The study of twins and their families provides a highly useful tool for disentangling the genetic and environmental origins of traits. The Cardiff Study of All Wales and North West of England Twins (CaSTANET) has followed children and adolescents over time into early adulthood, assessing a wide range of aspects of behavior and psychopathology using self-, parent and teacher reports. Four main waves of data collection have taken place to date, which have provided a wealth of information on the contributions of genetic and environmental risk factors to the psychological health of young people. This article first describes the CaSTANET register and subsequently presents some of the findings that have emerged from this resource, with a focus on depression and anxiety, chronic fatigue, attention-deficit/hyperactivity disorder, conduct problems and prosocial behavior. We describe in somewhat more detail the 4th wave of data collection, which has recently been completed and has provided us with extensive information on substance use and problem use as well as associated risk factors in the twins and their families, including longitudinal data on conduct problems and the relations between family members. Because of the wealth of data already collected and the opportunity for genetically informative analyses over time, CaSTANET provides a valuable resource for understanding the complexities of the psychological development of young people.

The Cardiff Study of All Wales and North West of England Twins (CaSTANET) is a longitudinal study, following children and adolescents over time into adulthood. The population-based CaSTANET register was established in Cardiff in 1991 by Anita Thapar and Peter McGuffin, and included twins born between 1976 and 1991 in the greater Cardiff area of South Wales. It was subsequently expanded, with the help of Jane Scourfield and Neilson Martin, to include twins born between 1976 and 1991 in all of Wales and the north west of England (see Figure 1 for the location of these specific areas in the United Kingdom [UK]). Although the north west of England area looks relatively small on the map, it represents an urban, densely populated area. Wales, on the other hand, includes both cities and rural areas and is less densely populated. For example, the current population of Greater Manchester in the north west of England (2,482,328) is nearly equal to the entire population of Wales (2,903,085) and considerably larger than the current population of the capital of Wales, Cardiff (305,353; Office for National Statistics, 2006).

Following the first wave of data collection in 1991 to 1993, three subsequent waves took place in 1996 and 1997 (Wave II), 2000 (Wave III), and 2004 and 2005 (Wave IV). There are approximately 6000 twin families on the register, although not all of these have been invited to participate in studies as yet. Rather, different subsets of twins have been targeted for different studies depending on their age or area of residence. In subsets of families, in addition to self-report and parental report, information from teachers or neuropsychological data has been obtained. Both questionnaire-based and interview-based (face-to-face and telephone) assessments have taken place and information has been collected from parents as well as self-reports for twins aged 11 and older. Parental reports were usually provided by the mother, but in a small subset of families by the father or another main carer.

Addresses of the twin families were initially obtained through Birth Registers and the UK National Health Service (NHS). For each new wave of data collection, addresses were updated and families were invited to participate.

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Zygosity was assigned using a twin similarity questionnaire (see Table 2) completed by the parents and, in a subsample, validated by genotyping DNA markers (Payton et al., 2001). The sample is representative of the local populations in terms of ethnicity and socioeconomic status (Rice et al., 2002; Scourfield et al., 1997; Thapar & McGuffin, 1996a; Thapar & McGuffin, 1996c; Thapar et al., 2000).

In this article, we describe the CaStANET study and the four waves of data collection that have taken place to date and subsequently summarize some of the findings this resource has yielded. We acknowledge the wealth of findings that have emerged from other twin registers across the world, but for the purposes of this article, we are focusing on the history of CaStANET and the findings based on this sample.

Data Collection in CaStANET Sample

Table 1 provides information on sample sizes, response rates and the age range of the twins for the four waves of data collection. Some assessments have been completed at several waves of data collection, while new information has also been obtained at each occasion. Table 2 details information on which assessments were conducted at each of the waves.

During Wave I (1991–1993), which included twin families from South Wales, the focus was on the etiology of childhood psychopathology with an emphasis on depression (Thapar & McGuffin, 1994). During Wave II (1996–1997), the register was expanded to include twin families in the north west of England as well as a larger region of South Wales. The aim of this study was to examine the etiology of externalizing behavior (attention-deficit/hyperactivity disorder [ADHD] and antisocial behaviors). During Wave III, which took place in 2000, twin families where twins were aged between 8 and 17 years were contacted. Some of the twins who had participated in Waves I or II were out of the age range of this study (i.e., over the age of 17). The focus was on emotional problems (depression and fatigue).

The most recent wave of data collection, Wave IV, took place in 2004 and 2005. Twin families who had participated at Wave II and/or Wave III with twins aged between 12 and 20 years were contacted. Data collection focused on use and problem use of alcohol, cigarettes and illicit drugs by the twins and their family members as well as related risk factors. Risk factors we assessed included antisocial behavior, relations between family members, peer influences and peer substance use, school adjustment and personality. Choice of risk factors was informed by our epidemiological and developmental research and earlier twin studies (Harold & Conger, 1997; Harold et al., 1997; Miles et al., 2002; van den Bree, 2005; van den Bree & Pickworth, 2005; van den Bree, Svikis, et al., 1998; van den Bree, Whitmer, et al., 2004). Information was obtained from twins and their parents.

Longitudinal information was obtained at Wave IV on conduct problems using the Strengths and Difficulties Questionnaire (Goodman, 1997) and the Rutter A-Scale (Rutter et al., 1970) as well as on family risk and protective factors, using the Moos and Moos and McMasters devices (Moos & Moos,
Selected Findings From CaSTANET

Studies based on CaSTANET have focused on the following phenotypes: depression and anxiety, life events, chronic fatigue, ADHD, conduct problems, prosocial behavior and relations between family members. Main findings from these studies are summarized below. During the most recent, fourth, wave of data collection, we have focused on substance use and problem use and associated risk factors, including family relations and conduct problems. The measures and methods of analysis we have used are also described.

Depression and Anxiety

We have found that for depression symptom scores, assessed by maternal ratings of the Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988), common environmental influences play a greater role for children than adolescents, while depression scores for adolescents are significantly moreheritable than for children. We have found this across different waves of data collection (Rice et al., 2002; Scourfield et al., 2003; Thapar & McGuffin, 1994, 1996a, 1996c). This age-related finding has been shown in other samples, for example, among female twins (Silberg et al., 1999). Both parent and adolescent reports of depression and neurotic symptoms were found to be heritable (Rice et al., 2002; Thapar & McGuffin, 1994, 1996c). High self-ratings appeared to be more strongly influenced by shared environmental factors (Rice et al., 2002). It has been well-established that there is cross-generational transmission of depression, but it was not clear to what extent genes and environment contribute to the links between maternal and child depression. We found that both were important using an extended twin family design (Rice et al., 2005). Finally, by undertaking research diagnostic interviews with high scoring twins and a sample of those with scores within the normal range, we showed that the MFQ is a valid measure of depressive disorder in the general population (Thapar & McGuffin, 1998).

Results for anxiety were less clear-cut in that there were differences in etiology according to rater. Genetic factors contributed to parent ratings of anxiety whereas self-reports of anxiety were mainly influenced by shared environmental factors. Cross-sectional (Thapar & McGuffin, 1997) and subsequent longitudinal (Rice et
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Measures Collected on CASTANET Sample Over the Four Waves of Data Collection That Have Taken Place to Date

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Note:  
1 Investigators were Anita Thapar and Peter McGuffin and funding was supplied by the Medical Research Council.  
2 Investigators were Anita Thapar, Peter McGuffin, Richard Harrington, Jane Scourfield and Neilson Martin and funding was supplied by the Medical Research Council.  
3 Investigators were Frances Rice, Tom Fowler, Anita Thapar, Gordon Harold and Anne Farmer and funding was supplied by the PPP Foundation and Cardiff University.  
4 Investigators were Marianne Van de Bree, Anita Thapar, Michael Neale, Gordon Harold, Jane Scourfield, Kate Lifford, Katherine Shelton and Tom Fowler and funding was supplied by the Wellcome Trust, the European Advisory Board (ERAB) and Higher Education Funding Council for Wales (Biostatistics/Bioinformatics Unit).  
5 Self-report by twins was collected in those aged 11 and older. At Wave IV all twins were aged 11 and older and supplied self-report.  
6 Iowa Youth Family Project Scales (Mezey & Conger, 1999)  
7 Moos and Moos family scale (Moos & Moos, 1976)  
8 McMasters family assessment device (Epstein et al., 1983)  
9 Hospital Anxiety and Depression Scale (HADS; Bjelland et al., 2002)  
10 SCL-90 (Derogatis, Lipman, & Covi, 1973)  
11 Add Health questionnaire (Robins et al., 1997)  
12 Twin zygosity questionaire (Nichols & Bilbro, 1969)  
13 Twin zygosity questionaire (Cohen et al., 1975)  
14 A subsample of twins were also genotyped to confirm zygosity status  
15 Environmental sharing (Loehlin & Nichols, 1976)  
16 Twin pregnancy information (Lewis & Murray, 1987)  
17 DuPaul scale (DuPaul, 1991a)  
18 Conners scale (Conners, 1973)  
19 Strengths and Difficulties Questionnaire (Goodman, 1997)  
20 Oweus scale (Oweus, 1989)  
21 Rutter A-Scale (Rutter et al., 1970)  
22 Mood and Feelings Questionnaire (MFQ; Costa & Angold, 1988)  
23 Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds & Richmond, 1978)  
24 CAPA depression scale (Angold et al., 1998) was used. In addition, a phone interview was conducted to obtain information about the period(s) of fatigue (including the type and degree of impairment in functioning) and information to determine whether the young person had experienced a symptom profile, duration and impairment similar to the Centers for Disease Control operational criteria for chronic fatigue syndrome in adults (Fukuda et al., 1994).  
25 Social cognition scale (Skuse et al., 1997)  
26 Junior Trait and Character Inventory (J-TCI; Luby et al., 1999)  
27 Life events checklist (Johnson & McCutcheon, 1980)  
28 Twin Inventory of Relationships and Experiences (TIRE; Carbonneau et al., 2001)  
29 Social support scale (Kessler et al., 1993)  
30 Coping strategies scale (Jose, Caffasso, & D’Anna, 1994)  
31 Adolescent Substance Abuse Questionnaire (ASAQ; Sutherland & Willner, 1998)
analyses showed that anxiety and depression share a common genetic etiology.

Life Events
We examined life events in the twins because they represent an important risk factor for depression. First, we found that whereas dependent life events were heritable, independent life events were not (Thapar & McGuffin, 1996b). Subsequent bivariate genetic analysis showed evidence of gene–environment correlation for life events with depression (Thapar et al., 1998). Furthermore, dependent life events were found to occur more commonly among adolescents and there was evidence of stronger gene–environment correlation in adolescents than in children (Rice et al., 2003). These results suggested that our previous finding of increased heritability in adolescence may be partially explained by increased gene–environment correlation of negative life events with depression in adolescents (Rice et al., 2003).

Chronic Fatigue
We have also studied chronic fatigue in the CaSTANET sample. Nearly half of all long-term medical absence from school is due to unexplained fatigue (Dowsett & Colby, 1997), making this an important but understudied component of childhood/adolescent health. One of the first twin studies of fatigue in children was conducted in CaSTANET and showed that genetic influences contributed to episodes lasting at least a week as well as longer periods (Farmer et al., 1999). Further studies of the lifetime prevalence of fatigue in twins aged 8 to 17 were conducted, using parent questionnaire report as well as a detailed semistructured telephone interview with the parents (see Table 1). Our questionnaire measure of fatigue was validated against the interview information. Using the interview information, prevalence estimates were found to range from 2.3% for disabling fatigue lasting 3 months to 1.3% for a disorder resembling adult operationally defined chronic fatigue syndrome (Farmer et al., 2004). Using a broader definition of disabling fatigue in childhood based on parent questionnaire report, we found evidence that it is familial (Fowler et al., in press.). Although depression and fatigue tend to co-occur, we also found that the genetic and environmental etiology of disabling fatigue is mostly independent from that of depression (Fowler, Rice, et al., 2006).

ADHD
ADHD is a childhood-onset psychiatric condition characterized by developmentally inappropriate inattention, hyperactivity, and impulsiveness. Our twin studies have indicated that parent and teacher reports of ADHD symptom scores are highly heritable (Thapar et al., 2000; Thapar et al., 1995). Using the ADHD items on the Rutter A-Scale (Rutter, et al., 1970), we found evidence of sibling interaction/rater contrast effects (Thapar et al., 1995) and this finding has since been widely replicated (Thapar et al., 1999). However, other measures (DuPaul ADHD scale; DuPaul, 1981) did not yield the same finding (Thapar et al., 2000).

We also found that high ADHD symptom scores in the general population are associated with neurodevelopmental problems (Thapar et al., 2000) and that categorically defined ADHD is heritable. Finally, we found evidence that a categorically defined, broad measure of ADHD showed similar clinical and demographic correlates to that of clinical ADHD and was highly heritable (Thapar et al., 2000).

Associations between environmental risk factors and ADHD symptom scores have also been examined in the CaSTANET sample. We found a significant association between maternal smoking during pregnancy and offspring ADHD, taking into account birthweight, family conflict, family size, social class and conduct disorder symptom scores (Thapar et al., 2003). We also used structure equation modeling to test whether the association between maternal smoking in pregnancy with conduct problems is mediated through its relationship with ADHD and this was not found to be the case (Button, Thapar, et al., 2003).

Martin et al. (2002) have used multiple informant data to show that, whilst both parent- and teacher-rated data show a high degree of heritability for ADHD, the ratings reflected the effects of different genes. Self-report data from twins aged 11 to 16 years, however, showed no evidence of genetic effects.

Information on neuropsychological scales commonly used in studies of psychopathology was obtained in a subset of twins at wave II. The scales used included the Matching Familiar Figures Test (MFFT) and the Continuous Performance Task (CPT; Holmes et al., 2002). In this pilot study, we examined the heritability of these tests, with preliminary results suggesting a heritable component for the MFFT but not the CPT. These results were used to inform our molecular genetics research of ADHD (Langley et al., 2004).

Finally, we examined the association between a functional variant (VNTR) in the dopamine D4 receptor (DRD4) gene and the dopamine transporter gene (DAT) and ADHD in a subsample of twins (92 pairs; Payton et al., 2001). We found a trend towards an association between the DRD4 7 repeat allele and the DAT allele 10 (both of which have since been shown to be associated with clinical ADHD in pooled analyses; Faraone et al., 2005; Thapar et al., 2005).

ADHD and Conduct Problems
ADHD and conduct problems commonly co-occur and we have found that they share a common genetic etiology (Thapar et al., 2001). Conduct problems in ADHD are known to index greater clinical severity (Thapar et al., 2005) and familiality of ADHD (Faraone et al., 2000). We found in our twin sample that conduct problems in ADHD indexed higher genetic loading (Thapar et al., 2001) and this finding again has informed our molecular genetics research (e.g., Holmes et al., 2002; Thapar et al., 2005).
Conduct Problems, Antisocial and Prosocial Behavior

We have previously found that both antisocial and prosocial behavior in childhood is significantly heritable but that shared environmental influences may also play a role (McGuffin & Thapar, 1997; Scourfield, John et al., 2004; Thapar et al., 2001; Thapar & McGuffin, 1996c). Bivariate analysis of aggressive and nonaggressive antisocial behavior showed a partial genetic overlap between the two types of symptoms although there was a specific genetic effect contributing to the variance of aggressive antisocial behavior as well as a gender effect, with stronger genetic influences on aggression in females than males (Button et al., 2004). When we combined data on conduct problems experienced by the twins as obtained from parent, teacher and self-reports, we found that the common underlying phenotype of pervasive conduct problems rated by all three informants was entirely influenced by genetic factors (Scourfield, van den Bree, et al., 2004).

Another multivariate study focused on the link between conduct problems and social cognition (Scourfield, Martin, et al., 2004). Parent-reported accounts of their twins’ conduct problems and social cognition were found to be highly correlated and to share common genetic influences that accounted for about half the covariance in scores. Each phenotype was subject to its own environmental influences that were not shared.

Family Risk and Protective Factors

In our studies evaluating family-related risk factors, we have found evidence for the importance of social class (Thapar & McGuffin, 1996c) and family dysfunction on antisocial behavior (Button, Scourfield, et al., 2005). In the latter study, using a cross-sectional analysis, the genetic variance of antisocial behavior was found to differ according to the level of family dysfunction. In a longitudinal analysis of overt family conflict and depressive symptoms, we have found evidence of significant gene–environment interaction. Specifically, the influence of family conflict in predicting depressive symptoms was increased in individuals at genetic risk for depression and the genetic component of variance in depressive symptoms increased as levels of family conflict increased (Rice et al., 2006). These findings confirm earlier accounts of gene–environment interaction in depression (Caspi et al., 2003; Silberg et al., 2001).

Wave IV Data Analysis

CaStANET has provided the opportunity for the first UK-based twin study of substance use and problem use. Substance use by adolescents is a major cause for concern in the UK, with reported rates of alcohol use, drunkenness and illicit drug use being higher than in most European countries (Hibell et al., 2004). We found rates of substance use in the CaStANET sample to be broadly in line with previously reported prevalence rates in UK-based samples (Fowler et al., submitted).

Our analyses of the Wave IV substance use data have included new theoretical approaches, including the causal-common-contingent (CCC) model and multivariate extensions of it (Neale et al., 2006). The CCC model establishes the extent to which substance initiation and progression can be considered to be independent liabilities and estimates genetic and environmental influences separately on initiation versus progression. The model also corrects for age, by calculating age-dependent thresholds for each twin pair and using a computational procedure to account for individuals not yet having reached the threshold for progression because, due to their younger age, they have not yet initiated substance use. These features are of particular importance in adolescent samples. These types of analyses have been applied to data on alcohol, cigarette and marijuana use (Fowler et al., in press).

We have explored the relationships between these risk factors in studies of conduct problems, family-related risk factors and adolescent substance use (Shelton et al., 2006) as well as longitudinal analyses of conduct problems as rated by parents and teachers and the initiation and progression of marijuana use 8 years later (Shelton et al., in press).

Finally, we have conducted analyses to examine to what extent the strong correlations between alcohol use by adolescents and their best friends are explained by genetic and environmental influences (Fowler, Shelton, et al., in press).

Exploring the Impact of In Vitro Fertilization Treatment

Finally, we have examined the impact of in-vitro fertilization (IVF) treatment on twin study findings. Increasingly, twins are being born by means of IVF treatment and will be included in twin registers, but it is poorly understood whether these twins differ from those born by natural conception. Within the CaStANET sample, we therefore examined the two groups separately and found some differences in terms of pregnancy variables and social factors. There were also some differences in terms of twin correlations for psychopathology. We have highlighted the need to be aware of these differences (Goody et al., 2005).

Summary

There are a number of different, excellent twin registries across the world and findings from studies based on these samples have made important contributions to insight into the genetic and environmental influences on behavior and illness. The CaStANET sample has contributed particularly to understanding of psychological health in children and adolescents. Studies from our register have focused mainly on depression and anxiety, chronic fatigue, ADHD, conduct problems, substance use and problem use and related risk factors. With four main waves of
data now available, CaStANET provides a rich resource for the study of the contributions of genetic and environmental influences over time to the complex origins of the development of psychopathology. New studies will allow us to refine our twin and epidemiological analyses by the incorporation of measured genotypic data, thus enhancing the specificity and informativeness of the models. By extending data collection into adulthood, the links between childhood/adolescent risk factors and psychological and other problems later in life can be explored, using a genetically sensitive design.

Acknowledgments

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Finally, we are grateful for the contribution of Peter McGuffin in initially starting the register. We would also like to acknowledge the late Richard Harrington, Neilson Martin and Tanya Button who were subsequently involved in the expansion of CaStANET and in papers that have originated from it.

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Finally, we are grateful for the twins and their families.

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