Published in final edited form as:

Am J Speech Lang Pathol. 2007 May ; 16(2): 169–178. doi:10.1044/1058-0360(2007/021).

Genetic etiology in cases of recovered and persistent stuttering in an unselected, longitudinal sample of young twins

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Abstract

Purpose—The contribution of genetic factors in persistence and early recovery from stuttering was assessed..

Method—Data from the Twins Early Development Study were employed. Parental reports regarding stuttering were collected at ages 2, 3, 4 and 7 years and were used to classify speakers into recovered and persistent groups. Of 12,892 children with at least two ratings, 950 children had recovered and 135 persisted in their stutter.

Results—Logistic regressions showed that the rating at age 2 was not predictive of later stuttering, whereas ratings at ages 3 and 4 were. Concordance rates were consistently higher for monozygotic than for dizygotic twin pairs (with the exception of girls at age 3). At 3, 4 and 7 years, the liability to stuttering was highly heritable (h^2 estimates of between .58 and .66). Heritability for the recovered and persistent groups was also high, but did not differ from each other.

Conclusion—Stuttering appears to be a disorder that has high heritability and little shared environment effect in early childhood and for recovered and persistent groups of children, by age 7. The clinical implications of the findings are discussed.

Stuttering is a condition that is characterized by an abnormally high frequency or long duration of stoppages in the forward flow of speech (Peters & Guitar, 1991) that cause difficulties in communication for those affected. There is high variability in the phenotypic expression and severity of signs of stuttering. Despite a long history of research into this disorder investigators are still mystified as to the causes of the disorder, which led one leading authority to conclude recently that “(1) its cause is unknown, (2) its essential nature is not understood, and (3) there is no known cure” (Wingate, 2002, p.11).

A number of epidemiological findings are consistent with the notion of strong genetic influences in the etiology of stuttering, but concerted efforts to find specific genes that account for the susceptibility, and heredity patterns, are still in their infancy (see for instance Felsenfeld, 2002 for a review). Most stuttering begins in childhood and the majority of children recover by the early teenage years. Consequently, prevalence varies as a function of age: Approximately 5% of pre-school children are affected, but by the end of primary school (equivalent to junior high school in the US) this percentage drops to 1% and remains at this level throughout life (Yairi & Ambrose, 1999). Even though estimates for spontaneous remission in the pre-school years are high (ranging from 39% to 89% - see Cooper, 1972;

Peters & Guitar, 1991; Yairi, Ambrose, Paden, & Throneburg, 1996) the reasons for such recovery are unknown, nor do we know whether these forms of recovery differ from therapy-assisted recovery. More than 75% of cases of stuttering report an onset of between 3 and 6 years, with almost no new cases being reported after age 12 years (Bloodstein, 1995). The question has been raised, but not definitively answered, as to whether there are genetic differences between recovered and persistent cases (see Ambrose, Yairi, & Cox, 1993; Shugart, Mundorff, Kilshaw, Doheny, Doan, Wanyee et al., 2004; Viswanath, Lee, & Chakraborty, 2004, for family and linkage studies). One finding that has been reported is that persistence and recovery runs in families (Ambrose, Cox & Yairi, 1997). These authors showed that a persistent proband had a higher proportion of persistent relatives and a smaller proportion of recovered relatives compared with recovered probands who had a higher proportion of recovered relatives and a lower proportion of persistent relatives.

The ratio of male to female individuals who stutter varies with age. Boys are about twice as likely to stutter as are girls among pre-school children, but by around age 9 this ratio increases to about four affected males for every affected female. This pattern has been interpreted as showing that girls are more likely to recover than are boys (Yairi & Ambrose, 1999). From a genetic perspective this could mean that there is a difference in the pattern of inheritance for boys and girls (or sex-modified transmission), which is one of the issues that this study addresses. Because girls are more likely to recover in earlier childhood it is possible that there is higher heritability for boys than girls earlier on for stuttering.

Another issue indicating genetic influences in the disorder is the reported pattern of familial aggregation. Two research groups have provided evidence that prevalence is significantly higher among the biologically-related family members of probands who stutter than among the relatives of control cases or compared to population rates for the condition (Ambrose et al., 1993; Cox, Kramer, & Kidd, 1984). Both these studies conducted segregation analyses. Although the studies were consistent in reporting higher prevalence rates in families with a history of stuttering, other findings were not consistent. Cox et al. (1984) found a multiple gene transmission model fitted best, whereas Ambrose et al.'s (1993) findings supported a single gene model. A recent segregation analysis also favors the single gene model (Viswanath et al., 2004). However, family studies cannot determine whether familial aggregation is genetic or environmental in nature. This issue can be addressed by twin research.

An early study on adult twins in which at least one member of the pair was affected by stuttering reported that identical (monozygotic-MZ) twins were more concordant for the presence of stuttering than were fraternal twins (dizygotic-DZ) (Howie, 1981). Two additional studies of adult twins used unselected community-based adult twin samples (Andrews, Morris-Yates, Howie, & Martin, 1991; Felsenfeld, Kirk, Zhu, Statham, Neale & Martin, 2000) and obtained similar results, i.e. higher concordances for MZ as compared to DZ twin pairs. Both of these studies carried out formal statistical (ACE) modeling of data. ACE modeling is a technique that allows estimates of additive genetic (A), common environmental (C) and unique environmental (E) influences. Non-additive dominant genetic (D) effects can be estimated in ADE modeling (C and D cannot be estimated within the same model). The two studies reported that about 70% of variance in liability to stuttering could be attributed to additive genetic effects (A) with the remaining 30% attributable to the individual's unique environment (E). The most recent twin analysis has been carried out in Japan (average age of participants was 11.5 years). Using questionnaire data it was reported that heritability was 80% for boys and 85% for girls in this age group (Ooki, 2005).

Behavioral genetic analyses have begun to go beyond estimating heritability alone and have also considered other issues such as developmental change and continuity (Bishop, Cherny,

Corley, Plomin, DeFries & Hewitt, 2003). For example, in general cognitive abilities (“g” or general intelligence), it has been reported that genetic factors play an increasingly important role throughout the lifespan (McGue, Bouchard, Iacona, & Lykken, 1993; Plomin, 1995). Whether there are also developmental changes in the heritability of stuttering, and what these might indicate, are issues explored here for the first time.

The above review highlights the need for further clarification of the hereditary processes involved in stuttering during early childhood. Three particular questions that have not been addressed to date are: 1) What are the patterns of heritability and shared environment in early childhood? 2) Are there different genetic and environmental influences for children who recover from stuttering and those who persist? 3) Is the inheritance pattern the same or different for boys and girls at such an early stage in stuttering? The present study sought to address these questions.

Method

Participants

Data came from the Twins Early Development Study (TEDS), a longitudinal, UK-based study of all twins born between 1994 and 1996 (Trouton, Spinath, & Plomin, 2002). After checking for infant mortality, all families identified by the UK Office for National Statistics (ONS) as having twins born in these years were invited to participate in TEDS when the twins were about 18 months old. Information was gathered from parental report booklets when the twins were 2, 3 and 4 years old. The response rate of those that received questionnaire packs at these ages was 59% (6285 of 10646 packs sent out), 64.8% (6059 of 9350 packs sent out) and 65% (8148 of 12528 packs sent out - this included for the first time the cohort with those twins born in 1996), respectively. Between 2001 and 2003, when the twins were aged 7 years there was a 62.4% (12,902 active families) response rate. Number of individual twins and breakdown of twins in zygosity groups is given in Table 1. Individual children with a specific medical syndrome, such as Down Syndrome, Fragile X, and other chromosomal anomalies, including cystic fibrosis, and cerebral palsy were excluded, as were cases where zygosity data were unavailable, where consent was not given and where first contact data had not been supplied.

Zygosity

One issue frequently queried in larger twin studies is how zygosity is determined. In TEDS twin zygosity has been assigned using parent questionnaire ratings of twins’ physical similarity. A TEDS study (Price, Freeman, Craig, Petrill, Ebersole & Plomin, 2000) indicates that even at 18 months of age zygosity was correctly assigned by parent ratings in 94.4% of cases as validated against zygosity assigned by identity of polymorphic DNA markers. When questionnaire ratings of twin similarity were readministered at 3 years of age, the parent rating of zygosity at 18 months showed a high degree of stability over the intervening period.

Measure of Stuttering

Each questionnaire contained at least one question specifically regarding stuttering/stammering. At age 2 this question was embedded in an adapted scale using wording employed in the Preschool Behavior Questionnaire (Behar, 1977). Although more detailed evaluations are desirable, the general nature of the TEDS survey precluded obtaining more detail. In order to check on report accuracy of parents, comparisons were made with extant estimates of incidence, prevalence, and to see whether males have different rates of recovery to females, all of which have been reported in other studies (Yairi & Ambrose, 2005). The Preschool Behavior Questionnaire which was used at ages 2, 3 and 4 queried behavioral

patterns and was phrased to be answered with the responses *not true/sometimes true/certainly true*. One of the questions directly referred to stuttering (see Table 2). At ages 3 and 4 years there was an additional question regarding stuttering which was part of a specific section on language concerns. For these two ages, children were only assigned to the stuttering group analyses when both of these were answered affirmatively (i.e. at least 'sometimes true' in the first question and 'YES for language concerns plus s/he stutters' in the subsequent follow up) or when one answer was missing and the other was affirmative. At age 7 a question regarding stuttering only appeared in the language concern part of the parent booklet (this was the same as the question about language concerns at both years 3 and 4-see second question above).

Coding for recovered versus persistent stuttering

The measures described above, taken at the four different ages, were also coded to designate whether each child had persisted or recovered from their stutter by age 7. The designation as recovered/persisted was made in the following manner. First, only children with more than one year's data were included in this part of the investigation. This was a group of 12, 892 children. These were then classified as having a reported incidence of stuttering at only one age or at two or more of the four ages. Any of those that fell into the latter category (i.e. had at least twice been rated as stuttering) and had an affirmative parental report at age 7 were classified as persistent, whereas those that had only been rated as stuttering once, or those rated more often as stuttering but who were rated by their parents as no longer stuttering at the age of 7, were classified as recovered. Recovery and persistence were categorized only on those individuals who had data at age 7. Those who had been classified as stuttering but did not have data at age 7 were excluded from the recovered/persistent part of the analysis as well as those who were recorded as stuttering for the first time at age 7.

Analysis

Logistic regression—Logistic regressions were conducted to ascertain the extent to which stuttering at the age of 7 years can be predicted by stuttering reported at earlier ages. This method was carried out in a single step entering ages 2, 3 and 4 into a regression together to predict age 7 outcome.

Twin concordance—In line with the three previous twin studies using adult twin pairs (Andrews et al., 1991; Felsenfeld et al., 2000; Howie, 1981) both the pairwise and the probandwise concordance rates are reported. The ratio of the number of pairs of probands to the total number of twin pairs is called the *pairwise concordance* rate:

$$\frac{\text{Number of where both twins are affected}}{\text{Number of concordant twin pairs + number of discordant twin pairs}}$$

In contrast the ratio of the number of probands in concordant pairs to the total number of probands is termed the *probandwise concordance* rate:

$$\frac{\text{Twice the number of concordant twin pairs}}{\text{Twice the number of concordant twin pairs + number of discordant twin pairs}}$$

As such the probandwise concordance rate is the probability that the co-twin of a proband twin will also have the disorder. Because the earlier twin studies reported pairwise concordances these will also be given here. However, they will not be discussed in detail because they cannot be interpreted without knowing how cases have been selected from the

population and so they have been described as a measure that is now ‘obsolete’ (Rijsdijk & Sham, 2002, p.129), and the probandwise concordances are the focus. The analysis was carried out separately for MZ and DZ twins and is commonly used as an index of twin resemblance. However, concordances themselves cannot be used to estimate genetic and environmental parameters because they do not take into account population prevalence rates.

Liability threshold modeling—Genetic models were fit to the raw data using the *Mx* statistical package (Neale, Boker, Xie, & Maes, 2002). This provides parameter estimates and confidence intervals for the models. Genetic and environmental parameters were estimated from the case-classification data using liability threshold (LT) modeling techniques (for a more detailed introduction to twin modeling techniques see Rijsdijk & Sham, 2002). This method assumes that the risk of being affected by a disorder (in this case stuttering) is normally distributed, and that the disorder occurs when a certain threshold, or liability, is exceeded. For liability threshold models twin resemblance is summarized as tetrachoric correlations, which are used to describe the relationship between two variables (i.e. one for each twin) each of which is categorized as unaffected or affected. More specifically, tetrachoric correlations between two dichotomous measures are estimates of the Pearson’s correlations that would be obtained if the two constructs were measured continuously.

The model-fitting process then estimates the MZ and DZ correlations for that liability. As with continuous data, variance is decomposed into additive genetic (A), either shared environmental (C, referring to experiences that make children growing up in the same family similar) or non-additive dominant genetic (D), and non-shared environmental influences (E, referring to influences that make children growing up in the same family different).

Univariate sex limitation models were used to test for sex differences. These are modeled in the following manner. Models include a term (r_G) that represents genetic relatedness between twins in a pair. This is fixed to the value of 1 in same-sex MZ groups because MZ twins are assumed to share all their genetic make-up whereas in same-sex DZ groups this value is fixed at 0.5, because DZ twins share half their segregating (i.e. those identical copies of a gene inherited from a common ancestor) genes. There is also a shared environment coefficient (r_C), which is fixed to the value of 1 for both MZ and DZ same-sex groups assuming that twins growing up in the same family have the same shared environment. For DZ twin pairs, r_G and r_C are individually allowed to vary below this fixed value in order to test that males and females share less than half their segregating genes and that their shared environment is less similar to that of same-sex twins (*qualitative sex differences*). To test whether there are different magnitudes of genetic or environmental influences for boys and girls, the parameters for A, C or D, and E in each trait are allowed to vary according to gender group; this represents a *quantitative sex difference*.

Initially full models (i.e. ACE or ADE models) are compared to a model that estimates all possible parameters (called the *saturated* model) using the log likelihood fit statistic (-2LL). When models are nested (meaning that parameters of one set are a subset of the parameters of another set) these can be differentiated using the -2LL. If for example the fit of the simpler (i.e. the one with fewer estimated parameters such as an AE compared to an ACE) is not significantly worse than that of the full model then the simpler (AE) model is selected since it provides a more parsimonious explanation of the data.

Results

Incidence and prevalence

The incidence of children who had been rated by their parents as stuttering ranged between 1.1-3.5% for different ages (see Table 2). The Table shows that it was lowest at the age of 2 highest at ages 3 and 4 and at an intermediate rate at 7. The sex ratio trend increased slightly: For each girl who stuttered at ages 2 and 3 there were 1.6 boys whereas at ages 4 and 7 there were 1.8 boys for every girl who stuttered (same value for the two ages).

Overall prevalence was 1812 (7%), with 1029 boys (4%) and 783 girls (3%), who had been rated as stuttering from all of the twins in the entire dataset that had been contacted (N=25830) over the 7-year period. This included cases where stuttering had been affirmatively answered at any age for any question, i.e. even those where stuttering was only indicated once in the two questions at ages 3 and 4 (it would be expected to be closer to 5%, Bloodstein, 1995). Of the 12,892 children with at least two ratings 950 (7%) children were classified as the recovered group, comprising 429 girls (45%) and 521 boys (55%). Of the 135 (1%) children who persisted, 35 (26%) were female and 100 (74%) were male, i.e. 2.9 boys for every girl who stuttered.

Logistic regression

Numbers of children who stutter at age 7 who had been stuttering at previous ages are presented in Table 3. It can be clearly seen that most children who had been rated as stuttering at age 2 were no longer reported to have such a problem at age 7. Consistency in parental rating increased in ages 3 and 4. Ignoring missing cases from earlier to later ages, this corresponds to a 69% recovery rate at age 2 and 79% and 53% for ages 3 and 4 of, respectively.

Logistic regressions were performed to examine whether reports of stuttering at early ages were predictive of stuttering at the age of 7 years when entered together into a regression as predictors. Results are presented in Table 4.

The results show clearly that reports of stuttering at ages 3 and (especially) 4 predict stuttering at age 7 years. From the very low Wald chi-square value for age 2 it can be deduced that knowing whether a child stuttered at age 2 does not provide any additional information if we also have information on whether or not the child stuttered at age 3 or age 4. Furthermore it can be seen that even though ratings at both ages 3 and 4 were significant predictors (*Wald chi-square* = 24.42 and 96.35, $p < 0.001$) the odds ratios indicate that there were many children rated as stuttering at these ages, particularly at the age of 3, who were no longer rated as stuttering at 7 years (*odds ratios* of 11.64 and 56.23 respectively).

Twin concordances

The age 2 data were not predictive of later stuttering, so twin concordances and modeling results are not reported for this age group. However, because the above results might indicate that children who stutter at age 2 were more likely to recover these data were used in the recoding of both the recovered and persistent groups. MZ twins were more concordant (for all ages and also recovered and persistent groups) than were DZ pairs, with increasing genetic influence from age 3 to 4. Averaging across sexes (including also DZ opposite sex twin pairs), the probandwise concordances for combined MZ and DZ pairs can also be seen in Table 5. Because the DZ concordances were less than half the MZ concordances at ages 3 and 4, no shared environmental influences are suggested. The results for boys and girls are generally similar and suggest substantial heritability and no shared environment, although the pattern of results is less consistent across the sexes, probably because of reduced power.

Liability threshold modeling for stuttering at 3, 4 and 7 years

The tetrachoric correlations needed for liability threshold modeling are presented in the last column of Table 5. These are quite similar to the probandwise concordances shown in the penultimate column of Table 5. All analyses estimated separate threshold parameters for boys and girls because of the different stuttering prevalence rates for males and females. Table 6 presents fit statistics from the best fitting models for the two genders.

As suggested by the twin concordances (Table 5), substantial genetic influences and no shared environmental influences are found at 3, 4 and 7 years (see Table 7). There was an increase in heritability estimates from age 3 to 4 (h^2 estimates were .58 and .65 respectively) although the overlapping confidence intervals indicate that this was not significant. No significant quantitative or qualitative sex differences were found. Models also estimated threshold values for boys and girls separately. These correspond to z-values for population parameters. This was the only sex difference in the modeling of the data. Table 7 (and the data on Table 9 that model persistent and recovered cases as discussed below) clearly show that girls' thresholds are always significantly higher than those for boys (non overlapping confidence intervals), indicating that fewer girls are affected than boys, at each age as well as for the recovered and persistent group.

Liability threshold modeling for persistent versus recovered stuttering

The longitudinal data ($N=12,892$; all had at least two data points as described in the method section) were coded to categorize children as persistent or recovered. As already highlighted in Table 5, for both of these groups there was a higher concordance rate for MZ as compared to DZ groups: MZ and DZ probandwise concordances were .40 and .20 respectively, for the recovered group, and .19 and .00 for the persistent group. Table 8 presents fit statistics from the best fitting models for recovered and persistent groups. For the liability threshold modeling recovered and persistent were coded individually as categorical variables (either 0 or 1). This meant that in case of persistence, children who had recovered were coded as 0 and vice versa (to be in line with concordance results as presented in Table 5).

Parameter estimates (Table 9) for both the recovered and persistent groups are similar (h^2 estimates of .67 and .60, respectively), suggesting substantial genetic influence and no influence of shared environment for both groups. Because there were fewer cases in the persistent group, the confidence intervals are larger than for the recovered group; nonetheless, the overlapping confidence intervals for the parameter estimates for the recovered and persistent groups indicate that the estimates do not differ significantly.

Cross-concordance of recovered and persistent cases by zygosity

Looking at recovery and persistence as purely categorical variables in the manner described in the last section for liability threshold modeling, does miss out on those pairs where recovery and persistence occurred within one twin pair. Whether and how frequently this pattern is present in the current dataset is broken down into MZ and DZ twin groups in Table 10.

The Table shows that in most pairs where one child had been affected by stuttering (either recovered or persisted) most often the other twin was unaffected. Clearly this pattern is even more apparent in the DZ twins compared to MZ pairs. As described above in relation to Table 5 it again shows higher concordances for MZ than DZ twins, and thus genetic influences. Cross concordance is also shown in the Table for both MZ and DZ pairs. Eyeballing the numbers of these pairs does not suggest a vastly different number of pairs where one twin has recovered and the other persisted for MZ than DZ pairs.

Discussion

The current study set out to estimate developmental and gender effects in the genetic liability to stuttering. The longitudinal parental rating data for the twins allowed categorization into recovered and persistent groupings of children with the aim of estimating genetic and environmental influences for these two groups individually.

Even though there were very limited data available at each age, there does not seem to be substantial over-reporting by parents of stuttering in childhood, as incidence/prevalence and gender ratios fell well into the regions of those reported by previous studies for these age groups. The slightly higher incidence rates for ages 3 and 4 are possibly due to the double questioning at these two ages, which could have led to a slight over-reporting. The sex ratios are also in agreement with previous research for the pre-school years as well as the increase as a function of age (see Bloodstein, 1995). Furthermore, the percentage of those that persist in their stutter is exactly that reported in the literature (see Yairi & Ambrose, 1999). The language studies in TEDS have also shown that when intensive testing was carried out in the children's home setting it provided excellent validation of previous parental report measures (Plomin, Colledge, & Dale, 2002).

In developmental terms the twin analyses showed that even as early as 3 years MZ concordance rates were consistently higher than DZ rates, suggesting substantial genetic influence and little evidence of shared environmental influence, which was verified by formal twin modeling of the data. Consequently, this study provided evidence for the heritability of stuttering and early recovery from stuttering in childhood. By age 4 these estimates fall within the same confidence intervals as those previously reported for adults who stutter (0.71 and 0.70 as reported by Andrews et al., 1991, and Felsenfeld et al., 2000, respectively). Though the current study was on children, the estimates correspond roughly with those found in two studies on adults (Andrews et al., 1991; Felsenfeld et al., 2000). These studies on adults reported that about 70% of variance in liability to stuttering were attributable to A and 30% were attributable to E. Previous twin studies on stuttering have been carried out on adults as well as older children who stutter, mainly not to complicate data with transient cases. The current study is the first to provide evidence that even as early as age 3 stuttering is heritable even though a vast number of those children later recover. This again suggests that the path of this impairment is genetically influenced to some extent, which is also supported by the finding that recovery from stuttering is heritable.

There was a trend for a developmental increase in genetic influences from age 3 to age 7 which was, however, not significant. It is possible that these changes could be due to gene-environment interplay, for instance the onset of the problem has a likely change in unique environmental influences as a consequence. For instance other children's, as well as the child's own, reactions to an onset of speech / pronunciation difficulties could be part of a child's unique environmental influences.

With regards to the genetic effects throughout, it also needs to be emphasized that, even though substantial (i.e. over .60) estimates of heritability were obtained, many monozygotic twin pairs were discordant for stuttering. This is further evidence for the importance of the child's unique environmental influences, in that specific stressors have unique effects when a genetic liability is present. Future research should include the detailed study of discordant MZ twin pairs to establish which influences might have contributed to the onset of speech problems in only one of two children with the same genetic liability to the disorder.

With regards to gender differences, the hypothesized quantitative sex differences were not found to be significant in the twin modeling process. In this way it is important to note that the factors that increase liability to stutter do not appear to be significantly different for male

and female children. This is consistent with results reported in previous adult twin studies and is possibly due to the lower prevalence in girls. Differences in prevalence are possibly linked to sex-modified transmission of stuttering as suggested in other studies. With fewer cases in girls the power to detect possible differences is low and larger samples would be needed. However, the overall number of girls who were rated as stuttering is comparatively high for twin studies and the same argument could be applied to any of the other previous twin studies on this issue (none of which reported sex differences in model fitting). Furthermore in the recovered group proportions of boys and girls are almost equal. This is consistent with Ambrose et al.'s (1997) findings, and indicates that girls are more likely to recover than boys.

Finally, the data provided unique opportunity to classify recovered and persistent groups of twins which in turn allowed for formal estimation of the heritability of recovery or persistence of stuttering. Previous work has shown that both recovery and persistence of the disorder are familial in nature (Ambrose et al. 1997), but only in the present data can the contributions of genetic and environmental influences be estimated. Shared environmental influences have often been misinterpreted as being either inside or outside the family home environment (as discussed in detail by Rutter, 2006). The 'shared' influences are those that make children within the same family more alike, whereas non-shared factors make children less like each other. As such, the current findings do not discount the importance of parental behaviors in recovery or persistence per se, but highlight that these factors may have unique effects on different children within a family and/or suggest that environmental factors besides those shared by siblings may be important. Unique environmental events could include in utero or birth events, low birth-weight and/or perinatal hypoxia as well as childhood illnesses, for instance. Cross-concordant cases of twin pairs where one recovered and the other persisted by age 7 seem to be a little less clear cut. Because the numbers between MZ and DZ pairs for these pairs are not strikingly different it suggests that genetic factors acting on this relationship are lower. It highlights however that there are substantial environmental influences on the relationship between early recovery and persistence of stuttering. A clearer understanding of this relationship with larger numbers of recovered and persistent twins should be done in future. The goal should be to find out whether both shared and non-shared environmental factors play a role in the relationship between recovery and persistence.

The question of whether the same or different sets of genes are involved, or whether recovered cases might be a milder form of the persistent condition, cannot be established from the current data. Future molecular work might shed more light on the issue of whether different sets of genes or specific additional genes are involved in persistence of stuttering.

Clinical Implications

Yairi and Ambrose (2005) argue that genetic information can be employed at diagnostic, prognostic, treatment and counseling levels. They argue that a clinician should be alerted to the fact that a child may be prone to stuttering when there is a strong family tendency. The current results showing a large genetic component can be taken as support for that view. Ambrose et al.'s (1997) results that persistence and recovery run in families would have obvious application to prognosis of the disorder. Most children recover from stuttering and treatment resources are limited. Thus anything that improves the ability to determine risk of persistent developmental stuttering, such as environmental and genetic factors, is potentially important and can be used to prioritize cases. According to the present data, a positive family history may play a role in risk-assessment, and the fact that both early recovery and persistence are heritable, which is consistent with Ambrose et al. (1997). Future clinical research may lead to new forms of treatment that recognize and incorporate what is known about the influence of the shared environment on recovery and persistence. Such a

development would have the potential to significantly reduce treatment time for pre-school age stuttering children. A first step would be to estimate the relative contribution of environmental and genetic factors at different points during the course of treatment.

Acknowledgments

The first author was funded by a National Alliance for Autism Research project grant. TEDS is funded by an MRC program grant G9424799. Anna Remington and Peter Howell are funded by the Wellcome Trust program grant 072639. Many thanks for the support of the TEDS staff group and to Susan Felsenfeld and two anonymous reviewers for their helpful comments. We also thank the parents of the TEDS twins for their participation. Parts of these data were presented at the 5th Speech Motor Control Conference in Nijmegen, June 2006.

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Table 1

Total number of individual twins and breakdown of zygosity groups.

Age (years)	N	Monozygotic		Dizygotic		Opposite sex	
		Male	Female	Male	Female	Male	Female
2	11121	1744 (15.68%)	2060 (18.52%)	1868 (16.80%)	1772 (15.93%)	3677 (33.07%)	
3	10567	1702 (16.11%)	1927 (18.24%)	1773 (16.78%)	1661 (15.72%)	3504 (33.16%)	
4	14828	2179 (14.70%)	2504 (16.89%)	2301 (15.52%)	2367 (15.96%)	4645 (31.33%)	
7	13838	2508 (18.12%)	2814 (20.34%)	2370 (17.13%)	2504 (18.10%)	4632 (33.47%)	

Note. These are the numbers included in the study after exclusion criteria were applied as outlined in the Method.

Table 2

Questions used to code for stuttering

Time of Questionnaire	Questions/Statement referring to stuttering	Incidence of stuttering
Age 2	Has a stammer <i>not true/sometimes true/certainly true</i>	118 (1.1%)
Ages 3 and 4	Has a stammer <i>not true/sometimes true/certainly true</i> Do you have concerns about your child's speech and language? <i>YES/NO</i> . If Yes, what are your concerns?- option 6: <i>s/he stutters</i> "	227 and 493 (2.0% and 3.5%) respectively *
Age 7	Do you have concerns about your child's speech and language? <i>YES/NO</i> . If Yes, what are your concerns? - option 6: <i>s/he stutters</i> "	218 (1.6%)

* when the first two questions were answered affirmatively (see text)

Table 3

Cross tabulation of stuttering at age 7 and stuttering at each measured age group.

		Stuttering at age 7	
		No	Yes
Stuttering at age 2	No	7164	93
	Yes	82	1
Stuttering at age 3	No	7616	68
	Yes	180	33
Stuttering at age 4	No	10514	64
	Yes	262	87

Note. Numbers do not add up to the numbers in the prevalence section because of different combinations of missing cases.

Table 4

Logistic regression results predicting age 7 stuttering from age 2-4 stuttering as rated by parents (predictors entered together).

<i>Predictors</i>	<i>Wald Chi square</i>	<i>df</i>	<i>p</i>	<i>Odds Ratio (95% Confidence Interval)</i>
stuttering at age 2	<.001	1	.998	<.001
stuttering at age 3	24.415	1	<.001	11.63 (CI 4.40 - 30.81)
stuttering at age 4	96.349	1	<.001	56.226 (CI 25.15 - 125.71)
Constant	323.185	1	<.001	.004

Table 5

Number of affected individual children by zygosity (pairs with missing values here excluded), concordance rates and tetrachoric correlations.

	ZYGOSITY	CONCORDANT PAIRS	DISCORDANT PAIRS	PAIRWISE CONCORDANCE	PROBAND WISE CONCORDANCE	TETRACHORIC CORRELATIONS
AGE 3	MZM	12	41	.23	.37	.42
	MZF	3	41	.07	.13	.18
	DZM	4	54	.07	.13	.25
	DZF	3	32	.09	.16	.25
	DZO	3	76(M) 40(F)	.025	.05	.05
Combined	All MZ	15	82	.15	.26	
	All DZ	10	202	.04	.09	
AGE 4	MZM	19	63	.23	.38	.41
	MZF	8	54	.13	.23	.36
	DZM	10	71	.12	.22	.27
	DZF	3	54	.05	.1	.16
	DZO	5	111(M) 37(F)	.03	.06	.10
Combined	All MZ	27	117	.19	.32	
	All DZ	18	273	.06	.12	
AGE 7	MZM	6	37	.14	.20	.33
	MZF	6	20	.23	.38	.49
	DZM	1	40	.02	.05	.08
	DZF	0	17	.00	.00	-0.01
	DZO	1	56(M) 16(F)	.01	.03	.07
Combined	All MZ	12	57	.17	.29	
	All DZ	2	129	.02	.03	
Recovered group	MZM	34	99	.25	.41	.38
	MZF	34	104	.25	.40	.38
	DZM	20	111	.15	.26	.24
	DZF	13	114	.09	.19	.17
	DZO	23	149 (M) 70 (F)	.10	.17	.17
Combined	All MZ	68	203	.25	.40	

	ZYGOSITY	CONCORDANT PAIRS	DISCORDANT PAIRS	PAIRWISE CONCORDANCE	PROBAND WISE CONCORDANCE	TETRACHORIC CORRELATIONS
	All DZ	56	444	.11	.20	
Persistent group	MZM	2	15	.12	.21	.40
	MZF	1	10	.09	.17	.38
	DZM	0	23	0	0	-.14
	DZF	0	11	0	0	-.06
	DZO	0	36 (M) 8 (F)	0	0	-.17
Combined	All MZ	3	25	.11	.19	
		0	78	0	0	

Abbreviations: MZM = monozygotic male, MZF = monozygotic female, DZM = dizygotic male, DZF = dizygotic female, DZO = dizygotic opposite sex

Note. In DZO pairs the two numbers in the discordant column refer to pairs with affected male (M) or female (F) children (i.e. of the 116 discordant DZO pairs at age 3, in 76 of pairs, the male was the stutterer and in the other 40 pairs the female was the stutterer). Tetrachoric correlations are estimated in the modeling and indicate the strength of correlation between members of twin pairs for two normally distributed variables that are both expressed as a dichotomy (affected / unaffected).

Table 6

Best-fitting liability threshold model results for categorical data on stuttering (unaffected /affected) by age.

Models	Par	-2LL	df	LRT(df)	AIC
AGE 3					
Saturated model	15	2923.973	11132		
AE model equated across boys and girls	4 (+ 2 constraints)	2940.503	11145	16.53 (13)	-9.47
AGE 4					
Saturated model	15	4237.520	14576		
AE model equated across boys and girls	4 (+ 2 constraints)	4257.588	14589	20.07 (13)	-5.93
AGE 7					
Saturated model	15	2136.411	14091		
AE model equated across boys and girls	4 (+ 2 constraints)	2146.991	14104	10.58 (13)	-15.42

Abbreviations: Par = Parameters estimated in the model. -2LL = Log likelihood fit statistic. df = Degrees of freedom. LRT(df) = Likelihood ratio χ^2 test with Δ df comparing reduced models to the full model. AIC = Akaike's information criteria (as computed by $LRT - 2*df$), the smaller the AIC the better the fit of the model. Nonsignificant p- values indicate a good model fit.

Note: Models tested were: ACE full sex limitation model allowing both qualitative and quantitative sex difference, ACE common effect submodel allowing only quantitative sex differences, ACE allowing no qualitative or quantitative sex differences, AE allowing no qualitative or quantitative sex differences and dropping the shared environment parameter, equivalent ADE models were also tested but did not lead to a better fit.

Table 7

Standardised parameter estimates for best fitting models with 95% confidence intervals (CIs) in different age groups (unaffected /affected) for the best-fitting models (as indicated in Table 5).

	A	C	E	Threshold
AGE 3				
Boys				1.78 (1.72 - 1.85)
	.58 (.44 - .71)	n/a	.42 (.29- .56)	
Girls				2.00 (1.92 - 2.07)
AGE 4				
Boys				1.68 (1.63 - 1.73)
	.65 (.54 - .74)	n/a	.35 (.26 - .46)	
Girls				1.97 (1.91 - 2.04)
AGE 7				
Boys				2.00 (1.93 - 2.07)
	.66 (.51 - .78)	n/a	.34 (.22 - .49)	
Girls				2.38 (2.29 - 2.47)

Abbreviations: A = additive genetic influences, C = common (shared environmental influences), E = unique environmental influences

Note: Threshold values refer to equivalent cutoff values in normal distributions (i.e. a threshold value of 1.78 refers to the top 3.7% of the distribution). The non-overlapping threshold values for boys and girls indicate the fact that affected girls are at the higher end of the distribution compared to boys.

Table 8

Best-fitting liability threshold model results for the recovered and persistent groups of children (1 threshold model - unaffected /affected).

Models	Par	-2LL	df	LRT(df)	AIC
RECOVERED GROUP					
Saturated model	15	6502.854	12742		
AE equated across boys and girls	4 (+ 2 constraints)	6520.398	12755	17.54 (13)	-8.46
PERSISTENT GROUP					
Saturated model	15	1410.555	11927		
AE equated across boys and girls	4 (+ 2 constraints)	1426.514	11940	15.96 (13)	-10.04

Note: Models tested were: ACE full sex limitation model allowing both qualitative and quantitative sex difference, ACE common effect sub-model allowing only quantitative sex differences, ACE allowing no qualitative or quantitative sex differences, AE allowing no qualitative or quantitative sex differences and dropping the shared environment parameter. Non-significant p-values indicate that the model tested is a good fit for the data.

Table 9

Standardised parameter estimates (with 95% confidence intervals) for best fitting models (recovered and persistent groups of children).

A	E	Threshold 1
RECOVERED GROUP		
Boys		1.36 (1.31 - 1.40)
.67 (.60 - .74)	.33 (.26 - .40)	
Girls		1.53 (1.48 - 1.58)
PERSISTENT GROUP		
Boys		2.09 (2.01 - 2.17)
.60 (.28 - .82)	.40 (.18 - .72)	
Girls		2.54 (2.42 - 2.66)

Note: Threshold values refer to equivalent cutoff values in normal distributions (i.e. a threshold value of 1.78 refers to the top 3.7% of the distribution). The non-overlapping threshold values for boys and girls indicate the fact that affected girls are at the higher end of the distribution compared to boys.

Table 10

Cross - concordance of recovered and persistent twin pairs.

Zygosity	Recovery or Persistence- Twin 2					
	Missing	Unaffected	Recovered	Persistent	Total	
MZ						
Recovery	301	40	10	1	352	
or						
Unaffected	34	1959	98	11	2102	
Persistence	8	105	68	4	185	
- Twin 1	0	14	5	3	22	
Total	343	2118	181	19	2661	
DZ						
Recovery	546	74	7	0	627	
or						
Unaffected	59	3466	223	41	3789	
Persistence	7	221	56	6	290	
- Twin 1	2	37	8	0	47	
Total	614	3798	294	47	4753	