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Genomewide Association Analyses of Electrophysiological Endophenotypes for Schizophrenia and Psychotic Bipolar Disorders: A Preliminary Report

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Abstract

Several event-related potentials (ERP), including P3, sensory gating (P50), and gamma oscillation, are robustly impaired in patients with schizophrenia (SCZ) and bipolar disorder (BIP). Although these ERPs are known to be heritable, little is known about the specific genetic loci involved and the degree to which they overlap with loci influencing mood and psychotic disorders. In the present study, we conducted GWAS to a) identify common variants associated with ERP endophenotypes, and b) construct polygenic risk scores (PRS) to examine overlap between genetic components of ERPs and mood and psychotic disorders. The sample consisted of 271 patients with SCZ or psychotic BIP diagnosis and 128 controls for whom ERP and genomewide data were available. GWAS were conducted using the full sample. PRS, derived from the Psychiatric

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Genomics Consortium (PGC) analyses of SCZ, BIP, and major depressive disorder were applied to each ERP phenotype. We identified a region on chromosome 14 that was significantly associated with sensory gating (peak SNP rs10132223, $P = 1.27 \times 10^{-9}$). This locus has not been previously associated with psychotic illness in PGC-GWAS. In the PRS analyses, patients with a higher load of SCZ risk alleles had reduced gamma response whereas patients with a higher load of BIP risk alleles had smaller P3 amplitude. We observed a genomewide significant locus on chromosome 14 for P50. This locus may influence P50 but not psychotic illness. Among patients with psychotic illness, PRS results indicated genetic overlap between SCZ loci and gamma oscillation and between BIP loci and P3 amplitude.

Keywords

schizophrenia; bipolar disorders; event-related potentials; genowide assoication; polygentic risk score; endophenotypes

INTRODUCTION

Event-related potentials (ERPs) reflect synchronized neuronal activities during cognitive processing [Luck, 2005]. Investigators have used various ERPs phenotypes to probe cognitive and information processing deficits in major neuropsychiatric disorders. Several ERP deficits are robustly observed in patients with schizophrenia (SCZ) and bipolar disorder (BIP), including reduced P3 amplitude and delayed latency [Hall et al., 1996; Bramon et al., 2004; Hall et al., 2007; Hall et al., 2009a], impaired sensory gating [Freedman et al., 1996; Hall et al., 2008], and reduced gamma oscillation [Kwon et al., 1999; Spencer et al., 2008b; Roach et al., 2013]. P3 amplitude is related to attention and working memory capacity [Polich and Kok, 1995] whereas its latency reflects stimulus processing speed [McCarthy and Donchin, 1981]. Sensory gating indexes aspects of inhibitory function needed for filtering out repetitive or irrelevant incoming sensory stimuli [Freedman et al., 1994]. Gamma oscillations are believed essential for integrating information within neural circuits and appear to play an important role in perceptual and cognitive processes [Uhlhaas and Singer, 2010]. Deficits in these ERPs aggregate in families of patients with psychotic disorders.[Clementz et al., 1998; Schulze et al., 2008; Perez et al., 2013] Twin studies have demonstrated that these ERPs are heritable [Hall et al., 2006; Hall et al., 2011a] and are genetically correlated with liability to SCZ or psychotic BIP. [Bramon et al., 2005; Hall et al., 2009b] Taken together, these findings suggest that ERP impairments are endophenotypes for psychosis [Turetsky et al., 2007; O'Donnell et al., 2013].

Genome-wide association studies (GWAS) have proven successful in identifying common single nucleotide polymorphisms (SNPs) associated with disease risks for SCZ [Schizophrenia Working Group of the Psychiatric Genomics C, 2014] and BIP [Sklar et al., 2011]. GWAS have also been used for identify SNPs associated with quantitative traits that are putative endophenotypes of SCZ and BIP, including general cognitive ability [Lencz et al., 2014] and gray matter volume [Wang et al., 2013]. However, to our knowledge, no GWAS of sensory gating, gamma, or P3 ERPs in patients with psychotic disorders have been reported to date. On the other hand, studies have used ERP endophenotypes as a tool

for characterizing functional or neurobiological effects of risk variants identified by GWAS. For example, Quednow et al. reported that variants of the SCZ risk locus *TCF4* are associated with sensory gating deficits [Quednow et al., 2012], and we recently found that the *TCF4* SNP rs17512836 risk allele was associated with reduced auditory P3 amplitude and, to a lesser degree, with its latency component [Hall et al., 2013].

GWAS have also demonstrated that a substantial proportion of the heritability of SCZ and BIP is explained by a polygenic component consisting of thousands of common SNPs of small effect [Purcell et al., 2009; Sklar et al., 2011; Schizophrenia Working Group of the Psychiatric Genomics C, 2014]. In addition, cross-disorder GWAS have documented overlapping polygenic risk among SCZ, BIP, and major depressive disorder (MDD), with the strongest effects for BIP and SCZ, indicating pleiotropic effects of some risk variants across conventional diagnostic classifications [Cross-Disorder Group of the Psychiatric Genomics C et al., 2013a; Cross-Disorder Group of the Psychiatric Genomics C et al., 2013b]. The degree to which these risk loci overlap with loci influencing ERPs remains unknown and such knowledge could provide important support for the ERP's status as putative endophenotypes.

In the current study, our aims were 1) to carry out genome-wide association analyses identifying common variants associated with P3, sensory gating, or gamma oscillation endophenotypes, and 2)to test genetic relationships between the aggregated disease-associated SNP's effect on each ERP phenotype by constructing polygenic risk scores (PRS) in our case-control sample based on summary statistics from the Psychiatric Genomics Consortium (PGC) of SCZ, BIP, and MDD GWAS. We hypothesized that cumulative polygenic risk for SCZ, BIP, or MDD would predict ERP deficits in our sample.

METHOD

Sample

The sample prior to genetic quality control procedures consisted of 280 patients with psychotic illness and 134 healthy controls (HC). All subjects were assessed using the SCID-IV [First et al., 1997]. Cases were clinically stable patients with a DSM-IV diagnosis of SCZ or schizoaffective disorder (n = 148), BIP type I with psychotic features (n = 129), or psychosis NOS (n = 3). All participants were between 18 and 65 years old with no known neurological disorder, no prior head injury with loss of consciousness, normal hearing confirmed by audiometry, and normal intellectual ability based on the North American Adult Reading Test (NAART) or years of education (high school level or higher). Patients were included if they had no substance abuse (excluding nicotine) in the preceding 6 months or dependence in the preceding 12 months and no history of seizures or ECT treatment in the preceding 12 months. The HC sample was recruited through local advertisements. Additional inclusion criteria for HC were: no current or past history of psychotic disorder, BIP, or a SCZ spectrum disorder, no affective disorder in the preceding 12 months, no substance abuse in the preceding 12 months or previous chronic dependence, and no first-degree relative with a history of psychosis or BIP. All subjects self-reported European ancestry. This study was approved by the McLean Hospital Institutional Review Board.

After a complete description of the study, written informed consent was obtained from each subject.

Table I presents demographic and clinical information for the final sample. After genetic quality control procedures (see below), 399 participants were included in the analyses (271 patients and 128 controls). SCZ and BIP patients were older, had fewer years of education, and smoked more cigarettes than control subjects. BIP patients were younger than SCZ patients, included more females, and were receiving a lower mean chlorpromazine (CPZ) equivalent daily dose of antipsychotic medication compared with the SCZ sample (see Table I). The two patient groups did not differ in mean age of illness onset or proportion of current smokers. All but 14 patients (SCZ = 8, BIP = 6) were receiving psychotropic medication. Medicated and non-medicated patients did not differ significantly on any of the ERP measures. The most commonly prescribed non-antipsychotic medications in our sample were: lamotrigine (N = 45), lithium carbonate (N = 58), divalproex sodium (N = 34), bupropion (N = 24), lorazepam (N = 33), and clonazepam (N = 26). The doses of mood stabilizers, antidepressants, anxiolytics, and antipsychotics (in CPZ equivalent daily dose) were not significantly associated with any ERP variable, with the exception of bupropion, for which dose was significantly correlated with P3 latency ($R^2 = 0.25$, P=0.02). SCZ patients who were treated with clozapine antipsychotics (n = 37) did not differ significantly from those who were treated with other antipsychotics in any of the ERP measures.

Electrophysiological Recording and Analysis

We applied the same EEG recording and processing procedures as described previously [Hall et al, 2006; Hall et al., 2013]. Briefly, EEG was recorded using the BioSemi Active Two system at a digitization rate of 512 Hz, with a bandpass of DC-104 Hz and a Common Mode Sense (CMS) as the reference (PO2 site). Blinks and eye movements were monitored through electrodes placed on the left temple and above and below the left eye. The EEG data were re-referenced off-line to the averaged mastoid. Subjects were not allowed to smoke for a minimum of 40 min prior to the recordings.

The sensory gating ERP was elicited using the dual-Click paradigm (160 pairs of identical click stimuli, 5-ms duration; 2-ms rise/ fall; 500-ms inter-click interval; 10-s inter-trial interval). Signal processing was performed off-line using NEUROSCAN software (4.3) [Hall et al, 2006; Hall et al, 2011b]. EEG signals were segmented (−100–400ms), filtered (1-Hz high-pass filter), baseline corrected, and artifact rejected if activity exceeding 50 μV between 0 and 75 ms post-stimulus. S1 and S2 waveforms were averaged, digitally filtered (10-Hz high pass), and smoothed. P50 sensory gating ERP are reported at the Cz site and calculated as a ratio (S2/ S1) **x** 100. A higher ratio reflects more impairment.

P3 amplitude and latency ERPs were elicited by the auditory Oddball paradigm (400 binaural tones; 50-msec duration, 5 ms rise/fall times; 15% 1500 Hz target tones; 85% 1000 Hz standard tones). All participants had >90% accuracy. Signal processing was performed off-line using Brain Vision Analyzer software (Brain Products, Inc, 2000). EEG data were segmented (−100–1000 ms), low-pass filtered (8.5 Hz), baseline corrected, eye-blink corrected using [Gratton et al., 1983], and artifact rejected if activity exceeding >100 μV. P3 amplitude and latency components were automatically detected from the average wave for

target tones between 280 and 650 ms at the Pz site [Hall et al., 1999; Salisbury et al., 1999; Hall et al., 2009a].

Auditory steady-state response (ASSR) of gamma oscillation was elicited by the auditory steady state 40-Hz click stimulation paradigm (150 trains of 1-ms white noise clicks, 500-ms duration, 1100-ms stimulus onset asynchrony, 40-Hz stimulation rate) [Spencer et al., 2008a]. Signal processing was performed off-line using Brain Vision Analyzer software (Brain Products, Inc., Germany 2000). Time-frequency analyses were performed using the IDL program (EXELIS Visual Information Solutions, Boulder, Colorado). Single-trial epochs were extracted (−250–800 ms), eye-blink corrected, and artifact rejected if activity exceeding >100 μV. Phase locking and evoked power at Cz were analyzed with the Morlet wavelet transform using the IDL program. Average spectral measures were computed at 20–520 ms and wavelet frequencies between 38–47 Hz, where both evoked phase locking and power were maximal [Spencer et al., 2008a; Spencer et al., 2009]. The evoked phase locking measure at Fz was used for the PRS analyses.

Genotyping and Quality Control Procedure

DNA from blood samples was extracted at the Massachusetts General Hospital Center for Human Genetic Research and geno-typed at the Broad Institute using the Illumina OmniExpress Infinium Platform. Quality control included the following steps: removing individuals with discordant sex information (n = 5), missing genotype rate >5% or heterozygosity rate >3SD (n = 4), shared IBD >0.125 (n = 5), or were non-European ancestry based on principal component analyses (n = 1), resulting in a final sample of N = 399. Exclusion criteria for SNPs were as follows: SNPs on the X or Y chromosome, MAF<0.05, call rate <98%, and $P < 1 \times 10^{-6}$ for deviation from Hardy-Weinberg equilibrium. A total of 664,907 autosomal SNPs passed QC Quality control steps were carried out with PLINK [Purcell et al., 2007].

We performed genotype imputation using a 2-step prephasing and imputation procedure implemented in SHAPHIT and IM-PUTE2 on a total of 1,293 psychosis patients and 381 healthy controls collected at McLean Hospital that included the 399 samples described above [Howie et al., 2011; Delaneau et al., 2012]. We divided the genome into 3 Mb partitions and performed pre-imputation quality control and imputation with the default parameters of the software. The pre-imputation quality control filters include discordant sex information, missing genotype rate per individual, heterozygosity rate, call rate per SNP, deviation from Hardy-Weinberg equilibrium. We used phased haplotypes from the full 1,000 Genomes Project data set as the imputation reference panel. The final imputed dataset comprised 9.7 million autosomal SNPs.

Statistical Analyses

Logistic or linear regression analyses were used to compare the case and control groups on demographic characteristics and each ERP phenotype using STATA (STATA version 12; Stata Corp., College Station, TX). Sex and age were included as covariates.

GWAS analyses

Genome-wide association tests were performed on each ERP phenotype (P3 amplitude, P3 latency, sensory gating, ASSR gamma) in our case-control sample using PLINK. We used linear regression under an additive model to test for association. We adjusted for 10 principal components (PC)in the regression models to correct for potential population stratification. The principal components were obtained using EIGENSOFT [Price et al., 2006].

Polygenic Risk Score Analyses

We used GWAS summary results from the Psychiatric Genomics Consortium (PGC) of SCZ (i.e., SCZ2), BIP, and MDD clumped datasets (http://www.med.unc.edu/pgc/) to derive PRSs for each disease condition. In each disease dataset, we applied five different association *P* value thresholds ($P_T < 10^{-5}$, $P_T < 10^{-4}$, $P_T < .001$, $P_T < .05$, and $P_T < .5$) and selected SNPs according to these threshods to produce five sets of PRSs for each study participant in our sample. PRS was calculated as a weighted sum of risk allele counts (0,1,2) for each sample in our study. The log of the association odds ratios were used as the weight for PRS [Purcell et al., 2009].

Associations between each of the PRS for SCZ ($PRS\text{-}_{SCZ}$), BIP ($PRS\text{-}_{BIP}$), or MDD ($PRS\text{-}_{MDD}$), and each of the ERP phenotypes (P3 amplitude, P3 latency, sensory gating, ASSR gamma) were tested in our case-control sample using linear regression models in R (R 2.15.3; R Core Team, Vienna, Austria). Effects of diagnosis and diagnosis by PRS interaction were included in the regression model. Age, and the first 10 PC were included as covariates. Partial correlations at each threshold were calculated to estimate the percent of variance explained by the PRSs. *P*-values ≤0.0125 ($\alpha = 0.05$ corrected for four phenotypes) were considered statistically significant after multiple testing correction. We also examined the associations of PRSs stratified by cases and control samples separately. All PRS analyses were adjusted for age.

RESULTS

Supplementary Table 1 shows summary statistics for each ERP phenotype by diagnostic group. Compared with HC, patients with SCZ or BIP showed a highly significant impairment of sensory gating (both $P < 0.0001$), reduced P300 amplitude (both $P < 0.0001$), evoked gamma responses (both $P < 0.0001$), and prolonged P3 latency (SCZ: $P = 0.001$, BIP $P < 0.0001$). SCZ and BIP patients did not significantly differ on any ERP variable.

A total of 392 subjects who had P3 ERPs and sensory gating data and a total of 331 subjects who had ASSR gamma data were included in the GWAS analysis. There was no evidence for genomic inflation in each GWAS analysis (P3 amplitude, $\lambda = 0.9916$; P3 latency, $\lambda = 1.007$; sensory gating, $\lambda = 1.000$; sensory gating, $\lambda = 0.9953$). As shown in the Manhattan plot (Fig. 1) and Table II, nine SNPs reached the genome-wide significance level of $P < 5 \times 10^{-8}$ for the sensory gating phenotype, with the strongest signal at imputed SNP rs10132223 ($P = 1.27 \times 10^{-9}$). However, rs10149105, a genotyped SNP in strong linkage disequilibrium (LD) with the peak SNP ($r^2 > 0.8$) showed a similar level of association ($P = 5.12 \times 10^{-9}$).

Figure 2 shows the regional plot for associated SNPs at the chromosome 14 locus; as shown, all significant SNPs are in strong LD and reflect a single association signal. The nearest gene to this genome-wide significant locus is *FLRT2* (located 400 kb from the peak SNP).

No genomewide significant associations were observed for the other ERPs. However, three SNPs on chromosome 4 approached genomewide significance for ASSR gamma (rs181531738, P = 9.77 E-08; rs146360492, P = 9.05E-08; and rs114213960, P = 8.47E-08, (see Fig. 3). These SNPs were in high LD with each other ($r^2 > 0.8$) and the associated alleles were inversely related to ASSR gamma. These SNPs are located in the intronic region of *CORIN* and are very close to *ATP10D* (ATPase, class V, type 10D) and *GABRB1* (γ-Aminobutyric acid A receptor, β1)(Fig. 3). Results for SNPs with $p < 10^{-5}$ for each of the four ERP phenotypes are given in Supplementary Tables 2–5.

Polygenic Score Analysis

The results of the PRS analyses are shown in Figure 4. The $PRS\text{-}_{BIP}$ was nominally associated with reduced P3 amplitude at two thresholds: P_T 1e-5 (P = 0.03, R^2 = 1%) and P_T 1e-4 (P = 0.03, R^2 = 1%). Higher genetic risk scores were associated with smaller P3 amplitude. PRS-BIP was also nominally associated with reduced ASSR gamma response at the threshold of P_T 0.05 (P = 0.02, R^2 = 1.3%). Higher genetic risk scores were associated with smaller ASSR gamma response. These associations did not remain significant after multiple testing correction. Significant interactions between PRS and case-control status were observed in $PRS\text{-}_{SCZ}$ with ASSR gamma at P_T 1e-4 (P = 0.04) and P_T 1e-5 (P = 0.008), as well as in $PRS\text{-}_{BIP}$ with ASSR gamma at P_T 0.05 (P = 0.047) .

Analyses of case and control cohorts separately (Supplementary Figure 1 and 2) revealed that $PRS\text{-}_{scz}$ was associated with reduced ASSR gamma in cases at P_T 1e-4 (P = 0.04, R^2 = 2%), and P_T 1e-5 (P = 0.003, R^2 = 4%); the latter remained significant after multiple testing correction. $PRS_{\text{-}BIP}$ was associated with reduced P3 amplitude in cases at P_T 1e-4 (P = 0.02, R^2 = 2%) and P_T 1e-5 (P = 0.005, R^2 = 3%); the latter survived multiple testing correction, though the interaction between $PRS\text{-}_{BIP}$ and case-control status was not significant [Supplementary Figure 1]. No significant associations were found in controls.

DISCUSSION

We conducted a GWAS of four heritable ERPs that have been implicated as endophenotypes for psychotic illness: P3 amplitude, P3 latency, P50 sensory gating, and ASSR gamma in a sample of patients with SCZ and psychotic BIP and healthy controls. We observed a single genomewide significant locus associated with sensory gating, including the genotyped SNP rs10149105. Risk alleles were associated with impaired auditory sensory gating (i.e., worse inhibitory control). The observed allele frequencies of these SNPs in control were similar to those reported in the HapMap 3 CEU reference samples. The closest gene, approximately 400 kb upstream, is fibronectin leucine rich transmembrane protein 2 (*FLRT2*). *FLRT2* is expressed in the mammalian developing neocortex [Yamagishi and others 2011] and is important for modulating cortical neuron migration. During development, *FLRT2* & FLRT3 ectodomains are shed from neurons and act as repulsive guidance molecules for axons and somata of Unc5-positive neurons [Yamagishi and others 2011]. Deletion of either *FLRT2* or

Unc5D causes a subset of neurons to migrate prematurely, whereas over-expression of Unc5D has opposite effects. Sensory gating is present at birth and cerebral inhibition develops perinatally, influenced by genetic and *in utero* factors [Ross and others 2013a; Ross and others 2013b]. A possible link between sensory gating and *FLRT2* during development warrants further investigation.

The locus associated with P50 was not associated with SCZ or BIP in the most recent large-scale GWAS of these disorders by the PGC [Schizophrenia Working Group of the Psychiatric Genomics 2014; Sklar and others 2011]. Specifically, the p value for the peak SNP rs10132223 was 0.27 in the PGC-SCZ GWAS and 0.22 in the PGC-BIP GWAS. Thus, this locus appears to influence impairment in sensory gating, but not risk for psychotic illness. The alpha-7 neuronal nicotinic receptor subunit gene (*CHRNA7*), localized at 15q13–14, has been linked to the P50 sensory gating deficit in SCZ [Freedman and others 1997; Stephens and others 2009]. In our sample, SNPs in the *CHRNA7* region were not associated with the P50 sensory gating phenotype (smallest P value = 0.04).

Three SNPs on chromosome 4 approached genomewide significance for the ASSR gamma (see Fig. 3). These SNPs are located in the intronic region of *CORIN* and are very close to *ATP10D* (ATPase, class V, type 10D) and *GABRB1* (γ-aminobutyric acid A receptor, β 1) (Fig. 3). Although the function of *CORIN* in the brain is largely unknown, *GABRB1* has been linked to beta oscillation in families with alcoholism [Porjesz et al., 2002]. Beta (13–30Hz) and gamma (>30 Hz) oscillations are tightly coordinated in the brain [Uhlhaas and Singer, 2013] and generation of beta and gamma oscillations rely critically on gamma-aminobutyric acid (GABA) ergic N-methyl-D-aspartate (NMDA) networks [Arai and Natsume, 2006; Uhlhaas and Singer, 2013]. Alterations of GABAA receptor gene and expression level are implicated in the pathogenesis of SCZ [Rotaru et al., 2012]. Our preliminary result will need to be confirmed in a larger independent sample, since SNPs associated with gamma oscillation did not survive correction and were relatively rare.

Our second aim was to investigate the overlapping genetic relationships between aggregate effects of SCZ-, BIP- and MDD-SNPs on four ERP phenotypes. Studies of ERPs have characterized P3, sensory gating and ASSR gamma deficits as endophenotypes for SCZ [Bramon et al., 2005; Hall et al., 2007; Hall et al., 2011b] and for psychotic BIP [Muir et al., 1991; Hall et al., 2008; Rass et al., 2010]. Our observations that SCZ and BIP patients did not significantly differ on any ERP variable are consistent with the notion of shared genetic susceptibility between SCZ and BIP [Hall et al., 2012] and that these ERP impairments are endophenotypes for psychosis [Olincy and Martin 2005; Sanchez-Morla et al., 2008; Spencer et al., 2008b; Cross-Disorder Group of the Psychiatric Genomics C et al., 2013a; Cross-Disorder Group of the Psychiatric Genomics et al., 2013b].

We tested the hypothesis that polygenic risk scores for SCZ, BIP, or MDD would associate with ERP phenotypes. In the whole case-control sample analyses, we did not observe a significant correlation. However, analyzing cases and controls separately, we found that a SCZ polygene score was significantly and inversely correlated with ASSR gamma in cases ($P = 0.003$) at the most stringent P_T threshold. [Supplementary Figure 1]. The association explained 4% of the variance in ASSR gamma. A total of 93 SNPs was included in this PRS

at *P* value $<10^{-5}$ threshold. We also found that BIP-associated SNPs were significantly and inversely associated with P3 amplitude in cases ($P = 0.005$) at the most stringent threshold [Supplementary Figure 1]. The observed association explained about 3% of the variance in P3 amplitude and only four independent SNPs were included in this threshold cutoff. In fact, the variance explained in P3 amplitude or ASSR gamma dramatically decreased when more SNPs with higher cutoff P_T were added [Supplementary Figure 1]. These results suggest that the overlap between common variants so far involved in disorders and ERP phenotypes is restricted to a small subset of SNPs and is seen for ERP variance only among cases. It is possible that the observed SNP effects on P3 amplitude or gamma oscillations are indexing illness severity or some other clinical characteristic. However, the relatively small sample size of ERP subjects may well have limited our ability to detect more extensive overlap. In addition, our sample may not capture the full spectrum of ERP variation because most cases (68% of the sample) were recruited from clinical settings and are thus enriched for more severely ill patients.

Our study has several limitations: first, as noted above, our sample size was modest, raising the possibility of Type II error. For our sample of 399 and alpha level at 0.0125 for the polygenic score analysis, we had 50% power to detect a locus or polygene score accounting for 1.5% of the variance in each phenotype we examined. Nevertheless, our results provide the first genomewide analysis of multiple ERP phenotypes and can inform future, larger studies. Second, we were unable to identify a suitable sample to attempt replication and our results will need further confirmation in independent samples. While cases in our sample were significantly older than controls, age was included as a covariate in the regression models and in the PRS analyses.

In summary, we found genomewide significant association between a locus on chromosome 14 near *FLRT2* and the auditory sensory gating phenotype. However, this locus does not appear to be associated with SCZ or BIP based on the largest available GWAS of those disorders. In case-only PRS analyses, we found that a risk score comprising BIP-associated loci (at $P_T < 10^{-5}$) is also associated with reduced P3 amplitude, and a risk score comprising SCZ-associated loci (at $P_T < 10^{-5}$) is associated with reduced ASSR gamma response. Our results provided useful information for future ERP-genetic studies. Larger studies will be needed to clarify the genetic relationships among these phenotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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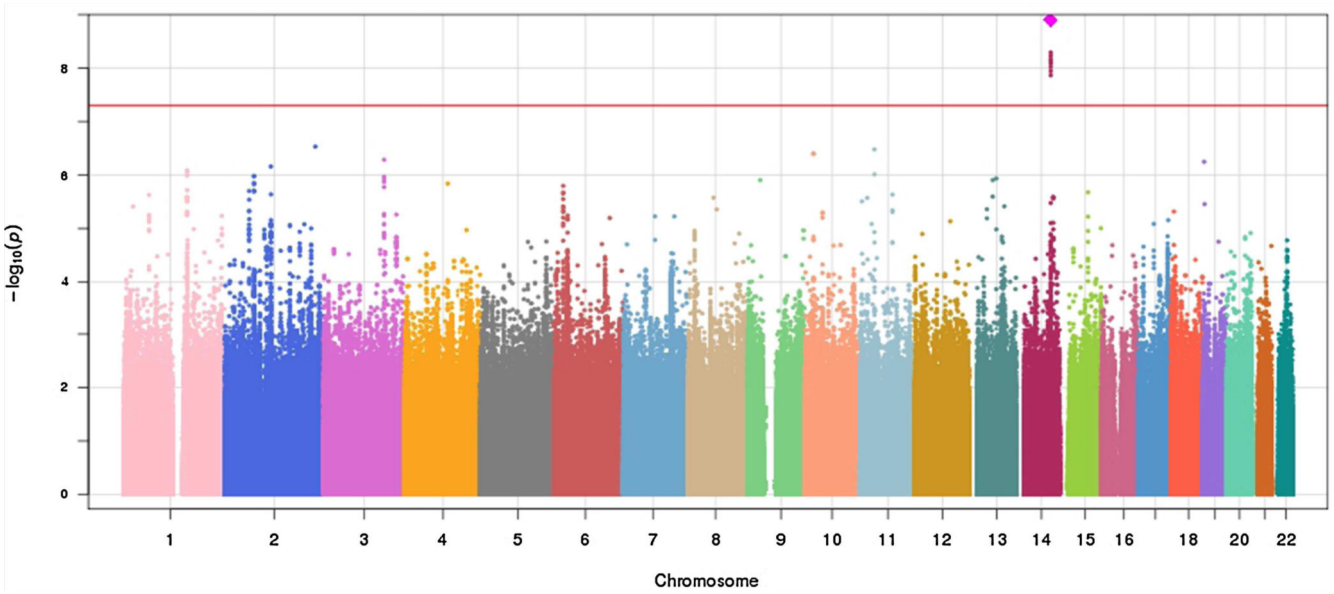

FIG. 1.
Manhattan Plot of GWAS results for sensory gating (P50).

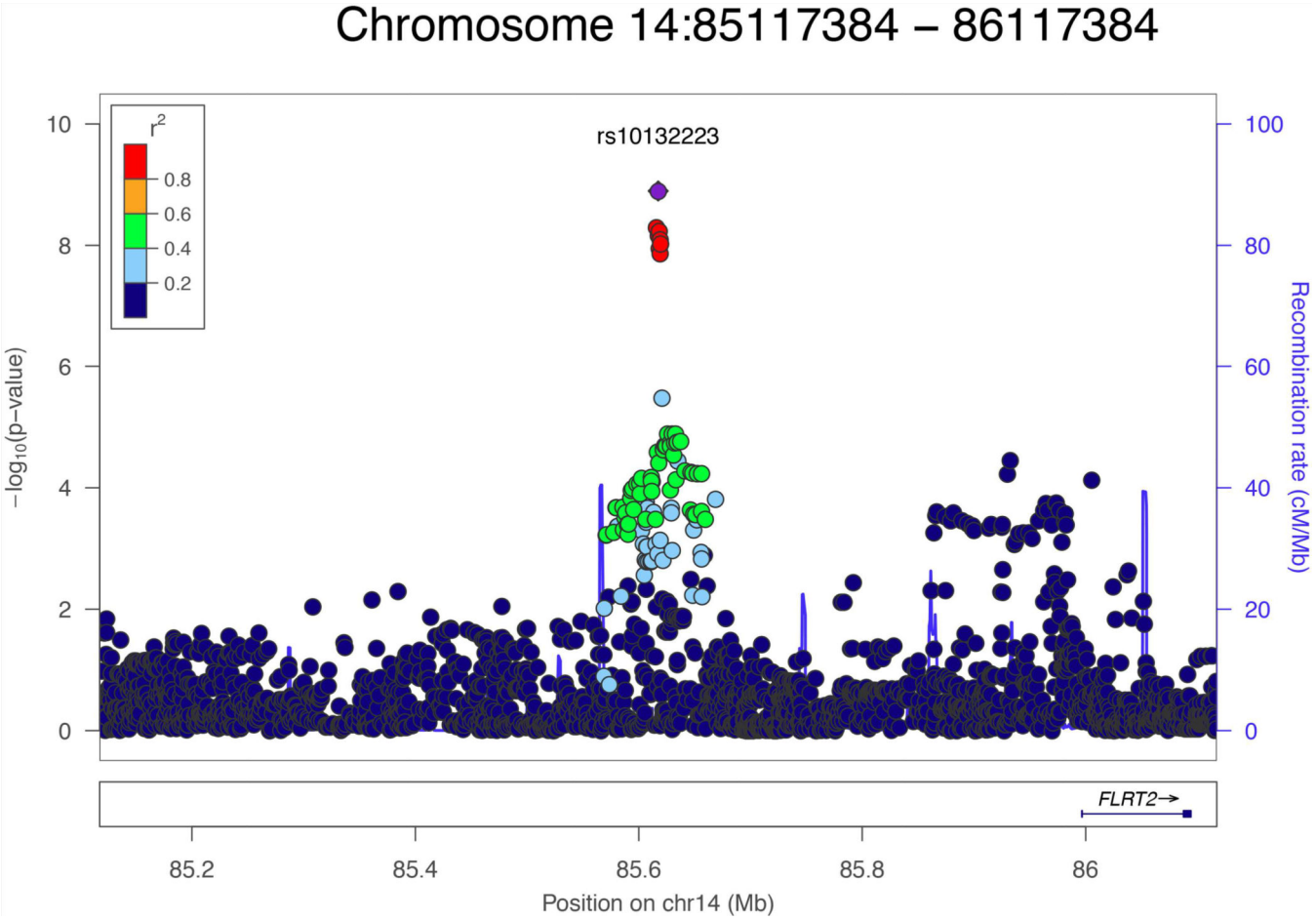

FIG. 2.
Regional plot for Chromosome 14 locus associated with Sensory gating.

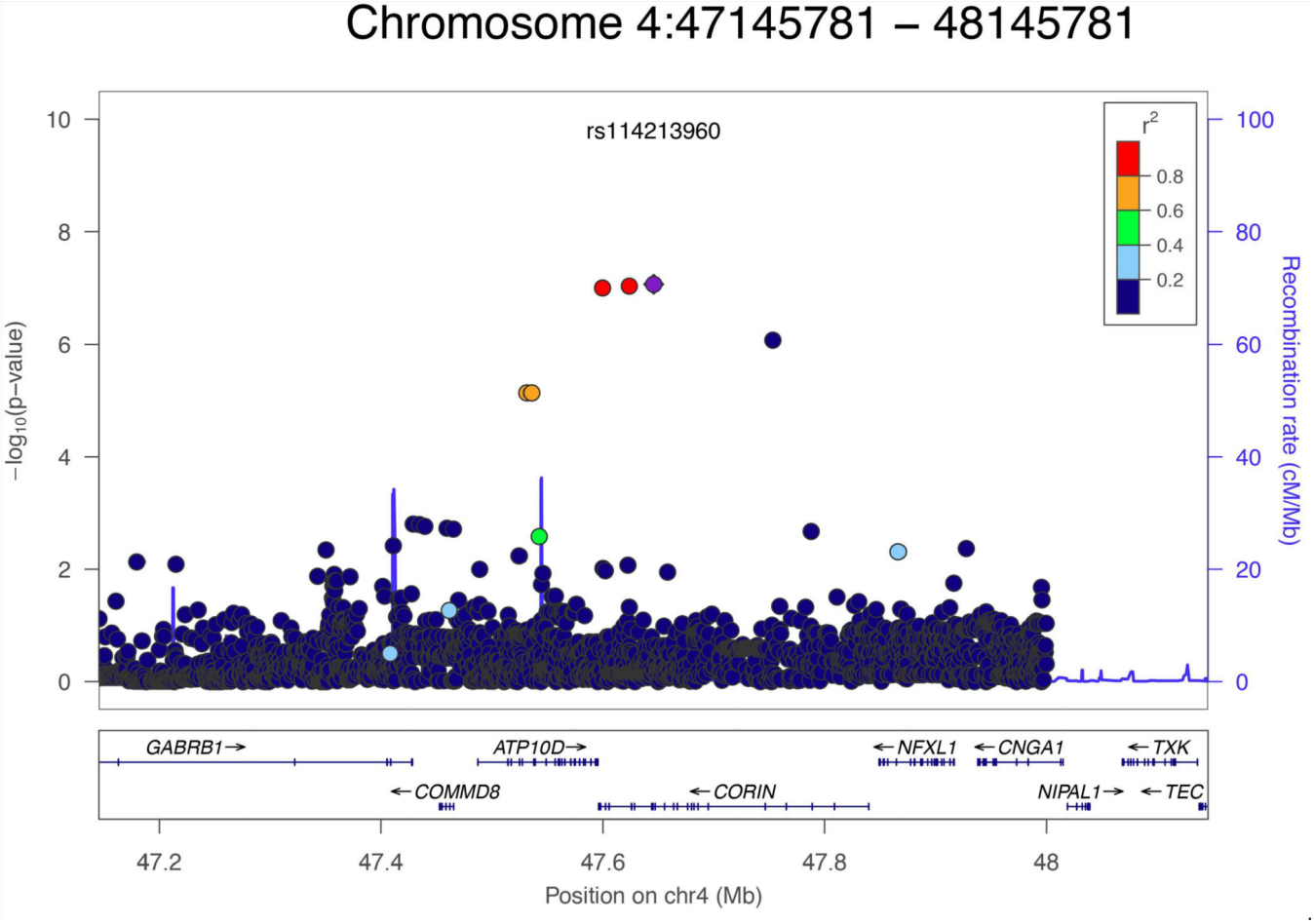

FIG. 3.
Regional plot for Chromosome four locus associated with ASSR gamma oscillaton.

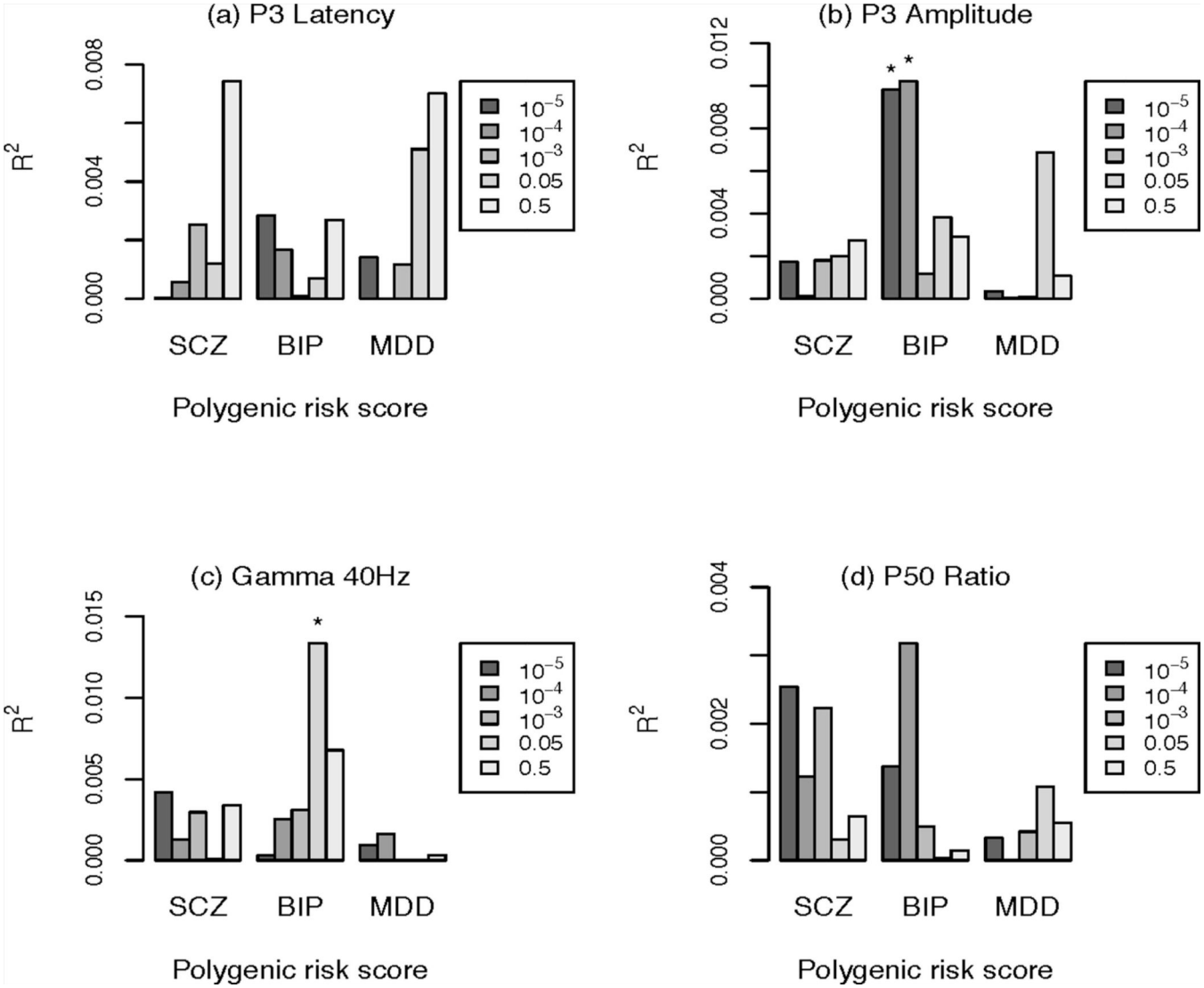

FIG. 4.

The variance explained of different phenotypes by polygenic schizophrenia score (PRS-$_{SCZ}$, left), bipolar score (PRS-$_{BIP}$, middle), and major depressive disorder (PRS-$_{MDD}$, right) for different p-cutoff single nucleotide polymorphism sets (box, right); y axis explained variance by the PRS of this phenotype. SCZ schizophrenia; BIP, bipolar disorder; MDD, major depressive disorder. *$P < 0.05$. PRS-$_{BIP}$ was nominally associated with reduced P3 amplitude at $P_T < 10^{-5}$ and $P_T < 10^{-4}$. Higher genetic risk scores were associated with smaller P3 amplitude. PRS-BIP was also nominally associated with smaller ASSR gamma response. These associations did not remain significant after multiple testing correction.

TABLE I

Demographic Characteristics of the Sample

	SCZ (n = 141)	BID (n = 127)	Controls (n = 128)	SCZ vs. HC	BID vs. HC	SCZ vs. BID
Age, yrs	43.9 (12.5)	40.0 (13.7)	33.2 (12.5)	$P < 0.001$	$P < 0.001$	$P = 0.01$
Female sex, N (%)	47 (33)	67 (53)	71(55)	$P < 0.001$	$P = 0.66$	$P = 0.001$
Education, yrs	14.3 (2.1)	15.1 (2.0)	15.6 (2.1)	$P < 0.001$	$P = 0.04$	$P = 0.004$
Smoker, N (%)	44 (39)	38 (35)	9 (9)	$P < 0.001$	$P < 0.001$	$P = 0.48$
Age of illness onset	22.9 (7.8)	22.4 (8.8)	N/A	N/A	N/A	$P = 0.59$
CPZ*	726.5 (910)	359.2 (338)	N/A	N/A	N/A	$P = 0.002$

Data are presented as mean (SD) unless otherwise indicated. (SCZ schizophrenia, BID bipolar disorder, CPZ chlorpromazine equivalent).

*SCZ n=120, BID n=85.

TABLE II

GWAS Results of Significant SNPs Associated With Sensory Gating

CHR	Location (BP)	SNPs	BETA	SE	P-value	Risk allele	Ref. allele	Risk allele frequency	INFO	Genotyped
14	85615940	rs10149105	20.1793	3.3717	5.12E-09	T	C	0.2212	1.0503	Yes
14	85617384	rs10132223	21.3939	3.4342	1.27E-09	T	G	0.2072	1.056	No
14	85617393	rs10144282	−20.0177	3.3748	6.90E-09	T	G	0.7783	1.0475	No
14	85617703	chr14_85617703_I*	20.0052	3.375	7.06E-09	GT	G	0.2217	1.0473	No
14	85618302	rs10135204	19.8278	3.3937	1.13E-08	T	C	0.2202	1.0409	No
14	85618459	rs10147584	−19.9705	3.3506	5.87E-09	T	C	0.7698	1.032	No
14	85619165	rs9652388	19.9258	3.3752	8.06E-09	A	G	0.2216	1.0474	No
14	85619232	rs7157801	19.9104	3.4278	1.36E-08	C	G	0.2158	1.021	No
14	85619625	rs7158211	19.826	3.3742	9.39E-09	T	C	0.2216	1.0482	No

INFO, imputation quality score.

Genomic positions are in UCSC hg19/NCBI Build 37.

*Chr14_85617703_I is a GT vs. G insertion variant.