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Genetic influences on handedness: Data from 25,732 Australian and Dutch twin families

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ABSTRACT

Handedness refers to a consistent asymmetry in skill or preferential use between the hands and is related to lateralization within the brain of other functions such as language. Previous twin studies of handedness have yielded inconsistent results resulting from a general lack of statistical power to find significant effects. Here we present analyses from a large international collaborative study of handedness (assessed by writing/drawing or self report) in Australian and Dutch twins and their siblings (54,270 individuals from 25,732 families). Maximum likelihood analyses incorporating the effects of known covariates (sex, year of birth and birth weight) revealed no evidence of hormonal transfer, mirror imaging or twin specific effects. There were also no differences in prevalence between zygosity groups or between twins and their singleton siblings. Consistent with previous meta-analyses, additive genetic effects accounted for about a quarter (23.64%) of the variance (95%CI 20.17, 27.09%) with the remainder accounted for by non-shared environmental influences. The implications of these findings for handedness both as a primary phenotype and as a covariate in linkage and association analyses are discussed.

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1. Introduction

Handedness is first demonstrated between 9 and 10 weeks gestation, as embryos begin to exhibit single arm movements (Hepper, McCartney, & Shannon, 1998). The archaeological record of cultural and skeletal remains provides evidence of population level biases towards right-handedness in early humans (Steele, 2000; Toth, 1985). It has been hypothesized that lateralized behaviors either arose *de novo* in early *Homo sapiens* (Annett, 2002; Corballis, 1997; McManus, 2002) or evolved from ancestral population level behavioral asymmetries (Vallortigara & Rogers, 2005). From a neuropsychological perspective, lateralization in the form of hand or foot preference remains the best behavioral predictor of cerebral lateralization. Left-hemisphere language dominance is reported in approximately 95% of right-handers and 70% of left-handers (Elias & Bryden, 1998; Pujol, Deus, Losilla, & Capdevila, 1999) and behavioral laterality has also been found to predict emotional lateralization (Elias, Bryden, & Bulman-Fleming, 1998).

Although there is evidence that behavioral laterality develops prenatally (Hepper, Wells, & Lynch, 2005), the extent to which this population level bias can be explained by genetic effects has been the topic of much debate. One method by which this may be explored is through the comparison of relatives who differ in the amount of genetic information they share. Twin studies, in which

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the similarity of identical (monozygotic; MZ) and non-identical (dizygotic; DZ) twin pairs are compared, provide estimates of the relative magnitude of genetic and environmental influences and have proved popular in studying behavioral laterality. Since the first study by Siemens (1924) there have been thirty-seven twin studies of handedness published (for reviews see McManus, 1980; Medland, Duffy, Wright, Geffen, & Martin, 2006; Sicotte, Woods, & Mazziotta, 1999).

Unfortunately, the results have been mixed and as handedness is typically analyzed as a binary trait (left or non-right vs. right) the issue of sample size is nontrivial. For example, for a trait with a 10% prevalence (which is typical of left-handedness) where 30% of the variance is accounted for by an additive genetic effect, about 1000 pairs of twins would be required to reject a purely unique environmental model with 80% power (Neale, Eaves, & Kendler, 1994). Larger samples are required to distinguish between genetic and shared environmental influences (Neale et al., 1994). However, the median sample size of the 35 studies reviewed by Medland et al. (2006) was 189 pairs indicating a general lack of statistical power due to small sample sizes within the literature. Thus, with few exceptions (Basso et al., 2000; Medland et al., 2003; Neale, 1988; Orlebeke, Knol, Koopmans, Boomsma, & Bleker, 1996; Ross, Jaffe, Collins, Page, & Robinette, 1999), sample sizes have not been adequate to detect genetic or environmental effects that account for less than 50% of the total phenotypic variance with 80% power.

The aim of the present study was to characterize the heritability of hand preference (defined as writing/drawing hand or self reported preference) in a large genetically informative sample. To this end we used data from 54,270 twins and their non-twin siblings from 25,732 Australian and Dutch twin families. Previous twin studies of handedness have typically only compared the similarity of mono- and dizygotic twins. By using an extended twin and sibling design, the present study allowed tests of special twin effects both on the prevalence of left-handedness and the covariation between siblings, thus also providing a test of the generalizability of these findings to the general population.

Behavioral laterality may be modified by cultural and environmental effects (Laland, Kumm, Van Horn, & Feldman, 1995) potentially masking genetic effects. Within western cultures, the prevalence of left-handedness (as defined by writing-hand) has gradually increased over the last century from around 2% in 1900 to between 10 and 15% in more recent samples (1990–2000) (Annett, 2002; McManus, 2002; Perelle & Ehrman, 1994). While cultural pressures have been hypothesized to decrease the prevalence of left-handedness, exposure to adverse environments and pathogenic insults has been hypothesized to increase the prevalence of left-handedness (Satz, Orsini, Saslow, & Henry, 1985). In addition, subtle neurological insults may also result in lasting changes in hand preference without deficits in other neuropsychological domains (Triggs, Tesar, & Yong, 1998). A wide range of pathogenic risk factors have been proposed, including, low birth weight, birth stress and ultrasound exposure (Bailey & McKeever, 2004; Bakan, Dibb, & Reid, 1973; Salvesen, 2002). Previous studies have typically found that lower birth weights were associated with higher rates of left-handedness (Hay & Howie, 1980; Orlebeke et al., 1996; Powls, Botting, Coooke, & Marlow, 1996). To account for these effects, birth cohort (year of birth) and birth weight were included as covariates in the current study.

2. Methods

2.1. Participants and measures

The data were collected within a number of twin studies conducted in Australia and the Netherlands. The focus of these studies, the number of participants, the method of data collection and method of zygosity determination are summarized in Table 1. In the Netherlands twin registry Older twins study, self classification (left-handed, right-handed or either) was used to determine handedness. In the Australian Twin ADHD Project and the Younger Netherlands twin study handedness was assessed by asking which hand is used for drawing. In all other studies, handedness was assessed as the hand used for writing. Following Annett (2002) and McManus (2002) reports of mixed handedness or ambidexterity, which were less than 1% of total reports, were classed as left-handed. Previous studies have shown self report (left-handed, right-handed or either) and hand used for writing (left vs. right) to be highly correlated .97 (data from Perelle & Ehrman, 1994). Similarly, drawing hand and writing hand are highly correlated .97 (estimated from parental report of drawing hand from the Australian Twin ADHD Project and self-reported writing hand from the Brisbane adolescent study as described below).

As the majority of Australian studies recruited twins from the Australian Twin Registry which uses a centralized identification number system we were able to check for overlap between the Australian studies. When an individual had participated in more than one study or wave of data collection the most recent report was used (as described in the following paragraph we used the multiple reports of hand preference to assess the reliability of the measure). For one of the Australian studies (the Sex study) we were only able to identify the individuals who had returned a consent form, as the data in this survey were collected anonymously. To account for this we excluded the data from individuals who had returned a consent form for this study from any other data set (1215 individuals).

The large number of participants who contributed on multiple occasions within the Australian data set, and the longitudinal nature of the Netherlands adult twin study, afford an excellent opportunity to assess the test–retest reliability of hand-preference. Within the Australian data 1509 individuals reported their hand preference twice, while an additional 256 individuals reported their hand preference three times. The polychoric correlation between the multiple reports was .994 indicating the high reliability of self reported hand preference. Within the Netherlands adult twin study test–retest data were available for 6361 individuals (2948 reported twice, 1863 three times, 1206 four times, and 344 five times). As in the Australian data the polychoric correlation between the multiple reports of .993 supported the high reliability of this measure, which has been previously demonstrated to remain virtually unchanged in the absence of injury or insult (Liederman & Healey, 1986; Raczkowski, Kalat, & Nebes, 1974).

In addition, parent and self-reported handedness was available for 60 pairs of twins who had participated in both the Brisbane adolescent study and Australian Twin ADHD Project. The polychoric correlation between parent and self-reported handedness of .970 indicates the high reliability of parental report in these data (which may be expected as twins are allowed to help the parents complete the questionnaires). These results suggest that parental report is a valid method of data collection and comparable with self-report in terms of accuracy when the measures of handedness are salient. Based on these results it was decided that parental reports collected in the Australian Twin ADHD Project and younger Netherlands twin studies could be used to assess the handedness of their offspring.

2.2. Statistical analyses

To model the binary hand preference data we employed the multifactorial threshold model which describes discrete traits as reflecting an underlying normal distribution of liability (or predisposition). Liability, which represents the sum of all the multifactorial effects, is assumed to reflect the combined effects of a large number of genes and environmental factors each of small effect and is characterized by phenotypic discontinuities that occur when the liability reaches a given threshold (Neale & Cardon, 1992). The distribution of hand preference assessed for multiple items is J-shaped. However, for self classification or writing hand the distribution is effectively binary. It is not difficult to conceptualize hand preference as reflecting the continuous and normally distributed measure of relative hand skill with a mean shifted towards the right as measured by a peg moving task (Annett, 1985).

All data analyses were conducted using maximum likelihood analyses of raw data within Mx (Neale, Boker, Xie, & Maes, 2006) which maximise the natural log of the following likelihood of the data:

$$L = \prod_{i=1}^{M} (2\pi)^{-k_i/2} |\Sigma_i|^{-1/2} e^{-1/2[(y_i-\mu_i)' \Sigma_i^{-1} (y_i-\mu_i)]},$$

with respect to Σ_i and μ, where k is the number of data observations for family i (which in this case is equal to the number of siblings for whom data is collected), Σ_i is the expected covariance matrix among the variables for family i, y_i is a vector of observed scores obtained for the k variables for family i, μ_i is the vector of expected means for family i, and M is the number families. Corrections for known covariates, Sex, Year of Birth (both linear and quadratic effects), and birth weight were included with the threshold models in all data analyses. Year of birth ranged from 1906 to 2002 (median 1981) in the Australian data and from 1914 to 1998 (median 1989) in the Dutch data. To avoid computational difficulties year of birth was rescaled by subtracting 1950 and dividing by 10. Birth weight ranged from 454 to 5675 g (mean 2647.76, S.D. 604) in the Australian data and from 580 to 5500 g (mean 2594.60, S.D. 580) in the Dutch data. Birth weight was converted to a z-score before analysis.

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