The Australian Twin ADHD Project: Current Status and Future Directions

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This article describes the Australian Twin Attention-deficit/hyperactivity disorder (ADHD) Project (ATAP), the results of research conducted using this database and plans for future studies. Information has been actively collected from Australian families with twin children since 1991 for the ATAP database. The value of assessing siblings as well as twins is emphasized. Much work has gone into continuing the involvement of families in the study though this does become more difficult when twins reach maturity. The main focus of the project is ADHD in children and adolescents plus comorbid conditions including conduct disorder, oppositional defiant disorder, and generalized anxiety disorder. A major challenge has been how to retain continuity in the assessments, while at the same time covering changes in psychiatric classification, such as the move to Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association, 1994). Changes in the scale can affect the reports of twin similarity. Over the years, these twins have become part of other twin studies and future plans include linking different twin databases to investigate the relationships between childhood behavior and adult conditions. Recruitment, assessment and retention of twin families require a major commitment but create a significant resource for collaboration in areas outside the original aim.

Origins of the ATAP

The Australian Twin Attention-deficit/hyperactivity disorder (ADHD) Project (ATAP) was started in 1991 by David Hay and Florence Levy. The main aim of this database was to follow a group of twins and their siblings over a 10-year period to determine the developmental pattern of ADHD. The database was designed to have sufficient sample size for robust quantitative genetic analyses of the genetic and environmental contributions to ADHD. A secondary aim of the database was to examine related conditions such as conduct disorder (CD), oppositional defiant disorder (ODD), and generalized anxiety disorder (GAD). In 2004 a new cohort of families with twins was approached to participate in the study. These families were approached so that ADHD and comorbid conditions could be investigated in a new group of young twins and twins discordant for ADHD identified for a number of studies. The ATAP database serves as a resource for research performed at Curtin University of Technology and numerous collaborative projects with other universities and medical centres.

Participant Recruitment

There have been four phases of data collection over 15 years in (1) 1991, (2) 1994 to 1995, (3) 1999 to 2000, and (4) 2004 to 2005. In each of the data collection phases, parents completed a questionnaire about their twins and similar aged siblings, using the Twin and Sibling Questionnaire (Hay & Levy, 1994; Hay & Levy, 1999c; Levy & Hay, 1991). This questionnaire covers areas including development, behavior, and education. In the third phase of data collection (1999–2000) adolescent twins also completed a self-report questionnaire entitled Behaviour Questionnaire for Young People (Aged 12 Years and Older), (Hay & Levy, 1999a) and parents completed a self-report questionnaire entitled Parent Behaviour Questionnaire (Hay & Levy, 1999b).

Data Collection 1991

In the initial phase of the ATAP study 3215 families of eligible 4- to 12-year-old twin pairs were approached and 1938 parents participated through the completion of the Twin and Sibling Questionnaire (Levy & Hay, 1991). This number represents a response rate of 73.5% of all families initially contacted. Families were recruited through the Australian Twin Registry (ATR), a voluntary registry of Australian twins of all zygosity types and ages. Additional recruitment was conducted using a series of media campaigns, maternity services, and The Australian Multiple Birth Association. Families were extensively screened and children identified with a
significant disability were excluded from the study due to the evidence that a disability has a major impact on the development of both internalizing and externalizing behaviors in children (Cuskelly et al., 1998). The Dillman (1991) protocol utilizing reminder cards, resending questionnaires, and follow-up phone calls, was used to maximize participation by families. A detailed description of the recruitment process is provided in Hay et al. (2002).

Data Collection 1994–1995
In 1994–1995, when the twins were aged 8 to 16 years, parents were once again approached and asked to complete a modified version of the Twin and Sibling Questionnaire (Hay & Levy, 1994). The questionnaire was updated from an earlier version to reflect changes in ADHD diagnosis since the introduction of *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) and some of the field items which were considered for inclusion in DSM-IV were also included (Todd et al., 2004). A detailed description of the modification of this scale can be found in Levy et al. (1996). Families were again screened for eligibility and an additional 27 families were excluded, in some cases due to developmental disorders, which were undiagnosed at the time of the first data collection. A total of 1885 families were mailed the study questionnaire and 1550 families completed the questionnaire, reflecting an 82% response rate.

Data Collection 1999–2000
In 1999 and 2000, a third wave of data collection began with an approach to 1515 contactable families. Six hundred and fifty-nine families completed the questionnaires giving a response rate of 43%. A lower response rate was found during this phase of data collection despite following the Dillman (1991) protocol. This may be explained by the fact that many of the families had joined the ATR at the birth of their twins and had subsequently lost contact or interest, perhaps because in many cases the twins were now adults.

In this third phase of data collection parents were asked to complete the Twin and Sibling Questionnaire (Hay & Levy, 1999c). This questionnaire was modified from earlier versions to address some additional research questions and ensure that the questions remained age appropriate. This questionnaire also included a new measure of ADHD entitled The Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior (SWAN) Scale (Swanson et al., unpublished), which measured both the below average and the above average performance of children in the areas of attention and activity (Hay et al., in press). Additionally, twins over the age of 12 years were asked to complete a self-report questionnaire called Behaviour Questionnaire for Young People (Aged 12 Years and Older), (Hay & Levy, 1999a). This questionnaire covers a range of areas including ADHD symptomatology and was used to investigate differences in self versus parent report. To further investigate family issues that may influence ADHD, parents were asked to complete a questionnaire measuring their own behavior entitled the Parent Behaviour Questionnaire (Hay & Levy, 1999b). The large number of questions and questionnaires in this phase of data collection may have influenced participation rates. There was a markedly lower response from adolescents with only 535 completing the self-report questionnaire compared to 685 questionnaires completed by parents.

Data Collection 2004-2005
In order to continue to examine ADHD in children a new cohort of twins was recruited through the ATR in 2004 and 2005. A total of 2827 eligible families with twins born between 1989 and 1998 agreed to participate in the study, reflecting a 60% response rate. The response rate in this phase was lower than expected given previous data collections responses. One possible reason may be the large size of the questionnaire families were asked to complete. A similar low response rate was found in the third phase of data collection when a large questionnaire was administered. To ensure the samples would be comparable with previous phases of data collection, families were asked to complete the Twin and Sibling Questionnaire (Hay & Levy, 2004) and were followed up using the Dillman (1991) protocol. Additionally, families were screened and where children were identified with a significant disability, the whole family was excluded from the study.

Twins and Siblings
ATAP has always obtained data from singleton siblings as well as twins for four different but related reasons:

1. To identify twin-singleton differences (Levy et al., 1996) since siblings provide a group matched on so many family environmental variables;
2. Twins impose additional demands on the family and the possible effects of this on siblings need to be recognized (Hay et al., 1988);
3. Siblings add power to genetic analyses (Ehringer et al., 2006) and also provide an important means of checking genetic analyses based on twins alone where there may be biases that exaggerate or minimize differences within twin pairs (Levy & Hay, 2001);
4. With studies of twins discordant for ADHD, the use of siblings allows the differentiation of how much is due to simply being the sibling of an affected child (Cuskelly et al., 1998) and how much is related to being the twin of such a child and the additional pressures this may create (McDougall et al., 2006).

Measures
Parents in all four phases of data collection were asked to report on their children’s behavior using the Twin
The Twin and Sibling Questionnaire (Hay & Levy, 1994; Hay & Levy, 1999c; Levy & Hay, 1991). Table 1 outlines the areas that have been measured by ATAP during the data collection.

The Twin and Sibling Questionnaire covers a range of areas including:

- **Birth history.** Parents were asked to provide information about their children’s birthweight, the number of days each child spent in hospital after delivery, the type of delivery, and to list any complications associated with the birth of the twins. Apgar scores were also collected but in our experience parental reports are problematic.

- **Behavior.** The symptoms of ADHD, CD, ODD, depression, separation anxiety (SA), and GAD were measured using a 4-point scale. Each symptom was rated as occurring 1 (not at all), 2 (just a little/sometimes), 3 (pretty much/often), or 4 (very much/very often). Symptoms were based on the diagnostic criteria of DSM-IV and informants were asked to record a symptom only if it was noticeable for at least 6 months. As impairment criteria were not measured, and as data were collected using mailed questionnaires, the scales are used only as an approximation of DSM-IV diagnoses. From 1999 on ADHD was also assessed using the Swanson, Kotkin, Agler, Mylnn, and Pelham (SKAMP) Rating Scale of impairment and the SWAN Scale (Swanson et al., unpublished). While also based on the 18 ADHD items in the DSM-IV, these scales are designed to measure a wider range of population variation by extending the 4-point severity rating scale to 7 points, using

### Table 1

<table>
<thead>
<tr>
<th>Measures</th>
<th>Data Collected</th>
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<td>Birth history</td>
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<tr>
<td>Behavior</td>
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<tr>
<td>ADHD — 18-item DSM-IV based scale</td>
<td>X</td>
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<td>ADHD — SWAN and SKAMP scales</td>
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<td>CD — 15-item DSM-IV based scale</td>
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<td>ODD — 8-item DSM-IV based scale</td>
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<td>Depression — 4-item DSM-IV based scale</td>
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<td>SA — 8-item DSM-IV based scale</td>
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<td>GAD — 9-item DSM-IV based scale</td>
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<td>Remedial reading and speech</td>
<td>X</td>
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<td>ADHD medication</td>
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<td>Subtest use</td>
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<td>Behaviour Questionnaire for Young People (Aged 12 Years and Older) (1999)</td>
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<td>Behavior</td>
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<td>ADHD — 18-item DSM-IV based scale</td>
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<td>CD — 15-item DSM-IV based scale</td>
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<td>Depression — 4-item DSM-IV based scale</td>
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<td>Substance use</td>
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<td>Parent Behaviour Questionnaire (1999)</td>
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<td>Depression Anxiety Stress</td>
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<td>Personality</td>
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<td>Substance use</td>
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Note: ADHD: attention-deficit/hyperactivity disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th ed.); SWAN: Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior Scale; SKAMP: Swanson, Kotkin, Agler, Mylnn, and Pelham (SKAMP) rating scale; CD: conduct disorder; ODD: oppositional defiant disorder; SA: separation anxiety; GAD: generalized anxiety disorder.

¹ Scales used in 1991 were DSM-III-R based but have significant overlap with DSM-IV. The 1994–1995 study included the field items which were considered for inclusion in DSM-IV.
Zygosity. Zygosity was determined by discriminant function analysis, using a zygosity questionnaire based on an earlier version by Cohen et al. (1975). The questionnaire contained six questions on similarity and features and six on frequency of confusion by the mother, father, and other relatives. A more detailed description of this process of assessment of zygosity is described in Levy et al. (1997) and Hay et al. (2001). These families are increasingly part of other studies (e.g., National Institute of Mental Health funded study entitled The Molecular Genetics of Inattention in Australia) where DNA is obtained. Zygosity testing on these samples can be used to confirm the high validity of the zygosity questionnaire.

• **Movement ability.** A 17-item version of The Developmental Coordination Disorder Questionnaire (Wilson et al., 1998) was modified to fit the Australian sample. This scale was used to assess parents’ perceptions of their children’s motor ability.

• **Substance use.** Parents were asked to indicate whether they believed their children had used alcohol, tobacco, cannabis, or other hard drugs within the last 6 months using a yes/no response (Barton & Hay, in press). Information on the amount of alcohol and tobacco parents believed their children were using was also collected.

In the third phase of data collection (1999–2000), twins were asked to complete a self-report questionnaire entitled Behaviour Questionnaire for Young People (Aged 12 Years and Older; Hay & Levy, 1999a). This questionnaire covered a range of areas including:

• **Behavior.** Measures of ADHD, CD, and depression were collected. Adolescents were asked to rate their levels of symptoms on a 4-point scale ranging from 1 (not at all), 2 (just a little/sometimes), 3 (pretty much/often), and 4 (very much/very often). Adolescents were asked to record a symptom only if it was noticeable for at least 6 months.

• **Substance use.** Adolescents were asked to indicate whether they used alcohol, tobacco, cannabis, or other hard drugs within the last 6 months using a yes/no response. Additional information on the amount of alcohol and tobacco they were using was also collected.

Additionally, parents were asked to complete a self-report questionnaire entitled Parent Behaviour Questionnaire (Hay & Levy, 1999c). This questionnaire covered the following areas:

• **Behavior.** Two measures of parent ADHD behavior were collected. A 44-item version of the Wender Utah Rating Scale (Ward et al., 1993) was used to obtain parents’ descriptions of their own childhood behavior. This scale retrospectively assessed ADHD-relevant childhood behaviors and symptoms in adults. Parents were also asked to complete an 18-item measure of their own current level of ADHD symptomatology based on the diagnostic criteria in DSM-IV.

• **Depression, anxiety and stress.** The emotional state of parents was assessed using a short 21-item version of the Depression Anxiety Stress Scales (DASS-21). The DASS-21 consists of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress (Lovibond & Lovibond, 1995). It is widely used in Australia and available free of charge.

• **Family functioning.** The 12-item General Functioning subscale of the McMaster Family
Assessment Device (Miller et al., 1985) was used to examine family functioning. This self-report scale measures emotional relationships and functioning within the family on a 4-point scale.

- **Personality.** The Tridimensional Personality Questionnaire (Cloninger, 1987) was used to measure three major personality dimensions in parents: novelty seeking, harm avoidance, and reward dependence.

- **Substance use.** Parents were asked to describe their drinking behavior on a 10-item scale and asked to indicate if drinking had ever had a harmful effect on their life using a 4-item scale. Where relevant, the average daily tobacco use and age when smoking commenced was also measured.

**Other Areas**

As collaboration with other researchers has been encouraged during the ATAP study, data have also been collected in a diverse range of areas, some possibly related to ADHD such as motor and/or vocal tics, aggression (Dent et al., 2005) and smoking behavior during pregnancy. Other questions dealt with issues where ATAP was a convenient means of screening a large sample of twin families, such as handedness (Medland et al., 2003) and epilepsy (Berkowitz et al., 1998).

**Major Findings From the ATAP Database**

Data from the ATAP has been used in numerous research studies. For example it has been used to show that ADHD is inherited as a behavioral dimension rather than as a discrete disorder (Levy et al., 1997). In this paper the authors were the first to demonstrate the existence of ADHD as a continuum by using the DeFries and Fulker method to demonstrate that the heritability of ADHD defined as a continuum was not significantly different from that defined as a disorder. This suggested that ADHD was best measured as a continuum and that cut-off thresholds in the definition of ADHD were arbitrary. This remains one of the most widely cited papers from twin studies of ADHD. Additionally, the ATAP databases were actively used in the development of a textbook on the genetics of ADHD entitled Attention, Genes and ADHD (Levy & Hay, 2001). A review in the British Journal of Psychiatry (Chen, 2002) acknowledged this text as a comprehensive manual for child psychologists and psychiatrists, which outlines both the methodology and future direction of behavior genetics. Further information about research utilizing the ATAP database can be found at www.twinsandmultiples.org

**Uses for the ATAP Database**

As Table 1 depicts, many of the areas measured during the ATAP study have been replicated over the four phases of data collection. This replication allows comparisons to be made within the database to identify developmental changes in individuals. For example, a paper by Hay et al. (2004) examined the changes in ADHD symptomatology in the same children over several years to determine the genetic components of ADHD throughout childhood and into adolescence. Using the ATAP longitudinal data it was demonstrated that much of the consistency in behavior during childhood and early adolescence is due to genetic influences, but also that there were some genetic influences unique to specific ages.

The design of the ATAP database allows for comparisons to be made between different cohorts. For example, levels of parent-rated CD were collected from 8- to 16-year-old twins (mean = 11.16, SD = 2.29) born between 1979 and 1988 and again from 8- to 16-year-old twins (mean = 12.55, SD = 2.49) born between 1989 and 1999. The findings show that the levels of parent-rated CD did not change significantly between the phases of data collection. In contrast, rates of ADHD were different between the two samples with 393 out of 2235 children identified as having six or more ADHD symptoms in the early sample and only 204 out of 3380 children identified in the more recent sample (chi-square = 149.74, p ≤ .05). Although there may be many reasons for the difference in the number of ADHD symptoms in children, including changes in parent perception about ADHD over time, the design of the ATAP database and the repeated use of measures allow these issues to be examined. One thought had been that there may be more children with ADHD in the earlier group due to the improved ability to keep very preterm multiples alive, but there was no major difference between the two cohorts in gestational age and birthweight.

**Collaborative Work**

The ATAP data has provided opportunities to explore other topics related to ADHD and to foster collaboration with multiple international groups. Two doctorate theses from Emory University, Atlanta, have used the ATAP database to study gender differences in the determinants of ADHD (Rhee et al., 1999) and separation anxiety (Feigon et al., 2001). A postdoctoral fellowship to Washington University, Missouri, has resulted in increased collaboration on a latent class analysis (LCA) approach to ADHD (Rasmussen et al., 2002, 2004). LCA offers a uniquely powerful means of confirming the value of collaboration. The Missouri sample of twin families was identified via state records and interviewed about ADHD telephonically. That the same latent structure of ADHD and similar genetic determinants were identified in both samples is powerful justification for the ability to extrapolate results across both studies and countries.

Collaboration also exists with the Free University of Amsterdam where the ATAP database is being used to investigate the relationship between ADHD and developmental co-ordination disorder (DCD) through an Australian Research Council International Linkage
grant (Martin, Piek et al., 2006; Sergeant et al., 2006) with a particular focus on the neuropsychological assessment of monozygotic (MZ) twins discordant for ADHD and DCD.

**Data management**

Data collected in the various phases has been housed in separate databases at secure facilities at Curtin University of Technology and the sites of the collaborators. On ascertainment each family is made anonymous (names and addresses are not stored with the data) and given a unique ID with individual codes to identify each member (mother, father, twins and siblings). This ID can then be used to link data from all databases for each family. While this may appear straightforward, there are two problems, namely how to deal with families with two sets of twins and how to handle the increasingly complex blended families — her children, his children and their twins.

Due to the nature of the unique IDs, each database can be merged to provide a 'virtual' longitudinal study in which data taken on the same measures at different times can be merged into a single database for analysis. It can also be used to add data on particular measures from one study to data on other measures from another. This is a key feature of our data structure to facilitate ongoing and future collaborations. Recently it was employed to merge data held at Curtin on adult ADHD measures with data held on alcohol use and abuse, for the same families, held at Queensland Institute of Medical Research.

A merge of data for a virtual longitudinal study can be used to study the lifetime prevalence and etiology of symptoms recorded by the various measures. This can be used to observe patterns of phenotypic change from childhood into adulthood and elucidate the changes in the underlying causative genotypic expression. It can also be used to investigate the changing contribution of genetic and environmental factors and their interactions to the symptoms of interest.

The flexibility of the database structure means that in addition to single discrete studies, which can be treated as 'snapshots' at a particular time-point, we can also look at data spanning over 40 years of the individual's life. In addition, as there are 4642 families (12,537 individuals) we can select subsets (e.g., by age) for study and still obtain a sample large enough to maintain reasonable statistical power. This is due in part to the structure of the database and the unique characteristics of the population ascertained by ATAP.

To handle management of the data, only the data manager can access the full database. Specific subsets of the data are exported to smaller files for researchers, containing only the measures in which they are interested. This makes analysis more efficient and also keeps track of what data are in use. Generating the subfiles is handled in-house written custom scripts. An application has also been created in-house to handle the transfer of data between several data formats for different software packages. Files can be prepared for import into SAS (SAS Institute Inc., 2003), or SPSS (SPSS Inc., 2004) for the common statistical analyses. They can also be exported to Mx (Neale, 1997) for structural equation modeling or LCAP (Neuman et al., 1999) for latent class analyses. In addition, the results from LCAP can be converted to a format ready for SPSS or Microsoft Excel ready for visualization.

**Support for Families and Professionals**

Fundamental to recruiting families and keeping them engaged have been our resources targeted at families with twins in the age group most likely to be involved in ATAP. The booklet *Twins in School* based on our surveys of parents and teachers of twins (Gleeson et al., 1990) has been around for many years and was replaced in 2001 with our website (Hay & Preedy, 2002, 2006). This allows much easier access by families and agencies and enables us to update information and to include details of new research as they emerge. The website has been extensively publicized to schools, with articles in the professional journals which go to all primary (elementary) and secondary school principals in Australia and New Zealand. As National Patron of the parents’ organization, the Australian Multiple Birth Association, David Hay provides a regular feature for their quarterly journal and there is a system in place for providing information and referral of multiple birth families with particular needs. Organizations that fund our research do not see this as a cost they should bear, but it is fundamental to ensuring the continued participation of families.

**Future Work**

The Australian twin research scene is unusual in that multiple overlapping registers have been created over more than 30 years. Thus many child twins in the LaTrobe Twin Study of the 1970s (Hay & O’Brien, 1983) are now part of the ATR and as adults may have taken part in our other studies, such as that of psychosis-proneness (Hay et al., 2001). Western Australia has a unique population-based twin registry, the Western Australian Twin Child Health (WATCH) database (Croft et al., 2002), that to an extent overlaps with the ATR. There are at least 10 twin studies undertaken by different research groups covering this period and a current initiative is to link these, creating a unique longitudinal twin database.

**Discussion**

By definition, longitudinal studies of behavioral problems are beset with multiple challenges including:

2. There are new questions that were not considered when the study began. A good example is DCD, first defined in 1987 in DSM-III-R. Our work shows it is common in young people with ADHD (Piek et al., 1999; Martin, Piek, et al., 2006) and given the high rate of cerebral palsy in multiples (Petterson et al., 1993), less serious motor control problems may actually be a significant problem in this population.

3. Children grow up. This poses two significant issues for longitudinal studies such as ATAP. First is that of consent. The most recent Australian Ethics guidelines, The National Statement of Ethical Conduct in Human Research (National Health and Medical Research Centre, 2006), refers to children giving consent ‘consistent with their cognitive abilities’. In practice, the parents initially gave consent and provided information on their twin children and siblings. We are now faced with asking young adults to provide ongoing information for this study when they may not have been aware that their parents were providing information about them. It is perhaps no surprise that the response rate in the third phase of the ATAP study was not what we had experienced in earlier collections.

4. Longitudinal studies require measurement over the course of development, which raises difficult questions about the measurement instruments. One solution adopted by the very large Netherlands twin study has been to focus on the Child Behavior Checklist (CBCL) and its versions for different informants and ages (Bartels et al., 2004). The downside of such an approach is that the strength and also the weakness of the CBCL is that it is based on a statistical approach for identifying the dimensions of childhood behavioral disorders, and does not map precisely onto the clinical categories of DSM-IV or International Classification of Diseases (10th revision; ICD-10). This is not the venue to debate the contrasting approaches to the definition of psychopathology. The issue cannot be resolved as simply as getting families to complete questionnaires or interviews that encompass both approaches. With some 130 CBCL item requiring completion for each individual, not only for twins but preferably also for their siblings, the demands on the informants can become excessive.

**Acknowledgments**

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