The Enrichment Study of the Minnesota Twin Family Study: Increasing the Yield of Twin Families at High Risk for Externalizing Psychopathology

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The Enrichment Study (ES) was designed to extend the Minnesota Twin Family Study (MTFS) by oversampling 11-year-old twins at especially high risk for substance use disorders by virtue of having a childhood disruptive disorder. The sample was ascertained from Minnesota birth records. To identify high-risk twins, we conducted telephone screening interviews for parent-reported symptoms of attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) as well as indications of academic disengagement. Twins who exceeded a predetermined threshold were invited to participate. To facilitate comparison with the previously ascertained MTFS participants, a random sample of 11-year-old twins was also recruited. As part of the ES study, 499 twin pairs, and their parents, visited the University of Minnesota, where each participant completed a clinical interview, psychophysiological evaluation, and thorough assessment of environmental risk. We were highly successful in recruiting at-risk twins; 52% of the screened male twins and 41% of the screened females met criteria for a diagnosis of ADHD, CD, or oppositional defiant disorder (ODD). At the pair level, 63% of the screened pairs had at least one member with a childhood disruptive disorder. This article provides an overview of the study design and includes a review of recent findings using this sample of twins.

Keywords: twin-family research, high-risk longitudinal designs, childhood disruptive disorders, externalizing psychopathology

Conceptual Overview

Substance use disorders typically co-occur with each other (Stinson et al., 2005) and with other risk behaviors and mental health disorders (Kessler et al., 1997; Krueger, 1999; Regier et al., 1990). The association of childhood disruptive disorders and substance misuse is reflected in studies showing that attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) are both comorbid with substance use disorders and forecast their development (Armstrong & Costello, 2002; Disney et al., 1999; Flory & Lynam, 2003; Kim-Cohen et al., 2003; Weinberg et al., 1998). These phenotypic associations have led several researchers to posit the existence of an underlying vulnerability to disinhibitory behavior, characterized in preadolescence by undersocialized behavior and low levels of dispositional constraint. Our own research supports the existence of this latent factor, which is highly heritable (Hicks et al., 2007; Krueger et al., 2002; Young et al., 2000) and transmitted from parent to child (Hicks et al., 2004). Moreover, this general factor accounts, in large measure, for the covariance across a broad range of indicators of externalizing psychopathology, including childhood disruptive disorders, substance abuse and dependence, antisocial personality, and personality measures of behavioral undercontrol (Button et al., 2006; Button et al., 2007; Dick et al., 2005; Krueger & Markon, 2006; Slutske et al., 1998) as well as precocious social deviance and substance misuse (Keyes et al., 2007; McGue & Iacono, 2008; McGue et al., 2006).

While there is unequivocal evidence for a heritable component to substance use disorders (Dick et al., 2009), the importance of environmental contributions cannot be disputed (Hawkins et al., 1992). For example, disruptive adolescents are more likely to experience a number of the known environmental risks for substance use disorders, including weak attachment to and conflicted relationships with parents (Barkley et al., 1991a; Burt et al., 2005a, 2005b; Danforth et al., 1991) poor performance in and less strong attachment to school (Barkley et al., 1991b; Hinshaw, 2002; Lambert, 1988), and affiliation with

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deviant peer models (Keyes et al., 2007). A consequence of these exposures is an acquired greater tolerance for behavioral deviance, the rejection of conventional norms against rule breaking and substance use, and resulting elevated rates of substance disorders (Jessor et al., 1991). Longitudinal approaches are needed to explore how inherited vulnerability affects an adolescent's profile of environmental risk and the subsequent development of substance use disorders.

An additional body of research is concerned with measuring psychophysiological activity and responses to laboratory stimuli to assess the degree to which different psychophysiological measures may serve as endophenotypes for externalizing psychopathology (Iacono et al., 2008). Because they are thought to be more proximal to genetic influence than, for example, clinical diagnoses, endophenotypes may help researchers identify genes that contribute to the development of psychological disorders (Gottesman & Gould, 2003) as well as provide insight into the nature of genetic risk underlying those disorders (Iacono et al., 2008). Our work, as well as that of others, has indicated that one promising endophenotype, P300 amplitude reduction (P3AR), appears to serve as an endophenotype for the spectrum of externalizing disorders (Iacono et al., 2002b; Patrick et al., 2006), and that the association between P3AR and externalizing psychopathology is genetically mediated (Hicks et al., 2007). In addition, investigators have begun to explore other measures of electroencephalography (EEG) activity that appear to relate more directly to specific neural processes, which in turn may be linked to relevant genes. Indeed, some of this work has identified potential candidate genes associated with spontaneous or event-related oscillatory activity, such as genes coding for receptors for the neurotransmitters GABA (Porjesz et al., 2005), acetylcholine (Jones et al., 2004), and glutamate (Chen et al., 2009).

Method

Design Overview

The Enrichment Study (ES) is a component of the Minnesota Twin Family Study (MTFS), a longitudinal investigation of the adolescent origins of substance abuse using a developmental behavioral genetic perspective.

Initial MTFS Recruitment

The MTFS, which began in 1990, includes a representative population-based sample of 1382 pairs of like-sex twins and their parents. Participating MTFS families were originally ascertained from Minnesota state birth records for the years between 1972 and 1984. Families were eligible to participate if they lived within a day's drive of the University of Minnesota and if the twins had no physical or psychological disability that would interfere with their completing an assessment. Using publicly available data bases (e.g., phone books, Internet directories), we located addresses for over 90% of those twins still alive, and invited them to participate in a study of the maturation and health of twins.

The initial MTFS sample includes two cohorts: one initially assessed at age 11 (the younger cohort) and one initially assessed at age 17 (the older cohort). Intake and follow-up assessments are scheduled to coincide with major transitions in the lives of adolescents and young adults. Assessments were also completed by 99% of biological mothers, 91% of living biological fathers, and over 85% of stepparents, thus providing comprehensive information on the biological and rearing backgrounds of the twins. Analysis of participation and non-participation at study intake and follow-up has indicated little evidence of participation bias (Iacono et al., 1999; Iacono & McGue, 2002a; Iacono et al., 2006).

ES Recruitment

To enrich our sample with twins at high risk for the development of substance abuse, we began, in 2000, to recruit ES twin families in which at least one member of the pair was likely to be diagnosed with a childhood disruptive disorder. This sample was ascertained from Minnesota birth records of 2717 like-sex twin pairs born between 1988 and 1994. Of these, 82% (2226 total pairs; 1073 male and 1153 female) were successfully located and, in the year they became 11 years old, were recruited to participate in our study. The overall sampling plan was intended to maximize the number of high-risk twins while achieving our target sample of 500 families from the relevant birth years.

The ES recruitment strategy included random assignment to one of two samples. Seventy-six percent (1697 total pairs; 855 male and 842 female) of the twin pairs were randomized to the screened sample. In this sample, a parent (usually the mother) was contacted by phone and interviewed regarding symptoms of ADHD and CD as well as indications of academic disengagement (e.g., 'Lacks interest in school work') in each twin. ADHD symptoms and academic disengagement items were assigned weights of one; CD symptoms were assigned weights of three. The entire set of ES screening items is provided in Table 1. Only those pairs in which at least one member met or exceeded a threshold of five were invited to participate in the study (e.g., the threshold could be attained by having five symptoms of ADHD or one symptom of CD plus several symptoms of ADHD). This threshold was chosen, based on an analysis of data already collected from our existing 11-year-old cohort, to maximize both the sensitivity and specificity for predicting a twin having either a diagnosis of ADHD at age 11 or a diagnosis of CD by the age-14 follow-up.

The remaining twin pairs (529 total pairs; 218 male and 311 female) were randomly assigned to the unscreened sample. These twin families were recruited without prior screening, other than for physical or intellectual disability that precluded completing the assessment or for living within a day's drive of the

Table 1

DSM-IV and DSM-III-R Symptoms of ADHD and Conduct Disorder and Academic Items Assessed in Enrichment Screening Interview

ADHD symptoms (Give 1 point for each symptom coded full, based on examples of frequency and severity)
Often easily distracted by extraneous stimuli (III-R and IV)
Often fidgets with hands or feet or squirms in seat; in adolescents, may be limited to subjective feelings of restlessness (III-R and IV)
Often leaves seat in classroom or in other situations in which remaining seated is expected (III-R and IV)
Often has difficulty sustaining attention in tasks or play activities (III-R and IV)
Often interrupts or intrudes on others (III-R and IV)
Often loses things necessary for tasks or activities at school or at home (III-R and IV)
Difficulty playing (or engaging in leisure activities-IV) quietly (III-R and IV)
Often does not seem to listen (when spoken to directly-IV) to what is being said to him/her (III-R and IV)
Often talks excessively (III-R and IV)
Difficulty following through on instructions from others; not due to oppositional behavior or failure of comprehension (III-R and IV)
Often shifts from one uncompleted activity to another (III-R)
Often engages in physically dangerous activities without considering possible consequences; not for the purpose of thrill-seeking (III-R)
Often has difficulty organizing tasks and activities (IV)
Often forgetful in daily activities (IV)
Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school work or homework; IV)
Often runs about or climbs excessively in situations in which it is inappropriate (IV)
Often fails to give close attention to detail or makes careless mistakes in school work, work, or other activities (IV)
Often 'on the go' or often acts as if 'driven by a motor' (IV)
Difficulty awaiting turn in games or group situations (III-R and IV)
Often blurts out answers to questions before they have been completed (III-R and IV)
Conduct disorder symptoms[a] (Give 3 points for each symptom coded full, based on examples of frequency and severity)
Often lies (III-R) to obtain goods or favors or to avoid obligation (IV)
Used a weapon in more than one fight (III-R) with the potential for causing serious harm (IV)
Often initiates physical fights (III-R and IV)
Deliberately engaged in fire-setting (III-R) with the intent of causing serious damage (IV)
Stolen without confrontation of a victim on more than one occasion (III-R); items stolen are of nontrivial value (IV)
Physically cruel to animals (III-R and IV)
Deliberately destroyed others' property (other than by fire-setting; III-R and IV)
Often bullies, threatens, or intimidates others (IV)
Physically cruel to people (III-R and IV)
Often stays out at night despite parental prohibitions, beginning before age 13 (IV)
Often truant (III-R); truancy must begin before age 13 (IV)
Broken into someone's house, building, or car (III-R and IV)
Academic items (Give 1 point for each item answered in indicated direction)
Lacks interest in schoolwork (true)
Is well liked by his/her teachers (false)
Enjoys attending school (false)
Turns in homework on time (false)
Studies or completes homework at night without being told to do so (false)
Likes his/her teachers (false)
Is motivated to earn 'good' grades (false)
Has a good attitude about school (false)

Note: [a]Due to their extremely low endorsement in our existing 11-year-old cohort, some CD symptoms were omitted from the screening interview, but were assessed during the visit.

university. The recruitment of the unscreened ES sample was designed to mirror MTFS twin recruitment. The proportion of the total sample randomized to the unscreened and screened samples was set to ensure that all pairs that screened above threshold and were willing to participate could be accommodated in the 500 recruitment slots available, while inclusion of an unscreened sample facilitated comparison with the unselected MTFS twins.

We successfully interviewed 84% of the families in the recruitment pool to determine eligibility in the study and to collect basic demographic information. The eligibility interview could not be scheduled with some families before our target recruitment goals were met or the twins had become too old (8.6%), and some families refused the eligibility interview (7.6%). Sixty-seven twin pairs in the unscreened sample and 205 in the screened sample did not meet basic inclusion criteria (i.e., disability-free, family lived within a day's drive of our lab). An additional 930 twin pairs in the screened sample did not meet the pre-determined symptom threshold. In all, 663 twin pairs were eligible to participate in the ES study and

were invited to do so (336 in the unscreened sample and 327 in the screened sample). Eligible families who did not participate included those that refused (17%) as well as those we were unable to schedule before our recruitment goals were met (7%). The ES refusal rate is virtually identical to that for the original MTFS cohort (Iacono et al., 1999). Participation rates did not vary by screening status.

To investigate sampling bias, we compared demographic measures from participating and eligible non-participating families. Neither the percentage of parents remaining married, mean family income, father's years of education, nor mother's occupational status differed significantly between participating and nonparticipating families. Years of education, however, were significantly higher among participating mothers (M = 14.3, SD = 1.9) than among nonparticipating mothers (M = 13.8, SD = 2.0) ($p < .01$), and occupational status indicators (codes ranged from 1 to 7, with 7 reflecting the highest status) were higher among participating fathers (M = 4.7, SD = 1.7) when compared with nonparticipating fathers (M = 4.2, SD = 1.8) ($p < .01$). While this indicates some degree of positive selection, the effect appears to be slight. Standardized effect-size estimates equal .26 and .29 for mother's education and father's occupational status, respectively. Thus, the sample is generally representative of the population from which it was drawn.

ES Participants

Five-hundred ES families visited the university to complete our day-long assessment. A single twin pair was later excluded due to intellectual limitations evidenced at the visit, resulting in a final sample of 499 twin pairs, with 48% drawn from the screened sample (101 unscreened male and 156 unscreened female pairs; 138 screened male and 104 screened female pairs). At the time of their intake visit, the mean age was 11.9 for both boys (SD = .41) and girls (SD = .44); ages ranged from 10.9 to 13.0 years. Ninety-one per cent of the twins are Caucasian, which is representative of Minnesota-born children from the relevant birth years. Zygosity was determined through comparison of three estimates: (1) parental reports of physical similarity on a zygosity questionnaire, (2) staff evaluation of physical similarity, including similarity of the eyes and ears, and (3) zygosity diagnosis obtained by an algorithm using ponderal index, cephalic index, and fingerprint ridge count. When these estimates were inconsistent, DNA-based confirmation of zygosity was obtained using a panel of highly polymorphic short tandem repeat markers. The sample includes 300 monozygotic (MZ; 162 unscreened and 138 screened pairs) and 199 dizygotic (DZ; 95 unscreened and 104 screened pairs) twin pairs.

Like the original MTFS 11-year-old cohort, the ES sample is being followed every 3 years, with the age-14 assessment concluded and the age-17 assessment more than half complete. The participation rate for the age-14 assessment exceeds 90%, and we anticipate that age-17 participation will be similarly high. We have just begun a third follow-up at age 20. In addition, DNA samples are currently being collected from all twins and their parents as part of the National Institute on Drug Abuse Genes, Environment, and Development Initiative (GEDI; DA024417), an effort that focuses on the role of the interplay between measured genes and environments in the development of substance use disorders.

Overview of Assessments

An overview of our entire assessment protocol is given in Table 2; additional detail on our clinical and psychophysiological measures is given below.

Table 2

Overview of Design and Measures Used in the Enrichment Study

Participants	A population-based sample of 260 female and 239 male twin pairs, located from birth certificates spanning 1988–1994 and over-selected for the presence of externalizing behavior, completed an in-person assessment after reaching age 11. Biological and step-parents of the twins were assessed regarding their own mental health history.
Longitudinal design	For twins, the intake (ages 11–12), first (ages 14–15), second (ages 17–18), and third (ages 20–21) follow-ups consist of a full-day assessment involving interview and lab sessions. Both parents visit at intake and at the second follow-up; only the primary caregiver visits at the first follow-up. At each assessment, structured interviews are administered to children and parents to generate diagnoses. Most measures are obtained from multiple raters (e.g., parent, child, and teacher).
	Description of domains measured in twins
Substance abuse	
Substance use disorders	DSM-IV and DSM-III-R nicotine dependence, alcohol use disorders, and 12 categories of drug use disorders at ages 11 and 14 with revised version of the Diagnostic Interview for Children and Adolescents (DICA-R); at ages 17–20 with expanded Substance Abuse Module (SAM), from the WHO's Composite International Diagnostic Interview (CIDI).

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Table 2 (continued)

Overview of Design and Measures Used in the Enrichment Study

Initiation of Substance Use and Escalation	Ages 11–17, private computerized questionnaire re: quantity, frequency, age onset, abuse for alcohol, tobacco, marijuana, street, and prescription drugs; cognitive factors re: expectancies and benefits/detriments of alcohol/drug use (AEQ-A). Ages 17–20, questions added to SAM re: age of first use and quantity and frequency of use (for all substances), including maximum drinks in 24 hours, patterns of binge drinking, and Fagerstrom Test for Nicotine Dependence.
Related DSM-IV and III-R psychopathology, personality, and behavior	
Mental Health Assessment	ADHD, CD, ODD, depression, and anxiety disorders in twins (with parent report) at intake and adolescent follow-ups with DICA-R. Mood/anxiety disorders via SCID at ages 17–20; Inventory of Depression/Anxiety Symptoms (IDAS) at age 20. Antisocial personality disorder at ages 17–20 with Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II); borderline personality disorder via SIDP-IV borderline interview module and PAI-BOR questionnaire.
Personality	Ages 11–17, teacher ratings of personality; adolescent self-reports on Tellegen's Multidimensional Personality Questionnaire (MPQ; at ages 14 and 17 to assess personality change during adolescence), State-Trait Anxiety Inventory (STAI), and Piers-Harris (P-H) Self-Concept Inventory. Age 20 disinhibition measure (from CPI Socialization scale).
Behavioral Deviance	Trouble with police, arrests, incarceration, age at first sexual intercourse, self-report of risky sexual behaviors. Ages 11–17, Delinquent Behavior Inventory (DBI) ; measures of relational aggression and victimization; Opinions and Attitudes, consisting of Antisocial Attitudes and Aggressive, Family, and Prosocial Orientations. Ages 11–20, Minnesota Eating Behavior Survey (MEBS) re: eating pathology (also: diagnostic interview for females).
Environmental risk and social outcomes	
Demographics	Parent SES; other objective indices (e.g., census data) re: neighborhood and school (e.g., poverty status, urban vs. rural).
Substance Exposure	Nicotine, alcohol, and illicit drug use during pregnancy asked of mother at intake. Cumulative indices of ingestion of substances across development obtained at ages 11–20.
Access, modeling, pressure to use	Ages 11–17, self-report of access to substances, pressure from friends/siblings to use alcohol, tobacco, or marijuana, parental attitudes towards substance use, and timing of puberty (which may accelerate exposure to risky environments).
Family and peer relationships	Parental Environment Questionnaire (PEQ) at ages 11–17; Peer affiliation (Friends) measure at ages 11, 14, 17, and 20; Sibling Relationship Scale regarding twin relationship at ages 11–14.
Parental functioning	Parental functioning indexed via clinical diagnostic assessment (similar to that given to twins at ages 17–20). Parental knowledge/monitoring of children's activities, quality of parents' marriage (DAS), opinions on child-rearing.
Academic achievement	Ages 11–17, academic engagement, school behavior, grades, and parental expectations for academic achievement. WRAT-3 reading and math achievement at age 14.
Life events/ trauma	Comprehensive life events interview for parents and twins at each assessment; childhood experiences of harsh discipline, neglect, physical/sexual abuse, retrospectively at age 20 with items from Trauma Assessment for Adults (TAA), Childhood Life Events (CLE), and Colorado Adolescent Rearing Interviews.
Social support	Ages 11–20, social adjustment interview re: social support provided by relatives/friends, romantic experiences, educational outcomes, involvement in activities; religious activities and involvement questionnaire.
Psychophysiological measures of risk (note: most measures obtained in lab assessments of parents as well)	
Brain physiology	Rotated heads oddball task used to elicit event-related potential waveforms and a P300 response at ages 11, 14, 17, 20. Task modified to include frontally-mediated novelty P3a. Time-frequency decomposition applied to P300 data to determine event-related oscillations (EROs). Error-related negativity (ERN) examined with Eriksen flanker task. Spontaneous EEG recorded at ages 11, 14, 17. All assessments use a 64-channel recording system.
Cognitive functioning	Fluid and crystallized intellectual functioning with Block Design and Vocabulary at age 11 (WISC-R) and 17 (WAIS-R). Age 20, measures of attention (Digit Span from the WAIS-III), memory (Rey Auditory-Verbal Learning Test), and cerebellar functioning (time estimation) assess consequences of substance use.

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Table 2 (continued)

Overview of Design and Measures Used in the Enrichment Study

Other relevant psychophysiological domains	Autonomic nervous system (ANS) reactivity, habituation, and modulation of ANS responses to predictable and unpredictable aversive lab stressors. Verbal and spatial working memory. Assess degree to which the emotional content of affectively laden images modulates startle eye blink reflex elicited by loud noises. Eye tracking tasks, including antisaccade and smooth pursuit tasks.
Molecular genetic (DNA) measures	
	Blood drawn from twins and parents; DNA extraction/storage; Genome-wide association study in progress.

Clinical Assessments

At every assessment, each parent and twin is interviewed separately by a different interviewer. Interviewers have a BA or MA in psychology and have completed extensive training and observation. Our approach to diagnosis is based on DSM-IV, but to maintain comparability to previous MTFS samples, our interviews assess both DSM-IV and DSM-III-R criteria. Diagnoses at intake were lifetime, whereas diagnoses at the three-year follow-up assessments focus on symptoms occurring since the last assessment. Past 12-month diagnoses are available for some disorders as well (e.g., substance use disorders). The clinical assessment of parents was very similar to that described below for twins at their second (age 17–18) follow-up. Phone interviews are conducted only with those who are unable to visit; otherwise, all follow-up assessments are done during in-person visits to our laboratory.

At the completed intake (age-11) and first follow-up (age-14) assessments, maternal reports of each twin's symptoms of ADHD, CD, ODD, major depressive disorder (MDD), substance use disorders, and anxiety disorders (separation anxiety at intake; generalized and social anxiety disorders at follow-up) were obtained with a modified version of the Diagnostic Interview for Children and Adolescents — Revised (DICA-R; (Reich, 2000; Welner et al., 1987)), updated based on DSM-IV criteria. Child reports of the same disorders were obtained using a parallel child version of the DICA-R. Eating pathology, which may be elevated in girls with ADHD (Mikami et al., 2008), was assessed via structured interview diagnoses of anorexia and bulimia and with the 30-item Minnesota Eating Behavior Survey (von Ranson et al., 2005).

At our ongoing second follow-up, when the twins are approximately 17 years old, portions of the DICA-R (i.e., ADHD and ODD) are re-administered to the twins and to their primary caretaker. As shown by Barkley et al. (2002), persistence of ADHD may be substantially underestimated if the parental report is dropped during adolescence. However, instruments that are more developmentally appropriate for older adolescents and adults are substituted for other disorders. Because an increase in CD symptoms during adolescence (along with comorbid ADHD) exerts a strong influence on heavy drinking (Molina et al., 2007) and other substance outcomes (Elkins et al., 2007), an interview adapted from the Structured Clinical Interview for DSM-III-R Personality Disorders (Spitzer et al., 1987), assessing DSM-IV and DSM-III-R criteria for antisocial personality disorder (ASPD), has been modified to cover CD since the age-14 follow-up. DSM-IV and III-R substance use disorders are assessed using a modified version of the expanded Substance Abuse Module (SAM) developed by Robins et al. (1987) as a supplement to the WHO's Composite International Diagnostic Interview (Robins et al., 1988). We have added questions to the SAM covering quantity and frequency of use, the Fagerstrom Test for nicotine dependence (Heatherton et al., 1991), maximum drinks in 24 hours, patterns of binge drinking, and an expanded list of prescription drugs that may be abused. Finally, we comprehensively assess mood and anxiety disorders, using the Structured Clinical Interview for DSM-III-R and IV (Spitzer et al., 1992) to assess MDD, mania/hypomania, specific/social anxiety, panic disorder, agoraphobia, and generalized anxiety disorder.

For the recently initiated third follow-up at age 20, we repeat the clinical assessment in twins, who now visit without their parents. We have supplemented their DICA-R ADHD assessment with probes reflecting adult manifestations of ADHD symptoms (Adler et al., 2006). In addition, to enhance our assessment of risk in females, we have added an assessment of borderline personality disorder using the borderline module from the SIDP-IV (Pfohl et al., 1997) and the PAI-BOR scale from the Personality Assessment Inventory (Morey, 1991).

Following the assessment, each interview is reviewed by two individuals with advanced clinical training (supervised by a Ph.D. clinical psychologist) blind to other family diagnoses. Symptom presence is determined through review of severity and frequency criteria for each behavior followed by consensus regarding whether it constitutes a symptom. A symptom is considered present if either the primary caretaker or twin reported it as present, using a best-estimate procedure (Leckman et al., 1982) that we have found results in greater validity than relying on either report alone (Burt et al., 2001). To maximize sensitivity in our population-based sample of adolescents, diagnoses in the twins are made at two levels: definite (all diagnostic criteria satisfied) and probable

(all but one diagnostic criteria satisfied). This strategy avoids problems with underreporting of lifetime symptoms in population-based samples (Iacono et al., 1999), and is essential for detecting emerging substance use disorders during adolescence (Martin & Winters, 1998; Pollock & Martin, 1999). Further, it does not appear to inflate our rates of ADHD and CD (Elkins et al., 2007). For example, our DSM-IV lifetime prevalence of ADHD is still lower than other community-based samples that include probable cases (Smalley et al., 2007). We have examined reliability of our consensus procedure by disorder, informant, subject age, and instrument. Interviews of approximately 600 participants were reviewed by two independent, blinded pairs and produced kappas > .74, with all SUD kappas > .90. An independent consensus team re-evaluates every 25th case to ensure continued reliability and to control drift; we continue to have over 90% diagnostic agreement.

Psychophysiological Assessments

At every assessment, ES twins participate in a psychophysiological laboratory assessment. Fathers complete this assessment at their intake and second follow-up visits, while mothers complete this assessment at their first follow-up. The ES study employs developmentally sensitive laboratory tasks designed to tap genetic risk for substance use disorders and childhood disruptive disorders, individual differences in inhibitory control, and putative frontal lobe indices of executive functioning relevant to adolescent brain development. We also include procedures tapping autonomic nervous system (ANS) function and measures of negative affect, which have received considerably less attention in the substance abuse literature, both for their potential as endophenotypes and for illuminating mechanisms underlying the role of affect dysregulation in the development of substance use disorders (see Table 2).

All assessments include measures of brain activity. Although most MTFS research on EEG and event-related brain potentials (ERPs) has been conducted using a 5-channel system, we employ 64-channel EEG recording in the ES study. We use the same 'rotated heads' visual oddball task (Begleiter et al., 1984) used in the previous MTFS cohorts to elicit ERPs. We and others have demonstrated that amplitude of the P300 wave is reduced in individuals with disorders in the externalizing spectrum as well as those at risk for such disorders (Iacono et al., 2002b; Porjesz et al., 2005). P3AR also predicts the subsequent development of substance use disorders (Carlson et al., 2004; Habeych et al., 2005; Iacono et al., 2002b). Because certain aspects of spontaneous and task-related EEG oscillations may also prove valuable as endophenotypes for substance use disorders (Gilmore et al., in press; Porjesz et al., 2005) and are associated with ADHD (Barry et al., 2003), we also extract event-related oscillations (EROs) from our ERP data and examine the spectral components extracted from our recordings of spontaneous EEG.

The assessment includes other psychophysiological procedures that are thought to tap mechanisms involved with the development of substance use disorders. These assessments include measures of smooth pursuit and antisaccade eye tracking, working memory, ANS habituation, ANS reactivity in anticipation of a stressor, and the emotional modulation of the startle eye-blink response. Because functioning of anterior brain structures may be particularly relevant to understanding the effects of adolescent-onset substance abuse, we have added new measures of brain function likely to be sensitive to the effects of substance misuse at the age-20 follow-up.

Results

Success of the ES Recruitment Strategy

We can evaluate the success of the ES recruitment strategies in two ways. First, because the recruitment and assessment of the ES unscreened sample was intended to parallel the MTFS younger cohort, we can assess the overall similarity between these two groups. Second, we can determine the extent to which we have enriched the sample for the presence of childhood disruptive disorders. Table 3 reports the number of cases and the prevalence of DSM-III-R diagnoses (the diagnostic system in place when the study began) for the MTFS younger cohort, ES unscreened, and ES screened samples, all assessed at age 11. These data are shown for ADHD, ODD, and CD, at the definite and at the definite plus probable levels. The differences in diagnostic prevalence for childhood disruptive disorders between the ES unscreened and earlier MTFS samples are negligible, suggesting that we are justified in pooling cases across these samples. In addition, the data shown in Table 3 further demonstrates that we have been highly successful in recruiting at-risk twins; 52% of the ES screened males and 41% of the screened females met criteria for a childhood disruptive disorder diagnosis at the probable or definite level. At the pair level, 63% of the screened pairs had at least one member with a diagnosis of ADHD, CD, or ODD. Combining across all samples, the addition of the ES study has effectively doubled the number of at-risk twins available for analysis (n = 650). The unusually large sample of affected females (n = 232) ensures that this high-risk sample is well suited for the investigation of gender effects. Moreover, by age 11, 165 twins (105 males and 60 females) were receiving pharmacological treatment for ADHD (e.g., methylphenidate), giving us a large sample with which to explore iatrogenic effects of ADHD treatment. Finally, we can expect the number of CD and ODD cases to increase when the age-14 follow-up assessment is complete.

Weighting the ES Sample

By design, twins in the ES unscreened and screened samples had different probabilities of selection into the

Table 3

A Comparison of Number of Cases (and Prevalence per 100) by Gender: MTFS Younger Cohort, ES Unscreened, and ES Screened Samples at Age 11

	Males			Females		
DSM-III-R Diagnoses	Younger cohort sample (*N* = 755)	ES unscreened (*N* = 202)	ES screened (*N* = 276)	Younger cohort sample (*N* = 762)	ES unscreened (*N* = 312)	ES screened (*N* = 208)
ADHD						
Definite only	51 (6.8)	9 (4.5)	52 (18.8)	27 (3.5)	10 (3.2)	27 (13.0)
Probable and definite	69 (9.1)	20 (9.9)	68 (24.6)	33 (4.3)	19 (6.1)	39 (18.8)
CD						
Definite only	55 (7.3)	10 (5.0)	50 (18.1)	11 (1.4)	5 (1.6)	9 (4.3)
Probable and definite	143 (18.9)	35 (17.3)	95 (34.4)	34 (4.5)	11 (3.5)	38 (18.3)
ODD						
Definite only	68 (9.0)	14 (6.9)	44 (15.9)	38 (5.0)	14 (4.5)	19 (9.1)
Probable & Definite	112 (14.8)	21 (10.4)	71 (25.7)	76 (10.0)	25 (8.0)	32 (15.4)
Any Disruptive Disorder						
Definite Only	118 (15.6)	27 (13.4)	103 (37.3)	63 (8.3)	22 (7.1)	47 (22.6)
Probable & Definite	216 (28.6)	58 (28.7)	144 (52.2)	109 (14.3)	38 (12.2)	85 (40.9)

Note: Any Disruptive Disorder includes Attention-Deficit/Hyperactivity Disorder (ADHD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD).

study. This violates the assumption of equal probability of selection for all observations that is fundamental to simple random samples. Unequal selection probabilities, however, can be accommodated by means of sampling weights, which commonly represent the inverse of the probability of selection into the sample (Kalton, 1983). The ES design effectively oversampled for high-risk pairs, which therefore make up a greater percentage of the total sample than they would in the population. If we assume that the unscreened sample is representative of the population, it is possible to derive weights that adjust the screened male and female samples relative to the unscreened ones, and thus effectively equate them. More specifically, it is possible to assign weights that mathematically adjust for differences between unscreened and screened samples in the number of twin pairs above the screening threshold. This results in assigning greater weight to the unscreened pairs and less weight to the screened ones. Because selection in the ES sampling frame occurred at the level of twin pairs, each twin within the same pair is assigned the same weight.

Table 4 provides the prevalence of DSM-III-R diagnoses in ES twins, adjusted for the ES sampling plan. We also present rates for the younger cohort of MTFS twins. The two are quite comparable, attesting to the success of the weighting scheme. For comparison, we also present the simple, unweighted rates. These are substantially higher than the weighted rates, as expected given the large number of cases in the ES screened sample.

Table 4

Comparison of Prevalence (per 100) by Gender: ES Weighted, MTFS Younger Cohort, and ES Unweighted Samples at Age 11

	Males			Females		
DSM-III-R Diagnoses	ES Weighted Sample (*N* = 478)	Younger Cohort Sample (*N* = 755)	ES Unweighted Sample (*N* = 478)	ES Weighted Sample (*N* = 520)	Younger Cohort Sample (*N* = 762)	ES Unweighted Sample (*N* = 520)
ADHD						
Definite Only	7.0	6.8	12.8	3.8	3.5	7.1
Probable & Definite	10.8	9.1	18.4	6.1	4.3	11.2
CD						
Definite Only	6.6	7.3	12.6	1.3	1.4	2.7
Probable & Definite	15.9	18.9	27.2	4.7	4.5	9.4
ODD						
Definite Only	8.0	9.0	12.1	4.4	5.0	6.3
Probable & Definite	13.2	14.8	19.2	7.7	10.0	11.0
Any Disruptive Disorder						
Definite Only	16.2	15.6	27.2	8.1	8.3	13.3
Probable & Definite	28.0	28.6	42.3	14.5	14.3	23.7

Note: Any Disruptive Disorder includes Attention-Deficit/Hyperactivity Disorder (ADHD), Conduct Disorder (CD), and Oppositional Defiant Disorder (ODD).

Discussion

As we have demonstrated, the ES study has successfully recruited and retained a large sample of twin families enriched for offspring being at high risk for childhood disruptive disorders. Following the methods outlined here, studies involving ES twins have already contributed substantially to our understanding of childhood disruptive disorders and more broadly to the development of externalizing psychopathology. In what follows, we highlight findings from reports employing ES families.

Using ES twin families, Herndon and Iacono (2005) extended our earlier MTFS work demonstrating familial transmission of externalizing disorders (Hicks et al., 2004) by showing that parental antisociality is associated with increased risk for childhood disruptive disorders at age 11 and a wide range of externalizing disorders by age 17. Similar effects are evident for the offspring of parents with alcohol and illicit drug use disorders (Marmorstein et al., 2009). Personality profiles are also deviant in children with childhood disruptive disorders, with low constraint and high negative emotionality a common feature (Cukrowicz et al., 2006).

In a series of related studies that include ES families, Burt and colleagues (Burt et al., 2003; 2005a; 2005b) have shown that as adolescence unfolds, CD and the comorbidity among the childhood disruptive disorders can be attributed in part to the family environment, particularly as it relates to parent-child conflict. Association with antisocial peers, by contrast, does not appear to be causal, indicating instead that disruptive adolescents select or shape (either intentionally or inadvertently) subsequent environmental experiences to increase affiliation with deviant peers (Burt et al., in press).

Our large sample of ES females with disruptive behavior disorders has provided an opportunity to pursue novel hypotheses concerning gender-specific risks. For example, Burt et al. (2006) showed that the heritability of CD varies as a function of age of menarche, with heritability being greatest when menarche occurs at a normative age rather than early age. This result is consistent with the notion that CD in early maturing girls reflects psychosocial environmental mediation. Puberty may also be important to understanding the etiology of eating disorders, which we have shown to predict increases in externalizing behavior during adolescence (Marmorstein et al., 2007). In a research program that has been extended by the use of ES twins as a replication sample, researchers (Culbert et al., in press; Klump et al., 2007) have shown that the heritability of disordered eating increases as girls enter puberty. This finding supports the possibility that the increase in ovarian hormones at puberty in girls activates or moderates genetic effects on disordered eating. These results are also consistent with a possible role for active genotype-environment correlation leading to an increase in genetic effects after pubertal onset.

Reduced P300 amplitude has been identified as an important candidate endophenotype for externalizing psychopathology (Iacono et al., 2002b), including the childhood disruptive disorders, substance use disorders, and ASPD. Our recent work with ES twins has helped refine and further delineate this endophenotype. Given the possibility that alcohol use can affect adolescent brain development, an important question concerns the degree to which the reduced P300 amplitude observed in adolescents reflects the underlying genetic risk for developing substance abuse as opposed to the effects of alcohol misuse. In Perlman et al. (2009), we found that the heritability of P300 amplitude in adolescent twins was not moderated by alcohol consumption. This finding is consistent with the hypothesis that reduced P300 amplitude reflects genetic risk rather than the effects of adolescent alcohol consumption.

Our initial work examining older-cohort twins with a lifetime diagnosis of ADHD indicated significant reduction in P300 amplitude (Iacono et al., 2002b). However, when 'pure' ADHD cases (those with no comorbid externalizing diagnosis) were examined, P300 amplitude was not significantly reduced, suggesting that the P3 effect observed in ADHD may be attributable to its overlap with other externalizing disorders. Further, because this study was carried out with 17-year-old twins, many of whom had already initiated substance use, it was not possible to rule out substance exposure as a factor in the P3AR of the comorbid group. We therefore extended this work using 11-year-old ES and MTFS twins for whom substance use is uncommon. In this younger-cohort sample, Yoon et al. (2008) found that ADHD cases showed reduced P300 only in the presence of comorbid CD and/or ODD. These results suggest that ADHD in the absence of other externalizing disorders may reflect a different underlying genetic mechanism than comorbid ADHD because individuals with 'pure' ADHD did not show the characteristic P3AR. Thus, ES twins have helped us to further refine this endophenotype. Moreover, in Gilmore et al. (in press), we showed that the EROs comprising the P300 response can be used to capture risk for externalizing disorders beyond that which is possible using P300 alone.

Our work with ES twins has also contributed to two international collaborative efforts. In Hur et al. (2008), we combined forces with other twin registries to show that differences in the variances for height, weight, and body mass index distributions that exist between Caucasian and East Asian populations are attributable to genetic factors. These findings indicate that the genetic mechanisms underlying these variables, important in part to understanding obesity, are different in these two populations, and suggest that association studies can therefore expect to identify different genes in each population. In Haworth et al.

(2009a), a collaboration pooling data from 11,000 twins, we showed that the heritability of general cognitive ability increases substantially from childhood to young adulthood. These findings support the hypothesis that as children grow up they select, modify, and create opportunities to accumulate knowledge and educational experience, reflecting the effects of gene–environment correlation. These results also suggest that adult samples, rather than those composed of children, are likely to be better for finding genes associated with cognitive ability.

Other studies with ES twins have shed additional light on the development of cognitive ability and educational attainment. We have reported that high cognitive ability is heritable in adolescence. A modest shared environmental effect is also evident, both for cognitive ability in general and for especially high ability (Haworth et al., 2009b; Kirkpatrick et al., 2009). Academic achievement has been examined in a series of studies, Johnson and colleagues (2005; 2006; in press). This work has explored the complexity of gene–environment interplay associated with the development of academic achievement from pre-adolescence through adolescence and into young adulthood.

Collectively, these studies highlight the many ways in which this enriched twin-family sample has contributed to better understanding of important phenotypes. The first follow-up assessment of the ES families at age 14 has just been completed, an important milestone that will further facilitate the incorporation of ES twins in our longitudinal studies of the development of externalizing behavior and related outcomes.

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