

The inheritance of left-handedness

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Abstract. Left-handedness occurs in about 8% of the human population. It runs in families and an adoption study suggests a genetic rather than an environmental origin; however, monozygotic twins show substantial discordance. The only genetic models that successfully explain the family and twin data are those of McManus and Annett, which share the feature of incorporating a random component reflecting the biological phenomenon of 'fluctuating asymmetry'. The models have each been modified to explain the greater incidence of left-handedness in males. The McManus model is more successful at explaining the maternal effect—left-handed mothers have more left-handed offspring than do left-handed fathers. Both models explain the association of handedness with cerebral language dominance. The models differ principally in their conception of the phenotypes of handedness: Annett proposes a unimodal continuum, McManus proposes two discrete categories of handedness. Finding the gene for handedness and hence for language dominance would unlock the neurobiology of language. Two ways of finding the gene for handedness are proposed: searching the pseudoautosomal region of the X chromosome or invoking a specific evolutionary model of lateralization in which the handedness gene has evolved from the *situs* gene then searching the human genome for homologues to the mouse *situs* gene.

1991 Biological asymmetry and handedness. Wiley, Chichester (Ciba Foundation Symposium 162) p 251–281

'The existence of a dominant hemisphere raises a number of problems, the most fundamental of which is why it should exist. . . . A question of major interest is the relationship between cerebral dominance for speech and handedness. . . . It may be possible for the geneticists to settle this question . . .'.

Lord Brain, (at the Ciba Foundation Symposium,
Disorders of Language, 21st May, 1963)

About 8% of the human population is left handed, using the left hand preferentially for complex skilled activities such as writing. Art historical evidence suggests the incidence has been constant for five millenia (Coren & Porac 1977); patchier palaeontological evidence suggests that human brain asymmetry has existed for a million years or so. Handedness is therefore a stable, behavioural polymorphism.

In 1865 Paul Broca showed that most individuals have language functions localized in the left cerebral hemisphere. Although left-handers were once thought to show the mirror image of this pattern, the relationship is actually more complex, 5% of right-handers and 30% of left-handers have language functions localized in the right hemisphere. Handedness and language localization are therefore interconnected, albeit not simply.

If any cognitive ability is typical of mankind, it is language; understanding language's biological bases would illuminate much of cognitive neuroscience. Handedness is another peculiarly human characteristic. Rats, mice, cats and dogs all show individual handedness (or strictly pawedness) in that each animal has an individual preference for using the right or the left paw. However, in those species there is no population preference, 50% prefer the left paw and 50% the right paw (e.g. Collins 1977). Recent claims that primates show population handedness preferences (MacNeillage et al 1987) have been much criticized and are not supported by thorough naturalistic studies such as those in the mountain gorilla (R. W. Byrne, J. M. Byrne, personal communication 1991).

The unique occurrence of handedness and language in humans, the lateralization of language and its association with handedness suggest that understanding the biology of handedness should illuminate the biology of language. Handedness is intrinsically simpler to study than language dominance, because of its ease of measurement. It is therefore an excellent surrogate for language dominance in the study of one of neurobiology's big problems.

The incidence of left-handedness

A meta-analysis of 284 665 individuals described in 88 studies in the literature (Seddon & McManus 1991) found an overall incidence of left-handedness of 7.78%. Variation between studies (Fig. 1) was not related to measurement methods (such as the numbers of items on inventories). The incidence was related to two background measures: the number of subjects, smaller studies reporting somewhat higher incidences, and the age of subjects, older subjects showing less left-handedness. Age and year of birth were highly correlated with each other across studies; the data did not allow disentanglement of an age effect from a cohort effect, although date of publication did not relate to the incidence. Of particular interest is the absence of geographical differences, a finding compatible with handedness being a balanced polymorphism present in all cultures. No cultural group has been found in which the incidence of left-handedness deviates substantially from 8%. As a single example of cultural uniformity, Professor Kevin Connolly (personal communication, 1991) has measured handedness in a pre-literate culture in a remote area of the Western Highlands of Papua New Guinea: of 188 individuals 21 (11.2%; 95% confidence interval = 6.7% to 15.7%) showed preferential use of the left hand.

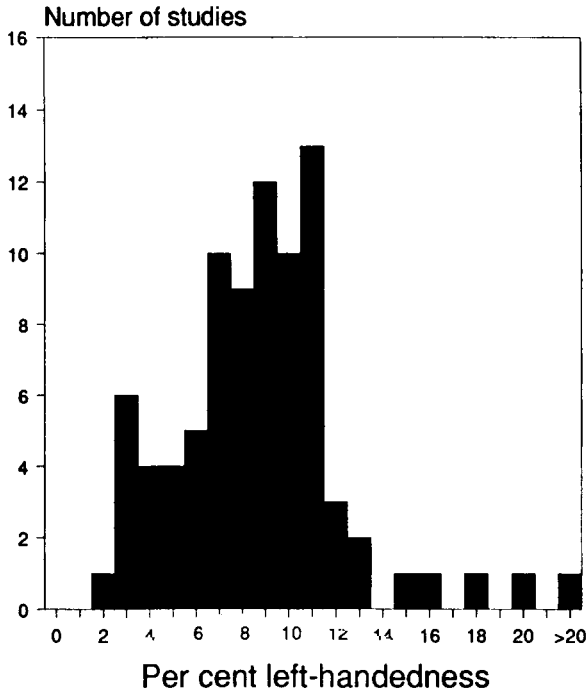


FIG. 1. Overall incidence of left-handedness from a meta-analysis of 100 populations examined in 82 studies. From Seddon & McManus (1991).

The measurement of handedness

To the person in the street, handedness is straightforwardly described; individuals are right handed if they write with the right hand, with the proviso that a natural left-hander who is forced by social pressure to write with the right hand is really left handed. However, the description of handedness has been complicated by more sophisticated measures (see Bishop 1990 for a good review).

Handedness is assessed as either *preference* or *skill*. These are highly correlated in normal individuals (although recently we have found that autistic children show no correlation of handedness/preference and handedness/skill; I. C. McManus, B. Murray, K. Doyle, S. Baron-Cohen, unpublished). Handedness/preference is often measured using a questionnaire that asks which hand is preferred for a range of tasks. In children handedness/preference is more often measured using performance tasks; the observer notes which hand a subject uses for a range of unimanual tasks. Handedness/skill is measured using manual tasks in which subjects use first one hand and then the other, for example to make marks with a pencil or to move pegs across a board:

handedness is expressed as either a difference score ($R - L$) or a standardized difference score ($(R - L)/(R + L)$).

Measures of handedness/preference usually show a bimodal distribution, with few subjects appearing truly ambidextrous (e.g. McManus 1979, McManus et al 1988). Handedness/skill measures are more controversial: some tasks, such as the Annett peg-board (Annett 1970) give a unimodal distribution, suggesting a continuum of handedness; whereas other tasks, such as putting dots in circles (Tapley & Bryden 1985) or squares (McManus 1985a), give a bimodal distribution, implying two discrete categories of individual, analogous to the two modes found in handedness/preference measures. Elsewhere (McManus 1985a), I have argued that measures of handedness/skill differ principally in the extent to which they share skills used in the most highly developed skill asymmetry—writing. Peg-moving appears to be a unimodal distribution because it is less dependent upon asymmetrical processes, so that the modes have become closer, one being subsumed within the other; nevertheless, statistical decomposition of the distributions shows it is actually a mixture of normal distributions, as predicted (McManus 1985a).

Handedness measures can be analysed in terms of *direction* and *degree*. Direction of handedness considers whether a subject is on the right or left side of the distribution; it is defined as $\text{sign}(R - L)/(R + L)$. Degree of handedness assesses whether subjects show weak laterality (i.e. are nearly ambidextrous) or strong laterality; it is defined as $\text{Abs}(R - L)/(R + L)$. Most genetic studies of human handedness have assessed direction of handedness; in this paper I will also do so. Familial studies of degree of human handedness show no parent-offspring correlation (McManus 1979, 1985b) or very weak correlations (Bryden 1982, Coren & Porac 1980). Collins (1985) has selected mice for high and low degrees of pawedness, resulting in two strains (HI and LO). Elsewhere (McManus, submitted), I have suggested that these strains are not evidence that degree of handedness is under direct genetic control. Selection may have been for overall heterozygosity, the LO mice being less heterozygous; this would also explain their lower birth weight, poorer reproductive fitness and the lower proportion of males.

Environmental influences on handedness

Although this paper argues principally for a genetic influence on handedness, there have been suggestions that environmental influences are also important. Perhaps most influential is the birth stress hypothesis, which states that pathological left-handedness results from intrapartum anoxia. The meta-analysis of Searleman et al (1989) has effectively disposed of this theory.

Since 1982, Geschwind's hypothesis (see Geschwind & Galaburda 1987) that fetal testosterone levels relate to handedness, cerebral dominance and a range of other conditions has received much attention. The hypothesis is complex

and difficult to present as a formal model (see McManus & Bryden 1991a). A final verdict is probably premature, although it is safe to say that many of the theory's postulated correlations have not been replicated (see McManus et al 1990, Marchant-Haycox et al 1991).

Evidence for a genetic basis for handedness

Family studies

Left-handedness undoubtedly runs in families. McManus & Bryden (1991b) reviewed 25 studies, based on 72 600 offspring, relating handedness of children to parental handedness (Fig. 2). Clearly, left-handedness is more common if one parent is left handed, and still more common if both parents are left handed.

Left-handedness is often reported to be more common in males than females. A meta-analysis by Seddon & McManus (submitted) of sex differences in 63 studies found a 27.4% higher incidence in males than females (Fig. 3); the difference was unrelated to any other measures. McManus & Bryden (1991b) also looked at parental and offspring handedness in relation to the sex of parents and offspring; eighteen studies were available (Table 1). Log-linear modelling (of individual studies not grouped data as in Table 1, which is purely for illustrative purposes) showed a higher incidence of left-handedness in male parents and male offspring; additionally, left-handed mothers had more left-handed offspring than did left-handed fathers, although there was no interaction with sex of offspring. This 'maternal effect' has been reported before in the literature (e.g. McGee & Cozad 1980, Annett 1985a); there seems little doubt of its reality and it must be explained by any adequate genetic model of handedness.

Adoption studies

Familial associations need not imply genetic transmission because families also transmit culture and environment. Adoption studies can separate genetic effects from environmental ones. Surprisingly, only a single, adequate adoption study has looked at children adopted early enough and assessed at a late enough age for handedness to be defined. Carter-Saltzman (1980) showed that, in contrast to that of normal, biological children, the handedness of adopted children showed no relationship to that of their adoptive parents. We may therefore interpret familial trends as reflecting genetic effects.

Twin studies

Twin studies have long been seen as the Achilles heel of the genetics of handedness. Table 2, from McManus & Bryden (1991b), summarizes 14 studies, collected since 1930. Data obtained earlier are biased because discordant

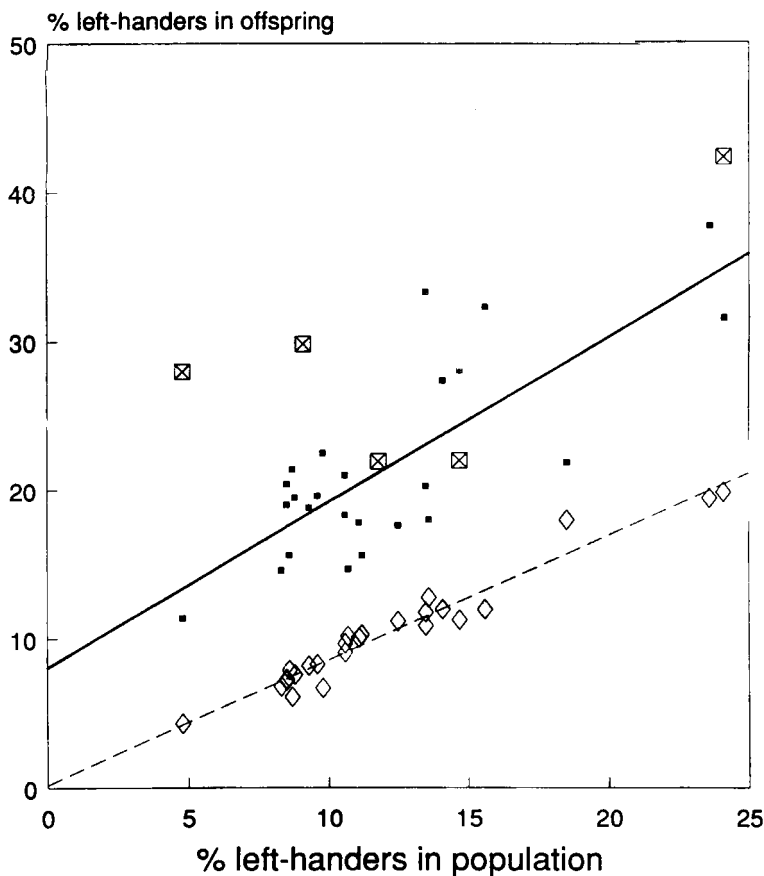


FIG. 2. Handedness in offspring of $R \times R$, $R \times L$ and $L \times L$ matings in relation to the overall incidence of left-handedness in the cohort. Offspring, parental and grandparental generations are plotted separately within studies, since the incidence of handedness is typically different in each. Dashed and solid lines represent best-fitting linear regressions through the offspring of $R \times R$ (\diamond) and $R \times L$ (\blacksquare) matings, respectively. Offspring of $L \times L$ (\boxtimes) matings are rare and therefore several studies with similar overall incidences of left-handedness have been amalgamated. From McManus & Bryden (1991b).

handedness was used as a criterion of monozygosity, in the belief that it represented 'mirror imaging' (McManus 1980). Discordance of handedness is frequent in monozygotic (MZ) and dizygotic (DZ) twins. Comparison of the expected proportions under a binomial distribution with the observed frequencies shows fewer discordant MZ pairs (90.1% of expected) than DZ pairs (99.3% of expected). MZ twins are therefore more similar than DZ twins. Nevertheless, the substantial amount of discordance requires explanation by any adequate genetic model.

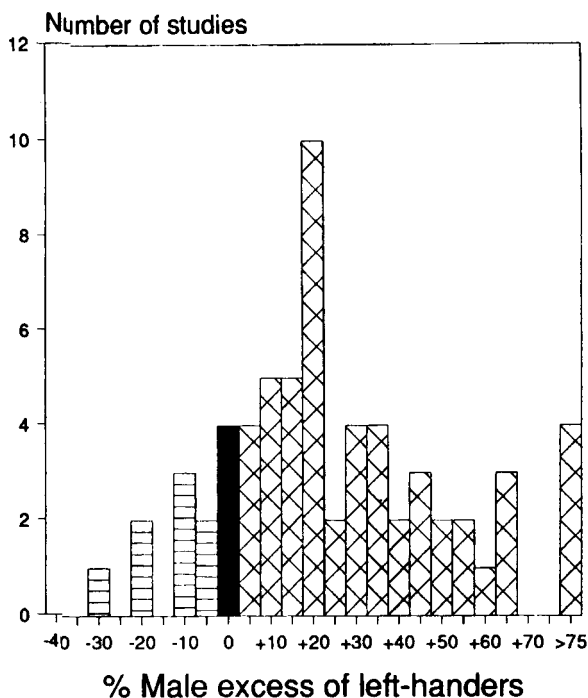


FIG. 3. The excess incidence of left-handedness in males expressed as a proportion of the incidence in females ($100 \times (\text{Male} - \text{Female}) / \text{Female}$) on the basis of a meta-analysis of 63 populations. Hatched, $M > F$; striped, $M < F$; black, $M = F$. From Seddon & McManus (1991).

TABLE 1 Handedness in families, according to maternal/paternal handedness and the sex of offspring

Parental handedness		Left-handed offspring		
Father	Mother	Sons	Daughters	Total
Right	Right	10.4% (30 268)	8.5% (26 020)	9.5% (63 250)
Right	Left	22.1% (1815)	21.7% (1688)	19.5% (8933)
Left	Right	18.2% (2308)	15.3% (2100)	
Left	Left	27.0% (215)	21.4% (168)	26.1% (417)

Overall totals ignoring sex are based on 25 sets of data; entries by sex of parents and offspring are based on 18 studies. From McManus & Bryden (1991b).

TABLE 2 Frequency of monozygotic and dizygotic twin pairs concordant and discordant for handedness, based on 14 studies

<i>Handedness of twins</i>	<i>Monozygotic</i>	<i>Dizygotic</i>
Right/Right	2184	1951
Right/Left	629	585
Left/Left	87	53
Observed/expected discordant pairs	0.901	0.993

The ratio of observed to expected discordant pairs is estimated by calculating for each study the ratio of the actual number of discordant pairs and the proportion expected under a binomial distribution, then averaging the ratios across studies. From McManus & Bryden (1991b).

Genetic models of handedness

Many genetic models of handedness have been published (see McManus & Bryden 1991b for a review). Most have failed because they predict that right-handers or left-handers 'breed true', or because they do not predict MZ twin discordance. At present there are only two adequate models: the 'right-shift' model of Annett (1978, 1985a) and my own genetic model (McManus 1979, 1984a, 1985b). These models were developed independently in the late 1970s. The success of each indubitably results from the same key feature—that one genotype does not control handedness in the strict sense, but results in randomness and hence right-handers and left-handers in equal numbers. This situation is known in biology as 'fluctuating asymmetry'; it is seen in the inheritance of *situs inversus* encoded by the *iv* gene of the mouse (Layton 1976) and in Kartagener's syndrome in humans. The 'inheritance' of non-human handedness depends entirely on this randomness that produces a 50% incidence of left-handedness and non-transmissibility to offspring.

McManus' genetic model

This model originally proposed two alleles, *D* (*Dextral*) and *C* (*Chance*), at a single, autosomal locus (Table 3). The *DD* genotype produces right-handedness in all offspring. The *CC* genotype results in fluctuating asymmetry, 50% of offspring being right handed and 50% left handed. The offspring are *not* ambidextrous—each is fully right handed or left handed, lateralization being absent at the level of the population not the individual. Model-fitting (McManus 1985b) showed that the effects of the alleles in the heterozygote, *DC*, had to be additive, producing 25% left-handers. The population gene frequency, $p(C)$, is estimated from the family and twin data to be 0.155, and is assumed to be identical in each study population. Differences between populations in the incidence of manifest left-handedness are assumed to represent response biases or criterion problems (McManus 1985b).

TABLE 3 The inheritance of handedness and cerebral dominance predicted by the genetic models of McManus and McManus & Bryden*(a) McManus' (1985a) genetic model*

<i>Genotype</i>	<i>% left-handedness</i>	<i>% right cerebral language dominance</i>
<i>DD</i>	0	0
<i>DC</i>	25	25
<i>CC</i>	50	50
	$p(C) = 0.155$	

(b) McManus & Bryden's (1991b) genetic model

	<i>Modifier gene in males</i>		<i>Modifier gene in females</i>		
	<i>M</i>	<i>m</i>	<i>MM</i>	<i>mM</i>	<i>mm</i>
<i>DD</i>	0	50	0	0	50
<i>DC</i>	25	50	25	25	50
<i>CC</i>	50	50	50	50	50
		$p(C) = 0.135$		$p(m) = 0.045$	

D (*Dextral*) and *C* (*Chance*) are alleles at an autosomal locus. *M* and *m* are alleles at a modifier locus on the X chromosome. The entries in (b) show the percentage left-handedness or right cerebral language dominance. $p(C)$ is an estimate of the frequency of allele *C* in the population; $p(m)$ of the *m* allele.

The model fits family data well. It predicts that $R \times R$, $R \times L$ and $L \times L$ matings (*R*, right-handed; *L*, left-handed) produce 5.97%, 17.42% and 28.87% of left-handers, values compatible with Fig. 2. Discordance in MZ twins is explained by assuming that chance processes in the *CC* and *DC* genotypes occur *independently* in each monozygotic twin, so that in 25% of *CC* MZ twin pairs both are right handed, in 25% both are left handed and 50% of pairs are discordant. Formal calculations using this model predict 11.02% of MZ pairs and 12.66% of DZ pairs to be discordant, each value being less than predictions under a binomial distribution of 14.29% discordance.

The model is extended to explain cerebral dominance by assuming that the genes also control language dominance; *DD* individuals are all dominant, *CC* individuals are right or left dominant with equal probabilities. The model predicts that 5.98% of right-handers and 28.88% of left-handers will be right-hemisphere dominant.

Originally, the McManus model did not attempt to explain sex differences or the maternal effect. In a recent modification it accounts for these problems (see below).

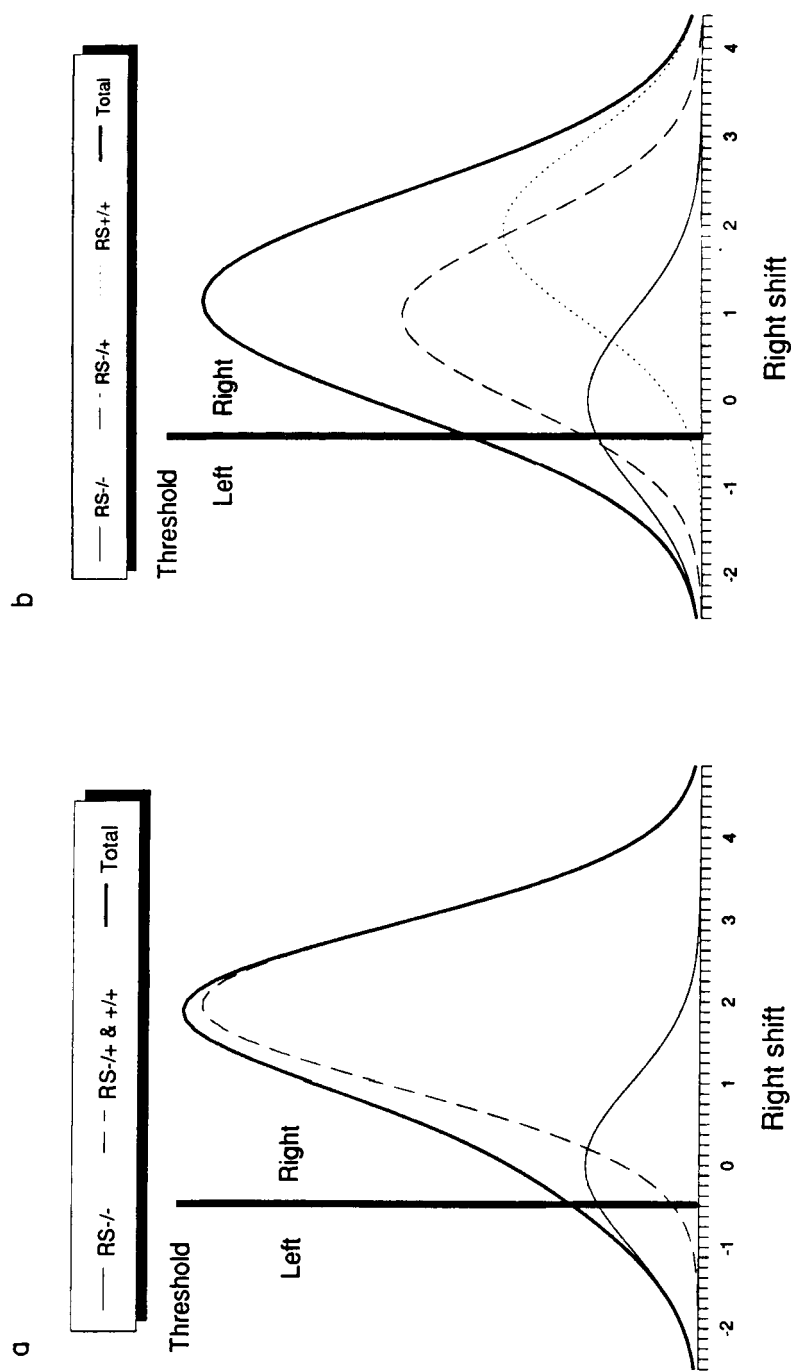


FIG. 4. The phenotypic distributions of the RS - / - , RS - / + and RS + / + genotypes, as predicted by (a) the Annett (1978) model, and (b) the Annett (1983) model (described in Annett & Kilshaw 1983). Distributions are shown only for singletons: those for twins are shifted somewhat less to the right.

Annett's right-shift model

Annett's right-shift model originates in the observed unimodal distribution of between-hand skill differences. In the 1978 model these were attributed to two populations: one, phenotype RS⁻, lacked a right shift (RS) and had a mean skill difference of zero; the other, RS⁺, had its mean shifted 1.96 standard deviations (S.D.s) to the right (see Fig. 4a). Populations differ in manifest incidence of handedness because survey methods use different criteria for 'left-handedness'. Phenotypes were determined by two alleles at an autosomal locus, with + dominant to -; -/+ and +/+ produced RS⁺ and -/- produced RS⁻ phenotypes. The model fitted various sets of family data, but did not fit twin data well. The problem was circumvented by the *ad hoc* assumption of a right shift of only 1 S.D. in RS⁺ MZ twins. The model accounted for language dominance by assuming a 50% chance of right hemisphere language dominance in RS⁻ phenotypes. The frequency of the - allele was calculated from a knowledge of the incidence of left-handers with right-hemisphere language dominance.

The right-shift model was modified in 1983 (Annett & Kilshaw 1983) to make the -/+ genotype additive, so that the R⁻/-, RS⁻/+ and RS⁺/+ phenotypes had right shifts of 0, 0.98 and 1.96 S.D.s (Fig. 4b). The model was further modified (Annett 1985a) with the proposal that males and females differed in their right shift; the RS⁻/-, RS⁻/+ and RS⁺/+ genotypes having shifts of 0, 1 and 2 S.D.s in males and 0, 1.2 and 2.4 S.D.s in females. The model then accounted for the excess of left-handed males, albeit by adding an additional parameter. However, as Annett (1985a; p. 327) recognized, the model still cannot adequately explain the maternal effect, the calculated effect being far smaller than the observed one (Table 4a).

The McManus and Bryden (1991) model

McManus & Bryden (1991b) have modified the McManus genetic model to account for sex differences and the maternal effect. The revised model proposes the same autosomal locus with *D* and *C* as previously, plus an additional X chromosomal modifier locus, with two alleles, *M* and *m*. (Modifier genes have also been invoked in the genetics of Tourette's syndrome (Comings & Comings 1986) and fragile X syndrome (Israel 1987).) The dominant gene, *M*, does not affect the function of *D* and *C* alleles. However, in the *m* genotype in males or the *mm* genotype in females, *m*, the rarer recessive gene, modifies *D* alleles to act as *C* alleles, substituting fluctuating asymmetry for directional asymmetry (Table 3b). The *C* allele occupies about 13.5% of its gene pool and the *m* allele about 4.5% of its gene pool. Not surprisingly, the model's extra parameter allows it to explain the excess of male left-handedness. More gratifying is that the model also predicts a substantial maternal effect (Table 4b), albeit not quite as large

TABLE 4 The predictions of the Annett (1985a) and McManus & Bryden (1991b) models of the inheritance of handedness

<i>Handedness of parents</i>		<i>% left-handedness in offspring</i>	
<i>Father</i>	<i>Mother</i>	<i>Sons</i>	<i>Daughters</i>
<i>(a) Annett (1985a) model</i>			
Right	Right	10.69	9.07
Right	Left	18.27	16.57
Left	Right	17.41	15.72
Left	Left	28.86	28.09
<i>(b) McManus & Bryden (1991b) model</i>			
Right	Right	10.49	8.63
Right	Left	21.50	19.55
Left	Right	18.49	17.44
Left	Left	29.40	28.39

Calculations are given for a population incidence of left-handedness of 6.7% in parents and 10.83% in offspring, the particular incidences found in Table 1, so that direct comparison is possible. For the model of Annett (1985a) the right shift is 2.4 and 2.0 for RS +/+ , 1.2 and 1.0 for RS +/- and 0 and 0 for RS -/- in females and males, respectively; the frequency of the RS- allele is 0.4306. The model of McManus & Bryden (1991b) is as given in Table 3b.

as that observed. However, the model has not yet been formally fitted and better parameter estimates may produce a better fit. McManus & Bryden have also noted that there is a cluster of conditions, such as stuttering, dyslexia and autism, characterized by a male preponderance and increased sinistrality; the modifier gene proposed here might explain such associations if it modified not only the cerebral dominance gene but also other autosomal loci involved in language or communication.

Comparing the McManus and Annett models

Both models succeed because they reflect the biology of asymmetry and especially of fluctuating asymmetry. Differences result from their conceptions of the phenotype of handedness: Annett sees a continuum of skill differences as the primary phenotype, preference occurring secondarily, whereas McManus sees a dichotomous, categorical measure of preference as primary, with skill differences of only secondary importance. The question is complex in its details (McManus 1985a, see also Annett 1985b), although I have argued that data on skill differences are more compatible with my own 'symmetric bimodal' model than with the right-shift model.

Formal comparisons of the McManus (1985b) model with Annett's 1983 model have been carried out using maximum likelihood fitting (McManus 1985b); my own model was generally a better fit.

Finding the gene for handedness and cerebral dominance

In the 1990s genetic models are properly tested by finding DNA and assessing its properties. That is difficult if one has no specific idea of where to look in the genome and there are no obvious routes through known chromosomal errors or obvious gene products. More seriously, the fundamentally random component in the models of handedness results in a substantial loss of power when searching for linkage with polymorphic markers. Two routes do seem possible and, I would suggest, worth pursuing: looking for the gene in the pseudoautosomal region and investigating whether it is a homologue of the *iv* gene.

Is the handedness gene in the pseudoautosomal region?

Crow (1990) has provocatively and imaginatively hypothesized that the atypical cerebral temporal lobe lateralization in schizophrenia could be explained if the schizophrenia gene were a mutation of the cerebral dominance gene. Additionally, Crow points out that the excess of schizophrenia in the sex chromosome aneuploidies would be explained if the schizophrenia/cerebral dominance gene were in the X chromosome's pseudoautosomal region. If this is so, schizophrenia should be more likely to occur in siblings of the same sex when transmitted by the father, but there should be no such association when the mother transmits the condition. Crow et al (1989) reported data that supported that prediction. I. C. McManus & T. S. Crow (unpublished) have analysed a similar prediction for handedness. A large sample of families showed an effect in the predicted direction, although it was not statistically significant; however, power calculations suggested the need for extremely large studies. Nevertheless, the pseudoautosomal region may be an interesting area to explore for the handedness gene.

*An evolutionary model of the origins of handedness and cerebral dominance: the handedness gene as a homologue of the *iv* gene*

Humans show several independent, uncorrelated asymmetries, all seemingly under genetic control: *situs*, handedness and cerebral dominance, hand-clasping, arm-folding (see McManus & Mascie-Taylor 1979) and eye dominance. Of these, only handedness, *situs* and perhaps eye dominance are of functional importance, the others showing wide geographical variation in incidence. *Situs* is the only asymmetry shared with other vertebrates and hence is probably evolutionarily the oldest of the human asymmetries. Palaeontological evidence suggests that

vertebrate asymmetry originated perhaps 500 million years ago in a sub-group of the deuterostomes, the dextiothetica, which eventually formed modern vertebrates, chordates and echinoderms (see Jefferies, this volume). It is probable that the wild-type allele of the mouse *iv* gene (see Brueckner et al, this volume) is closely related to, if not the same as, the gene for dextiothetism (see Fig. 5).

Genes controlling anatomical and functional asymmetry are rare, and hence unlikely to have evolved separately. The handedness/cerebral dominance gene is therefore probably a mutation of the wild-type *iv* gene, which no longer causes cardiac asymmetry (see Brown et al, this volume) but causes cerebral asymmetry, perhaps by subtly altering a protein's tertiary structure. If this is true, then the handedness gene should be very similar to the *iv* gene. Other human asymmetries, of hand-clasping, arm-folding and eye dominance, being of less biological consequence than handedness but still acting on cerebral tissue, are most likely mutations of the handedness gene.

Such an evolutionary scenario suggests a straightforward way of finding the handedness gene. Firstly, find the *iv* gene in the mouse (see Brueckner, this

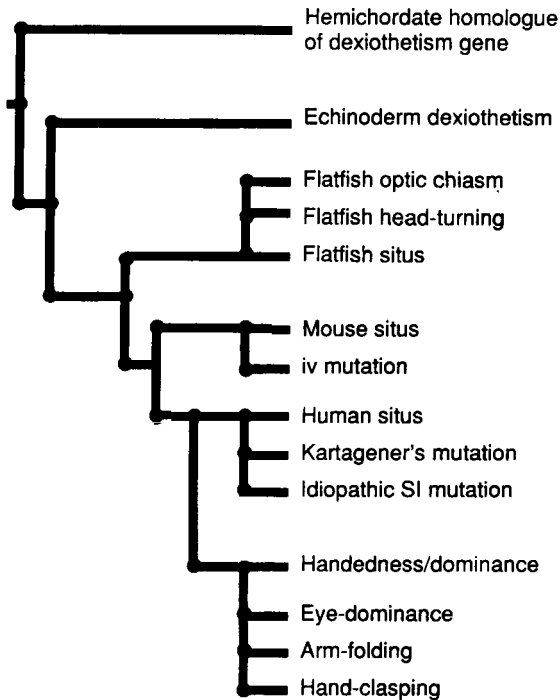


FIG. 5. A hypothetical evolutionary tree for the origins of the genes controlling handedness, hand-clasping, arm-folding, eye dominance, *situs* in humans, mice and flatfish, and dextiothetism.

volume), then hybridize the mouse *iv* gene to human DNA and search for partial homologues; one, probably very similar to the mouse gene, should be the human *situs* gene. Others of lesser homology should be the genes for handedness and the other asymmetries. Once the handedness gene has been found, it will be straightforward to determine its genetics, and to evaluate the McManus and Annett models. Other analyses are also possible. By studying *iv* gene homologues in flatfish, the evolution and inheritance of flatfish asymmetry (McManus 1984b) can be assessed. The evolutionary model of Fig. 5 can also be tested by looking for homologues in modern echinoderms. Last, but not least, identifying the handedness gene would allow *in situ* hybridization in embryos to determine when the gene is expressed and the sites of its action in embryogenesis.

It is probably not hyperbole to suggest that finding the gene for handedness and cerebral dominance would unlock the molecular biology and neurobiology of the characteristic which is most peculiar to humans, that of language.

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DISCUSSION

Fujinaga: I am asking this question because English is not my native language. Is there any difference in nuance between sidedness, handedness and laterality?

Wolpert: Sidedness is where there is a difference between one side and the other. Handedness would be where this sidedness is consistently specified with respect to right and left.

Collins: There is also lateralization, which we use to describe the degree of asymmetry without respect to the direction.

Wolpert: Lateralization is like sidedness—a difference between left and right but no preference for left or right.

Fujinaga: Both models described by Dr McManus ignore ambidextrous people.

Annett: No. There are many people who show no difference between hands in skill. A basic assumption of the RS theory is that there is a continuous distribution of differences between strong right and strong left for hand preference and hand skill.

Frankel: Could you please explain how these models deal with the nearly binomial distribution of handedness in identical twins?

McManus: My model is formally identical to Marian Annett's; I will explain in terms of my own model. Consider a pair of monozygotic twins who have the CC genotype. Chance determines whether an individual is right or left-handed: therefore there is an independent chance process going on in each twin, so 25% of twin pairs will both be right handed, 25% both left handed and 50% discordant. Complete calculations give almost exactly the numbers actually observed.

Frankel: What about DD twin pairs?

McManus: They are all right handed; therefore they are all concordant for right-handedness and for left-brainedness for language.

Annett: There is no gene for right-handedness in the RS theory; only a gene ($RS+$) which displaces the chance distribution to the right. Some monozygotic twins of $RS++$ genotype could differ in their handedness, but the proportion would be small.

Galaburda: I am not sure one needs a genetic theory for directionality of handedness. We know that Nature has to have these biases. You can disturb the system in many ways—by the products of many genes or by changing the uterine environment—to explain the observed maternal effect. That produces randomness; it produces symmetrical brains which will include those of left-handed people. The anatomical observations could be reconciled with the directionality of functional handedness by proposing a system where one is either right handed or random. Then you could postulate almost anything non-genetic or genetic in the sense of products of other genes to determine that. Why does one need genetics?

McManus: My model doesn't tell us where the directional effect comes from; the system is simply reading a pre-existing asymmetry. The model is therefore strictly a theory of the genetics of the variation in lateralization. It says there is variation in lateralization and that variation seems to run in families and therefore to be genetically transmissible. The model does not say why the brain is asymmetrical in the first place.

The brain asymmetry can also be disrupted. That may be due to a failure to read the system, which I am arguing can occur because of a fairly specific major gene. The system can also be overridden by other things; for instance, anything that produces developmental noise seems to increase the incidence of left-handedness. Almost every cause of mental retardation is associated with a higher incidence of left-handedness. But I would argue that those are phenocopies of true left-handers.

Burn: I don't think your genetic models need to explain twin studies. Francis Galton (1876) accepted that twins could be strongly contrasting. I would agree with Bronson Price (1950) who pointed out that twins are different from singletons. There are a whole series of potential primary biases—shared circulation, potential disturbance of laterality and so on—which mean that twins are morphologically different from singletons. You don't have to explain with the single model such as yours or Marian's the fact that monozygotic twins don't quite conform to your predictions. Monozygotic twins have their own reasons for being different. As Lotze said (1937), they are a malformation to whom Nature was kind.

McManus: That's not entirely reasonable. Galton was one of the first to propose the use of statistical tests in evaluating hypotheses. Handedness in monozygotic twins does not occur in binomial proportions; by any significance test the association is highly significant. This association of handedness between monozygotic twins has to be explained.

There may be an additional mechanism operating in twins: Marian Annett's model says that quite specifically. I would prefer to have a single process that

doesn't need to invoke these additional factors which we don't know about. We can model the data quite adequately using a single gene.

Burn: Biologically, one would expect there to be other factors that could influence handedness in twins, as they do in malformations in other areas.

McManus: But you have to predict the similar incidence of left-handedness in twins and singletons. If you argue that there is an additional mechanism acting in twins, you have to explain why the incidence of left-handedness is similar to that found in singletons. If there is something different happening in twins, the models for singletons become rather different, because the permissible models for singletons are constrained by the permissible models for twins.

Burn: I doubt whether they need to be.

Annett: Surely the geneticists could be rather worried about this meta-analysis putting all these very different studies together. When you do such a meta-analysis, I am not surprised that you come out with a mean value that looks reasonably appropriate.

McManus: When I am fitting the models, I am not fitting them to average data. I have fitted each separate study individually. I agree that all formal model fitting has to be done on the basis of individual sets of data, not on aggregated data sets.

Peters: I agree with Marian Annett that if you do a meta-analysis, real problems can arise. I looked at the sex ratios in a number of studies on handedness. Using the single criterion of which hand is used for writing, some studies found twice as many male left-handers as female left-handers, other studies found no difference.

Lewis: There was a time when left-handers were taught to write with their right hand, which would account for some of the discrepancy.

Peters: There is still a bias in this direction: just because teachers and parents do not overtly force a left-handed child to write with its right hand does not mean that pressures towards right-handedness are no longer present. For instance, a child may observe that it does things differently from other children and may quietly, without being told to, try to imitate the other children. Because left-handed parents are more accepting of left-handed preferences in their children, it is important that findings of a raised prevalence of left-handed offspring of left-handed mothers are not immediately interpreted solely in terms of genetics.

Burn: Looking at the age-related factor and also the temporal shift over this century, presumably the skill level of the task brings out the left-handedness. If you do something that requires more skill, it will expose your left-handedness; whereas something with a low skill level may not. Many girls in the 19th century were taught to write their name but little more. Writing one's name with the 'wrong' hand is relatively easy. Ask those girls to write fast in an exam and their laterality might become more exposed. The observed sex difference could be related to the degree of literacy.

McManus: Kevin Connolly's study in Papua New Guinea shows that the same prevalence of left-handedness occurs in a non-literate society.

Meta-analysis is a much criticized technique. People argue that if you put garbage in, you get garbage out. Michael Peters has effectively taken a number of studies and made individual *ad hoc* hypotheses that explain the different studies. With n studies, if you can find $n - 1$ characteristics, you can explain away all the variance and it is just a matter of deciding which remaining study is the 'correct' one.

The other way of comparing studies is effectively to say that these measurable characteristics do relate to the incidence of left-handedness, then to measure the characteristics of the way the study has been done. Statistical analysis of the results then estimates the association of the characteristic with left-handedness. I was well aware that in early studies there was a lower incidence of left-handedness, so I put the date of the study into the meta-analysis. I also put the estimated response rate to questionnaires into the meta-analysis. If we believe that left-handers are responding differentially, those studies with 100% response rates should have a different incidence of left-handers from those studies with a 20% response rate. But response rate doesn't come out of the analysis as being a significant predictor. Meta-analysis is no more than a formalization of what we do whenever we review any complex set of data.

Annett: The more important test of the model is to go back to the threshold idea which is inherent in my model and ask whether you can predict the outcome equally well if there is an incidence of 3% left-handers in the parents as if there is an incidence of 20% in the parents. Because it is a threshold model, the RS theory successfully predicts all the findings in the literature, wherever the thresholds fall, for parents and children. Because you want to stick with a single incidence in your model, you have to average the data to get it.

McManus: You are right and I have to argue that studies differ in their observed incidences of left-handedness for all sorts of extraneous social reasons; people deciding at different times, for instance, to say they are more likely to be left handed rather than right handed.

Your model says there are certain types of people who are more likely to swing across the threshold. We need to argue about why that threshold is moving. What it is about the threshold that allows such a change? Your model says it is those individuals with small skill asymmetries who can be described as right handed in one study and left handed in another; those are the people around the threshold.

Such a model assumes that the degree of handedness is inherited. I can't convince myself on the basis of the studies that two strongly right-handed parents tend to have strongly right-handed children. The threshold model does make that prediction, as far as I understand it.

Annett: I don't think that is the case at all. I do straightforward Mendelian genetics, having cut the distribution at whichever point, and find that the model predicts the incidence of left-handedness in the offspring.

Professor Wolpert discovered at the beginning of this symposium that only two of the participants are left handed. When assessing handedness, if we ask about more than one action, then we find many more people who prefer to use their left hand. I would like to ask people in this room to imagine they are dealing playing cards.

(Everyone deals imaginary cards)

Wolpert: Three from 28.

Annett: I would have expected about one in six from previous studies on students. I ask people 12 standard questions and find the incidence of left-handers to be about 35–36%.

McManus: But does that mean they are left handers?

Annett: That is semantics.

McManus: No, it is not. If I ask 28 questions on a handedness questionnaire, almost everybody finds some task at which they are left handed. This does not mean they are all left handed or that the phenomenon of right-handedness has disappeared; I think we are measuring two separate classes of individual, right- and left-handers.

Peters: When determining whether or not someone is left handed on the basis of which hand they use for certain activities, it is crucial to consider the nature of the activity. Some actions require no particular skill, such as picking up a book from a table. In those cases, it means little when people say they prefer their left or right hand. Other activities require a degree of skill and the preference expressed is important.

Wolpert: Which skills are the relevant ones?

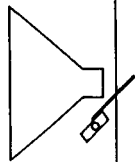
Peters: Ludwig said the preferred hand moves more quickly, more accurately and more forcefully. Tasks that demand any of these qualities are more likely to reveal the truly preferred hand.

Wolpert: Chris, it would be enormously helpful to those of us not in the field if you could summarize very briefly the difference between your model and Marian's.

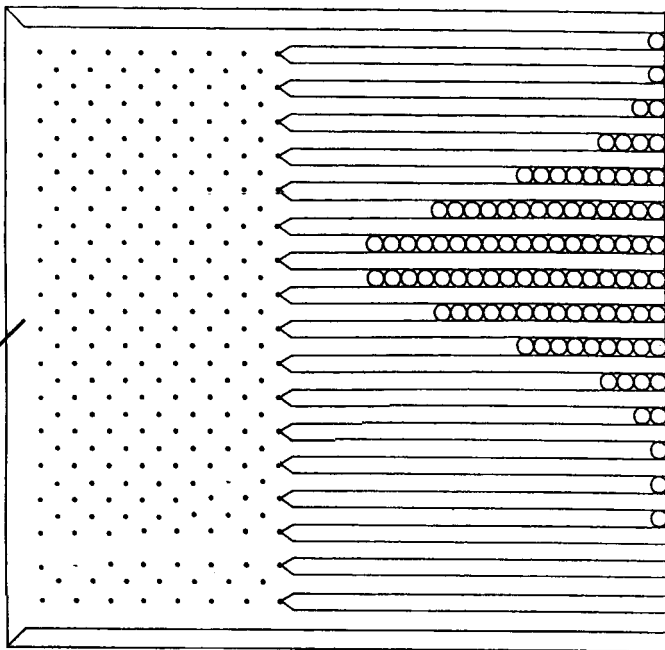
McManus: There is a series of differences. Marian proposes that the phenotype is a continuum of skill differences and an individual can be anywhere along it; the arbitrary division of the continuum into two groups divides the population into left- and right-handers. I propose that the phenotype is categorical: there are two types of individual, left-handed and right-handed, and skill differences are secondary to preference differences, owing to practice. The principle difference therefore concerns the definition of the behavioural phenotype. Marian argues that it is principally a skill difference with preference being a secondary phenomenon. I argue that the behavioural phenotype is principally preference and skill differences are secondary.

GALTON "MACHINE"

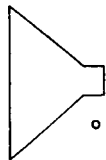
Demonstration of the
Right Shift Theory



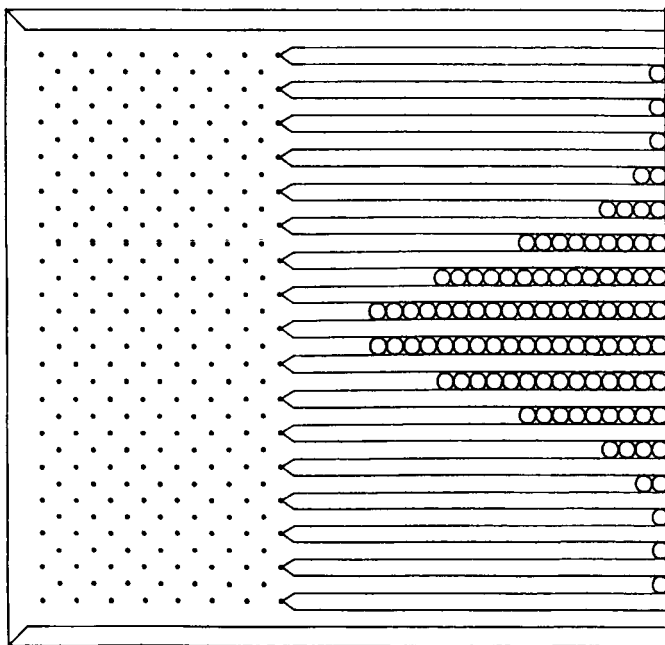
Right Shift
Present

**GALTON "MACHINE"**

Demonstration of the
Right Shift Theory



Right Shift
Absent



Galaburda: Then you are talking about different things! Marian is talking about magnitude, you are talking about directionality. According to Marian's model, as an individual becomes less right-biased, he or she becomes more random.

McManus: We are both talking principally about direction of handedness. Neither of us says that degree (or magnitude) need not be explained. However, I argue that degree of handedness does not need to be explained by genetic models.

Annett: The twins are a very important issue. Chris says that my model needs an extra postulate to account for the twin data. His model also does not account for twins unless a second randomness postulate is introduced.

McManus: No, I do exactly as you do: I assume that the phenotype of one twin is determined independently of the phenotype of the other twin, according to its genotype. Since in some genotypes there is a chance component in determining the phenotype, those random processes are independent of each other, according to both my model and yours.

Annett: I have a Galton machine which I use to explain the theory (Fig. 1). There is a funnel at the top, you drop ball bearings in at the top and they fall down and make a nice normal distribution.

My right-shift model basically grew from evidence which suggests that our primate cousins have a normal distribution of those who are better on the left and those who are better on the right, with the majority in the centre. For humans, I insert a bias which displaces the distribution to the right. If you have the same threshold for humans and for other primates—this is what convinced me that this is not just a model but a revelation—the percentages of pure left-handers, mixed handers and right-handers are exactly the same as found in monkeys and in humans, provided humans have this shift to the right.

If we assume that the same biasing factor puts speech on the left side of the brain, that is all we need to account for the main phenomena. My parameters for genetic calculations were derived entirely from the literature on patients with dysphasia after unilateral left- and right-sided lesions, not from the genetic data.

Wolpert: So you have a biasing factor where Chris has a phenotype which is random.

McManus: I see the bias as already there. I am not proposing a mechanism for the fundamental asymmetry but for the disruption of that asymmetry which sometimes results in left-handedness and right-brainedness.

FIG. 1. (*Annett*) The 'Galton' machine demonstration of the right shift theory. When the RS factor is absent, differences between the hands in skill are thought to be due to chance alone. Left and right hand preference are equally likely, with the majority having mixed hand preference. When the RS factor is present, the distribution of differences between the hands in skill is due to chance, as before, but is displaced to the right.

Morgan: It seems quite inappropriate to talk about a gene for right handedness. We have seen no evidence that any such gene exists. I am not even sure it is a meaningful concept. At best, there is evidence for some factor related to genetic variance that can interfere with the system and reduce the amount of right-handedness. The variants could be doing anything—raising the level of a neurotransmitter, decreasing receptor sensitivity, many things that have nothing to do with handedness but which fortuitously interfere with coding.

You accept that there are major environmental sources of variation which could add to the genetic variation. That means there are some people who are *DD* genotypically in your terminology who are phenotypically left handed. In that case your model shouldn't work and the fact that it does work is a bit suspicious because you haven't taken account of it in predicting the relative proportions of left- and right-handers.

McManus: You have to work out the incidence of pathological left handedness. Dorothy Bishop (1990) has calculated that the proportion of left handers who are left handed due to pathological factors is probably about one in 20. If one in 20 left-handers is left handed for non-genetic reasons, it hardly alters the calculations and therefore the models continue to show a good fit with the data.

I am not saying that 100% of the variation in handedness is genetic, but that the large proportion is. There is a major gene there. Other factors might be important, but birth stress is not one of those.

Morgan: When you compared the observed frequencies with those predicted by the model, you were talking about differences of 1.9% as evidence against a model. So why doesn't this additional 1/20 randomness coming from the environment make it impossible to discriminate between these different models?

McManus: If I took all the left-handers in my study and randomly made 1/20 of them right-handed, it would have an equivalent effect across all groups, irrespective of the handedness of the parents; thus it would average out in the calculations. The differences between the groups are not affected by an environmental insult which is affecting individuals at random. Unless the environmental insult is itself genetically transmitted, the insult shouldn't be related to the familial patterns.

Crow: I would like to present an argument that the human directional factor, which I assume is genetic, is pseudoautosomal (Crow 1989). The argument is based on the neuropsychology of sex chromosome aneuploidies (Netley & Rovet 1982, 1987).

Patients with Turner's syndrome lack an X chromosome (XO) and those with Klinefelter's have an extra X chromosome (XXY). Patients who are XXX resemble those with Klinefelter's and not Turner's. XXX are females and Klinefelter's are males, which diminishes any interest you might have in hormones and suggests that genes are more important in these differences.

The measures were of verbal and performance IQ. 100 is the expected value: patients with Turner's syndrome have a performance deficit (88, $n = 35$) and no verbal deficit; conversely, those with Klinefelter's have a verbal deficit (83, $n = 24$) and a normal performance IQ. These are substantial deficits. Other studies show deficits that are not as great; this difference between studies may depend on the age of the patients being tested.

Performance tests are mostly right sided and verbal tests are mostly left sided. Therefore, it is difficult to resist the conclusion that on the X chromosome there is some factor that is affecting the relative development of the two hemispheres. One of the things that Marian Annett and Chris McManus agree on is that the right-shift factor is autosomally transmitted, which doesn't fit with this conclusion.

The pseudoautosomal region is the small region at the tip of the short arms of the X and Y chromosomes within which there is recombinational exchange of genetic material. This was postulated by C. D. Darlington 40 years ago and its existence has been clearly established by the work of a number of geneticists. In male meiosis, these regions of the X chromosome and the Y chromosome are apposed and there is exchange of material, so that within this region genes on the X and the Y are homologous. Genes within this region appear to be autosomally transmitted, even though they are on the sex chromosomes.

The pseudoautosomal region is quite small; it is 2.6 Mb, less than 0.1% of the genome. So if there is anything in this hypothesis, the problem of identifying the handedness gene is simplified. There are a limited number of genes in this region; as judged by HTF islands it is probably seven or eight, of which three have been identified. Two of them are quite interesting: the MIC2 gene, which is a primate-specific membrane antigen, and the pineal enzyme, hydroxy indole-*o*-methyl transferase.

Burn: Recent evidence suggests that the pseudoautosomal region is not confined to the upper region of the short arm; other areas on the X chromosome behave in a pseudoautosomal fashion. So the mapping exercise might not be quite as simple as you assumed.

Crow: That's not quite true. There are homologies, but those regions do not exchange between X and Y. Nevertheless, the possibility that the handedness gene is not pseudoautosomal but in a region in which the X and Y chromosomes carry sequence homology deserves consideration.

Wolpert: Tim, you imply there is a significant difference between left and right sides of the brain. Earlier, I had a feeling from several speakers that the idea of left brain, right brain is rapidly disappearing.

Galaburda: We used the language very differently. That patients with Turner's syndrome have difficulty with visual things which ultimately show up in the performance IQ tests doesn't say anything about right hemisphere asymmetry as far as I am concerned. There is no reason to suspect that the only change between the normal karyotype and that in Turner's syndrome is a change in

asymmetry. A lot of other things are likely to be happening to the brain in Turner's syndrome.

All you may have to do is make smaller brains and bigger brains. For visual systems and visual analyses you may need big networks; for phonological and syntactic aspects of speech and language you may need small networks because learning of rules is the crucial step. All you may need to do is make the brain bigger in individuals who are XXY, which appears to be the case, and make the brains smaller in Turner's syndrome, which they are. You don't have to change the asymmetry. It is not that all the left and right differences can be dismissed, but they are part of a more interesting biological process that also includes brain size, connectivity and strategies for completing a task.

Crow: Surely it's not true that people with small brains have defective spatial abilities or that people with large brains have defective verbal abilities?

Galaburda: I don't know, but it is an empirical question. I would imagine that people with large visual networks will tend to be more symmetrical and better at visual spatial abilities, and people with severe asymmetry of language areas, which are then smaller, may be good at phonological and syntactic tasks.

McManus: I know the asymmetries in brain sometimes look small and they can sometimes be explained away. We must never forget what Broca found in 1865. If the left middle cerebral artery is occluded, 95% of right handers become aphasic, they stop speaking. If the right middle cerebral artery is occluded, those people probably carry on talking. That to me is the fundamental thing that has to be explained.

Galaburda: I believe my model begins to explain exactly that. It is the asymmetry of the assembly that is important. If you damage most of the assembly, wherever the assembly is, you cause the deficit. In most subjects, this is on the left.

McManus: Nevertheless, the basic phenomenon is indisputable. We cannot argue that there is a random combination of possible brain types and we just happen to be seeing some of them. There is clearly directional asymmetry that has to be explained.

Corballis: We should probably dismiss the pop psychology notion that there are two fundamentally different and opposite kinds of processing on the two sides of the brain. The critical thing is the left dominance in most people (not everybody) for language and perhaps for some kind of praxis that is reflected in handedness. The so-called right hemispheric specialization for spatial representation is not nearly as absolute or pronounced.

Peters: Chris's observation may be rephrased to say that the most salient and clearly observable aspects of language and speech are affected after left hemisphere damage. Because the characteristic changes in linguistic behaviour after right hemisphere damage are much more subtle and less easily detected, it is often asserted that right hemisphere damage has no effect on language.

Wolpert: The story that we left-handers are more liable to autoimmune diseases, more intelligent, etc, is it all nonsense?

Galaburda: There is no evidence to support the claim in the original observations that left-handers are more vulnerable to autoimmune diseases in general, although they may be more susceptible to some types of allergies. Among left-handers there is a greater proportion who are very bad at mathematics and a greater proportion who are very good than in the general population.

Annett: There is something in the theory that left-handers have certain advantages. Some people have to have two copies of the right shift gene, so the bias for them is a bit stronger. My model suggests that these people ($RS++$) are at risk. There are about 32% in the population who carry a double dose of the right shift gene. If you take any talented population, remove the 32% who are $RS++$, then the incidence of 8% left-handers in the total population becomes 8/68. If the best people are selected from the $RS--$ and $RS+-$ genotypes and the $RS++$ are missing, you come up with 11–12% left-handed. This explains the increased proportion of left-handed tennis players, other top sports people and surgeons. It is not that being left handed is particularly good for you, but that it is bad to be too right handed.

Collins: I have tried to gain a better understanding of the inheritance of asymmetry through experimental studies on genetically defined mice. I have focused on studies of handedness in the hope that they may lead to a more general perspective of genetic influences affecting other asymmetries of function and structure.

If mice are placed in individual testing cubicles in which rolled wheat is available in a feeding tube attached to the front wall, they will reach for the food. These reaches can be observed easily and scored with patience. I usually assess handedness in mice by measuring 50 reaches for each mouse. The 'right-paw entry score' (RPE) is a useful measure and ranges from 0 to 50. High scores indicate dextrality, whereas those near zero indicate sinistrality. Mice scoring in the region of 25 RPEs may be judged ambilateral. Mice may alternatively be classified as dextral or sinistral if their RPE scores are greater or less than 25 RPEs, respectively. The handedness of mice is extremely reliable when assessed within-session, across several days, or over several months (Collins 1968).

What happens when you observe the hand preferences of many members of a highly inbred strain? I tested 709 C57BL/6J mice that had, at that time, been inbred for more than 100 generations. The distribution of their RPE scores was markedly U shaped (Collins 1975). Approximately half the mice were strongly right handed, and half were strongly left handed; very few were ambilateral. This finding presents us with a puzzle. The maximum phenotypic variance is observed in a population that possesses minimum genetic variance.

It might be suggested that C57BL/6J mice still harboured a residue of genetic heterogeneity despite more than 100 continuous generations of brother-sister inbreeding. If so, this residue should be responsive to bidirectional selection.

I tested this by selectively breeding for right-handedness and left-handedness in C57BL/6J mice (Collins 1969). Through three generations of selection there was no change in the proportions of dextral or sinistral mice or in the RPE averages. Half the offspring from dextral-dextral matings remained left handed. Clearly, the maximum variance in directionality of handedness observed in C57BL/6J mice does not appear to be maintained by a residue of heritable genetic variation that escaped prolonged inbreeding. Nor does it appear that the handedness of mouse pups is learned from their mother, because if there were a cultural inheritance of directionality, the selection programme would have detected it. However, a cultural diffusion of behavioural asymmetry is possible. One example of observational learning for a novel behavioural asymmetry in mice has been presented (Collins 1988).

I observed a sex difference in the degree of asymmetry in the large-sample study of C57BL/6J mice (Collins 1975). Female mice, on average, showed a stronger hand preference than did male mice.

I believe the interest of researchers has been so focused on questions of directionality, we have tended to forget that asymmetry is a mathematical vector with a degree of magnitude as well as a direction. Perhaps the inheritance of the degree of asymmetry will be better behaved. I addressed this by initiating a long-term bidirectional selective breeding study for the degree of handedness in mice.

First, a foundation population possessing large potential genetic variability was established. It was derived from an 8-way crossing plan using the following inbred strains and partially inbred stocks of wild mice: BALB/cJ, C57BL/6J, DBA/2J, LP/J, RF/J, SM/J, *M. molossinus* and *M. castaneus*.

The distribution of RPE scores for the foundation population was markedly U shaped (Collins 1985). To provide a measure of the degree of asymmetry I used the 'preferred-paw entry' (PPE) score. This is a non-monotonic transformation of the RPE score in which the RPE distribution is cut at 25 and the left portion (0-24) is folded and superimposed as a mirror image on the right portion (26-50). The PPE score ranges from 25 to 50 and measures the degree of handedness without regard to its direction.

A HI-selected line was formed by mating mice with PPE scores of 48-50; a LO-line was produced from mice with PPE scores of 25-40. By the third generation of selection, there was a statistically significant separation in mean PPE performance in the selected lines. This difference increased as selection continued. Maximum separation was observed at the tenth generation (G10). At this time, approximately 45% of HI-line mice exhibited strong lateralization (PPEs of 48-50) compared to 8% of LO-line mice. The degree of lateralization of both lines was distinct from that of the unselected HET reference population (Collins 1985).

The selection pressure was relaxed for 17 generations, then selective breeding was reinstated at G28 for three consecutive generations. The HI- and LO-lines

retained their distinctive patterns of lateralization throughout this long period of random mating. There was no evidence of counter-selection for average effect or of regression toward the mean (R.L. Collins, unpublished).

Thus far I've considered only mice tested for handedness in unbiased or 'U-worlds', testing situations in which the food tube is located equidistant from the right and left walls. What happens when mice are tested in biased worlds in which the food tube is placed flush against either the right wall as faced by the mouse (R-world) or the left wall (L-world)? The distribution of RPE scores now changes from being bimodal and U shaped, to being unimodal and J shaped. Approximately 90% of a large sample of naive C57BL/6J mice tested in an R-world could be classified as dextral, only 10% as sinistral. The mirror-image pattern was obtained for mice tested in an L-world (Collins 1975). Such a bias in the environment may exert a profound effect on manifest laterality. However, this effect would be impressed on an already laterally dichotomized population. The external bias does not create laterality, it shifts an already lateralized equiprobable population into a non-equiprobable distribution of directions.

Let us now consider genetic models of asymmetry. In developing any genetic model of laterality it is necessary to map phenotype functionally to presumptive genotype by a series of probability statements for each of the genotypes in the model. I propose that as we do this, we map the probability of right as equal to the probability of left for each genotype considered. This is another way of saying that genes maintain an asymmetry lottery in which right and left are stochastic outcomes, and that genes do not specify the outcomes of a given gamble. Any observed uniformity in direction or a non-equiprobable distribution of directions, arises not because of differing gene frequencies for 'right' and 'left' alleles, but rather through an interaction of the stochastic outcomes with an external gradient of asymmetry. Consider the case of situs inversus in mice. In *iv/iv* mice the side of the midline on which the stomach lies appears to be determined randomly. In *iv/±* and *±/±* mice there is apparent uniformity of sidedness. Does this mean that the wild-type allele codes for 'stomach on the left'? I submit that it codes for directionality in the same way as does the *v* allele. The wild-type allele could lead to uniformity of directionality in one of two ways. It could code for a receptor that detects the external asymmetry gradient. Or it could code for an effector that translates information about an environmental bias into movement towards polarity.

The advantage of considering the distribution of directional forms arising through interaction with external world biases lies in our ability to manipulate the asymmetry gradients. If a gradient points one way, perhaps it can be made to point in the opposite direction. Or it could be removed. There are two experimental examples of the use of manipulated asymmetry gradients. One is the biased world studies of handedness in mice already discussed (Collins 1975, 1977b); the other is the series of elegant experiments by Leslie Rogers and her

collaborators on lateralization of function in the chick forebrain. In these, a null gradient was applied which abolished an existing directional distribution of neural and behavioural lateralization (Rogers & Anson 1975, Rogers 1982, Rogers & Bolden 1991).

Peters: In the initial task where the food was in the middle of the chamber, it might be inappropriate to talk about 'pawedness'. When the mouse reaches into the tube, it has to twist its body to be able to extend its paw and leg into the tube. Could the selection have been for the direction of twisting of the torso? If so, does this have anything to do with 'pawedness'?

Collins: I believe axial torsion does not play a major role in mouse handedness or in the response to selection. For example, if we put the food tube on the side opposite to the mouse's native hand preference, most mice will try to use their preferred paw even though it is very difficult for them posturally. Secondly, when mice were tested in a circular apparatus with the food hole through the floor, the correlation of RPE scores between the two tests was 0.96 (Collins 1970). The motor response topographies and the axial postures of mice in the two tests are each quite different.

Peters: When you said 90%, were those both HI-lines?

Collins: In the original biased world studies, C57BL/6J mice were directly placed into biased worlds and tested twice and then once in biased antiworlds (test sequences R-R-L or L-L-R). In the first two tests approximately 90% of mice exhibited a preference consistent with the world bias, whereas 10% resisted it. But we must remember that each group was an equal mix of dextrals and sinistrals, so that the proportion of mice resisting the bias was much higher. If we first test mice in an unbiased world and then twice in worlds biased opposite to their hand preference (sequences U-R-R or U-L-L), the proportions of mice resisting the bias can be quite high. For example, when we used HI-line mice in this challenge paradigm, the median PPE score remained flat across the initial and two biased world challenges.

Peters: If humans were presented with this sort of task, they would simply reach for the food with the arm that was most appropriate, i.e. for an opening that was to the left of the body midline, even a right-handed human would not twist the body to use the right arm. In this sense, these results reflect an unusually powerful lateral bias in the mice.

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