The Minnesota Center for Twin and Family Research (MCTFR) houses a collection of longitudinal, community-based twin-family and adoptee-family projects that focus on the mental health outcomes of adolescent youth with a special focus on the development of substance use and related behavior disorders. The Minnesota Twin Family Study includes epidemiological investigations of 11- and 17-year-old twins, an examination of 11-year-old twins selected for being at high risk for having a childhood disruptive behavior disorder, and a supplemental registry of young adult twins age 18 years and older who are not enrolled in these longitudinal studies. Also, part of the MCTFR is the Sibling Interaction and Behavior Study, a complementary prospective investigation of adolescent sibling pairs in families with adoptive and biological offspring. MCTFR participants from these various projects are assessed in person and through multiple informants to provide comprehensive coverage of psychological adjustment, mental health, and psychosocial risk/protective factors. Measurement of EEG and autonomic nervous system reactivity is also part of the assessment battery for twin families. This article provides an overview of study design and includes a review of recent MCTFR findings.

Conceptual Overview

Although it is clear that a variety of biological and psychosocial risk factors combine to influence the development of antisociality and substance use disorders (SUD), the processes by which these varied factors combine to influence risk remain to be characterized. MCTFR research is based on the premise that characterizing mechanisms of risk is best achieved through longitudinal research that begins in preadolescence, prior to substance-use initiation, focuses on families, and uses a genetically informative design that includes comprehensive and careful assessment of both individual-level and psychosocial risk. We hypothesize the existence of a general inherited vulnerability to the expression of disinhibitory behavior, which can manifest in preadolescence as undersocialized behavior, low levels of dispositional constraint, and psychophysiological indicators of central nervous system (CNS) dysfunction in inhibitory control. Preadolescent disinhibition increases the likelihood of early involvement in adolescent problem behavior, such as substance use, sexual experimentation, and delinquent behavior, as well as decreases the likelihood of attachment to socializing agents that encourage sobriety and adherence to social norms (e.g., parents, school, good-peer models). Early-onset SUDs are hypothesized to be an expression of both this inherited vulnerability and the diminished association with socializing agents that accompanies adolescent problem behavior.

Design Overview

Minnesota Twin Family Study

Initiated in 1990, the MTFS began with two age cohorts, preadolescent 11-year-old twins recruited while still in elementary school, and late adolescent twins.
17-year-old twins were recruited typically during their last year of secondary education. Twins were identified from State of Minnesota birth certificates, and all located twins and their parents still residing in Minnesota or near the Minnesota border in neighboring states were invited to participate in the MTFS if they met minimal inclusion criteria (e.g., twins live with at least one biological parent, no disability that would make meaningful participation impossible). Over 90% of Minnesota-born twins were located, and of those meeting eligibility requirements, 83% agreed to complete a day-long in-person assessment. At study intake, twins and their parents (all available biological and step-parents were included) visited MCTFR laboratories, splitting their time between clinical interviews and psychophysiological assessments. Approximately every 3 to 4 years, the twins (and one or both of their parents if the twins are still teenagers) are reassessed in our laboratory in day-long follow-up visits. Eleven-year old twins have been recruited throughout the history of the MTFS, and the oldest members of this cohort are now in their mid-20s. Of those first recruited as part of the older twin cohort at age 17, many are now in their early 30s. By comparing participating to nonparticipating twin families (Iacono et al., 1999) and the demographic characteristics of participating families to United States Census data (Holdcraft & Iacono, 2004), we have shown that MTFS families are broadly representative of the Minnesota population.

In order to enrich the representation of twins at high risk for the development of substance abuse, in 2000 we began to recruit twin families when, based on a telephone screening interview with the mother, at least one of the twins was deemed at high risk for having a childhood externalizing disorder (e.g., conduct disorder, attention-deficit/hyperactivity disorder [ADHD]). To facilitate comparison to the original unselected age 11 MTFS cohort, a random sample of families of 11-year-old twins was also recruited. This enrichment process has led to the addition of 500 twin families to the 1383 unselected families already enrolled in the MTFS. These twin families are also revisiting our laboratories every 3 years or so.

**Sibling Interaction and Behavior Study**

The MCTFR also includes the community-based Sibling Interaction and Behavior Study (SIBS) project, an investigation of 617 families that complements and extends our twin research through the inclusion of adoptees and their foster parents. SIBS includes 408 adoptive families (about half of whom have children who were foreign born) and 209 biological families each composed of parents and two adolescent offspring whose age brackets that of the adolescent twins in the MTFS. Both same-sex and opposite-sex sibling pairs are included. Adoptive families were recruited through private agencies in Minnesota that had placed infant children in Minnesota homes. Biological families were recruited through birth records and selected to be broadly representative of the Minnesota population while matching the adoptive adolescents in age and gender. A more thorough description of the SIBS project can be found in McGue et al. (in press) which includes analyses demonstrating the appropriateness of relying on an adoption sample (where adoptive parents are screened in part for psychological fitness) to estimate shared environmental effects on measures of behavioral disinhibition in their adoptive children.

**MTFS Expansion: New Young Adult Same-Sex Twin Registry**

Recent work has further extended the MTFS by establishing an active registry of all same-sex twins born in Minnesota in the years 1971 to 1980 who were not included among those currently enrolled in MTFS longitudinal studies. Most of these twins were initially identified when they turned 11 or 17 years old along with the other MTFS participants. Although these located families have been counted in our registry, since initially contacting them, we have not asked them to participate formally in our research. This group included individuals who, although born in Minnesota, resided far away in other states. Many we could not assess as the number of twin families available each birth year exceeded the number of days available to test families in a given study intake year. It also included twins who had not been located previously if, for example, they came from birth years incompletely assessed due to the timing of grant funding. Working from birth certificates and the registry of already located twins, 2183 eligible twin pairs were identified, 87% of whom were successfully relocated or located for the first time. When those who were ineligible (e.g., due to the death of a twin or physical handicap) were removed from this group, a final sample of 1753 actively participating pairs was incorporated into the updated MTFS registry. Unlike the MTFS twins enrolled in our longitudinal studies, only limited information is available on these twins who were asked to complete via mail or over the Internet, biographical and personality questionnaires. In addition, the parents of these young adult twins are not currently active participants.

**Major Assessments**

All MCTFR children and parents complete structured interviews covering common child and adult mental disorders (based on *Diagnostic and Statistical Manual of Mental Disorders* 3rd ed., rev., and 4th ed. [DSM-III-R and DSM-IV] diagnostic criteria), individually administered Wechsler IQ tests, self-report personality scales, and psychosocial measures covering the quality of the family environment, peer groups, social adjustment, and life event stress. Teachers provide ratings of personality, peer group characteristics, externalizing behavior, and academic progress. All MTFS participants spend a half day in a psychophysiology laboratory where they engage in various psychological tasks while electroencephalography (Bernat et al., in
press; McGuire et al., 1998), event-related brain potentials (Iacono et al., 2002), eye movements (Malone & Iacono, 2002), eye-blink startle (Benning, Patrick, & Iacono, 2005), and autonomic nervous system activity (Iacono et al., 2000) are monitored. Instead of a psychophysiological assessment, SIBS participants complete videotaped family and sibling interaction tasks. DNA has been drawn on approximately 6000 MCTFR participants, with the eventual goal of obtaining blood or buccal samples on all children and parents.

Recent Findings

Our work supports the existence of a latent externalizing trait characterized by disinhibitory psychopathology, undersocialized behaviors, and personality characteristics indicative of low constraint (e.g., impulsivity, risk taking, and failure to adhere to generally accepted societal norms). This spectrum of disorders, behaviors, and traits is hypothesized to reflect the presence of a genetically influenced CNS diathesis that can be tapped by measuring psychophysiological endophenotypes. The candidate endophenotype most strongly associated with this diathesis concerns the P300 amplitude reduction observed in the brain event-related potential when performing a task that requires recognition of infrequently presented (so-called ‘oddball’) stimuli.

Behavioral Disinhibition in Late Adolescence and Early Adulthood

Our research indicates that this latent externalizing factor is highly heritable (Krueger et al., 2002), transmitted from parent to child (Hicks et al., 2004), and accounts for the covariance among childhood disruptive disorders, antisocial personality disorder (ASPD), and SUDs. Biometric models developed with our 17-year-old twins indicate that conduct disorder, antisocial personality disorder, adolescent/adult antisocial behavior (AAB; a syndrome characterized by the presence of ASPD antisocial behaviors with onset after age 15), nicotine dependence, alcohol use disorders, illicit drug use disorders, and the personality trait constraint all load strongly on this latent factor (Burcusa et al., 2003; Hicks et al., 2004; Krueger et al., 2002; McGuire et al., 2006). In the parents of MTFS twins, who are over the age of maximal risk for the development of externalizing psychopathology, direct comparisons of categorical and dimensional models of the latent externalizing liability demonstrated that the liability is continuous and graded, as opposed to delineating discrete categories of psychopathology in nature (Krueger et al., 2005). The amplitude of the P300 brain event-related potential, itself under strong genetic influence (Yoon et al., 2006), also loads on the latent externalizing trait (Patrick et al., 2006), an association that reflects shared genetic influence (Hicks et al., in press).

We have also learned that externalizing attributes present at age 17 predict the subsequent development of new nicotine, drug and alcohol problems by age 20, including alcohol use disorders (Malone et al., 2004), heavy drinking (King et al., 2005), AAB (Malone et al., 2004; Marmorstein & Iacono, 2005), low constraint (Elkins et al., 2006; King et al., 2005), and reduced amplitude of the P300 brain response (Carlson et al., 2002, 2004; Hicks et al., in press). In addition, Yoon et al. (2006) have shown that reduced P300 amplitude is broadly associated with adolescent misuse of cigarettes, alcohol, cannabis, and other drugs. Our work with the older twins thus indicates that these disorders, traits, and the P300 endophenotype share a strong, common genetic etiology and it is this general vulnerability that is inherited. These findings offer insights into the manifestations of behavioral disinhibition at age 17, a key period marking the end of adolescence and beginning of adulthood.

Behavioral Disinhibition from Preadolescence to Midadolescence

In preadolescence, childhood externalizing disorders appear to have some of the same correlates observed in the older cohort. Childhood disruptive disorders at age 11 predicted problematic substance-use behavior at age 14 (King et al., 2004). Likewise, teacher-rated oppositional-impulsivity, hyperactivity-impulsivity, and inattentiveness predicted drinking onset by age 14 (McGuire et al., 2001). Externalizing behavior evident by age 14 predicts later SUD development. McGuire and Iacono (2005) obtained this finding using retrospectively reported indices of early deviancy (defined as tobacco, alcohol or drug use, sexual intercourse, or police contact prior to age 13) from the 17-year-old twin cohort. Each deviancy indicator was associated with SUD development (and AAB). Moreover, the number of indicators present increased risk, such that 80% or more of males and 60% or more of females with at least four of these behaviors prior to age 15 developed a SUD by age 20. These indices of early deviancy all loaded strongly on the age-20 latent externalizing factor and were associated with reduced P300 amplitude (Iacono et al., 2003; Iacono & McGuie, 2006), providing strong support for the existence of a general mechanism that links adolescent problem behavior to adult externalizing.

Using mother’s ratings of her offspring’s personality at age 11, we found that compared to controls, conduct disorder and ADHD children’s scores on constraint were lowered by .5 to 1.5 standard deviations (Cukrowicz et al., 2006). We also found that paternal alcoholism and a quantitative index of problem drinking (maximum number of father-consumed drinks in 24 hours, net the effect of paternal alcohol-use disorders) were associated with elevated odds of childhood disruptive disorders in offspring at age 11 and substance misuse in offspring at age 14 (Malone et al., 2002). Parental AAB is similarly associated with childhood disruptive disorders at age 11 (as well as SUDs at age 17), with significant effects evident for each parent net the effect of the other parent’s diagnosis (Herndon & Iacono, 2005). Making use of the
longitudinal data from the age 11 cohort, Walden et al. (in press) found that both maternal and paternal SUDs were associated with accelerated substance involvement from age 11 to 17, especially in boys. Thus, the personality and familial transmission findings for childhood externalizing characteristics in early to midadolescence parallel those observed at age 17.

However, the etiologic underpinnings of childhood externalizing appear to differ, with shared environment more important to the interrelatedness of age-11 disorders. In a recent prospective study, Burt et al. (2006) found the heritability of conduct disorder to be strongest in girls with average timing of menarche and substantially weaker in those with an earlier or later onset. Shared environmental influences displayed the opposite pattern, highlighting a basic conceptualization of gene–environment interplay: the effect of the ‘average, expectable’ environment (Scarr & McCartney, 1983). Genetic influences are thought to be most strongly expressed under normal to optimal environmental conditions. More extreme or unfavorable conditions may act as ‘environmental main effects,’ such that differences in the trait are a function of differences in environmental circumstances, rather than differences in genetic make-up.

We have also found that the covariance among conduct disorder, oppositional defiant disorder, and ADHD was due to common environments (Burt et al., 2001), with a third of the covariation among these disruptive disorders accounted for by parent–child conflict acting via both genetic and environmental paths, suggesting a gene–environment correlation. In addition, Burt et al. (2001) found a reciprocal relationship such that both disruptive disorders and conflict at age 11 independently predicted each other at age 14. Furthermore, in an extension of this work, the association between psychopathology at age 11 and conflict at age 14 was mediated primarily by genetic mechanisms, while the association between conflict at age 11 and externalizing at age 14 was largely environmentally mediated (Burt et al., 2005). These results suggest a downward cycle of childhood externalizing exacerbation (see Patterson et al., 1998), and offer confirmation of an environmentally mediated effect of parenting on child behavior.

Other aspects of environmental risk are also likely to be important. Walden et al. (2004) examined parent and peer influences on age-14 use of tobacco, alcohol, and illicit drugs, using multiple independent informants to assess each variable. A poor relationship between the child and parents, and negative peer influences were associated with outcome. The covariation among parent-child relationship problems, peer deviance, and number of substances used was due largely to shared environmental influences, with peer deviance alone accounting for almost all of the shared environmental covariation with substance use. In Legrand et al. (1999), we found that 11-year-olds with low levels of environmental risk at study intake (e.g., strong attachment to church and school, good peer affiliations) were buffered against the initiation of substance use by age 14 despite having parents with a history of SUDs.

**Externalizing and Psychopathy**

One element associated with externalizing that receives scant attention in community samples is psychopathy. Our work has shown that measures of psychopathy can be derived from an omnibus personality questionnaire (Benning, Patrick, Blonigen, et al., 2005; Blonigen et al., 2006) and that those with psychopathy-related traits show psychophysiological response patterns like incarcerated felons identified as psychopaths (Benning, Patrick, & Iacono, 2005). Two heritable facets of psychopathy are evident: fearless dominance, which is associated with reduced genetic risk for internalizing disorders, and impulsive antisociality, which is associated with increased genetic risk for externalizing psychopathology (Blonigen et al., 2005).

**Behavioral Disinhibition Summary**

To summarize, these MTFS findings support a spectrum of co-occurring disinhibitory disorders, traits, and behaviors. When present at age 11, they increase the risk of substance misuse by age 14 and eventually are associated with adult SUDs and other forms of disinhibitory psychopathology. The co-occurrence of externalizing disorders in childhood and late adolescence appears to reflect different processes, with shared environmental factors important early and genetic factors important in late adolescence. Understood more fully, these causal differences may have prevention implications. Not everyone at high environmental (or genetic) risk at age 11 will ultimately develop SUDs. Investigating the progression of gene–environment interplay through adolescence and understanding how this relates to substance initiation, misuse, and abuse has obvious importance.

**Future Directions**

In the coming years, we plan to take advantage of MCTFR longitudinal data to explore how gene–environment interplay influences adjustment and the development of psychopathology through adolescence and into young adulthood. As DNA is available on most participants, we expect to continue preliminary candidate gene studies already under way. Our assessment protocol covers negative emotionality, including associated personality traits, major depression, and anxiety disorders. Although our work has begun to explore the relationship between the development of SUDs, negative emotion (Elkins et al., 2006, 2004), and internalizing psychopathology (Burcusa et al., 2003; Herndon & Iacono, 2005; King et al., 2004; Marmorstein & Iacono, 2003, 2004; Marmorstein et al., 2004; McGue & Iacono, 2005), we hope to expand our efforts in this important domain.
Most of our work with putative endophenotypes has dealt with P300 brain event-related potentials. We are expanding this work to explore how change in P300 amplitude with age may confer information about a developmentally sensitive endophenotype indexing genetic risk for disinhibitory psychopathology (Carlson et al., 2006). In addition, we are determining the dynamic EEG processes underlying P300 brain responses for their potential as endophenotypes (Bernat et al., in press). We are also developing autonomic indices of sensitivity to environmental stress that are likely to be under partial genetic control (Iacono et al., 2000; Taylor, 2004; Taylor et al., 1999).

Collaborative Opportunities

We have in place a set of guidelines and a formal review mechanism to facilitate collaboration with investigators at other universities. These guidelines call for the submission of a brief (2-page) proposal outlining the nature of the collaboration, contributions of the collaborators, hypotheses, research plan, and resources necessary to accomplish proposal aims. The MTFS is a member of the National Institute on Drug Abuse Genetics Consortium, and is contributing DNA and clinical data to the Consortium data base. We have made collaborative arrangements with investigators at a dozen different universities, and welcome inquiries from potential collaborators. We especially encourage collaborations with investigators who have skills and interests that complement ours, such as those with expertise in molecular genetics, brain imaging, or interests in pertinent topics that are not central to our major aims. Potential collaborations with investigators using similar measures who are interested in pooling resources to examine or replicate candidate gene effects are especially encouraged.

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References


