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# Twins Early Development Study (TEDS): A Multivariate, Longitudinal Genetic Investigation of Language, Cognition and Behavior Problems in Childhood

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The Twins Early Development Study (TEDS) focuses on the early development of the three most common psychological problems in childhood: communication disorders, mild mental impairment and behavior problems. The TEDS twins were assessed longitudinally at 2, 3, 4 and 7 years of age in order to investigate genetic and environmental contributions to change and continuity in language and cognitive development; it is multivariate in order to examine the origins of comorbidity; and it uses a large sample in order to study abnormal development in the context of normal development. The twins were identified from birth records of twins born in the UK in 1994–96. More than 15,000 pairs of twins have been enrolled in TEDS and the participating families are representative of the UK. The measures at 2, 3 and 4 years are administered by parents. At 7 years, children are assessed for language and cognitive development using telephone testing, parents and children are interviewed about behavior problems, and teachers also assess behavior problems as well as academic achievement. One set of findings is that the same genes largely contribute to both language and cognitive problems and the same genes affect normal and abnormal development, a result that suggests that general impairment may be a better target for genetic research than specific language impairment independent of nonverbal cognitive problems. DNA has been obtained so far for more than 4000 pairs and is being used initially in molecular genetic studies of language problems and hyperactivity.

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The Twins Early Development Study (TEDS) is the first large-scale population-based twin study in the UK, and the largest study by far ever conducted on language and cognitive development. One reason for its size is to enable TEDS to investigate the genetic and environmental etiology of abnormal development in the context of normal development. A related goal is to study developmental problems in a representative community sample rather than studying children who were identified clinically because the latter are unlikely to be representative of children with such problems. Another reason why a large sample size is needed is that TEDS was also designed to foster collaborative research in a new interdisciplinary research centre called the Social, Genetic and Developmental Psychiatry (SGDP) Research Centre whose goal is to bring together genetic and environmental influences in the study of behavioral problems of development.

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## Major Research Focus

Although communication disorders, mild mental impairment, and behavior problems represent the most common behavioral disorders of childhood, little is known about their genetic and environmental origins (Plomin & Dale, 2000). These disorders are frequently comorbid but nothing is known about the genetic and environmental links between them as they emerge in infancy and early childhood. Because these problems are often undetected until the school years, it is necessary to investigate them in a community sample in early childhood. These considerations provide the primary rationale for TEDS, the first large-scale study of this triad of common behavioral problems, which was launched in 1995 with program grant funding from the UK Medical Research Council. The goal of TEDS is to employ a multivariate design to investigate the genetic and environmental links within components of these disorders and links between the disorders — in other words, to work towards an aetiological rather than symptom-based nosology. The TEDS design is also longitudinal in order to analyze the genetic and environmental sources of change as well as continuity, that is, the transience of childhood disorders for some children as well as the persistence of disorders for others. As mentioned earlier, TEDS employs a large representative sample of twins in order to explore the extent to which these disorders represent the extremes of the same genetic and environmental factors that operate throughout the normal range of variability or whether these disorders are distinct etiologically from normal development. Measures of the home environment are also assessed in order to investigate the developmental interplay between nature and nurture.

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## Specifics of Recruitment and Sample Description

Twins born in England and Wales in 1994, 1995 and 1996 were identified through birth records. Their parents were

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contacted on behalf of TEDS by the UK Office for National Statistics after screening for infant mortality. 16,810 parents of twins responded that they were interested in participating in TEDS and were sent a certificate enrolling their twins in TEDS. After expressing their interest, usually when the twins were about 18 months of age, parents were sent a brief booklet that assessed general demographic data as well as information about zygosity, pregnancy and birth information about the twins and other siblings, medical problems, and consent to obtain hospital records regarding pregnancy and childbirth. Just before the twins' birthdays at 2, 3 and 4 years (except for the 1996 cohort which was only assessed at 4 years), parents were sent a similar booklet that updated demographic and medical information and obtained contact information for relatives and friends in order to facilitate follow-up. Parents were also asked to provide information focusing both on the twins' early experiences and the parents' own behavior towards their children. In addition, two test booklets, one for each twin, were included at 2, 3 and 4 years (described below). At present, data from 7528 twin pairs from the 1994 and 1995 birth cohorts tested at 2, 3 and 4 years are available for analysis. Additional data from the 1996 cohort are being processed. At age 7, data on approximately 2000 twin pairs from the 1994 cohort have been collected and will be ready for analysis together with additional data from the 1995 cohort at 7 by the end of 2002. A complete list of the measures administered in TEDS along with a more detailed sample description is available on request.

Considering the major burden imposed by the booklets on harried parents of young twins and our lack of pressure on the parents in order to avoid having families drop out of the study, a gratifyingly large number of parents completed the time-consuming booklets, which testifies to the well-known phenomenon of cooperation from parents of young twins. Each year parents were given the opportunity to indicate by ticking a box that they no longer wish to participate in the study; only 1102 families (6.6%) have so indicated. Considerable effort has been expended in recruiting and retaining families such as extensive follow-ups, sending certificates of enrolment, gifts (such as building blocks, colouring pencils and T-shirts with the TEDS insignia), hand-written birthday cards, a yearly newsletter and a freephone line (more than 7000 calls to date). Each year information is sought about friends and close relatives in order to facilitate tracing families who move house which happens frequently for families of twins. TEDS has also used commercial services which has made it possible to locate about half of the families who have gone missing. Nonetheless, a cost-benefit ratio must govern decisions about efforts to retain subjects. The cost would be considerable to go beyond the resources we have expended when the additional benefit would be marginal to our goal of obtaining a large representative sample in order to conduct twin analyses as contrasted with an epidemiological study whose goal is to estimate the incidence of disorders in twins.

TEDS families are reasonably representative as compared to UK census data for families with children. For example, 92% of UK mothers are white and 92% of mothers in the total TEDS sample are white. The percentage of mothers

with A-level exams, which are taken by students finishing secondary school who plan to go to university, is 32% for UK mothers and 34% for TEDS mothers. The percentage of working mothers is 49% for the UK and 41% for TEDS. Moreover, mothers who completed all test booklets at each age are similar to the total TEDS sample for ethnicity (94% white) and A-level exams (39%). The largest difference emerged for working mothers: mothers are somewhat less likely to be working both in the total TEDS sample (41%) and in the subsample who completed all the booklets (42%) compared to all mothers in the UK (49%), which is likely to reflect difficulties with rearing twins.

Data are obtained from parents for the triad of behavioral problems when their twins are 2, 3 and 4 years of age. At 4 years of age, home visits have been made to 516 pairs of twins whose booklet data suggested language and cognitive problems and to 310 pairs of control twins in order to administer standard measures of language and cognition. We are currently testing the entire TEDS sample towards the end of the first year of formal schooling (usually 7 years of age) using language and cognitive tests administered via telephone, as well as parent and teacher reports of behavior problems. Younger siblings of the TEDS twins are assessed in the same manner in order to test the generalisability of twin results to non-twin siblings and especially to test the hypothesis that twin estimates of shared environmental influence are inflated as compared to non-twin siblings.

In addition, DNA has been obtained from all cohorts which is currently being used in molecular genetic studies of language problems and hyperactivity. The TEDS molecular genetic analysis of language problems at 4 years of age includes a case-control analysis of all currently available non-synonymous single nucleotide polymorphisms (nSNPs) in coding regions of genes. In order to genotype large samples (400 low-language cases and 1000 unselected controls) for many DNA markers, DNA pooling is used in which small amounts of DNA from each individual are pooled for cases and for controls (Plomin et al., 2001). Positive results from the case-control screening will be tested for replication using the within-family comparison provided by DZ twins.

As mentioned earlier, an additional goal of TEDS is to foster collaborative research. Funded spin-off projects using the TEDS sample include the following: specific language disorders (Dorothy V. M. Bishop), children at environmental risk as defined by teenage motherhood (Terrie E. Moffitt & Avshalom Caspi), anxiety and obsessive-compulsive behavior (Derek Bolton, Thomas O'Connor, Thalia C. Eley), cognitive mechanisms underlying anxiety (Thalia C. Eley), food choices and eating behavior of children at genetic risk of obesity (Jane Wardle), and molecular genetics of hyperactivity (Philip Asherson, Sarah Curran, Eric Taylor). In addition to its focus on language, cognition and behavior problems, TEDS has also collected screening data to provide a resource for collaborative research on such topics as ear infections (Mark Haggard), bladder control (Richard Butler), feeding and eating (Jane Wardle), asthma and allergies (Jim Stevenson), and gender role differentiation (Melissa Hines, Susan Golombok, John Rust). TEDS is open to additional collaborations.

Philip S. Dale has been a co-investigator from the beginning of TEDS and constructed the parent-report instruments used in TEDS. Ian W. Craig oversees molecular genetics research and Pak Sham and Shaun Purcell provide statistical advice. The first coordinator of TEDS was Bonamy Oliver who now works on the project as a PhD student; Alexandra Trouton currently coordinates TEDS. The first postdoctoral students involved with TEDS were Thalia C. Eley and Stephen A. Petrill; Frank M. Spinath is currently a postdoctoral research fellow working with TEDS on leave from his teaching position at the University of Bielefeld in Germany. The first PhD student who also served as data manager/analyst for four years is Thomas S. Price; other PhD students whose research primarily involves TEDS include Kathryn Asbury, Essi Colledge, Nicole Harlaar, Gesina Koeppen-Schomerus, Emma Meaburn, Angelica Ronald, and Sheila Walker. Other collaborators who have been co-authors on TEDS papers include Kirby Deater-Deckard, Ginette Dionne, Michael J. Galsworthy, Francesca Happé, Alessandra Iervolino, Alison Pike, Michael Rutter, Kimberly J. Saudino, and Emily Simonoff. Current research staff include data manager Andrew McMillan and research assistants Sarah Hanratty, Clare Bodman, and Patricia Busfield.

### Major Achievements

One of the early findings within TEDS was that language problems even at 2 years of age are highly heritable, significantly more heritable than individual differences in the normal range of language development (Dale et al., 1998), suggesting that language impairment may be a good target for molecular genetic research. An issue at the core of many controversies in psycholinguistics is the relation between lexical and grammatical knowledge. Multivariate genetic analyses in TEDS indicate that these two domains (as assessed by vocabulary and grammar) are strongly linked genetically (Dale et al., 2000).

A key issue for TEDS is the extent to which the same genetic factors affect individual differences in language and non-verbal cognitive development in early childhood. A surprising finding from genetic research on cognitive abilities later in life is that the same genes are largely responsible for genetic influences on diverse cognitive abilities, which suggests a genetic basis to "g", general cognitive ability (Plomin, 1999). This finding is especially noteworthy because it goes against the assumption of genetic modularity in cognitive neuroscience (Plomin & Spinath, 2001). Multivariate genetic analyses in TEDS indicate that this genetic overlap begins to develop early. For example, not only are vocabulary and grammar substantially linked genetically, they are also linked genetically, albeit more moderately, with non-verbal cognitive measures (Dale et al., 2000). Genetic overlap between verbal and non-verbal cognitive measures occurs not only for the normal range of variation (Petrill et al., 2001; Price et al., 2000) but also for the low extremes (Purcell et al., 2001). Recent analyses of nine language measures administered during home visits at 4 years of age to 300 control pairs of twins yielded a general factor that accounted for 30% of the total variance (Colledge et al., in press). Multivariate genetic analyses

indicate that nearly half of the genetic variance on this general language factor overlaps with a non-verbal cognitive factor. These results suggest that molecular genetic research will find general language impairment a richer target than specific language impairment that excludes general cognitive ability.

In contrast to the strong phenotypic and genetic links between language and non-verbal cognitive development, overlap between behavior problems and language/cognitive development is modest phenotypically both for the entire distribution and for the lowest 5% and 10% of the distributions of the language and cognitive abilities. This overlap is more modest than expected based on the literature which usually involves clinic rather than community samples (Plomin et al., 2002). Nonetheless, genetic factors contribute moderately to the overlap for the entire distribution and even more strongly for the low end of the language/cognitive distributions.

TEDS has also provided the first behavioral genetic analysis of mild mental impairment. This research shows that across 2, 3 and 4 years of age mild mental impairment is substantially heritable, significantly more heritable than general cognitive ability in the normal range (Spinath et al., 2002). Children were selected on the basis of a robust general factor that accounts for about 50% of the variance at 2, 3 and 4 years and is remarkably stable but only modestly heritable (about 30%; Spinath et al., 2002). The lower heritability of general cognitive ability in early childhood is expected from the literature which indicates that heritability increases from about 20–30% in early childhood to about 40% in middle childhood to about 50% after adolescence (Plomin, 1986). Shared environmental influence, which is very high in TEDS (about 60%), is expected to decline during childhood. Moreover, preliminary analyses of data from younger siblings of the twins indicate that about half of the twin estimate of shared environmental influence is specific to twins (Koeppen-Schomerus et al., in press).

Other TEDS publications show high heritability and modest shared environmental influence for hyperactivity (Price et al., 2001), ear infections (Rovers et al., 2002), asthma (Koeppen-Schomerus, Stevenson, et al., 2001), and body weight and overweight (Koeppen-Schomerus, Wardle, et al., 2001). In contrast, modest genetic influence and substantial shared environmental influence were found for sex-typed behavior (Iervolino et al., 2002), and nocturnal bladder control (Butler et al., 2001). The first TEDS paper based on the assessments at 7 years shows substantial heritability and modest shared environmental influence for teacher ratings of school achievement (Walker et al., 2002). Other publications include univariate genetic analyses of the low extremes of cognitive and language ability (Eley et al., 1999; 2001), sex-limitation modelling using opposite-sex twins (Galsworthy et al., 2000), genotype-environment interaction involving prematurity (Koeppen-Schomerus et al., 2000), neighbourhood effects on behavior problems (Caspi et al., 2000), longitudinal analyses of change and continuity for language problems (Bishop et al., 2002), and DNA validation of zygosity assessed by physical similarity (Price et al., 2000).

Although most TEDS analyses use the twin method to disentangle genetic and environmental influences, the usefulness of its large dataset for phenotypic analyses is beginning to be realized. Three examples indicate the value of the longitudinal nature of TEDS. The first is an example of a prospective analysis: investigating the developmental outcomes for children with early language delays (Dale et al., 2002). The second is a type of retrospective analysis using prospective data. Children diagnosed as autistic at 4 years of age were perceived by their parents at 2 years of age as normal in many respects (e.g., perceived affectionateness), were like other children with developmental delay in others (e.g., ratings for solitary play and fussiness); and show some autistic-like symptoms (e.g., staring blankly and not liked by other children), even though few children are diagnosed as autistic before the age of 3 (Oliver, Happé, et al., 2002). A third example is a type of genetic "longitudinal" analysis from childhood (twins) to adulthood (the twins' parents) in which twins were selected on the basis of the body mass index of their parents in order to study the feeding and eating habits and preferences of young children at genetic risk for obesity but before the children are actually obese (Wardle et al., 2001). Another major phenotypic achievement of TEDS has been the development and administration to many thousands of children instruments for assessing cognitive development at 2, 3 and 4 years using parent-administered and parent-report measures (Oliver et al., 2001; Saudino et al., 1998) and at 7 years using tests administered by telephone (Petrill et al., 2002).

### Future Plans

Longitudinal and multivariate genetic analyses will continue to be conducted at 2, 3, 4 and 7 years of age, testing our hypotheses of increasing heritability of language and cognitive abilities, increasing genetic correlations between language and cognitive abilities, and increasing genetic links between normal and abnormal development. Molecular genetic research on language problems and on hyperactivity will continue and the TEDS dataset will continue to be used to foster molecular genetic research on other aspects of development.

One of the last remaining frontiers for genetic research is education, which has largely ignored the evidence for substantial genetic influence on cognitive abilities. We are currently exploring possibilities for extending TEDS in the direction of education especially as the TEDS children are now at the beginning of their formal schooling. By embedding analyses of school and classroom effects in a genetically sensitive twin design, it is possible to investigate the interface between nature and nurture similar to analyses during the past decade of the nature-nurture interface in relation to parenting. We will follow the sample again at least at 9 years with current funding and hope to obtain funding to continue following the TEDS sample into adolescence.

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