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ORIGINAL RESEARCH

Brain Electrophysiological Endophenotypes for Externalizing Psychopathology: A Multivariate Approach

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Abstract Abnormalities in electrophysiological measures of stimulus-evoked brain activity (including the P3 event-related potential (ERP) and its associated delta and theta time–frequency (TF) components), and intrinsic, resting state brain activity (including EEG in the beta frequency band) have each been associated with biological vulnerability to a variety of externalizing (EXT) spectrum disorders, such as substance use disorders, conduct disorder, and antisocial behavior. While each of these individual measures has shown promise as an endophenotype for one or more aspects of EXT, we proposed that the power to identify EXT-related genes may be enhanced by using these measures collectively. Thus, we sought to explore a multivariate approach to identifying electrophysiological endophenotypes related to EXT, using measures identified in the literature as promising individual endophenotypes for EXT. Using data from our large twin sample (634 MZ and 335 DZ, male and female same-sex pairs), and fitting multivariate biometric Cholesky models, we found that these measures (1) were heritable, (2) showed significant phenotypic and genetic correlation with a general vulnerability to EXT (which is itself highly heritable), (3) showed modest phenotypic and genetic correlation with each other, and (4) were sensitive to genetic effects that differed as a function of gender. These relationships suggest that these endophenotypes are likely tapping into neurophysiological processes and genes that are both common across them and unique to each—all of which are relevant to a biological vulnerability to EXT psychopathology.

Keywords Endophenotype · Antisocial behavior · Substance use · P3 · Beta · Time–frequency

Introduction

Decades of twin, family, and adoption research have established that genetic influences underlie substance use disorders (SUDs; e.g. alcohol, nicotine, and drug use/dependence) (Goldman et al. 2005). Elucidating the genetic etiology of SUDs would help to inform intervention and treatment strategies, greatly easing the public health impact of these disorders (Merikangas and Risch 2003). SUDs, however, rarely occur in isolation; disorders that commonly occur comorbidly with SUDs include a spectrum of disorders characterized by behavioral disinhibition, e.g., conduct disorder and antisocial behavior. Large-scale epidemiological studies with twins have shown that the common comorbidity among these disorders can be accounted for by an underlying externalizing (EXT) factor that is highly heritable (Kendler et al. 2003; Krueger et al. 2002; Young et al. 2000), and that the source of the comorbidity in these externalizing disorders can be largely attributed to common genetic factors (Hicks et al. 2004; Kendler et al. 2003). The high heritability and common genetic influence across these disorders suggest that a behavioral/clinical phenotype based on this EXT factor may be a better target in the search for genes underlying SUDs and related behavioral disinhibitory disorders in this spectrum than any of the disorders individually.

Efforts to discover genes underlying EXT spectrum disorders have reported significant results implicating genes for alcohol dependence and related phenotypes (e.g., ADH,

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GABRA2, GABRR1, GABRR2; Bice et al. 2008; Covault et al. 2008; Dick et al. 2006; Edenberg et al. 2004; Schuckit 2009; Wall et al. 2005; Xuei et al. 2009), other substance use disorders (Agrawal et al. 2006; Hopfer et al. 2007; Stallings et al. 2003), and behavioral disorders (Amin et al. 2009; Burt and Mikolajewski 2008; McGough et al. 2008; Rommelse et al. 2008). These findings, however, are tempered by the fact that psychopathological disorders are etiologically complex and multifactorial in origin, reflecting the combined influence and interactions of genetic, epigenetic, stochastic, and nongenetic factors (Cowan et al. 2002; Gottesman and Gould 2003; Schork et al. 2007). This complexity in etiology, coupled with an incomplete understanding of how best to identify and diagnose psychological disorders (e.g., Krueger et al. 2005), has hampered the search for psychopathology-related genes. This genetic and phenotypic complexity belies the need for phenotypes that are genetically simpler than clinical diagnostic categories, and that are less reliant on manifest behavior for diagnosing affected individuals (Gottesman and Gould 2003; Iacono 1998). Such traits, known as endophenotypes, are putatively less complex correlates of the disorder that, because they tap the neurobiological basis of gene effects, are closer to gene action, and can be powerful aids in discovering the disorder's genetic etiology.

Psychophysiological measures, particularly electroencephalography (EEG) based measures of neural activity, represent, in part, endogenous, biological attributes whose measurement relies neither on clinical diagnosis nor manifest symptoms of a disorder. EEG-based indices of both stimulus-evoked, task-related brain activity (namely, the P3 event-related potential [ERP] and its associated time–frequency [TF] components) and intrinsic, resting state activity (specifically, activity in the beta frequency band) have been associated with EXT spectrum disorders (e.g., Iacono et al. 2002; Porjesz et al. 2005), and have met criteria (e.g., Frederick and Iacono 2006; Iacono 1998) proposed to be necessary for status as an endophenotype: (1) heritability (van Beijsterveldt et al. 1996; van Beijsterveldt and van Baal 2002; Yoon et al. 2006), (2) association with multiple disorders in the EXT spectrum (Gilmore et al. 2010; Iacono et al. 2002; Porjesz et al. 2005; Rangaswamy et al. 2002), (3) presence in unaffected relatives of those with a disorder (Begleiter et al. 1984; Hill et al. 1995; Rangaswamy et al. 2004), and (4) in currently unaffected individuals, association with later development of an EXT spectrum disorder (Berman et al. 1993; Carlson et al. 2004; Hill et al. 2009; Iacono et al. 2002).

P3 event-related potential

The most robust association has been found between externalizing disorders and the P3 ERP. P3 is elicited by detection of a stimulus that deviates from the ongoing context of the task, and it is theorized to reflect context updating in working memory and the generation of subjective expectancies related to the probability of target occurrence (Donchin and Coles 1988; Duncan-Johnson and Donchin 1977; Soltani and Knight 2000). Reduced peak amplitude of the P3 has long been associated with alcoholism and familial risk of developing alcoholism (Begleiter et al. 1984; Hill 2004; Hill et al. 1995; Polich et al. 1994). Recent work, however, has expanded P3 amplitude reduction's (P3-AR's) association to other EXT spectrum disorders (e.g., Iacono et al. 2002), as well as to the underlying EXT factor (Patrick et al. 2006)—an association that is accounted for by shared genetic effects (Hicks et al. 2007).

These findings, however, have mainly involved only male subjects. Studies investigating the relationship between P3 and SUDs/EXT in females are fewer and the results equivocal. Some studies find reduced P3 in female alcoholics (Hill and Steinhauer 1993; Prabhu et al. 2001) and females at high-risk of developing alcoholism (Porjesz et al. 1998; Van Der Stelt 1999), while other studies find no significant P3-AR in female alcoholics (Hill et al. 1999; Parsons et al. 1990). Across genders, when P3-AR is present, it tends to be enhanced more for males than females (e.g., Iacono and McGue 2006; Porjesz et al. 1998; Yoon et al. 2006). Thus, evidence suggests a differential association between P3 and SUDs/EXT as a function of gender. Nonetheless, P3 has been shown to be strongly heritable (van Beijsterveldt and van Baal 2002; Yoon et al. 2006), and it has been linked to genes putatively underlying EXT spectrum disorders, particularly alcoholism. Williams et al. (1999) found that reduced P3 amplitude and an alcoholism diagnosis were jointly linked to a region on chromosome 4 near the alcohol dehydrogenase gene (ADH3), and Hill et al. (1998) found an association between lower P3 amplitude and presence of the dopamine receptor A1 allele in children from alcoholic families.

Event-related time–frequency components

While these findings support P3-AR's potential as an endophenotype for EXT psychopathology, at least for males, there is evidence that the P3 ERP is composed of multiple neurophysiological processes (e.g., Dien et al. 2003; Mantini et al. 2009). An emerging methodological approach that serves to represent the ERP in a more detailed way than standard measures (e.g., peak amplitude), and endeavors to delineate these multiple processes is time–frequency (TF) decomposition. For instance, TF decomposition has been used to show that ERP activity during the P3 can be characterized by TF components in the delta (0–3 Hz) and theta (3–7 Hz) frequency bands (Basar-Eroglu et al. 1992; Bernat et al. 2007; Jones et al.

2006; Yordanova et al. 2000), suggesting that TF representations may present a more detailed characterization of event-related brain activity.

Indeed, some recent efforts in the search for alcoholism-related endophenotypes have shifted focus away from time-domain P3 amplitude and toward TF measures of ERP activity. P3-related delta and theta power was shown to be reduced in adult alcoholics (Jones et al. 2006) and in high-risk adolescent and adult offspring of alcoholics (Kamarajan et al. 2006; Rangaswamy et al. 2007). Most recently, our group has extended these findings by utilizing a novel, data-driven, principal components analysis based TF analysis method (TF-PCA; Bernat et al. 2005) to reveal a more detailed representation of the multiple overlapping processes related to P3 activity (Bernat et al. 2007; Gilmore et al. 2010). In Gilmore et al. (2010), TF-PCA revealed five time- and frequency-specific event-related delta and theta components, each of which was able to discriminate those subjects with one of six externalizing spectrum disorders from those with no disorder (based on reduced amplitudes in the diagnostic groups) as well as or better than could P3 amplitude. These results demonstrated that TF-PCA derived components may capture more externalizing-related variance in the ERP than is indexed by P3 peak amplitude alone, suggesting that using these TF components in combination with P3 measures may optimize the measurement of this endophenotype.

Further evidence for TF activity's utility as an endophenotype comes from studies linking P3-related delta and theta activity to specific genes: CHRM2 (Jones et al. 2004; Porjesz and Rangaswamy 2007), a cholinergic muscarinic receptor gene, and GRM8 (Chen et al. 2009), a metabotropic glutamate receptor gene, both on chromosome 7. Both CHRM2 and GRM8 have been associated with alcohol dependence (Chen et al. 2009; Luo et al. 2005; Wang et al. 2004), while CHRM2 has also been implicated in drug dependence (Luo et al. 2005; Wang et al. 2004), and, most recently, in externalizing disorders (Dick et al. 2008).

Resting state EEG beta

In addition to these indices of evoked brain activity, measures of intrinsic, "resting state" brain activity as measured using EEG have also shown associations with alcoholism and other EXT-spectrum disorders. The spontaneous neural activity of the resting state is composed of dynamic combinations of delta (0–3 Hz), theta (3–7 Hz), alpha (7–12 Hz), beta (12–30 Hz), and gamma (>30 Hz) band frequencies (Buzsáki 2006). Activity in the beta frequency band, a putative index of the level of cortical arousal, has consistently shown associations with EXT-spectrum disorders. These associations may be affected, however, by the nature of the specific disorder and by gender. Increased beta power has been found in those with alcoholism (Bauer 1994, 2001; Costa and Bauer 1997; Rangaswamy et al. 2002), cocaine dependence (Costa and Bauer 1997), and those at high risk for developing alcoholism (Pollock et al. 1995; Rangaswamy et al. 2004), although the specific beta frequencies involved and their scalp topographies have been shown to differ as a function of gender (Rangaswamy et al. 2002, 2004). Beta power has been shown to be reduced, however, in adolescents with ADHD (Hobbs et al. 2007; Mann et al. 1992), ADHD with comorbid oppositional defiant disorder (Clarke et al. 2002), and young adults exhibiting impulsive and antisocial personality characteristics (Houston and Stanford 2005). Further, while boys' beta power is reduced more than that of girls relative to controls (Clarke et al. 2001), girls with ADHD show reduced beta more consistently (i.e., with less variability) than boys (Clarke et al. 2003).

Supporting its role as a potential endophenotype for EXT, resting state beta activity has been found to be highly heritable (McGuire et al. 1998; van Beijsterveldt et al. 1996), and has been linked to the GABRA2 gene, a GABA(A) neurotransmitter receptor gene on chromosome 4p (Edenberg et al. 2004; Porjesz et al. 2002), which itself has also been associated with a number of disorders in the EXT spectrum: alcohol dependence (Edenberg et al. 2004; Enoch 2008; Soyka et al. 2008), drug dependence (Agrawal et al. 2006; Dick et al. 2006), and conduct disorder (Dick et al. 2006). Thus, there is evidence that the GABRA2 gene may affect both beta frequency EEG power and a predisposition to develop various disorders in the EXT spectrum.

Multivariate approach to identifying endophenotypes for externalizing

Taken together, these results demonstrate that multiple stimulus-evoked and resting state electrophysiological measures show promise as endophenotypes for EXT psychopathology. Each of these measures has been shown to be heritable (e.g., van Beijsterveldt et al. 1996; van Beijsterveldt and van Baal 2002; Yoon et al. 2006), to be associated with genetic risk for one or more EXT disorders (e.g., Begleiter et al. 1984; Hill et al. 1995; Rangaswamy et al. 2004), and with specific, although different, genes associated with these disorders (e.g., Chen et al. 2009; Edenberg et al. 2004; Porjesz and Rangaswamy 2007; Williams et al. 1999). Thus, each of these brain electrophysiological measures, which putatively tap the neural bases of genetic risk, has demonstrated significant utility in the search for genes related to EXT psychopathology.

We propose that the power to identify EXT-related genes may be enhanced by using these measures in concert, effectively creating a multivariate endophenotype (e.g.,

Arya et al. 2001; Frederick and Iacono 2006; Iacono et al. 2000; Price et al. 2006), by capitalizing on the covariance among the multiple measures and EXT. The goal of this report was to explore a multivariate approach to identifying electrophysiological endophenotypes related to EXT psychopathology, using measures identified in the literature as promising individual endophenotypes for EXT. We specifically sought to address the following aims: (1) assess the magnitude of the phenotypic and genetic associations between each endophenotype and EXT, (2) determine if there is significant shared genetic variance among the multiple endophenotypes and EXT, and (3) determine if any of the endophenotypes share unique genetic variance with EXT (i.e., variance which is not also shared with the other endophenotypes). Also, because there is evidence for differential relationships between the brain activity measures and EXT disorders, we assessed potential gender effects. Finding significant relationships among the electrophysiological endophenotypes and EXT would suggest that, used in combination, they may be more optimal targets than any of the individual measures for studies investigating the genetic etiology of externalizing spectrum disorders.

Methods

Participants

Participants were adolescent male and female twins who participated in the Minnesota Twin Family Study (MTFS), a longitudinal and epidemiological study investigating the development of substance use disorders and related psychopathology. A comprehensive description of the MTFS is found in Iacono and McGue (2002). Two age cohorts compose the MTFS sample: a younger cohort initially recruited the year the twins turned 11 years old, and an older cohort recruited the year the twins turned 17 years old. Participants were identified through public birth records of twin pairs born in the years 1972–1978 in the case of the older male cohort, 1975–1979 for the older female cohort, 1978–1982 for the younger male cohort, and 1981–1984 for the younger female cohort. Zygosity (MZ = monozygotic; DZ = dizygotic) was determined by the agreement of three estimates: (1) a standard zygosity questionnaire completed by parents, (2) evaluation by MTFS staff of physical similarity based on eye, hair, face, and ear characteristics, and (3) similarity on fingerprint ridge count, cephalic index, and ponderal index. A serologic analysis was conducted if the three estimates did not agree. Twins return at roughly 3-years intervals for follow-up assessments.

For the present report, data were collected when members of both cohorts were at a similar age, specifically, the intake assessment for the 17-years-old cohorts (males: $M = 17.5$, SD = .4; females: $M = 17.5$, SD = .5) and the second follow-up assessment for the 11-years old cohorts (males: $M = 18.0$, SD = .7; females: $M = 18.3$, SD = .7). All study protocols and data collection methods remained consistent across the intake and second follow-up assessments. The current report included those participants for whom data on the psychophysiological measures of interest (see below for details) were available: 303 MZ and 153 DZ male twin pairs, 331 MZ and 182 DZ female twin pairs. Consistent with the demographics of Minnesota during the years the twins were born, almost all are Caucasian (98%). Written informed assent or consent (from the participant or from the parent of a minor child) was obtained as appropriate.

Diagnostic assessment

For participants in each of the two cohorts, lifetime presence of DSM-III-R (American Psychiatric Association 1987) disorders, the diagnostic system in place at the time the MTFS was initiated, was assessed via in-person, structured interviews by trained clinical interviewers. Members of each twin pair were assessed concurrently by separate interviewers. Symptoms of nicotine dependence, alcohol dependence, and illicit drug dependence (which included amphetamines, cannabis, cocaine, inhalants, opioids, PCP, and sedatives) were assessed using an expanded version of the Substance Abuse Module of the Composite International Diagnostic Interview (Robins et al. 1987). The substance for which the participant reported the maximal number of symptoms was used for their drug dependence variable. An interview designed by MTFS staff (Holdcraft et al. 1998) was used to assess symptoms of conduct disorder and adult antisocial behavior (i.e., the adult criteria for Antisocial Personality Disorder). Mothers reported on the presence of conduct disorder and substance use disorder symptoms in her twin children through interviews using the parent version of the Diagnostic Interview for Children and Adolescents (Reich 2000). A symptom was considered present if reported by either the mother or twin. Symptoms were assigned on the basis of a consensus, "best-estimate" approach (Leckman et al. 1982) combining mother and twin interview data.

Our measure of Externalizing consisted of the first principal component (which accounted for 59% of the variance) of the log-transformed symptom counts of conduct disorder, adult antisocial behavior, alcohol abuse/dependence, nicotine dependence, and illicit drug abuse/dependence (c.f. Hicks et al. 2007; Patrick et al. 2006).

Psychophysiological assessment

Resting EEG

Five minutes of resting EEG were collected while participants were instructed to relax with their eyes closed. The participants were seated in a comfortable chair in a dark room while listening to 55 dB white noise through headphones.

ERP task

A rotated-heads visual oddball task (Begleiter et al. 1984) was used. Subjects viewed 240 stimuli consisting of either an oval (two-thirds of trials—"standards") or a superior view of a stylized head (one-third of trials—"targets"), in which a nose and one ear were depicted on the oval. Subjects were required to respond to target trials by pressing a button on either the left or right armrest of their chair, corresponding to the side of the head on which the ear appeared. On half the target trials the nose pointed up (such that the left ear appeared on the left side of the screen; an easy discrimination), while on the other half of target trials the head was rotated 180° so that the nose pointed down (left ear appeared on the right side of the screen; a hard discrimination). Stimulus duration was 98 ms, and the inter-trial interval, during which subjects fixated on a dot in the center of the screen, varied randomly between 1 and 2 s.

Recording procedure

A Grass model 12A Neurodata Acquisition System recorded the EEG. Impedances were kept below 5 kΩ. Data were recorded at a sampling rate of 256 Hz during the ERP task and 128 Hz for the resting EEG, and filtered from .01 to 30 Hz (half-amplitude, 6 dB/octave rolloff) for both tasks. ERP task data were recorded from three parietal electrodes: on the midline at Pz, and over left and right hemispheres at P3 and P4, respectively, referenced to linked earlobes. Resting EEG was recorded using a bipolar montage from parietal-occipital sites, O1-P7 and O2-P8, over left and right hemispheres, respectively, and monopolarly, referenced to linked earlobes, from central-midline electrode Cz. Additionally, during both tasks, electrooculographic (EOG; used to screen for eye movement artifacts) data were recorded using a pair of biopotential electrodes arranged in a transverse montage, one electrode placed superior to the eye and the other at the outer canthus.

Data processing

Resting EEG

The resting EEG data were divided into 2 s half-overlapping epochs (i.e., the first second of each epoch overlapped with the last second of the preceding epoch). Epochs in which EOG amplitude >60 μV were eliminated from further processing. Fast Fourier Transform (FFT) was then applied to each artifact-free epoch using a Tukey-Hanning window, resulting in power spectra with .5 Hz resolution. The mean absolute power within the Beta frequency range (13–30 Hz) was then calculated for each of the three recording sites. Because the distributions of power within these bands were skewed, the data were log transformed.

ERP

For the ERP data, blinks and other ocular artifacts were corrected using the method of Gratton et al. (1983). Trials with activity >100 μV were excluded from further processing. ERP epochs, consisting of 2 s of data, including a 500 ms prestimulus baseline, were averaged over the easy and hard target conditions at each of the three electrode sites. P3 amplitude was defined as the point between 280 and 600 ms at which amplitude of the average waveform was maximal.

Time–frequency PCA decomposition of ERPs

The time–frequency PCA (TF-PCA) method has been detailed in previous reports (Bernat et al. 2005, 2007; Gilmore et al. 2010). Here, the primary features are outlined. Averaged target ERP data from each of the three electrodes, for each participant, were subjected to TF decomposition using the Cohen's class reduced interference distribution (RID) transform. This TF transform resulted in averaged TF surfaces, which are representations of the overall energy of the event-related activity, within a frequency range of 0–7.5 Hz (through the upper limit of theta) and a time range from stimulus onset (0 ms) to 1,000 ms post-stimulus. PCA, using the covariance matrix and varimax rotation, was then performed on these average TF surfaces to decompose the surfaces into separate TF-PCA components. The resulting TF surfaces represented each TF-PCA component's matrix of rotated component loadings for each TF point. Five components were retained, based upon inspection of the scree plot of singular values, representing the relative variance accounted for by each component, for a break, or elbow. In a final step, each participant's average TF surface was weighted using the extracted

TF-PCA components. To weight the original TF data, each time–frequency point is multiplied by the corresponding point in the matrix of rotated loadings for each component. This produces weighted data surfaces, for each participant for each TF-PCA component, whose data points represent energy in units weighted by the component loadings. For subsequent analyses, component scores representing the peak energy on the weighted TF-PCA surface were used.

Data analysis

Our main approach consisted in fitting multivariate biometric models using a Cholesky parameterization. This permitted us to determine whether adding candidate endophenotypes to our model would account for significant unique variance in EXT. Because our approach to decomposing time–frequency surfaces differs from that used in previous studies relating TF energy to externalizing psychopathology, yielding relevant dimensions not necessarily readily evident to the naked eye (Gilmore et al. 2010), it was not immediately apparent which features would be most relevant. We therefore conducted principal component analysis of the 15 TF-PCA measures (5 components, 3 electrodes) and EXT to identify TF-PCA components that are related to (load with) EXT (c.f. Patrick et al. 2006). We used the components that loaded with EXT in subsequent biometric models. PCA and all data manipulations were conducted using *R* (version 2.8.1; R Foundation for Statistical Computing).

We freely estimated means and covariances of P3 amplitude, beta power, the time–frequency components that emerged from the above analysis, and EXT without imposing any latent structure on the data (i.e., without the additive genetic (A), shared environmental (C), and nonshared environmental (E) latent factors). This served as a baseline model. We subsequently fit an ACE model using a Cholesky parameterization. Based on the strength of prior evidence regarding associations between the candidate endophenotypes and genetic risk for EXT, we entered them in the following order: P3 amplitude, time–frequency components, beta power, and EXT (see Fig. 1 for an illustration of the Cholesky model). We tested several submodels by fixing parameters at 0 in order to conduct significance tests of the importance of different parameters. Specifically, we constrained to 0 paths from EXT to the first three latent A factors to determine whether genetic influences on the endophenotypes account for significant genetic variance in EXT. We subsequently assessed whether genetic factors beyond A1 (which represent genetic variance in externalizing shared with all the endophenotypes) would be significant, and particularly whether there would be gender differences in this regard. We used several fit statistics to evaluate model fit: likelihood-ratio tests,

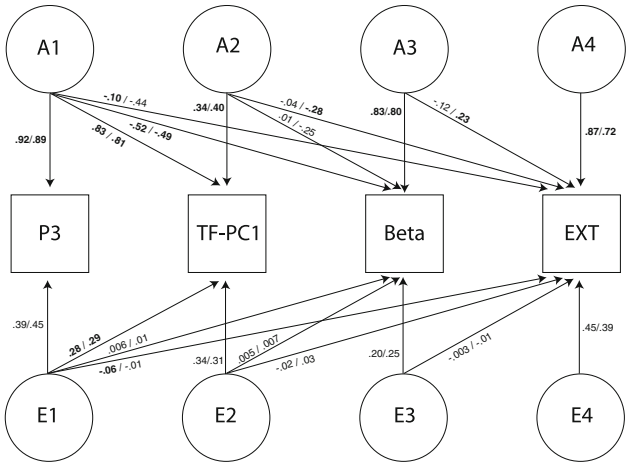

Fig. 1 Path diagram for the AE Cholesky model. Standardized path coefficients are shown for both males and females (males/females); significant paths ($p \leq .01$) are printed in *bold*. All paths should be squared to estimate the proportion of variance accounted for by the respective path. Summing all the squared coefficients pointing to each phenotype equals (within rounding error) the phenotypic variance which is standardized at 1. A1 and E1 represent the additive genetic and non-shared environmental variance, respectively, that is shared by all three endophenotypes and EXT. A2 and E2 are the variances shared by TF-PC1, Beta, and EXT, independent of that shared with P3. A3 and E3 are the variances shared by Beta and EXT, independent of that shared with P3 and TF-PC1. A4 and E4 are the variances unique to EXT. *Note*: Because E includes measurement error as well as other sources of nonshared influence, the paths from each E to its corresponding phenotype (E1 on P3, E2 on TF-PC1, E3 on beta, and E4 on EXT) could not be constrained to 0 for significance testing

Akaike's Information Criterion (AIC; Akaike 1974) and Draper's Information Criterion (DIC; Draper 1995).

Results

Before analyzing the data, we examined them for outliers using an *R* package (Fox 2009) that implements the regression diagnostic procedures of Cook and Weisberg (1982). We examined the bivariate distributions of twin scores, and deleted pairs producing significant residuals by Bonferroni-corrected *p* value. We also deleted pairs producing Cook's distance scores above the threshold suggested by Cook and Weisberg. This resulted in removing 20 pairs (2.1% of the total sample).

Stability of time–frequency components

For our TF-PCA components, we first wanted to confirm that the decompositions were stable across our different cohorts of subjects (i.e., across males and females in the 11 and 17 years old cohorts; see Fig. 2 which illustrates the ERP and the 5 TF components extracted from the TF-PCA

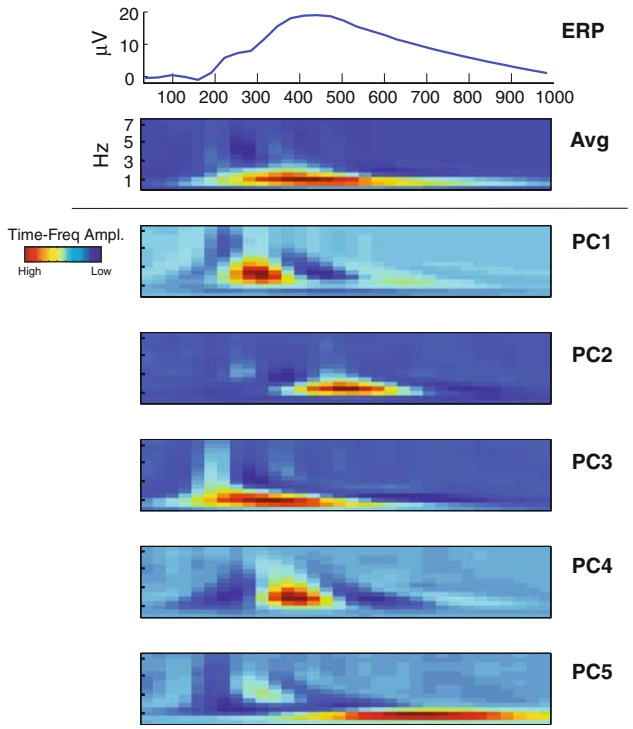

Fig. 2 Results of TF-PCA analyses. Grand-averaged ERP and TF (Avg) plots are presented at the *top*. ERP (from 0 to 1,000 ms) is from electrode Pz, grand averaged over all participants; P3 is the peak in the waveform occurring around 450 ms. The five time–frequency components (PCs 1–5) retained from the principal components analysis decomposition of the averaged TF surface are presented below the grand averages. For all time–frequency plots, data has been downsampled to 32 Hz; the *x*-axis is time from stimulus onset (0 ms) to 1,000 ms, and *y*-axes range from 0 to 7.5 Hz. Components are numbered (1–5: highest to lowest) based on the amount of variance for which they accounted in the varimax-rotated solution. PC1 (with peak energy centered around 2.5 Hz and 330 ms) is the TF component that loaded most strongly with EXT in a PCA analysis (see "Methods" and "Results" for details), thus, it is the TF-PCA component included in subsequent biometric analyses

decomposition). We assessed stability of the PCA solution across the independent cohorts of subjects by conducting the TF-PCA decomposition separately for each, and then computing Tucker's congruence coefficients (which measure the similarity of two factorial configurations by ascertaining the degree to which the magnitude of loadings on the two factors have a similar pattern; values in excess of .90 indicate high congruence). Congruence coefficients between matching components were uniformly high, ranging from .93 to .99 across age cohorts and from .93 to .95 across gender cohorts, indicating that the TF-PCA decompositions had highly similar patterns.

TF components most relevant for EXT

To determine which time–frequency components to include in our Cholesky model, we conducted PCA on the 15 measures (5 TF-PCA components, 3 electrodes) plus EXT, separately for each gender. The raw data were centered about the variable means and scaled by their respective standard deviations, equivalent to PCA on the correlation matrix. Although most of the variation in the data was due to the 15 time–frequency measures, the second (unrotated) component in both genders included a loading for the EXT composite in addition to certain TF measures, while the third component loaded almost entirely on the EXT composite. The pattern was clear: the TF measures and EXT each loaded on separate components, and one component included loadings for both, thus capturing covariance between the two domains. TF-PC1 (with peak energy centered around 2.5 Hz and 330 ms; see Fig. 2) and TF-PC4 (with peak energy also centered around 2.5 Hz, but occurring slightly later in time, around 400 ms; see Fig. 2) both loaded with EXT, with very similar loading patterns and magnitude of loadings for the two genders, thus indicating that these were the TF components most relevant to externalizing. In addition to loading with EXT, these components were highly correlated, with correlations between component scores for the different electrodes ranging from .76 to .91. Thus, to simplify our Cholesky model and avoid potential issues with collinearity, we elected to include in our model only TF-PC1, which loaded most strongly on the combined component in both genders.

Endophenotypic measures

For subsequent analyses, we created composite endophenotype measures. For those measures recorded from one primary scalp area (P3 amplitude and TF-PC1 peak energy, which were recorded from three closely spaced parietal electrodes) we averaged across the three electrode sites. For beta, we created a composite consisting of the first principal component of the covariance matrix of the three electrodes. Loadings for the bipolar occipital leads were approximately twice as great as the loading for the monopolar Cz recording. The scree plot clearly indicated that one component, which accounted for 78% of the variance, was warranted for beta.

Table 1 gives descriptive statistics for the endophenotypes and EXT. As the table indicates, MZ and DZ twins had similar mean levels and variances. Because beta and EXT are principal component scores, their values can be negative. There were small but consistent mean differences between male and female participants, with higher levels of the endophenotypes and lower levels of EXT in females. For instance, with an overall standard deviation of .92 on the EXT component, the difference between males and females corresponded to an effect size of $d = .51$ (not shown in Table 1, which is broken down by zygosity, but

Table 1 Descriptive statistics (Mean and SD) for each phenotype

	Males		Females	
	MZ	DZ	MZ	DZ
P3 amplitude	19.96 (6.69)	19.81 (6.76)	23.01 (8.04)	23.15 (8.21)
TF-PC1 energy	2.86 (.72)	2.84 (.75)	3.20 (.73)	3.19 (.75)
Beta EEG power	−.17 (.44)	−.19 (.43)	.16 (.43)	.16 (.45)
Externalizing	.19 (1.01)	.36 (1.10)	−.27 (.66)	−.12 (.85)

Values for P3 amplitudes are in μV; TF-PC1 values are log transformed peak energies. Values for Beta power and Externalizing are component scores for the first principal component, thus their values can be negative (see "Results" for details)

offered for illustrative purposes). In addition, although our analysis used the first principal component of the five disorders' symptom counts as our EXT measure, to insure that we had meaningful variance in EXT in this population-based sample, we determined the proportion of participants with three or more symptoms of each of the individual disorders making up the EXT score. This corresponds to those who are above the symptom threshold required to qualify for a diagnosis. Results showed that, overall, 24% of the sample had three or more symptoms of at least one disorder.

The phenotypic correlations among the variables are presented in Table 2. Lack of independence due to the fact that the sample consisted of twin pairs was accounted for in assessing the significance of correlations. For males, all the correlations were significant. For females, all but the P3-EXT correlation were significant. As might be expected from an epidemiological sample, the correlations between the endophenotypes and EXT were modest. Therefore, to further highlight their importance and to link our findings to the literature which often examines clinical samples or offspring of clinical samples compared to healthy controls, we conducted a quintile split on each of the endophenotypes, separately for males and females, and compared EXT scores between those high (top 20%) and low (bottom 20%) on each of the endophenotypes. Differences between groups

Table 2 Phenotypic correlations among the phenotypes

	P3	TF-PC1	Beta	EXT
P3	1	.76	.15	−.07
TF-PC1	.75	1	.15	−.10
Beta	.23	.21	1	−.10
EXT	−.15	−.14	−.10	1

Males are below the diagonal, females above it. For males, all the correlations were significant ($p \leq .05$). For females, all but the P3-EXT correlation were significant

Table 3 Intraclass correlations for each phenotype

	Males		Females	
	MZ	DZ	MZ	DZ
P3 amplitude	.66 (275)	.18 (145)	.66 (316)	.43 (169)
TF-PC1 energy	.61 (274)	.31 (145)	.66 (315)	.31 (169)
Beta EEG power	.76 (261)	.31 (139)	.68 (294)	.33 (156)
Externalizing	.79 (291)	.51 (149)	.64 (325)	.45 (176)

Numbers in parentheses are the number of twin pairs. All correlations are significant ($p < .05$). MZ correlations are significantly greater than DZ correlations in all cases ($p < .01$)

corresponded to effect sizes (Cohen's d; the mean difference between EXT scores) in the small to moderate range (P3: males $d = .31$, females $d = .20$; TF-PC1: males $d = .34$, females $d = .29$; Beta: males $d = .37$, females $d = .18$). These effect sizes, considered together with the modest phenotypic correlations, suggest that the correlations may underestimate the endophenotypes' abilities to differentiate between those high and low in EXT symptoms.

The intraclass correlations are more similar than different for the two genders, and indicate substantial genetic influence on all composite measures (Table 3); MZ correlations were significantly greater than DZ correlations in all cases (all z-statistics >2.80, p values <.01). Although the DZ correlation for EXT was substantial for both genders, suggesting some influence of shared environment, it was not significantly greater than half the MZ correlation ($p > .10$).

Cholesky decomposition model

For the biometric analyses, the Cholesky model provided improved fit relative to the unstructured base model (which estimated only the phenotype means and covariances) by both AIC and DIC, indicating that modeling the phenotypes in terms of latent ACE factors was reasonable, and in particular that the Cholesky version was adequate (results of model-fitting analyses are presented in Table 4). As Table 4 indicates, C influences on all phenotypes could be dropped without significant loss of fit, whereas A could not (i.e., relative to the ACE model, fit statistic values were significantly lower for the "No C" models, but not for the "No A" models). We subsequently adopted an AE model as our base model.

Univariate heritability estimates obtained from the AE model, given in Table 5, indicate moderately large heritable differences in all phenotypes, with estimates relatively similar for the two genders. Genetic correlations from the AE model are presented in Table 6. These were largely similar for males and females, and indicate substantial genetic overlap among the ERP measures (P3 and TF-PC1).

Table 4 Biometric model fit statistics

Model	−2LL	Parameters	AIC	DIC	$\Delta\chi^2$ (Δdf)	Δp
Unstructured base model (phenotypic means and covariances only)	11324.5	176	11676.5	12207.6		
ACE	11500.6	76	11652.6	11881.9	176.1 (100)	<.001
No C, males	11506.8	66	11638.8	11838.0	6.2 (10)	.799
No C, females	11508.8	66	11640.8	11840.0	8.2 (10)	.609
No A, males	11658.0	66	11790.0	11989.2	157.4 (10)	<.001
No A, females	11612.6	66	11744.6	11943.8	112.0 (10)	<.001
AE, both genders; base model	**11515.0**	**56**	**11627.0**	**11796.0**	**14.4 (20)**	**.810**
Significance tests of specific paths, males						
A1 on P3	11689.2	55	11799.2	11965.2	174.2 (1)	<.001
A1 on TF-PC1	11645.8	55	11755.8	11921.8	130.8 (1)	<.001
A1 on beta	11546.9	55	11656.9	11822.9	31.9 (1)	<.001
A1 on EXT	11521.6	55	11631.6	11797.6	6.6 (1)	.010
A2 on TF-PC1	11597.8	55	11707.8	11873.8	82.8 (1)	<.001
A2 on beta	11515.7	55	11625.7	11791.7	.7 (1)	.403
A2 on EXT	11515.7	55	11625.7	11791.7	.7 (1)	.403
A3 on beta	11597.8	55	11707.8	11873.8	82.8 (1)	<.001
A3 on EXT	11516.9	55	11626.9	11792.9	1.9 (1)	.168
A4 on EXT	11597.7	55	11707.7	11873.7	82.7 (1)	<.001
Significance tests of specific paths, females						
A1 on P3	11732.6	55	11842.6	12008.6	217.6 (1)	<.001
A1 on TF-PC1	11687.4	55	11797.4	11963.4	172.4 (1)	<.001
A1 on beta	11525.0	55	11635.0	11801.0	10.0 (1)	.002
A1 on EXT	11516.7	55	11626.7	11792.7	1.7 (1)	.192
A2 on TF-PC1	11649.7	55	11759.7	11925.7	134.7 (1)	<.001
A2 on beta	11516.7	55	11626.7	11792.7	1.7 (1)	.192
A2 on EXT	11522.5	55	11632.5	11798.5	7.5 (1)	.006
A3 on beta	11649.5	55	11759.5	11925.5	134.5 (1)	<.001
A3 on EXT	11519.3	55	11629.3	11795.3	4.3 (1)	.038
A4 on EXT	11631.8	55	11741.8	11907.8	116.8 (1)	<.001

A additive genetic, *C* shared environment, *E* nonshared environment; *df* degrees of freedom, −2LL is negative twice the model log-likelihood, *AIC* Akaike's information criterion. *DIC* Draper's information criterion. Smaller values of each indicate better model fit. $\Delta\chi^2$ and Δdf are relative to the base model

Shown in bold is the AE model adopted as the base model after determining that C influences on all phenotypes could be dropped without significant loss of fit

Table 5 Univariate heritability estimates

	Males		Females	
	A	*E*	*A*	*E*
P3	.65 (.58–.69)	.35 (.29–.42)	.66 (.60–.72)	.34 (.28–.40)
TF-PC1	.62 (.54–.68)	.38 (.32–.46)	.65 (.59–.68)	.35 (.30–.41)
Beta	.77 (.72–.81)	.23 (.19–.28)	.68 (.62–.73)	.32 (.27–.38)
EXT	.80 (.76–.82)	.20 (.17–.24)	.71 (.66–.75)	.29 (.24–.34)

Point estimates are standardized to unit variance (within rounding error), with 95% confidence intervals around them in parentheses

Overlap between these and beta was much more modest, and was approximately twice as great among males as among females. Genetic correlations with EXT are modest but significant with one exception: the P3-EXT correlation in females was not significant.

Figure 1 illustrates the path diagram of the AE Cholesky model. A1 and E1 represent the additive genetic and non-shared environmental variance, respectively, that is shared by all three endophenotypes and EXT. A2 and E2 are the variances shared by TF-PC1, Beta, and EXT, independent of that shared with P3. A3 and E3 are the variances shared by Beta and EXT, independent of that shared with P3 and TF-PC1. A4 and E4 are the variances unique to EXT. Shown are the standardized path coefficients, which, when squared, represent the proportion of variance accounted for by the respective path. To assess the significance of each path, we constrained it equal to 0 and assessed fit by means

Table 6 Genetic correlations from AE model

	P3	TF-PC1	Beta	EXT
P3	1	.79 (.73 to .83)	.18 (.07 to .29)	−.07 (−.18 to .04)
TF-PC1	.80 (.75 to .85)	1	.20 (.08 to .31)	−.16 (−.27 to −.05)
Beta	.34 (.23 to .45)	.31 (.19 to .42)	1	−.14 (−.25 to −.03)
EXT	−.15 (−.26 to −.04)	−.15 (−.26 to −.04)	−.12 (−.22 to −.03)	1

Correlations for males are below the diagonal, while those for females are above it. Ninety-five percent confidence intervals (CIs) are given in parentheses. All correlations are significant ($p < .05$), except the P3-EXT correlation in females (the CI includes zero)

of likelihood-ratio tests, AIC, and DIC. Significant likelihood-ratio tests and larger values of the information-theoretic fit statistics indicate significance of the path being tested. Results of these tests are presented in Table 4 for the genetic factors. The three fit statistics were consistent in showing a significant effect of A1 on the three endophenotypes, indicating shared genetic variance among them, for both males and females. The A2 influence on beta was not significant for either sex, indicating little genetic overlap between TF-PC1 and beta beyond what is also common to P3. Among males, only the A1 influence on EXT was significant, indicating shared genetic variance among all three endophenotypes and EXT. Among females, by contrast, the A1 influence on EXT was not significant but the influence of A2 and A3 both were. (The latter effect was somewhat marginal, in that setting this path to 0 resulted in a somewhat smaller value of DIC, although AIC was larger and the likelihood-ratio test was significant.)

Table 4 does not include similar statistics for the nonshared environmental effects. Because E includes measurement error as well as other sources of nonshared influence, the paths from each E to its corresponding phenotype (E1 on P3, E2 on TF-PC1, E3 on beta, and E4 on EXT) cannot be deleted. Constraining the remaining paths indicated that E1, the latent factor common to all phenotypes, had a significant influence on TF-PC1 in both males, $\Delta\chi^2 = 170.5, p < .001$, AIC = 11795.5, DIC = 11961.6, and females, $\Delta\chi^2 = 223.1, p < .001$, AIC = 11848.1, DIC = 12014.1. Among males, there was also a marginally significant effect of E1 on EXT, $\Delta\chi^2 = 4.6$, $p = .032$, AIC = 11629.6, DIC = 11795.6. (The latter actually represented a small decrease, indicating better fit.) None of the other paths was significant, with all chi-squared values less than or equal to 1.4.

Discussion

In the present report, we explored a multivariate approach to identifying electrophysiological endophenotypes related to EXT psychopathology, using a large sample of male and female adolescent twins and measures identified in the literature as promising individual endophenotypes for EXT. The P3 ERP, its associated TF components, and beta frequency resting state EEG have each shown promise as endophenotypes for various disinhibitory disorders in the EXT spectrum and/or a general EXT factor. Using composite measures and fitting multivariate biometric Cholesky models, we specifically addressed the following aims: (1) assess the magnitude of the phenotypic and genetic associations between each endophenotype and EXT, (2) determine if there is significant shared genetic variance among the multiple endophenotypes and EXT, (3) determine if any of the endophenotypes share unique genetic variance with EXT (i.e., variance which is not also shared with the other endophenotypes), and (4) explore potential gender differences.

Results indicated that there was substantial genetic influence on each of the endophenotypes and that each was highly heritable—to a similar degree in males and females. These results are consistent with previous reports on heritability estimates of and genetic influences on the individual ERP and EEG measures and EXT (e.g., Begleiter and Porjesz 2006; Hicks et al. 2007; van Beijsterveldt and Boomsma 1994; van Beijsterveldt et al. 1996). Extending these findings, we also demonstrated that these three endophenotypes (1) show significant negative phenotypic and genetic correlations with a general vulnerability to EXT disorders, (2) show modest to strong phenotypic and genetic correlations with each other, and (3) are sensitive to genetic effects that may differ as a function of gender. These relationships suggest that these three endophenotypes are likely tapping into neurophysiological processes and genes that are both common across them and unique to each—all of which are relevant to a biological vulnerability to EXT psychopathology.

In order to empirically explore the extent to which the EXT-related genetic influences were shared or unique among the three candidate endophenotypes, we performed multivariate biometric models using a Cholesky parameterization. Biometric models revealed that a substantial portion of the variance in each of these candidate endophenotypes was due to additive genes. Further, there was a significant (although modest) amount of genetic variance that was shared between EXT and each endophenotype, as well as between the endophenotypes themselves. Genetic correlations were strong within the ERP domain (i.e.,

between P3 and TF-PC1) for both genders, and were moderate across domains (i.e., between ERP measures and beta), being about twice as strong for males as for females. The only exception to these results was the non-significant P3-EXT correlation in females.

The Cholesky model allowed us to further assess the genetic variance shared among various combinations of the candidate endophenotypes and EXT, in order to determine if any endophenotypes shared variance with EXT independent of that shared with the other endophenotypes. Based on the literature, P3 has shown the most robust genetic associations with EXT (e.g., Hicks et al. 2007; Hill et al. 1998; Porjesz and Rangaswamy 2007), thus we entered P3 into the model first, followed by the P3-associated TF component, the beta power measure, and EXT. For both genders, there was significant genetic variance collectively shared among all the candidate endophenotypes, and for males this genetic variance was also shared with EXT. In males, this shared genetic variance was carried by the relationship between P3 and EXT, as there was no significant variance shared among the remaining endophenotypes and EXT independent of that shared with P3. In females, however, there was no significant genetic variance shared between P3 and EXT, whereas the TF component and beta power did share significant variance with EXT independent of their genetic overlap with P3. Further, the TF component and beta power each had significant independent genetic covariance with EXT in females.

Taken together, results suggest that these three endophenotypes are tapping into different neurophysiological and genetic substrates of EXT psychopathology. Results further suggest, however, that some of this genetic variance is common across the endophenotypes. These endophenotypes, then, are making independent, yet overlapping, contributions to the general genetic vulnerability to EXT (particularly in the case of females). This genetic variance that is shared among these measures is the key to their potential utility as a 'multivariate endophenotype' for EXT.

In the search for psychopathology-related genes, having an appropriate endophenotype is important for understanding the relationship between genes and behavior. Robust findings in genetic studies searching for gene-phenotype associations are generally hampered by a lack of statistical power due to the fact that (a) most subject samples are typically heterogeneous with regard to specific phenotypic characteristics, and (b) genes affecting any measured phenotype usually only account for a small proportion of variance of that phenotype (Plomin 2005; Plomin et al. 1994; Viding and Blakemore 2007). Also, the route from genes to behavior is typically complex, with multiple biological and cognitive pathways converging on the same behavioral phenotype (Viding and Blakemore 2007).

This potential complexity is evidenced in the present report by the significant genetic associations between brain electrophysiological endophenotypes from different domains (stimulus-evoked P3 and TF components, and intrinsic, resting state beta activity) and EXT psychopathology. Functionally, a genetic predisposition to disinhibitory disorders has been associated with central nervous system hyperexcitability (Begleiter and Porjesz 1999). Reduced amplitudes in the brain measures used in the present report theoretically reflect different manifestations of a dysfunction in the capacity for neuronal inhibition and in inhibitory control processes (Begleiter and Porjesz 1999; Iacono et al. 2000). Additionally, each endophenotype has been linked to different genes, all of which have also been associated with EXT-spectrum disorders (e.g., Chen et al. 2009; Dick et al. 2008; Edenberg et al. 2004; Jones et al. 2004; Williams et al. 1999). Thus, there is theoretical and empirical support for the measures in the present report with regard to their potential collective utility as a multivariate endophenotype for EXT.

Using these endophenotypes collectively, then, has the potential to overcome the problem of heterogeneous subject samples by increasing the ability to identify those in the population with the endophenotypes who are at especially high risk for EXT disorders (and, thus, more likely to be true gene carriers; e.g., Iacono et al. 2000). The small to moderate effect sizes we found when comparing EXT between those scoring high and low on the endophenotypes provides initial evidence supporting this hypothesis. A multivariate endophenotype could also be advantageous given the polygenic influences on the general vulnerability to EXT. Endophenotypes are putatively less genetically complex correlates of the disorder that, because they tap the neurobiological basis of gene effects, are closer to gene action. The extent to which the genetic influences overlap between the endophenotypes and EXT, then, may provide increased power to detect "hits" for genetic linkage and association studies that may account for exceedingly small proportions of variance in the EXT phenotype (Gottesman and Gould 2003). These are necessary avenues of future research in evaluating the utility of this multivariate approach to defining endophenotypes for EXT.

An important, novel finding in the present report was differential patterns of shared genetic variance as a function of gender. In males, the TF and beta endophenotypes accounted for an additional, yet non-significant, increment in genetic variance in EXT above that accounted for by P3; whereas in females, the TF and beta endophenotypes did account for significant variance above and beyond that shared with P3. Based on these results, the question arises as to the best way to utilize these endophenotypes collectively in genetic studies. Two possibilities emerge: (1) use a multivariate endophenotype that is specific to each

gender, thus requiring two "passes" in the search for EXT-related genes, each of which may be ideally suited for males or females, or (2) use the same multivariate endophenotype for both genders, which requires only one pass at the data, but may include a measure that is not associated with significant variance in EXT. Given the depth of information contained in the genetic code, we submit that the latter approach may be the more fruitful one (1) in terms of efficiency, and (2) because the genetic etiology of the individual measures themselves is also of interest. Including all the measures regardless of their gender-specific association with EXT may, nonetheless, yield interesting results. Further research is necessary to address these gender-specific issues.

Given the exploratory nature of the present report, it necessarily has some notable limitations. The brain electrophysiological measures were recorded from a limited number of electrodes: 3 parietal sites for P3 and its related TF components, and Cz and bilateral parietal sites for beta power. The implications are that we have limited topographic information and that we may not be capturing all measures that have been associated with EXT in the literature. For instance, a frontal theta TF component has been associated with alcoholism (Jones et al. 2006). It will be important to examine a denser array of electrodes in followup studies. Also, the sample consisted solely of twins in late adolescence and was not racially or ethnically diverse. This age ($\sim$17-years-old), however, is that at which the most is known regarding the endophenotypic relationship between the measures in the current study and EXT (e.g., Gilmore et al. 2010; Iacono et al. 2002; Rangaswamy et al. 2007). Thus, we initially focused our efforts on this age. Further research needs to be done, however, regarding the generalizability of the findings to other age, racial, and ethnic groups.

Conclusion

In the present report, we explored a multivariate approach to identifying electrophysiological endophenotypes related to EXT psychopathology. The P3 ERP, its associated TF components, and beta frequency resting state EEG were shown to be heritable and to collectively share genetic variance in EXT, suggesting that these measures may be tapping into common neurophysiological and genetic substrates associated with EXT psychopathology. This shared genetic variance, however, differed as a function of gender. P3 seemed to be more closely related to EXT in males, whereas beta and the TF component were more related in females. Regardless of the gender difference, however, current findings of significant relationships among these electrophysiological endophenotypes and EXT would suggest that a multivariate endophenotype including these measures constitutes a worthy target, in addition to consideration of any of the individual measures, for studies investigating the genetic etiology of externalizing spectrum disorders.

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