjects for the SPQ variables.

2.4.2 Association Analysis between Dimensional SPQ Symptom Clusters and SNPs—We performed linear regression using PLINK version 1.07 (Purcell et al. 2007) to explore associations between dimensional schizotypy symptoms from the SPQ, clustered by PCA, and SNP allele. Covariates included ancestry and gender.

2.4.3 Association Analysis between Categorical SPD Diagnosis and SNPs—To examine the relationship between single nucleotide polymorphisms (SNPs) and the categorical diagnosis of SPD, we performed a logistic regression using PLINK version 1.07 (Purcell et al., 2007), with SPD diagnosis (yes/no) as the dependent variable in the subsample of 108 subjects (20 HC, 31 SPD subjects, 32 BPD patients, and 25 OPD subjects) who had been diagnosed using SCID-I and SIDP-IV semi-structured interviews. Covariates again included ancestry and gender.

2.4.4 Relationship between Categorical SPD Diagnosis and Dimensional Schizotypy Symptoms—To examine the relationship between categorical diagnoses and dimensional schizotypy, we performed a multivariate analysis of variance (MANOVA), with the four SPQ symptom clusters (negative, paranoid, disorganized, and cognitive/perceptual) as dependent variables and diagnoses (SPD, BPD, OPD, and HC) as between-subject factors. For post-hoc analysis, univariate testing was performed.

3. Results

3.1 Principal Component Analysis of Dimensional Schizotypy Symptoms Measured with the SPQ

Factor loadings from the rotated component matrix are shown in Table 2. The Kaiser–Meyer–Olkin measure of sampling adequacy (0.88) and Bartlett's test of sphericity ($\chi^2 = 2501$, $df = 36$, $p < 0.0001$) indicated that the data were appropriate for factor analysis. Four factors emerged with Eigenvalues > 1, suggesting a multidimensional structure, and this four-factor solution accounted for 83.1% of the total variance (see Table 2). Our results are consistent with prior literature establishing a 4-Factor Model of SPQ symptoms (Fonseca-Pedrero et al., 2014; Stefanis et al., 2004). These included negative symptoms (lack of close friends, limited affect, social anxiety), paranoid symptoms (ideas of reference,

suspiciousness), disorganized symptoms (odd behavior and odd speech), and cognitive/perceptual experiences (magical thinking, perceptual experiences).

3.2 Association Analysis between Dimensional SPQ Symptom Clusters and SNPs

After QC, there were 880 SNPs and 137 individuals of European ancestry (43 healthy controls, 34 SPD subjects, 32 BPD subjects and 28 OPD patients). A Bonferroni corrected threshold of $\alpha = 5.682 \times 10^{-05}$ (0.05/880 markers tested) was used. Linear Regression revealed a significant relationship between the 3 SNPs, rs2915885 ($p=2.292 \times 10^{-05}$, MAF = 0.4234), rs11167557 ($p=3.235 \times 10^{-05}$, MAF = 0.4234), and rs1428159 ($p=5.063 \times 10^{-05}$, MAF= 0.4265), that are all positioned within the glycine receptor alpha 1 subunit (*GLRA1*), and dimensional traits related to the disorganized symptoms cluster. This relationship remained significant after Bonferroni correction (see Figure 1). These SNPs are found within a region of high Linkage Disequilibrium (LD) and were within 50 kb apart from each other ($r^2>0.8$), see Figure 2. Other symptom clusters were not found to be significant. For full results, see Supplement 1.

3.3 Association Analysis Between Categorical SPD Diagnosis and SNPs

In the subsample of 108 subjects (20 HC, 31 SPD subjects, 32 BPD patients, and 25 OPD subjects) who had been diagnosed using SCID-I and SIDP-IV semi-structured interviews there was no significant association between any SNPs (885 after the QC) and the categorical SPD diagnosis (see Supplement 2).

3.4 Relationship between Categorical SPD Diagnosis and Dimensional Schizotypy Symptoms

MANOVA of dimensional schizotypy (SPQ) symptom clusters by diagnosis revealed significant differences in symptom clusters across diagnoses, Pillai's Trace=0.469, F=4.769, df=(12,309), p=3.593×10^{-07}. In post-hoc univariate testing, SPD patients had significantly higher scores for the negative symptom cluster ($p=1.96 \times10^{-03}$), the paranoid symptom cluster ($p=2.97\times10^{-02}$), the disorganized symptom cluster ($p=5.88 \times10^{-03}$), and the cognitive symptom cluster ($p=3.22 \times10^{-02}$), in comparison to HCs. SPD subjects also had significantly higher scores for the cognitive symptom cluster in comparison to OPD subjects, ($p=1.09\times10^{-02}$). SPD subjects had higher scores for the negative symptom cluster, the paranoid symptom cluster, and the disorganized symptom cluster in comparison to OPD subjects, although scores did not differ significantly. SPD subjects had higher scores than BPD subjects for all subscales, although differences were not statistically significant. See Figure 3 for means of SPQ symptom clusters by diagnosis.

4. Discussion

Our main finding is that the minor allele of three SNPs, all positioned within the glycine receptor alpha 1 subunit *GLRA1*, rs2915885, rs11167557, and rs1428159, were significantly associated with dimensional schizotypy, specifically with the disorganized symptoms cluster. It is difficult to ascertain the mechanism at the molecular level that these *GLRA1* risk alleles may predispose to schizotypy. Glycine receptors are pentameric ligand-gated chloride ion channels that mediate inhibitory neurotransmission in the brainstem, spinal cord and retina

(Lynch 2009). Mutations in the glycine receptor alpha 1 subunit (GLRA1) have been shown to cause a neurologic disorder termed familial startle disease (STHE) or hyperekplexia (Shiang, Ryan et al. 1993). characterized by hypertonia, abnormal startle with triggered startle attacks. Some affected individuals suffer developmental delay and intellectual disability (Thomas, Drew et al. 2015). Interestingly, some data suggests that SPD patients have abnormal eye blink startle responses similar to those described in schizophrenia (Hazlett, Romero et al. 2007).

Other possible pathophysiological mechanisms may include alterations in NMDA glutamatergic receptor modulation, as GLRA1 mutations could lead to abnormal levels of glycine, a known coagonist of the glycine$_B$ site of NMDA receptors (Danysz & Parsons, 1998; Shim et al., 2008). Consistent with this theory, emerging data suggest that antipsychotic medications–the primary pharmacotherapy for schizophrenia spectrum disorders-lead to GLRA1 hypermethylation, which could induce GLRA1 downregulation which, in turn, could alter glycine levels and the glutamate pathway, via NMDA receptors. (Santoro, Ota et al. 2014)

Of note, SNPs located within the *GLRA1* gene were not found to be associated with schizophrenia in the most recently published GWAS cohort analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Our findings expand prior converging data suggesting a role of the NMDA pathway (Bharadwaj et al., 2014; Cherlyn et al., 2010; Jia et al., 2012; Ayalew et al., 2012; Martucci et al., 2006; Weickert et al., 2013) in schizophrenia. Our findings also support the possible therapeutic role for glycine in schizophrenia (Danysz & Parsons, 1998; Shim et al., 2008), and there is need for further multimodal research on the role of the GLRA1 pathway in the schizophrenia spectrum.

There are some limitations in this study. The SPQ is a self-assessment measure, and may be limited by insight of the subjects (Raine, 1991). Additionally, the sample size was limited in this study, and therefore the findings need to be replicated in a larger cohort. Moreover, the stringent inclusion/exclusion criteria employed in this study may limit the generalizability of the results to other samples.

The fact that we did not find a significant association between any SNPs and the categorical diagnosis of SPD may be due to the limited number of subjects in the sample who meet full DSM criteria for SPD assessed by SIDP-IV (n=31). Conversely, the dimensional schizotypy measure (i.e., SPQ), available for all subjects in the sample (n=137), allows us to capture more fine grained variability in schizotypy symptoms – even in those individuals with subthreshold symptoms that would not meet criteria for the categorical SPD diagnosis. This likely results in increased power to detect an association with the dimensional measure. (Kraemer, Noda et al. 2004) Thus, it would be of interest to include dimensional as well as categorical measures of schizotypy in future studies in larger samples.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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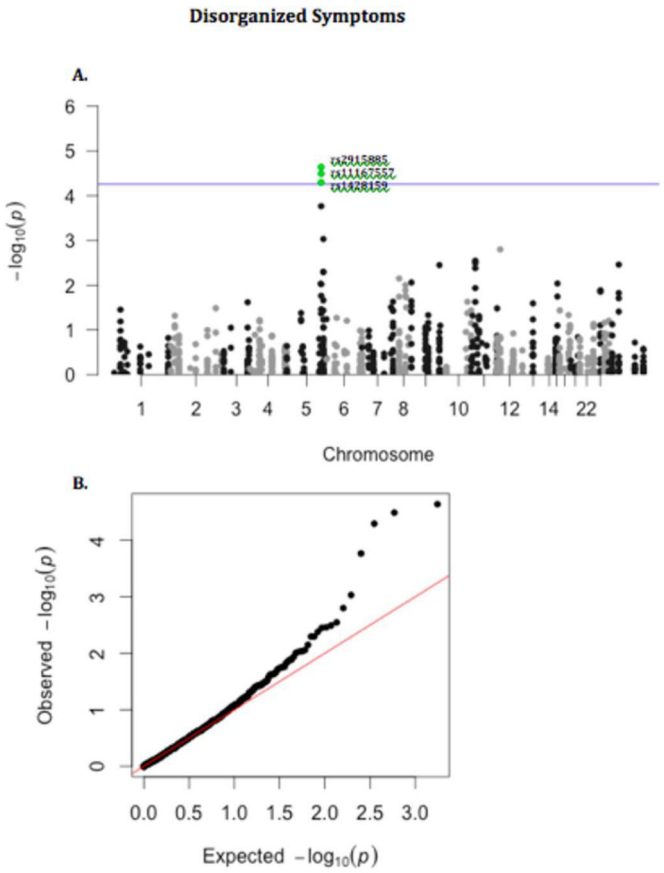

Figure 1.

(A) Manhattan plot, created by qqman R package (Turner S.D., 2014) showing the results of a linear regression exploring associations between 880 SNPs and dimensional schizotypy symptoms from the SPQ, clustered by PCA. The minor allele of three SNPs: rs2915885, rs11167557, and rs1428159, all within the glycine receptor *GLRA1*, were significantly associated with disorganized symptoms, after Bonferroni correction ($p<5.682 \times 10^{-05}$). **(B)** Q-Q plot, created by qqman R package (Turner S.D., 2014) supporting the significance of the finding.

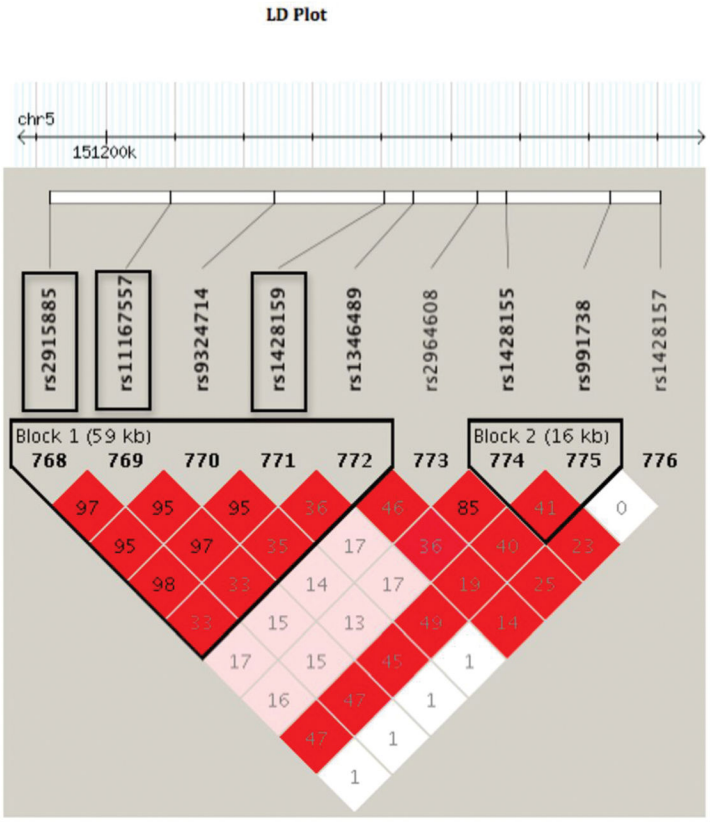

Figure 2.
LD plot including genotyped SNPs within *GLRA1*. Significant SNPs are highlighted with a box.

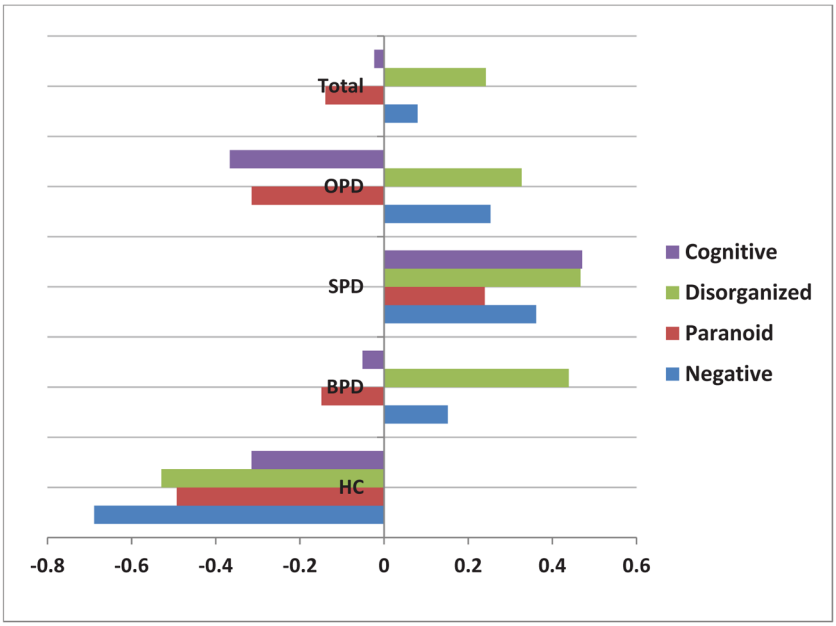

Figure 3.
Bar chart demonstrating means of SPQ symptom clusters by diagnostic group.

Table 1

Clinical and demographic variables for the final sample of 137 subjects of European ancestry included in the analyses.

	Group				Statistic
	HC (n=43)	SPD (n=34)	BPD (n=32)	OPD (n=28)	
Mean age in years (SD)	29.8 (9.2)	41.1 (10.4)	33.7 (9.0)	36.6 (11.9)	F=8.4, df=3, 133; p<0.001 Post hoc analyses (p<0.05) SPD>HC,BPD
Sex	21M/22F	21M/13F	16M/16F	18M/10F	n.s.

HC= Healthy control; SPD= Schizotypal personality disorder; BPD=Borderline personality disorder; OPD=Other personality disorder; n.s.=non-significant

Table 2

Factor loadings from the rotated component matrix

Principal component analysis (PCA) of individual items of the Schizotypal Personality Questionnaire (SPQ) - measuring dimensional schizotypy - was consistent with a previously described four-factor model (Stefanis et al, 2004). We used varimax rotation, converged in six iterations, with Kaiser normalization.

	PCA Factors			
SPQ subscales	**Negative**	**Paranoid**	**Disorganized**	**Cognitive**
Lack of close friends	0.863			
Constricted Affect	0.824			
Social Anxiety	0.78			
Ideas of reference		0.809		
Suspiciousness		0.782		
Odd Behavior			0.847	
Odd Speech			0.741	
Magical Thinking				0.925
Unusual perceptual Experiences				0.623