The Michigan State University Twin Registry (MSUTR): Genetic, Environmental and Neurobiological Influences on Behavior Across Development

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The primary aim of the Michigan State University Twin Registry (MSUTR) is to examine developmental differences in genetic, environmental, and neurobiological influences on internalizing and externalizing symptoms, with disordered eating and antisocial behavior representing particular areas of interest. Twin participants span several developmental stages (i.e., childhood, adolescence, and young adulthood). Assessments include comprehensive, multiinformant measures of psychiatric and behavioral phenotypes, buccal swab and salivary DNA samples, assays of adolescent and adult steroid hormone levels (e.g., estradiol, progesterone, testosterone, cortisol), and videotaped parent–child interactions of child and adolescent twin families. To date, we have collected data on over 1000 twins, with additional data collections underway. This article provides an overview of the newly developed MSUTR and describes current and future research directions.

The Michigan State University Twin Registry (MSUTR) is a new twin registry that began in 2001 within the Department of Psychology at Michigan State University. The registry currently includes 1090 (545 pairs) same-sex and opposite-sex twins reared together spanning childhood through young adulthood. The overall focus of the MSUTR is on understanding developmental changes in genetic, environmental, and neurobiological influences on internalizing and externalizing disorders. The primary internalizing phenotype examined is disordered eating (i.e., anorexia nervosa, bulimia nervosa, and disordered eating symptoms), while the primary externalizing phenotype is antisocial behavior (i.e., aggression, rule-breaking behaviors, and conduct disorder symptoms). Nonetheless, the registry includes abundant data on other psychiatric disorders and symptoms (e.g., depression, anxiety, attention-deficit/hyperactivity disorder symptoms, oppositional defiant disorder, substance use) that are comorbid with these conditions and are broadly representative of the internalizing and externalizing spectrums.

Several features of the MSUTR distinguish it from other twin registries. First, the registry takes a lifespan perspective by assessing twins during childhood, adolescence, and adulthood. This lifespan perspective ensures that genetic, environmental, and biological risk factors specific to particular developmental periods are identified and examined for their relevance for disordered eating and antisocial behavior.

Second, there is a focus on understanding mechanisms of etiologic effects. While standard twin biometric model-fitting analyses are used to examine relative contributions of genetic and environmental factors, these analyses are extended by the direct assessment of candidate genes, measured environmental factors (e.g., parent–child interactions), and biological risk factors (e.g., steroid hormone concentrations). These extended assessments allow for the examination of Gene × Environment interactions as well as the mediation of genetic effects by neurobiological factors. In the selection of these risk factors, particular attention was paid to developmental features of the disorders to allow for the identification of developmentally specific etiologies. For example, our adolescent twin studies include assessments of gonadal hormones that are known to become activated during puberty.

Third, the MSUTR has a particular focus on sex differences in psychopathology and the information that sex differences can convey about developmental changes and the genetic and neurobiological substrates of behavior. Eating disorders and antisocial behavior show opposite patterns of sex differences (i.e., eating disorders are more common in females while antisocial behavior is more common in males)

Received 18 July, 2006; accepted 3 August, 2006.

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and are thus ideal candidates for examining sex differences in etiological factors. We have intentionally assessed a range of phenotypic (e.g., personality characteristics; neuropsychological functioning) and biological (e.g., gonadal and stress hormone concentrations; ovarian hormone receptor genes) factors that are linked to sex differences in behavior.

Finally, whenever possible, the MSUTR has included multimethod assessments of phenotypes and environmental risk factors. Multiple informants (i.e., mother, twin, and/or teacher reports) are used in studies of child and adolescent twins, and co-twin reports are used in personality assessments of adult twins. Observational as well as survey methods comprise assessments of family environment variables, including assessments of parent–child interactions and family relationships. Our multimethod approach allows us to develop more rigorous phenotype definitions, examine informant effects on heritability estimates (Burt et al., 2005), and obtain a more fine-tuned understanding of environmental risk and its contribution to disordered eating and antisocial behavior.

In summary, the MSUTR is a new registry that seeks to use developmental features of psychopathology to understand the genetic, environmental, and neurobiological risk factors for internalizing and externalizing disorders across the lifespan. In the present paper, we describe this registry in greater depth including its recruitment methods, study assessments, and individual research projects.

Recruitment Methods

The MSUTR began as a university-based twin registry that assessed undergraduate men and women. Twins were initially recruited through flyers, paid advertisements, twin listservs, and recruitment mailings conducted by university registrar offices. Registrar employees identified student twin pairs through computer matches of last names, birth dates, ethnicities, citizenship, and counties of residence. Identified twin pairs were then sent recruitment packets from the registrars' offices that included descriptions of the studies and self-addressed, stamped postcards for the twins to indicate their interest in study participation. The postcards requested contact information from interested twins, as the registrars would not release this information to MSUTR researchers. Twins and their contact information therefore remained anonymous to MSUTR project staff until the twins indicated an interest in study participation.

Four recruitment mailings spaced approximately 1 to 2 months apart were sent. Response rates (i.e., 68%) were similar to those of other twin registries. Using a combination of advertisements and recruitment mailings, 294 same-sex female, 164 same-sex male, and 80 opposite-sex twins were recruited and assessed from 2001 to 2004.

By the start of 2004, the Michigan Department of Community Health (MDCH) had granted approval for the MSUTR to begin recruiting twins through birth records. The MDCH identifies twin pairs residing in lower Michigan who meet the study age criteria (see criteria below) and whose addresses or parents' addresses (for twins who are minors) can be located using drivers license information obtained from the state of Michigan. As birth records are confidential in Michigan, recruitment packets are mailed directly from the MDCH to eligible twin pairs. Twins indicating interest in participation via pre-stamped postcards or e-mails/calls to the MSUTR project office are then contacted by study staff to determine study eligibility and to schedule their assessments.

Two to four recruitment mailings are used for each study to ensure optimal twin participation. Overall, response rates (45%–52%) across studies are on par with those of other twin registries that use similar types of anonymous recruitment mailings. As of summer 2006, 246 child twins, 236 adolescent twins, and 64 adult twins had been recruited and assessed using these recruitment methods. Additional recruitment mailings for studies are ongoing.

Study Assessments

Table 1 presents a summary of the assessments that comprise each of the individual MSUTR projects. These projects include studies conducted with children (e.g., The Twin Study of Behavioral and Emotional Development in Children; Principal Investigator: SAB), adolescents, (i.e., The Adolescent Twin Study of Behavioral Adjustment and Development; Principal Investigator: KLK) and adults (i.e., The Adult Twin Study of Behavioral Adjustment and Development; Principal Investigator: KLK). Given the relatively low base rates of internalizing and externalizing symptoms and the correspondingly large sample sizes needed for twin biometric modeling, there is an emphasis on continuous data. There is also an emphasis on the use of developmentally appropriate measures for each twin population. This is particularly important for the MSUTR given its focus on examining developmental differences in etiologic factors. Finally, every effort is made to ensure that MSUTR projects use the same or similar measures of core phenotypes (i.e., disordered eating and antisocial behavior). This maximizes data collection efforts and allows for comparisons of etiologic effects across datasets and developmental periods.

Measures for eating disorders and related phenotypes

The primary measures used to assess disordered eating are the Minnesota Eating Disorder Survey (MEBS; von Ranson et al., 2005) and the Eating Disorders Examination Questionnaire (EDEQ; Fairburn & Beglin, 1994). Both measures assess a range of eating pathology (i.e., overall levels of disordered eating, weight preoccupation, body dissatisfaction, binge eating, the use of compensatory behaviors, dietary restraint) that have been shown to be risk factors for eating disorders (Jacobi et al., 2004). The MEBS and

https://doi.org/10.1375/twin.9.6.971 Published online by Cambridge University Press

Table 1

Summary of Existing MSUTR Project Assessments

	Informant reports				Assessment type		
MSUTR project	Twin	Mother	Teacher	Co-twin	Questionnaire	Interview/ tasks with twin	Observer ratings
Twin study of behavioral and emotional development in children (TBED-C)							
Zygosity determination		x			x		
Antisocial behavior	x	x	x		x	x	x
Disordered eating	x				x		
Other internalizing/externalizing symptoms	x	x	x		x	x	x
Parent–child relationship	x	x			x		x
Body mass index						x	
Maternal personality and psychopathology		x			x		
Child empathy	x	x			x		
Academic/verbal abilities			x			x	
Social-information processing						x	
Parent's marital relationship	x	x			x		
Peer deviance	x	x	x		x		
Twin DNA[1]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Adolescent twin study of behavioral adjustment and development:							
Zygosity determination	x			x		x	
Disordered eating	x				x		
Antisocial behavior	x	x			x		
Other internalizing/externalizing symptoms	x	x			x		
Temperament	x	x			x		
Finger-length ratios	x						
Body mass index and percent body fat					x		
Maternal personality, psychopathology, finger-length ratios, body mass index, and percent body fat		x			x	x	
Parent–adolescent relationship	x	x			x		
Separation/individuation difficulties	x	x			x		
Twin steroid hormones[2]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Adult twin study of behavioral adjustment and development:							
Zygosity determination	x				x		x
Disordered eating	x				x		
Antisocial behavior	x				x		
Other internalizing/externalizing symptoms	x				x		
Personality characteristics	x			x	x		
Finger-length ratios						x	
Body mass index						x	
Family history of psychopathology	x				x		
Nonshared environmental factors	x				x		
Attachment security	x				x		
DNA[1]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Twin steroid hormones[2,3]	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Note: [1] Twin DNA was collected using buccal swabs or saliva collection procedures.

[2] Steroid hormones for each twin were assayed from salivary, finger prick blood spot, and/or serum samples.

[3] Steroid hormones were collected for a subsample of female participants only.

https://doi.org/10.1375/twin.9.6.971 Published online by Cambridge University Press

EDEQ both show excellent psychometric properties (Fairburn & Beglin, 1994; von Ranson et al., 2005) and have been used in previous twin studies of eating pathology (Klump et al., 2000, 2003). The MEBS is particularly well-suited for the MSUTR, as it was developed for use in children as young as age 9.

Measures for antisocial behavior and related phenotypes

The primary measures used to assess antisocial behavior include the Child Behavior Checklist (CBCL) and Teacher Report Form (TRF; Achenbach & Rescorla, 2001), which show excellent psychometric properties and are the most frequently used measures of youth behavioral problems. However, because youth are motivated to conceal antisocial activities from parents and teachers, the incorporation of youth reports is also a critical component of any antisocial behavior assessment (Burt et al., 2005). In adolescents, we use the Youth Self-Report (YSR; Achenbach & Rescorla, 2001), while in children, we administer the Structured Clinical Interview for Children and Adolescents (SCICA; McConaughy & Achenbach, 2001) to each twin. Stories with ambiguous aggressive content (Hughes et al., 2004) are also read to each child twin and then coded for social information processing patterns (e.g., hostile attribution biases) important to aggression.

Zygosity determination

Zygosity is established using physical similarity questionnaires that show accuracies of 95% or better (see Lykken et al., 1990; Peeters et al., 1998). For several projects, the twin and/or mother complete the questionnaire in addition to a research assistant who independently evaluates the twins on physical similarity indices. Zygosities are then compared between the participant and research assistant reports and discrepancies are resolved through review of questionnaire data and twin photographs (when available) by one of the MSUTR principal investigators (KLK or SAB) or by DNA markers. On average, the physical similarity questionnaires used by the MSUTR have accuracy rates of 95% or better.

MSUTR Projects

Childhood

Investigations of risk factors for psychopathology must necessarily include an examination of childhood where internalizing and externalizing disorders are believed to have their earliest origins. In particular, childhood-onset antisocial behavior (found in roughly 5%–10% of children, primarily males) represents a relatively severe condition that is likely to culminate in negative adult outcomes (i.e., substance dependence, incarceration; Moffitt, 2003). In contrast, eating disorders are relatively rare in childhood. The primary focus of the MSUTR Twin Study of Emotional and Behavioral Development in Children (TBED-C) is thus on understanding the etiology of childhood-onset antisocial behavior and related phenotypes. Nonetheless, we include twin reports of disordered eating and assess internalizing symptoms, externalizing behaviors, and environmental risk factors that may represent precursors to antisocial and disordered eating symptoms.

The MSUTR TBED-C examines twins between the ages of 6 and 10, and to date, has assessed a total of 252 same-sex twins (124 female and 128 male). Our particular aims are to (1) examine genetic and environmental contributions to antisocial behavior and disordered eating, (2) perform genetic association studies, and (3) examine gene–environment interplay, using both biometric models (Purcell, 2002) and measured-gene × measured-environment analyses (Moffitt et al., 2005). As our final aim is to better understand how the environment may activate or suppress genetic predispositions, we measure multiple aspects of the twins' 'environment', including parent–child relationships, peer deviance, maternal personality and psychopathology, and the parents' marital relationship. Initial data collection for this project is nearing completion. Manuscripts will be forthcoming.

Adolescence

Adolescence is a critical time for the emergence of disordered eating and antisocial behavior. Eating disorders rarely occur in prepubertal individuals (Bulik, 2002) and demonstrate a sharp rise in incidence during adolescence (e.g., Killen et al., 1992). Importantly, data from the Minnesota Twin Family Study show that the heritability of disordered eating increases dramatically over the adolescent period (Klump et al., 2000, 2003). Puberty appears to be a particularly important developmental stage, as eating disorder symptoms show minimal heritability before puberty but significant genetic effects (i.e., greater than 50%) during and after puberty (Klump et al., 2003; Klump, Perkins, et al., 2006).

Adolescence is also a period of critical growth in antisocial behavior (Burt et al., 2007). The prevalence of nonaggressive delinquency is higher in adolescence (e.g., 20%–25%) than at any other point in the lifespan (Stanger et al., 1997). This surge in antisocial behavior belies its severity, however, as most antisocial adolescents ultimately transition into normative adult roles. This stands in marked contrast to childhood-onset antisocial behaviors (see above), which are infrequent but notably persistent (Moffitt, 2003). Understanding the etiological forces involved in the development of antisocial behavior during adolescence, and how they may differ from those in childhood, is thus a fundamental part of understanding the development of antisocial behavior.

The MSUTR Adolescent Twin Study of Behavioral Adjustment and Development examines genetic, environmental, and neurobiological risk factors for disordered eating, antisocial behavior, and related phenotypes during early adolescence. This study is ongoing, but has already assessed 236 twins (196 female and 40 male) between the ages of 10 and 14. Importantly, this study includes assessments of pubertal development, steroid hormone concentrations (i.e.,

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estrogen, progesterone, testosterone, follicular stimulating hormone, luteinizing hormone, and cortisol), and prenatal hormone exposure (assessed via finger-length ratios; see Manning, 2002). We hope to (1) determine whether the activation of gonadal hormones accounts for the dramatic increase in incidence and heritability of disordered eating during puberty, and (2) examine the extent to which gonadal hormones and Gene × Environment interactions account for sex differences in eating pathology and antisocial behavior. Data collection for this project is ongoing and thus, analyses and manuscripts will be forthcoming. Nonetheless, initial results in the female adolescent twins suggest that both disordered eating and antisocial behavior are related to levels of ovarian hormones during puberty.

Adulthood

Although disordered eating increases in incidence from childhood to adolescence, it is most prevalent in adulthood. Antisocial behavior, in contrast, is far less common in adulthood than in adolescence. Given these developmental shifts, the MSUTR includes assessments of young adults in order to capitalize on increased numbers of individuals with disordered eating and to compare etiologic effects across developmental periods.

The MSUTR Adult Twin Study of Behavioral Adjustment and Development has complete data on 602 twins (320 same-sex females, 168 same-sex males, and 114 opposite sex) between the ages of 18 and 30 years. The project has two primary aims. The first is to examine predictors of eating pathology and antisocial behavior and sex differences in etiologic influences on these and related phenotypes. Papers addressing this aim have been published (Munn & Klump, 2003) or are submitted for publication (Solomon et al., in press). One molecular genetic paper also has been presented at an international conference (Gobrogge et al., 2004). Importantly, biometric twin analyses have only recently begun, as data on adequate numbers of twins were not available until the end of 2005. Initial data are promising with regard to establishing genetic influences on prenatal androgen exposure (Gobrogge et al., 2006) and genetic associations between personality characteristics and attachment styles (Donnellan et al., 2006). Nevertheless, we anticipate several new analyses in the coming year that will investigate sex differences in genetic and environmental influences on disordered eating and antisocial behavior.

The second primary aim is to examine the role of gonadal hormones in the etiology and genetic diathesis of disordered eating. Two separate studies have examined this issue. In the first, a subsample of 25 same-sex female twins from the MSUTR who met strict inclusion/exclusion criteria (e.g., regular menstrual cycles, no oral contraceptive use) was used to examine whether gonadal hormones exhibit organizational and activational associations with disordered eating symptoms (Klump, Gobrogge, et al., 2006). Findings confirmed hypotheses and showed that higher levels of eating pathology were associated with lower levels of prenatal androgen exposure and higher circulating levels of estradiol. Taken together, results tentatively suggested that gonadal hormones may (1) organize sex differences in disordered eating via prenatal androgens, and (2) activate disordered eating postnatally.

In the second project, a sample of 12 female twins from the MSUTR collected *daily* behavioral and salivary ovarian hormone data for 94 days. The primary purpose of this study was to extend previous analyses by using a longitudinal design to examine whether natural changes in ovarian hormones across the menstrual cycle predict changes in disordered eating.

Findings showed that changes in estrogen and progesterone did significantly predict changes in disordered eating (Klump, Culbert, et al., 2006). Importantly, phenotypic associations appeared to be mediated by genetic factors, as monozygotic (MZ) cross-twin cross-trait correlations for ovarian hormones and disordered eating approached the within-person associations for these phenotypes.

Summary and Future Directions

In summary, the MSUTR projects are designed to augment our understanding of developmental influences on internalizing and externalizing disorders. Each study has a particular focus on disordered eating and antisocial behavior, with the relative emphasis depending upon the developmental stage investigated. As the MSUTR is a new registry, data collections are underway and/or recently completed. Nonetheless, initial findings are promising, particularly with regard to phenotypic and genetic associations with gonadal hormones. We are hopeful that the developmentally informed approach of the MSUTR will continue to yield data that clarifies the role of genetic, environmental, and neurobiological factors in the development of psychopathology across the lifespan.

New analyses and additional data collections are planned to help us achieve this goal. First, we plan to examine differences in genetic and environmental influences on disordered eating and antisocial behavior across childhood, adolescence, and adulthood. Our inclusion of the same (or parallel) measures across studies will allow us to examine developmental differences and identify key risk factors within each stage of development.

Second, we plan to conduct new data collections to enhance and expand the MSUTR. As initial findings in the adolescent twins are so promising (see above), we are currently collecting additional data on 360 adolescent same-sex twins (180 male, 180 female) between the ages of 10 and 15 years (co-investigators: SAB and KLK). These new twin pairs will allow for more powerful tests of genetic factors, neurobiological factors, Gene × Environment interactions, and Gene × Hormone interactions in the development of disordered

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eating and antisocial behavior during adolescence. In addition, grant applications to increase the number of participants in the TBED-C are currently in preparation.

We also plan to extend the MSUTR by including longitudinal data collections. Funding for a large MZ twin study of associations between ovarian hormones and disordered eating across the menstrual cycle is under review. Follow-up assessments of existing MSUTR samples (particularly those in childhood and adolescence) are planned with the intent of conducting cross-sequential analyses. Finally, we hope to secure funding for new longitudinal studies that include annual assessments of core phenotypes, DNA, and neurobiological risk factors across childhood and adolescence. We welcome collaborations with other twin researchers and registries on these new as well as existing MSUTR projects. Through such collaborations and prospective designs, we hope to further increase understanding of the etiology of disordered eating and antisocial behavior and their developmental trajectories.

Acknowledgments

This work was supported by grants from the National Institute on Mental Health (MH 63851, MH 70542) awarded to Dr Klump and by institutional grants from Michigan State University awarded to Drs Klump and Burt.

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