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Heritability and molecular-genetic basis of the P3 event-related brain potential: A genome-wide association study

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Abstract

P3 amplitude is a candidate endophenotype for disinhibitory psychopathology, psychosis, and other disorders. The present study is a comprehensive analysis of the behavioral- and molecular-genetic basis of P3 amplitude and a P3 genetic factor score in a large community sample (*N* = 4,211) of adolescent twins and their parents, genotyped for 527,829 single nucleotide polymorphisms (SNPs). Biometric models indicated that as much as 65% of the variance in each measure was due to additive genes. All SNPs in aggregate accounted for approximately 40% to 50% of the heritable variance. However, analyses of individual SNPs did not yield any significant associations. Analyses of individual genes did not confirm previous associations between P3 amplitude and candidate genes but did yield a novel association with myelin expression factor 2 (*MYEF2*). Main effects of individual variants may be too small to be detected by GWAS without larger samples.

Descriptors

P300; Endophenotype; Genome-wide association study; Gene-based tests; Heritability; GCTA; Molecular genetics

P3 (or P300) amplitude is often considered a robust endophenotype for disinhibited psychopathology, such as antisocial behavior, disruptive disorders, such as attention deficit hyperactivity disorder (ADHD) and conduct disorder, and substance use disorders (SUDs)

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Supporting Information
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(Hesselbrock, Begleiter, Porjesz, O'Connor, & Bauer, 2001; Iacono, Carlson, Malone, & McGue, 2002; Iacono & Malone, 2011; Porjesz et al., 2005). We have recently discussed endophenotypic properties of P3 (Iacono & Malone, 2011), and we refer the interested reader to this paper for details. In brief, P3 amplitude can be measured reliably (Hall et al., 2009; Turetsky et al., 2007; van Beijsterveldt, van Baal, Molenaar, Boomsma, & de Geus, 2001), it is stable over the course of development (Carlson & Iacono, 2006; van Beijsterveldt et al., 2001), and reliable individual differences in developmental trajectories are observed (Carlson & Iacono, 2006; Hill et al., 2013). P3 amplitude is heritable, with a meta-analysis reporting a heritability of .60 (van Beijsterveldt & van Baal, 2002). This is nicely illustrated by the finding that the correlation between P3 amplitude recorded over parietal cortex in one hemisphere in a monozygotic (MZ) twin and P3 amplitude from the homologous site in the other hemisphere of his or her co-twin is approximately as large as the correlation within the same individual (Katsanis, Iacono, McGue, & Carlson, 1997). In addition, the genetic influence on P3 amplitude appears stable over time in adolescence (van Beijsterveldt et al., 2001) and into early adulthood (Carlson & Iacono, 2006).

There are numerous reports of associations between P3 amplitude and the externalizing spectrum of disinhibitory disorders, including alcoholism and alcohol abuse (Baguley et al., 1997; L. O. Bauer, 2001a; Carlson, Katsanis, Iacono, & Mertz, 1999; Chen et al., 2007; Cohen, Wang, Porjesz, & Begleiter, 1995; Costa et al., 2000; George, Potts, Kothman, Martin, & Mukundan, 2004; Glenn, Parsons, & Smith, 1996; Justus, Finn, & Steinmetz, 2001; Koskinen et al., 2011; Malone, Iacono, & McGue, 2001; Rodriguez Holguin, Porjesz, Chorlian, Polich, & Begleiter, 1999; Steinhauer, Hill, & Zubin, 1987; Yoon, Iacono, Malone, & McGue, 2006), drug abuse or dependence (Attou, Figiel, & Timsit-Berthier, 2001; L. O. Bauer, 2001a; Biggins, MacKay, Clark, & Fein, 1997; Carlson et al., 1999; Gamma, Brandeis, Brandeis, & Vollenweider, 2005), smoking and nicotine dependence (Anokhin et al., 2000; Iacono et al., 2002), antisocial personality disorder (Barratt, Stanford, Kent, & Felthous, 1997; L. O. Bauer, O'Connor, & Hesselbrock, 1994; Costa et al., 2000; Hesselbrock, Bauer, O'Connor, & Gillen, 1993; Iacono, Malone, & McGue, 2003; Malone et al., 2001), conduct disorder (L. O. Bauer & Hesselbrock, 1999, 2001; Kim, Kim, & Kwon, 2001), and ADHD (Banaschewski et al., 2003; Johnstone & Barry, 1996; Szuromi, Czobor, Komlosi, & Bitter, 2011; Yoon, Iacono, Malone, Bernat, & McGue, 2008). The association between P3 amplitude and symptoms of different externalizing disorders can be accounted for by a single latent dimension (Patrick et al., 2006) and is due to shared genetic influences (Hicks et al., 2007).

Several studies have observed P3 amplitude reductions in first-degree relatives of individuals with an externalizing disorder (Begleiter, Porjesz, Bihari, & Kissin, 1984; Carlson & Iacono, 2008; Carlson, Iacono, & McGue, 2002; Gabrielli & al., 1982; Hesselbrock et al., 1993; Hill, Steinhauer, Zubin, & Baughman, 1988; Iacono et al., 2002; Polich, Pollock, & Bloom, 1994; van der Stelt, Geesken, Gunning, Snel, & Kok, 1998), as well as in abstinent former substance abusers (L. O. Bauer, 2001b; Branchey, Buydens-Branchey, & Horvath, 1993; Fein & Chang, 2006; Realmuto, Begleiter, Odencrantz, & Porjesz, 1993). Moreover, P3 amplitude predicts the subsequent development of externalizing psychopathology or behavior (Berman, Whipple, Fitch, & Noble, 1993; Carlson, Iacono, & McGue, 2004; Gao, Raine, Venables, & Mednick, 2013; Habeych,

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Charles, Sclabassi, Kirisci, & Tarter, 2005; Hill, Steinhauer, Lowers, & Locke, 1995; Iacono et al., 2002; Perlman, Markin, & Iacono, 2013).

Although the status of P3 amplitude as an endophenotype is perhaps strongest in relation to externalizing disorders, P3 amplitude reductions have also been observed in other psychiatric disorders, such as borderline personality (Houston, Ceballos, Hesselbrock, & Bauer, 2005), which shares some features with the externalizing spectrum. A large number of studies have examined associations between P3 amplitude and schizophrenia and risk for schizophrenia (Jeon & Polich, 2003), with P3 amplitude commonly considered both a state and trait marker of the disease (Ford, 1999; Mathalon, Ford, & Pfefferbaum, 2000; Turetsky et al., 2007). P3 amplitude is also reduced among patients with bipolar disorder and their relatives (Hall et al., 2009; Turetsky et al., 2007). Associations with major depression are inconsistent and appear to reflect primarily state characteristics, although at least one study has reported reduced amplitude in offspring of parents with major depression (Y. Zhang, Hauser, Conty, Emrich, & Dietrich, 2007). In addition, reduced P3 amplitude has been reported in neurodegenerative diseases such as Alzheimer's disease (Gooding & Aminoff, 1992; Polich & Corey-Bloom, 2005). Understanding the molecular-genetic basis of P3 amplitude is thus of broad clinical interest.

P3 amplitude appears to reflect the modulation of attention by noradrenergic activity originating in the locus coeruleus (Nieuwenhuis, Aston-Jones, & Cohen, 2005), which may facilitate a process whereby computations conducted in the hippocampal formation result in an updated representation of stimulus context (Donchin, 1981) in association cortex in the temporal-parietal junction (Polich & Criado, 2006). This permits the organism to classify a stimulus as relevant to behavior (e.g., a button press to stimuli designated as targets) or as familiar. The latter allows use of P3 amplitude as a probe of recognition memory in detecting deception (Iacono & Patrick, 2014). The process of information transfer from short- to long-term storage is reflected in the so-called remembered word effect, whereby words in a study session that are subsequently recalled elicit larger P3 amplitudes than words that are not successfully recalled (e.g., Fabiani, Karis, & Donchin, 1986). Although several neural areas are implicated in P3 generation (cf. Mulert et al., 2004), the relative uniformity of P3 latency across the scalp suggests that the P3 represents activity of a distributed neural circuit (Nieuwenhuis et al., 2005).

The search for genetic markers associated with P3 amplitude has met limited success. Linkage studies have implicated regions of several chromosomes, principally 4, 6, 7, and 12 (Begleiter et al., 1998; Hill et al., 2004; Williams et al., 1999; Wright et al., 2008; H. Zhang, Zhong, & Ye, 2005). However, linkage analysis by itself can only highlight relatively large segments on a given chromosome. A number of candidate gene studies have been conducted, especially in recent years. These have produced several leads but no well replicated findings (Berman et al., 2006; Blackwood & Muir, 2004; Bramon et al., 2008; Chen et al., 2010; Decoster et al., 2012; Hill et al., 1998; Johnson et al., 1997; Lin, Yu, Chen, Tsa, & Hong, 2001; Shaikh et al., 2013). For instance, several studies have investigated dopamine genes, but these have mostly produced null findings or specific interactions with gender, risk status, or other genes (Berman et al., 2003; Garcia-Garcia, Barceló, Clemente, & Escera, 2011; Hill, 2000; Strobel et al., 2004). Dopamine genes may

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be especially relevant to P3 amplitude recorded at frontal sites (Gallinat et al., 2003, 2007; Heitland, Kenemans, Oosting, Baas, & Bocker, 2013; Mulert et al., 2006), which would be consistent with the finding that dopamine depletion is associated with reduced frontal P3 (Neuhaus et al., 2009).

Several recent studies from the Collaborative Studies on the Genetics of Alcoholism (COGA) have examined stimulus-related activity in the theta and delta frequency bands during the P3 time window, an alternative method of quantifying P3-related activity. Initial studies consisted of genome-wide linkage analysis, which uses markers consisting of polymorphisms varying either in sequence or size in samples comprising families. If a marker is coinherited with a trait, the two are said to be linked, and the gene that influences the trait is thought to be located near the marker. Because such markers tend to be widely spaced, linkage analysis is limited to identifying a relatively large chromosomal region containing genetic markers related to a phenotype. However, finding a “hot spot” can be followed up by analysis of SNPs or candidate genes located in the region. Such analyses have yielded significant results for the *CHRM2* gene encoding a muscarinic acetylcholine receptor (Jones et al., 2006) and the *GRM8* gene encoding a glutamate receptor (Chen et al., 2009). A genome-wide association study (GWAS) of P3-related theta activity at a frontal site reported association with a serotonin receptor gene, *HT7* (Zlojutro et al., 2011), one SNP in which was also associated with alcohol dependence. A second, family-based GWAS of frontal theta activity reported associations with several SNPs in the gene *KCNJ6* (Kang et al., 2012), which encodes a potassium channel involved in the function of dopaminergic, cholinergic, GABAergic, and glutamatergic synapses. These findings accord with the notion that cholinergic and GABAergic activity influence P3 amplitude, perhaps by modulating the activity of glutamate (Frodl-Bauch, Bottlender, & Hegerl, 1999; Kenemans & Kähkönen, 2010).

P3-like waves have been elicited in animals, and the amplitude of the P3 response is reduced in strains of mice selectively bred to show a preference for alcohol relative to other strains (Ehlers & Somes, 2002). Findings of reduced P3 in animal models of alcoholism risk bolster the notion that P3 amplitude is an endophenotype for alcoholism and related psychopathology. That P3 is so ubiquitous but at the same time associated with heritable individual differences also suggests that a “common-disease [phenotype], common-variant” model of inheritance is likely applicable. The genotyping arrays used in GWAS primarily assess common variants, defined most often as those that occur in at least 1–5% of the population, and have permitted discovery of association between such variants and common diseases. However, there are no published GWASs on P3 amplitude itself, a surprising gap in the literature in view of the extensive interest in the genetic basis of this endophenotype that is apparent from reviewing the literature.

To address this gap, we examined in the present investigation 527,829 single nucleotide polymorphisms (SNPs) in a large population-based sample of adolescent and adult participants from three independent cohorts of the Minnesota Center for Twin and Family Research (MCTFR). The analysis plan for all GWASs in this special issue is described in depth in Iacono, Malone, Vaidyanathan, and Vrieze (2014). In brief, we used a four-pronged approach: estimate the heritability of P3 amplitude using twin and twin-family biometric

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models, estimate the total genetic variance in P3 amplitude accounted for by all SNPs in aggregate by means of genome-wide complex trait analysis (GCTA; Yang, Lee, Goddard, & Visscher, 2011), assess associations between each individual SNP and P3 amplitude in a GWAS, and assess associations between individual genes and P3 amplitude by aggregating the effect of all SNPs in a gene using VEGAS, a versatile gene-based test for association studies (Liu et al., 2010). Analyses of individual SNPs and genes comprised both purely atheoretical analyses of the whole genome as well as more targeted analyses of candidate genetic variants.

Our primary measure was of P3 amplitude at a midline parietal site (Pz). In addition, we took advantage of having recordings from two additional electrodes over lateral parietal scalp and the fact that our sample consisted of nuclear twin families to estimate genetic factor scores. Given standard assumptions behind the latent variable models used to decompose total variance in P3 amplitude into its additive genetic and environmental sources, observed phenotypic scores can be transformed into genetic and environmental factor scores (cf. Boomsma, Molenaar, Orlebeke, Rao, & Vogler, 1990). Because it is by definition based solely on the additive genetic influence on P3 amplitude, a P3 genetic factor score is arguably a more appropriate target for GWAS than measured P3 amplitude. We expected it to provide greater power, relative to P3 amplitude, to detect the influence of individual genetic variants on the P3 response.

Method

Participants

As described in Iacono et al. (2014), the sample is a subset of the larger sample in a recent family-based GWAS of substance abuse and related psychopathology conducted at the Minnesota Center for Twin and Family Research (MCTFR; McGue et al., 2013; M. B. Miller et al., 2012). Participants for the present investigation are from the older and younger cohorts and enrichment samples of the Minnesota Twin Family Study (MTFS; Iacono, Carlson, Taylor, Elkins, & McGue, 1999; Keyes et al., 2009; McGue et al., 2013). The cohort-sequential nature of the MTFS design is such that the two age cohorts of twins participate at partially overlapping assessment ages. The sample for this investigation was based on the age-17 laboratory assessment of twins and all parents who had completed an identical laboratory assessment. (See Iacono et al., 2014, for further details.) Participants in MCTFR studies gave written consent or assent, if under the age of 18, to participate in the initial study as well as to allow data used in GWASs to be placed in a public repository to be shared with other researchers.

The sample is broadly representative ethnically of the state of Minnesota during the relevant birth years; it is thus predominantly Caucasian (96%). To avoid population stratification, which confounds genetic analyses if allele frequencies and mean levels of a phenotype both vary by different subpopulations, we limited this study to Caucasian subjects, based on self-reported ethnicity corroborated by principal component analysis (PCA) of genotype data (Iacono et al., 2014). The mean age was 17.7 (range, 16.6–20.0) for adolescent participants and 44.6 (range, 28.4–65.3) for the parents. Fifty-seven subjects were excluded for serious head injury, neurological disorders, use of alcohol or illicit drug the day of the assessment,

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medication likely to affect psychophysiological responses, and not refraining from taking medications for ADHD, such as methylphenidate, as was requested of the twins (Iacono et al., 2014). We excluded an additional 126 for reasons specific to the data used in this particular report: recording problems, poor task performance (less than 75% accuracy), or insufficient data (fewer than 30 artifact-free sweeps). The final sample consisted of 4,211 individuals, 2,439 adolescents (1,180 males) and 1,772 adults (1,200 males) from 1,637 families. The majority of families were MZ twin families (1,053, or 64%).

Experimental Task

The Begleiter rotated heads task (Begleiter et al., 1984) served to elicit event-related potentials (ERPs). Subjects viewed 240 stimuli presented one at a time on a computer display in a Bernoulli sequence. A 500-ms baseline interval preceded stimulus onset. Stimulus duration was 100 ms. Responses were monitored during a response window of 1.5 s and a random intertrial interval drawn from a uniform distribution of 1–2 s. Superior views of stylized “heads” consisting of an oval, the nose, and one ear served as target stimuli (n = 80), with the head rotated 180° on half the trials. The subject’s task was to press a button on either the left or right arm of their chair to indicate whether they had viewed a left- or right-ear head. Stimuli for the remaining trials consisted of plain ovals (n = 160), which required no response.

EEG Recording

ERP data were collected over the course of more than 20 years using two different systems. For older- and younger-cohort MTFS participants[1] (74% of the sample), electroencephalogram (EEG) was recorded via Grass Neurodata 12 systems (256-Hz sampling rate, pass-band from .01 to 30 Hz with a roll-off of 6 dB). For each trial, 2 s of EEG, including a 500-ms prestimulus baseline, were written to disk. Hardware constraints limited the number of signals recorded to three: one from midline parietal scalp and two from left and right parietal cortex, respectively. Signals were referred to linked ear electrodes. Eye blinks and other eye movements were recorded by means of a transverse electrode arrangement, with one superior to the eye and one next to the outer canthus. For MTFS enrichment sample (ES) participants, a BioSemi ActiveTwo system was used to collect continuously recorded EEG data with a sampling rate of 1024 Hz. Stimulus delivery was controlled by a script written in E-Prime software 1.1 (Psychology Software Tools, Pittsburgh, PA) to mimic the original program and pass event triggers to the recording system. ActiveTwo amplifiers are DC coupled, and signals were low-pass filtered using a digital 5th-order Bessel antialiasing sinc filter with a cutoff frequency (3-dB attenuation) of 205 Hz. ActiveTwo signals are monopolar.

ERP Processing

Data processing was conducted in MATLAB (The Mathworks, Natick, MA) using identical methods for both systems, based on functions in the Psychophysiology Toolbox http://sourceforge.net/projects/psychophys/ and custom scripts. BioSemi data were transformed to

[1]There were 50 exceptions to this, with 39 ES fathers tested in the Grass lab and 11 MTFS fathers tested in the BioSemi lab.

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be comparable to the original data, as described in the online supporting information. Notes recorded at the time the data were collected guided us in visually identifying problematic data that might need to be excluded. In addition, specific trials containing transient artifacts and excessively small or large voltage deflections were tagged for exclusion by computer algorithm. To increase reliability of peak selection, target ERPs were low-pass filtered with a cutoff frequency of 10 Hz using a finite impulse response (FIR) filter with least-squared error to minimize the contribution of higher frequencies (Losada, 2004). A computer algorithm selected the largest peak within a window between 300 and 600 ms as the P3. Outliers with respect to amplitude and latency were identified and their data visually screened to determine whether outlyingness was due to problems necessitating subject exclusion. In addition, we identified multivariate outliers using the three parietal electrodes and a robust version of Mahalanobis distance from the *robustbase* package (Rousseeuw et al., 2011) in the statistical computing environment (R Development Core Team, 2010). The corresponding data were examined visually, and the algorithm's selection overridden if necessary.

Molecular Genetic Data

The pipeline for extracting and processing DNA as well as steps taken to ensure quality control are described in detail in Iacono et al. (2014) and in Miller et al. (2012). PCA was conducted on genotypes of non-Caucasian subjects using EIGENSTRAT (Price et al., 2006) in order to identify the major dimensions of genetic variation. Scores on the first 10 components were subsequently used in all analyses in order to control confounding due to any residual population stratification in allele frequencies (cf. Price et al., 2006).

Statistical Analyses

Our primary dependent measure was P3 amplitude at the midline parietal location (Pz). Generation (twin or parent), gender, chronological age, a dummy variable representing recording system (BioSemi or Grass) in order to account for possible mean differences between them, and the 10 PCs from EIGENSTRAT served as covariates in subsequent analyses. Additive SNP effects were modeled, with each SNP represented as a count of the number of minor alleles.

In addition, we examined genetic factor scores (Boomsma et al., 1990) derived from a biometric common pathway (Kendler, Heath, Martin, & Eaves, 1987) or psychometric factors (McArdle & Goldsmith, 1990) model, with P3 amplitude at the three parietal locations as indicators of a common factor, representing what is shared by the three P3 amplitude measures. Unique factors captured electrode-specific influences, including noise. Preliminary moderated factor analyses (D. J. Bauer & Hussong, 2009) indicated that the four primary covariates (age, gender, generation, and recording system) were significant influences on the common factor mean. In addition, gender and generation influenced both the unique and common factor variances. (Table S1 provides parameter estimates from the preliminary factor analyses, and the supporting information provides additional detail concerning the model.) Thus, our final biometric model allowed for gender and generation effects on common factor and unique variances, with effects on the factor mean accommodated through adjusting P3 measures for the four covariates (age, gender,

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generation, and recording system). Figure 1 illustrates the model for one individual, although data from all family members are used in estimating the model.

Biometric heritability—The amount of heritable variance in P3 amplitude and the P3 common factor was estimated using standard biometric approaches to modeling twin-family data (Neale, Boker, Xie, & Maes, 2003) and conducted using the OpenMx package for R (Boker et al., 2011). Our approach and the logic of biometric model fitting are described in Iacono et al. (2014). We fit models to twin data as well as data from the entire family. For both endophenotypes, models allowed for three latent factors, which influence ("cause") the endophenotype: additive genetic influences (A), common environmental influences (C), and unique, or unshared, environmental influences (E). Parameter estimates from the common pathway model, which is described in more detail in the supporting information, were used to derive genetic factor scores. Because genetic factor scores and genotype are identical for MZ twins, only one twin from each MZ pair was used in analysis of these scores. The correlation between the two (covariate-adjusted) P3 endophenotypes was .925.

SNP heritability—We used GCTA (Yang et al., 2011) to estimate the proportion of variance in P3 amplitude accounted for by the combined additive effect of all SNPs on the Illumina genotyping array (or in linkage disequilibrium [LD] with them). In a sample of genetically unrelated individuals, the degree to which any two are phenotypically similar must be due to the specific genetic variants they share. GCTA estimates genotypic similarity in the form of a genetic relatedness matrix (GRM), somewhat akin to a correlation matrix representing pairwise genetic similarity. In samples comprising families, Yang and colleagues (Yang, Lee, Goddard, & Visscher, 2013) have recommended filtering the sample on the basis of genetic relatedness, using several thresholds and looking for consistency across the resulting estimates. We used thresholds of .025, .05, and .10, which remove all but distant relatives. The same covariates were used as in all other analyses (age, gender, generation, recording system, and the 10 PCs from EIGENSTRAT). Because LD can bias SNP heritability estimates upward (Speed, Hemani, Johnson, & Balding, 2012), we repeated these analyses after weighting SNPs by local LD patterns using LDAK software (http://dougspeed.com/ldak). Yang and colleagues have more recently recommended using the entire sample when it consists of closely related subjects, and estimating the magnitude of genetic influence while simultaneously modeling the environmental influences family members share (the C latent variable in biometric models). This provides an estimate of genetic influence unconfounded by shared environmental effects (as well as an estimate of such effects). In addition to this, we conducted the same analysis without modeling shared environmental influences (i.e., without any threshold of genetic relatedness). The difference between the two provides a simple indication of the magnitude of such effects (which is also estimated directly by GCTA).

SNP effects: Genome-wide scan—Analyses of the association between each SNP in turn and our endophenotypes were conducted by means of the R package for rapid feasible generalized least squares (RFGLS; Li, Basu, Miller, Iacono, & McGue, 2011), a computationally efficient form of generalized least squares (GLS) developed for this purpose. GLS is useful with correlated data, such as the correlation that exists when subjects

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are nested in families (see Iacono et al., 2014, for details). Our sample comprised MZ and DZ twin families. In addition, the 74 stepparents in the sample (70 of them male) were treated as families of one. The conventional genome-wide significance threshold of 5×10^{-8} was used.

SNP effects: Candidate SNPs—Using the results of our genome-wide scan, we examined associations between each endophenotype and two target sets of specific candidate SNPs implicated in previous studies of P3 or P3-related activity ($N = 183$; P3-specific candidate SNPs) or in recent meta-analyses of disorders associated with the endophenotypes examined in this special issue ($N = 1{,}180$; endophenotype-general candidate SNPs). The latter included alcohol and drug dependence, cocaine abuse, smoking and nicotine dependence, ADHD, schizophrenia, bipolar disorder, and major depression, or related phenotypes, such as heavy drinking or excessive consumption, and the personality characteristic of excitement seeking (Iacono et al., 2014). SNPs in the candidate sets but not on the Illumina array were imputed (Iacono et al., 2014). Analyses of imputed SNPs used allele dosage as the independent variable, which is a count of the minor allele weighted by the posterior probability of each genotype. We used Bonferroni-corrected significance thresholds for both sets, with significance criteria of 2.73×10^{-4} and 4.24×10^{-5} for P3-specific and endophenotype-general SNPs, respectively.

Gene effects: Genome-wide scan—Gene-based tests can be a powerful alternative to tests of individual SNPs, especially when there are several causal SNPs in a gene. It is possible in such a circumstance that the *p* values might not be small enough to be distinguishable from noise. We conducted gene-based tests of 17,601 autosomal genes available in VEGAS (Liu et al., 2010). VEGAS aggregates the effects of all SNPs within a gene by converting the *p* values for each SNP into a chi-squared statistic and summing these into a single score, which is adjusted for LD between the SNPs (see Iacono et al., 2014). In order to capture SNPs with regulatory functions and SNPs in LD with those in the gene proper, VEGAS includes SNPs spanning a small region on each end of the gene. Because the *p* values were produced by RFGLS, they accurately reflect the clustered nature of our sample. A threshold of 2.84×10^{-6} was used for determining statistical significance, which corrects for the number of different genes.

Gene effects: Candidate genes—In analyses similar to our analyses of candidate SNPs, we evaluated three sets of candidate genes: 18 that have been implicated in P3 amplitude or related measures (P3-specific candidate genes, see first column of Table S4 for a list); 204 genes that are likely relevant to understanding the endophenotypes examined in this special issue because they are part of the major neurotransmitter and neuromodulator systems (dopamine, noradrenaline, acetylcholine, GABA, glutamate, and serotonin), they are part of the endogenous cannabinoid and opioid systems, or they are involved in metabolizing nicotine and alcohol (endophenotype-general candidate genes, see first column of Table S5); and 92 genes identified by the Consortium on the Genetics of Schizophrenia as related to similar endophenotypes (COGS candidate genes, see first column of Table S6). Bonferroni correction was used to determine the significance of genes in each set, with thresholds of 2.78×10^{-3}, 2.45×10^{-5}, and 5.43×10^{-4} for the three sets, respectively.

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Results

Descriptive statistics are provided in Table 2 in Iacono et al. (2014) in this issue. Mean amplitudes were 5% to 11% larger for females than males and 61% to 72% larger for adolescents than adults. Plots of the distribution of each endophenotype indicated that the assumption in regression analysis of normally distributed scores was reasonable (see Figures S1 and S2 in supporting information).

Heritability from Biometric Models

Table 1 gives family correlations produced by RFGLS for P3 amplitude and phenotypic factor scores from the common pathway model, which was the basis for estimating genetic factor scores. The pattern of correlations suggests substantial genetic influence and little shared environmental influence. This was confirmed by the results of biometric model-fitting analyses, summarized in Table 2. Heritability estimates for both endophenotypes (P3 amplitude and the P3 common factor) were substantial, indicating that between half and nearly two thirds of the variance in them was due to additive genetic influence. Heritability estimates were somewhat larger in magnitude for the common factor. Point estimates of C were nonzero in estimates obtained from twin data, although the confidence interval included 0. This indicated that shared environment is likely not a significant influence.

SNP Heritability

In order to obtain a subsample of unrelated individuals, we filtered the sample using genetic relatedness thresholds of .025, .05, and .1 (Yang et al., 2013), the most stringent of which corresponds approximately to the relationship between third or fourth cousins. Results for each subsample are given in Table 3, which also presents results for the same subsamples using a GRM based on SNPs weighted by LD patterns (Speed et al., 2012). The standard errors are large, a consequence of the fact that unrelated individuals are used, which also reduced the sample approximately in half. SNP heritability estimates vary somewhat, as would be expected due to sampling error across the subsamples, but are relatively consistent. The median estimates were .29 and .27 for P3 amplitude and the genetic factor score derived from parameters of the biometric common factor model, respectively. Standard errors in some cases were larger than the point estimates, making strong inferences ill advised. Table 3 also includes SNP heritability estimates for each endophenotype in the full sample (i.e., without imposing a threshold of relatedness, appearing in the row labeled “None” in the table), which is largely driven by the phenotypic relationships among family members and approximates the sum of factors that give rise to phenotypic resemblance (A and C) in Table 2. We also used the method of Yang and colleagues to model, and thereby control, shared environmental influence in family data while estimating the magnitude of genetic effects (see the column labeled “GCTA-Family”). Because there is by definition no such shared environmental influence in the genetic factor score, this was estimated only for P3 amplitude. Despite the fact that this second method accounts for C, it produced a point estimate that was identical to two decimal places (.57).

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SNP Effects: Genome-Wide Scan

Figure 2 presents the Q-Q plot for P3 amplitude, while Figure 3 presents the Q-Q plot for the genetic factor score. Substantial deviation from the expected line representing the null distribution can indicate inflated (or deflated) power, such as might result from population stratification. This was not the case, an inference corroborated by the genomic control statistics, which were close to 1 for both measures (with 1 indicating that the observed values conform exactly to expectation under the null hypothesis). Our analytic approach therefore appears to have appropriately accommodated the lack of independence in our family data, and there was no meaningful residual ethnic stratification. There was also no evidence for significant associations. None of the SNP effects on either P3 or the genetic factor score was genome-wide significant (p values $> 5 \times 10^{-8}$). An apparent excess of small p values, which appear as large values of $-\log_{10}(p)$, was evident in the Q-Q plots, especially for P3 amplitude. These subthreshold p values may indicate that there are true associations hidden in the GWAS signal. We list the results for all SNPs with p values less than 10^{-4} in Tables S2 and S3 for P3 amplitude and the genetic factor score, respectively. Ninety-six SNP associations with P3 amplitude produced p values less than 10^{-4}, whereas approximately 50 would be expected by chance (ignoring LD, which creates a correlation among SNPs). However, the degree of overlap between endophenotypes with respect to the specific SNPs producing small p values was limited (24 in all), especially considering the magnitude of the phenotypic correlation between the two.

Manhattan plots, which are presented in Figure 4 for P3 and in Figure 5 for the genetic factor score, order p values by location on each chromosome, thereby providing information about where in the genome variants with small p values occur. Although small p values (large $-\log_{10}[p]$) appear to cluster somewhat on a few chromosomes, on balance there is little evidence of significant or even suggestive associations.

SNP Effects: Candidate SNPs

Table S4 in the supporting information lists the results for P3-specific candidate SNPs. Two SNPs out of 176 were nominally significant for P3 amplitude ($p < .05$), while one SNP—a different one—yielded a p value less than .05 for the genetic factor score. None of the p values was close to the Bonferroni-corrected threshold of 2.73×10^{-4}. Table S5 gives results for SNPs in our endophenotype-general candidate SNP set of 1,180. None of the observed p values approached the Bonferroni-corrected threshold of 4.24×10^{-5}; the smallest, for P3 amplitude, was 5.38×10^{-4}.

Gene Effects: Genome-Wide Scan

A comprehensive evaluation of 17,601 autosomal genes provided by VEGAS yielded a genome-wide significant association ($\alpha = 2.87 \times 10^{-6}$) with both endophenotypes for *MYEF2*, myelin expression factor 2, $p \leq 6.79 \times 10^{-7}$, a gene on chromosome 15. The protein encoded by *MYEF2* is a repressor of transcription of the myelin basic protein gene (*MBP*). Gene Ontology annotations related to *MYEF2* include RNA binding and nucleotide binding. The next smallest p value was 7.50×10^{-5}.

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Gene Effects: Candidate Genes

VEGAS summary statistics for P3-specific candidate genes are presented in Table S6. Test statistics and associated *p* values for the 204 endophenotype-general candidate genes appear in Table S7, and summary statistics for the 92 candidate genes associated with endophenotypes for schizophrenia are presented in Table S8. None of the genes in these three candidate gene sets yielded *p* values that survive the respective Bonferroni-corrected threshold for each set.

Discussion

Additive Genetic Variance in P3 Amplitude

This study is the first published GWAS of amplitude of the P3 wave, the most widely studied ERP measure and a strong candidate endophenotype for disinhibitory behavior and psychopathology in particular (Iacono & Malone, 2011; Porjesz et al., 2005). We conducted biometric analyses in our sample of MZ and DZ twin families to determine the extent to which variation in P3 amplitude reflects heritable individual differences. Estimates of heritability from ACE models ranged from .50 to .66 for the two phenotypes, which is consistent with results of a meta-analysis that estimated P3 heritability as approximately .60 (van Beijsterveldt & van Baal, 2002). GCTA analyses provide estimates of SNP heritability, or phenotypic variance due to the measured genetic variants on our genotyping array (or variants in LD with them). Using several thresholds of pairwise genetic relatedness to select unrelated subjects from our family sample based on a weighted and unweighted GRM, we obtained median estimates of SNP heritability of .29 for P3 amplitude and .27 for genetic factor scores. This represents approximately 40% to 50% of the heritable variance in each trait. These estimates are imprecise; 95% confidence intervals around them are necessarily large when derived from genetically unrelated individuals. Nevertheless, results of GCTA analyses indicate that much of the additive genetic influence in both endophenotypes is due to common genetic variants. GCTA that accounted for shared environmental influences within families and GCTA with the full sample (without a threshold of genetic relatedness) produced nearly identical estimates (.571 and .570, respectively). These numbers cannot be considered SNP heritability estimates, because they are driven by all factors that cause highly related individuals to have similar values of P3 amplitude, such as nonadditive genetic influences and rare variants that are not tagged by the SNPs on the genotyping array. However, the fact that they were virtually identical indicates that shared environmental influences were minimal. This is consistent with the fact that the 95% confidence interval around the estimate of C in biometric models of both twin data and family data included 0.

Analysis of SNPs

Despite evidence from biometric analyses and GCTA that additive genetic influences on P3 amplitude and the P3 genetic factor score are substantial and due in large part to common variants, we failed to obtain genome-wide significant associations with any individual SNPs for either endophenotype, including those in our sets of candidate SNPs selected for having been reported to be associated with P3 amplitude or P3-related activity in previous genome-wide studies or because they are hypothesized to be relevant to disorders associated with our endophenotypes.

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Analysis of Genes

Genome-wide analysis of all autosomal genes produced one significant finding for both endophenotypes that survived Bonferroni correction. Myelin expression factor 2 (*MYEF2*) is a transcriptional repressor of myelin basic protein, which codes for a major constituent of the myelin sheath surrounding oligodendrocytes and Schwann cells in the central nervous system. In addition to increasing the velocity of the conduction of action potentials along axons, myelin is important for facilitating long-range connections among brain regions. P3 appears to be produced by a distributed neural circuit, and myelin may facilitate coherent activity in this circuit. This is a novel finding, although we are unable to find any previous links to P3 or related measures, which makes independent replication especially important.

Analyses of the 92 schizophrenia endophenotype candidate genes from COGS and the 204 candidate genes we hypothesized might be related to all the endophenotypes examined in this special issue did produce a handful of associations that were nominally significant for both endophenotypes ($p < .05$). However, these were few in number, and none survived Bonferroni correction. Our failure to find strong evidence of associations with neurotransmitter genes in the endophenotype-general candidate set of 204 is disappointing given empirical and conceptual evidence that P3 amplitude depends critically on several major neurotransmitters. We also did not corroborate previous findings regarding P3 amplitude or related phenotypes, such as event-related theta power. Although several associations were nominally significant ($p < .05$), this was not the case for both endophenotypes, despite the fact that they were very highly correlated.

Lack of Agreement with Previous Studies

That we failed to confirm recent findings from genome-wide studies might stem from the fact that the majority of recent studies reporting positive findings have primarily examined event-related theta power at frontal sites. P3 amplitude consists largely of stimulus-locked activity in the delta and theta frequency ranges (Başar, Başar-Eroğlu, Karaka, & Schürmann, 1999; Kolev, Demiralp, Yordanova, Ademoglu, & Isoglu-Alkaç, 1997), and one might expect some overlap in SNP associations. However, the correlation between frontal theta power and parietal P3 amplitude may not be large enough to be reflected in significant SNP associations. Previous genome-wide findings have also been based on the COGA sample (Chen et al., 2009, 2010; Jones et al., 2006; Kang et al., 2012; Zlojutro et al., 2011), which comprises alcoholic probands and relatives from families with a dense history of alcoholism. Although the density of alcohol dependence in our general population sample is not comparable to its density in COGA, problematic alcohol use is quite prevalent in the MCTFR in general (Hicks, Schalet, Malone, Iacono, & McGue, 2011; McGue et al., 2013), including MTFS twins (Hamdi & Iacono, 2014). Ascertainment in COGA on such high levels of genetic susceptibility is likely to increase the relative importance of rare variants with large effects in genetic analyses. It also may amplify the genetic signal common to P3 amplitude and alcoholism risk more than the P3-specific signal, which is small in population-based samples such as ours (Hicks et al., 2007).

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Limitations

Of course, the present investigation suffers from limitations. One is the number of electrodes used for recording P3 amplitude—one, or three in the case of the common factor approach. Although P3 amplitude is typically greatest at the site we used (Pz) and much of the relevant research establishing its status as an endophenotype has also used this site, several recent positive findings for individual SNPs or candidate genes, whether of P3 amplitude or event-related theta activity, have been for recordings over frontal brain regions. Our use of two different age cohorts, although allowing us to maximize sample size, may have obscured true effects that are expressed differently in late adolescence compared to adulthood. Even with the cohorts combined, the sample was small by current GWAS standards, if not when this project was first undertaken. We did not use bioinformatic methods that are designed to use additional information, such as knowledge about biological pathways and gene expression, to mine the *p* values produced by GWAS for patterns, or methods for selecting subsets of SNPs, although the approach we adopted is a reasonable starting point.

Conclusions

The aggregate additive effect of all SNPs accounted for a little less than 30% of the variance in P3 amplitude and the genetic factor score, which is between 40% and 60% of the heritable variation in these measures. Approximately half the heritable variation thus appears to be due to common genetic variants. Nevertheless, we did not obtain any statistically significant associations between endophenotypes and individual SNPs, and the association with *MYEF2*, despite being genome-wide significant, has no precedent in the literature and awaits replication. Moreover, although the P3 genetic factor score, because it specifically reflects the additive genetic variance in P3 amplitude, would seem to be advantageous in GWAS, its usefulness consisted primarily in allowing us to assess the degree of correspondence between analysis results for the two endophenotypes.

Endophenotypes have offered the promise of assisting scientists in identifying genes for psychiatric disorders, so much so that Miller and Rockstroh (2013) characterized the time since the publication of Gottesman and Gould's influential paper in 2003 as the "decade of the endophenotype." Against this backdrop, our failure to find genome-wide significant SNPs is disappointing. Null findings in individual GWA studies are commonplace, however. Assuming a two-tailed test at $p < 5 \times 10^{-8}$ and an effective sample size of 2,790, based on an intraclass correlation of .31 from a simple linear mixed model analysis with a random family-level intercept, we had 80% power to detect effects accounting for 1.4% of the variance in our phenotypes (Gauderman & Morrison, 2006). This is larger than the typical effect size in GWAS findings for quantitative traits (Visscher, Brown, McCarthy, & Yang, 2012). Although requiring one to argue that failing to reject the null hypothesis constitutes positive evidence, our findings support a polygenic model of inheritance, in which complex traits reflect the additive influence of many SNPs, each with very small effect. If the genetic influence on P3 amplitude truly conforms to such a model, we were underpowered to detect it. Much larger sample sizes than ours are necessary.

Due to the expense of collecting psychophysiological or similar measures, it is unlikely that large enough samples will be available to permit detecting variants that account for more

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than a trivial proportion of the variance (de Geus, 2010). Thus, what endophenotypes may offer in psychiatric genetics is less the promise of helping to identify novel genetic variants as helping scientists understand the neurocognitive characteristics of psychiatric disorders (Hall & Smoller, 2010). Alternative methods may be useful for increasing the sensitivity of genome-wide scans, such as Bayesian and network-based methods that make use of additional information or penalized regression approaches such as the lasso (Hastie et al., 2009), which permits selecting subsets of relevant SNPs. However, it may also be that different conceptualizations of the problem are required (de Geus, 2010; Hall & Smoller, 2010). For instance, trying to identify specific genetic influence on a phenotype, even an endophenotype, from a single cross-sectional snapshot may be somewhat akin to trying to understand the effects of gravity on a falling object while it is frozen in midair. Genes are expressed in particular environments over the course of development, yet our analytic approach ignores this interplay. Considering developmental trajectories may be fruitful. For now, however, the molecular-genetic basis of P3 amplitude remains to be determined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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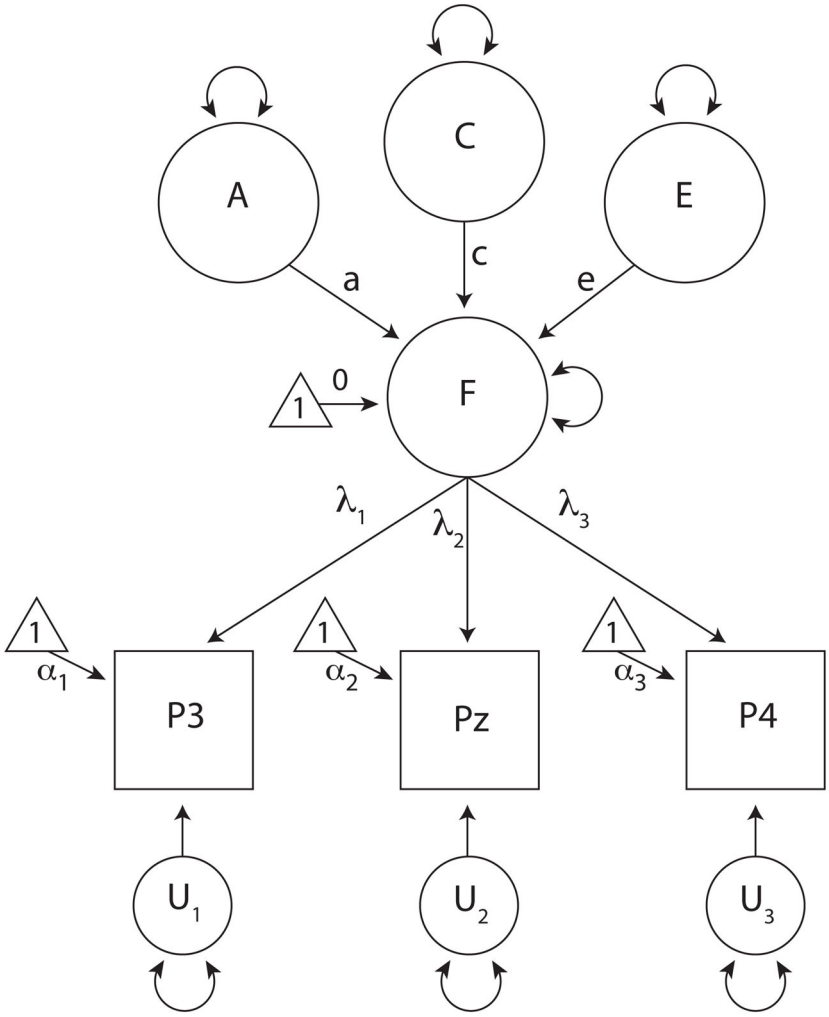

Figure 1.

Illustration of the common pathway model for deriving genetic and environmental factor scores. P3 amplitude at three sites (P3, Pz, and P4) is due to the influence of a common factor, F, as well as site-specific or unique influences (U_1–U_3). The factor loadings, λ_1 to λ_3, are estimates of the magnitude of the influence of F on the three measurements. To identify the model, the variance of F is fixed at 1 and the factor mean is fixed at 0. Under the model, amplitude at a given electrode site, j, equals $P3_j = \alpha_j + \lambda_j F + u_j$, where α_j are the intercepts for the amplitude measures (equivalent to the intercept in linear regression) and u_j is the unique (residual) influence on each amplitude measure. The common factor, F, is itself influenced (caused) by additional latent factors: A, representing additive genetic influence; C, representing common environmental influence; and E, representing specific environmental influence. Using family data, in which genetic and environmental correlations among family members are known, the magnitude of each latent variable's influence on F can be estimated, given standard assumptions. Factor variances are fixed at one (not shown), so the total variance in F can be represented as $a^2 + c^2 + e^2$, using standard tracing rules for path analysis. Because our interest is in the common genetic influence on F, we did not decompose the unique factors into A and C in addition to E.

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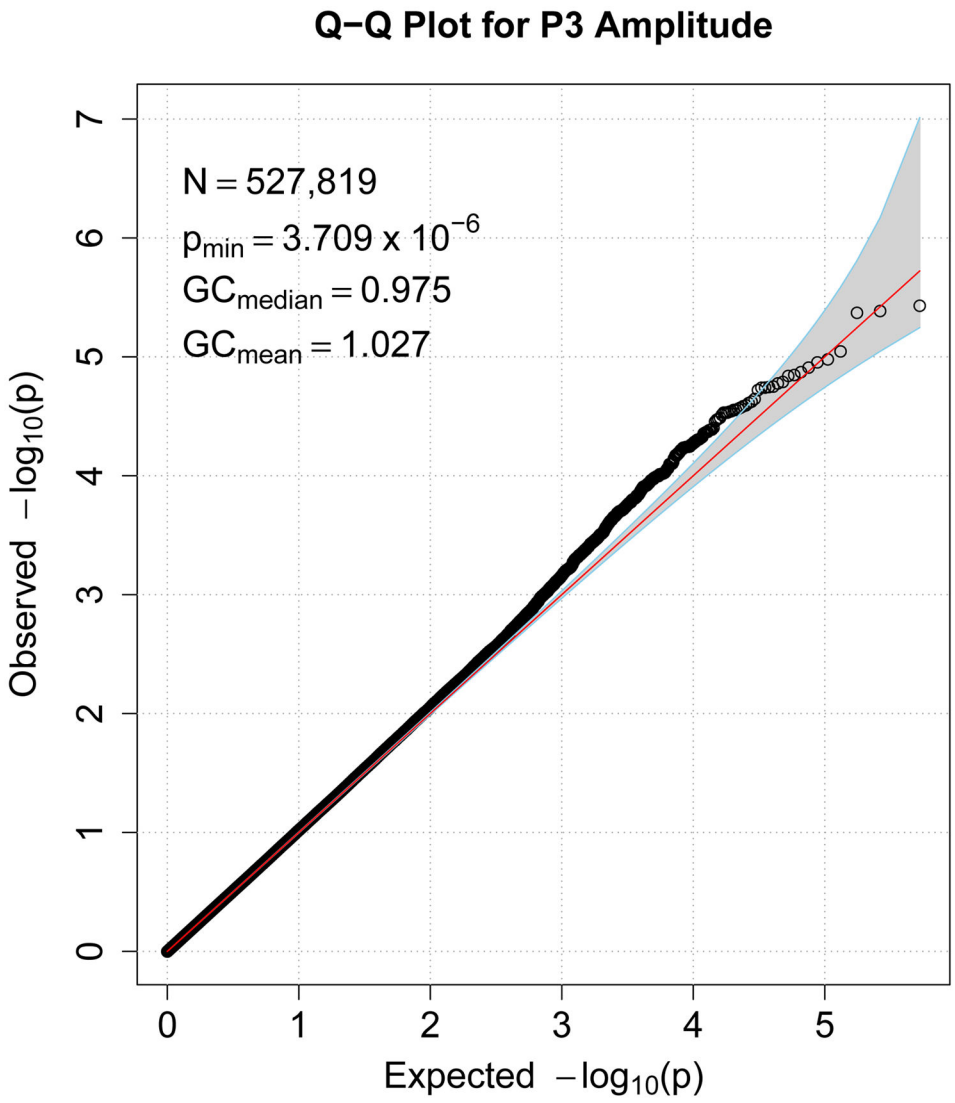

Figure 2.

Q-Q plot for SNP associations with P3 amplitude. The 45° line gives the expected value under the null distribution. The area shaded in gray corresponds to the 95% acceptance region. Median and mean genomic control values are given in the inset in the upper left. N refers to the number of SNPs, which is 10 fewer than the number of SNPs on the array because there was no variation for 10 SNPs in this sample. Q-Q plots in GWAS give the observed *p* values against the expected *p* values under the null distribution of no association, although the additive inverse of the common log of *p* values ($-\log_{10}$[*p* value]) is used in order to emphasize small *p* values. Because the vast majority of SNPs are not expected to be associated with a given phenotype, observed *p* values should conform closely to their expected values, falling on or very close to the 45° line depicted.

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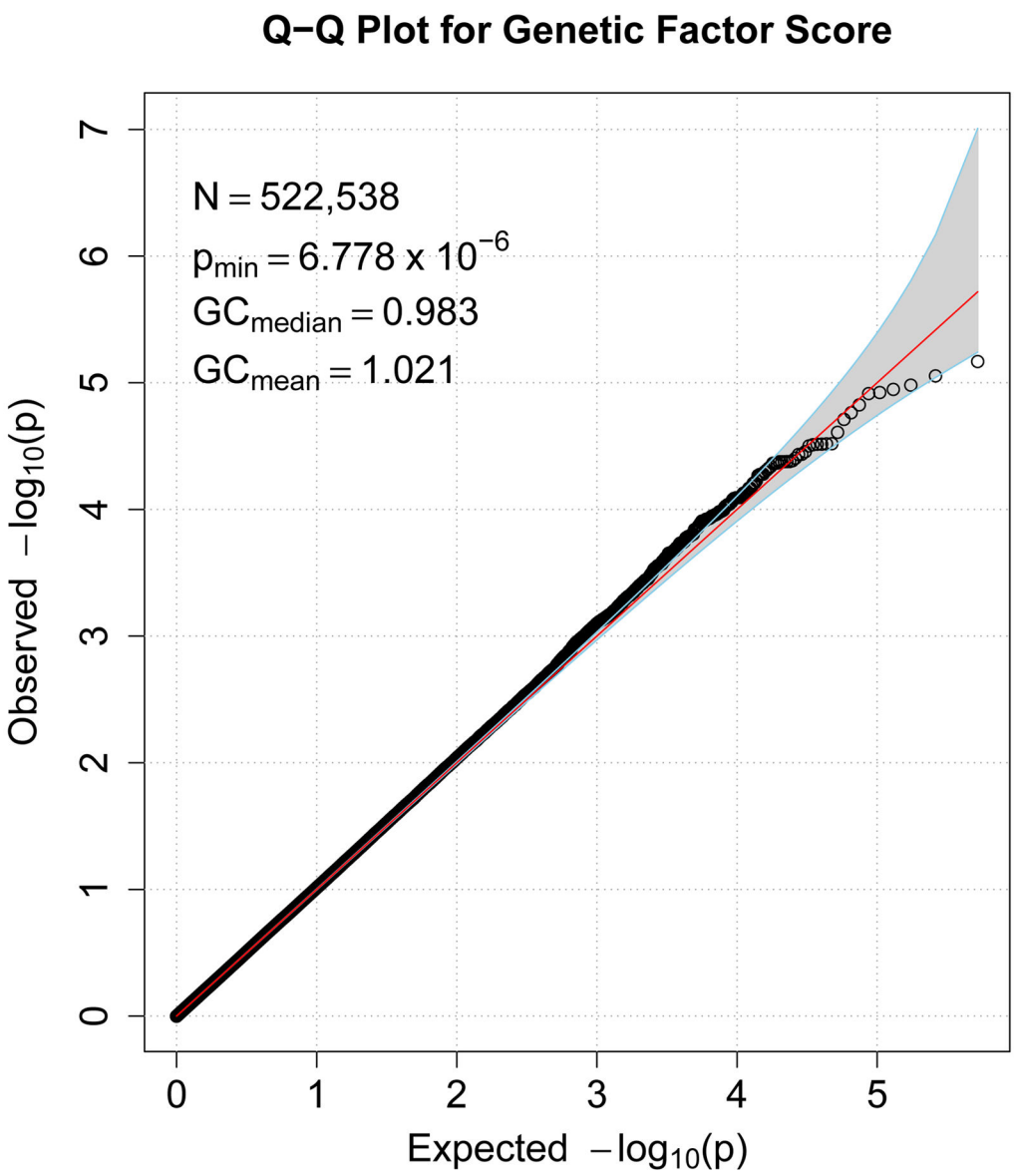

Figure 3.

Q-Q plot for SNP associations with the genetic factor score. The 45° line gives the expected value under the null distribution of no association. The area shaded in gray corresponds to the 95% acceptance region. Median and mean genomic control values are given in the inset in the upper left. N refers to the number of SNPs that were actually polymorphic in this sample, which is smaller than the P3 sample because subjects without amplitude values for all three parietal electrodes were dropped. Q-Q plots in GWAS give the observed *p* values against the expected *p* values under the null distribution, although the additive inverse of the common log of *p* values ($-\log_{10}$[*p* value]) is used in order to emphasize small *p* values. Because the vast majority of SNPs are not expected to be associated with a given phenotype, observed *p* values should conform closely to their expected values, falling on or very close to the 45° line depicted.

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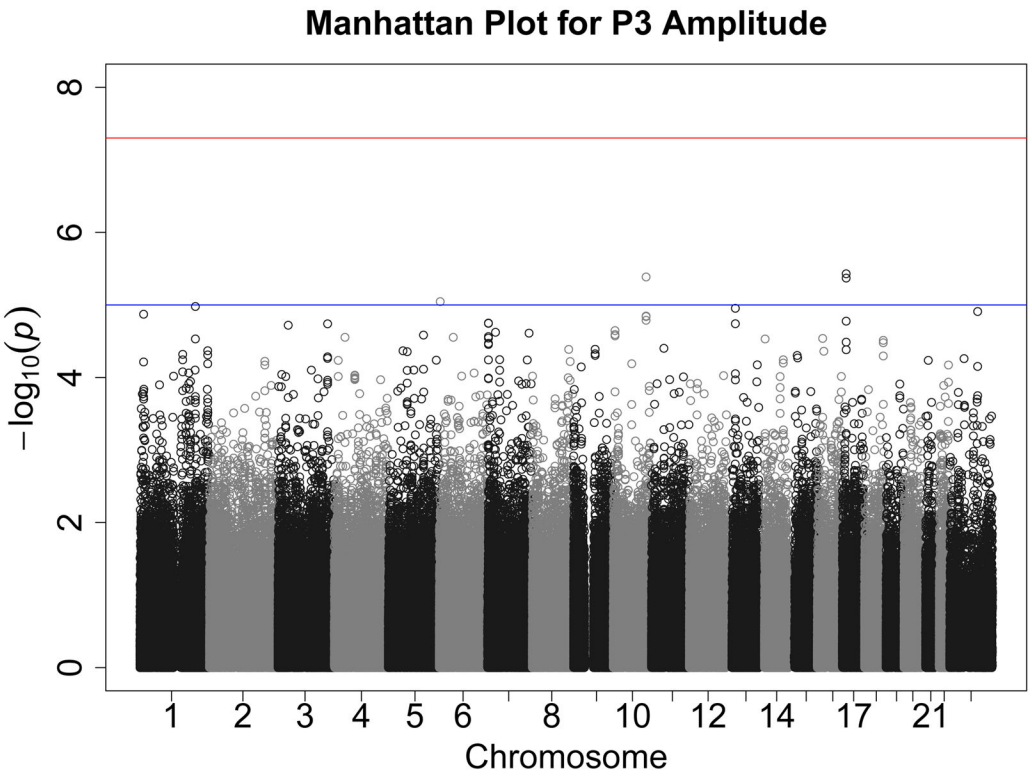

Figure 4.

Manhattan plot of individual SNP associations with P3 amplitude. Manhattan plots also depict the distribution of $-\log_{10}(p$ values) but are ordered by SNP location on a chromosome, which provides information about the location of any SNPs associated with small *p* values. The horizontal line at 7.3 indicates the genome-wide significance level (5E-08). The horizontal line at 5 indicates E-05, which is sometimes used to indicate "suggestive" significance.

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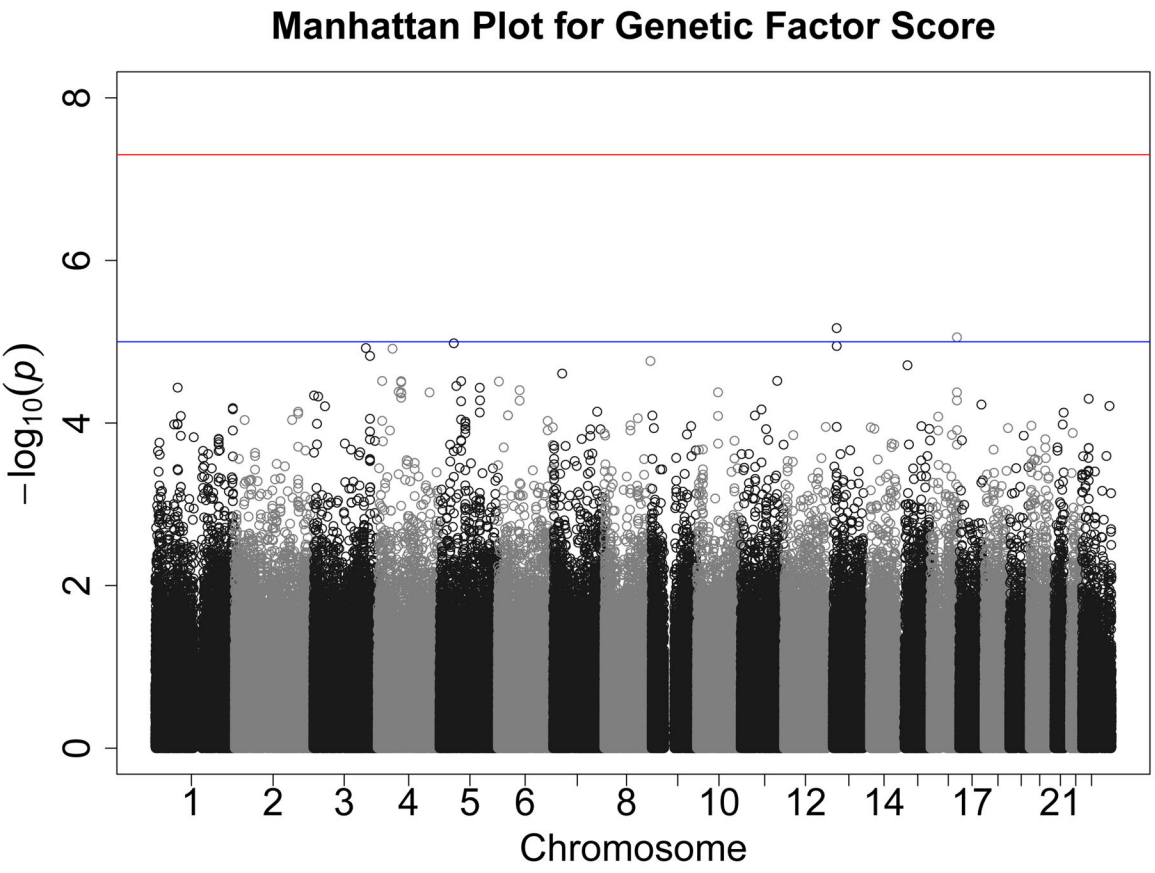

Figure 5.

Manhattan plot of individual SNP associations with the genetic factor score. Manhattan plots also depict the distribution of $-\log_{10}(p$ values) but are ordered by SNP location on a chromosome, which provides information about the location of any SNPs associated with small *p* values. The horizontal line at 7.3 indicates the genome-wide significance level (5E-08). The horizontal line at 5 indicates E-05, which is sometimes used to indicate "suggestive" significance.

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Table 1

Within-Family Correlations for P3 Amplitude

Pair	P3 amplitude	Common factor
MZ twins	.636	.662
DZ twins	.387	.413
Father-offspring	.193	.201
Mother-offspring	.257	.259
Mother-father	.005	.016

Note. "Factor" represents the common factor used for deriving genetic factor scores. P3 amplitude at the three parietal electrodes served as indicators of the factor (cf. Figure 1). All amplitude measures were adjusted for effects of age, sex, generation, recording system, and PCs from EIGENSTRAT.

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Table 2

Heritability Estimates from Biometric Model-Fitting Analyses

Data	Measure	A	C	E
Family	P3 amplitude	.602 (.556–.643)	.000 (.000–.025)	.398 (.357–.442)
	Common factor	.658 (.612–.699)	.000 (.000–.024)	.342 (.301–.386)
Twins	P3 amplitude	.497 (.324–.660)	.134 (.000–.295)	.369 (.331–.412)
	Common factor	.537 (.359–.713)	.150 (.000–.317)	.313 (.276–.355)

Note. Point estimates are provided for each variance component, with 95% confidence intervals in parentheses. These are standardized and sum to 1. Data = ACE model was estimated based on the entire family or only the MZ and DZ twins; A = additive genetic influence; C = common or shared environmental influence; E = unique or unshared environmental influence.

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Table 3

SNP Heritability of P3 Amplitude from GCTA Analyses

	P3 amplitude			Genetic factor score	
Threshold	**Unweighted GRM**	**Weighted GRM**	**GCTA-Family**	**Unweighted GRM**	**Weighted GRM**
.025	.190 (.186)	.251 (.256)		.274 (.199)	.249 (.321)
.050	.300 (.181)	.410 (.244)		.324 (.194)	.241 (.309)
.100	.279 (.179)	.366 (.240)		.370 (.193)	.273 (.305)
None	.570 (.020)	N/A	.571 (.041)	1.000 (.019)	N/A

Note. Standard errors associated with each GCTA are in parentheses. Sample sizes for P3 range from 1,991 to 2,054 for the three subsets and equaled 4,166 for the full sample. They ranged from 1,806 to 1,852 for the genetic factor score, with 3,125 in the full sample. Threshold = genetic relatedness threshold used for selecting unrelated individuals; None = no threshold was imposed and all subjects were included; Unweighted GRM = raw GRM; Weighted GRM = weights based on LD patterns to discount those SNPs in high LD (Speed et al., 2012). This is not used in the full sample, because the method was designed for samples of unrelated individuals or samples containing a small number of large pedigrees (Doug Speed, e-mail communication, May 4, 2014). GCTA-Family = all subjects used to estimate the total genetic variance related to P3 amplitude while simultaneously modeling, and thus controlling statistically, shared environmental influences. This was not relevant to the genetic factor score, which, by definition, is not influenced by the family environment.

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