Cerebral asymmetry in twins: Predictions of the right shift theory

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Abstract

A study of the heritability of lobar brain volumes in twins has introduced a new approach to questions about the genetics of cerebral asymmetry. In addition to the classic comparison between monozygotic (MZ) and dizygotic (DZ) twins, a contrast was made between pairs of two right-handers (RR pairs) and pairs including one or more non-right-hander (non-RR pairs), in the light of the right shift (RS) theory of handedness. This paper explains the predictions of the RS model for pair concordance for genotype, cerebral asymmetry and handedness in healthy MZ and DZ twins. It shows how predictions for cerebral asymmetry vary between RR and non-RR pairs over a range of incidences of left-handedness. Although MZ twins are always concordant for genotype and DZ twins may be discordant, differences for handedness and cerebral asymmetry are expected to be small, consistent with the scarcity of significant effects in the literature. Marked differences between RR and non-RR pairs are predicted at all levels of incidence, the differences slightly larger in MZ than DZ pairs.

Keywords: Twin concordance, cerebral dominance, handedness, genetics.

Findings for monozygotic (MZ) and dizygotic (DZ) twins have an important role in the evaluation of genetic theories because for most purposes MZ twins can be taken to be identical genetically, whereas DZ twins share fifty percent of their genes, on average. MZ twin pairs often differ for handedness, and this occurs with about the same frequency as in DZ pairs. These observations rule out mirror-imaging as the main cause of discordance for handedness in MZ twins. They also rule out direct genetic determination of right- and left-handedness. It has been widely believed that discordance for handedness in MZ pairs, and the similarity of levels of discordance between MZ and DZ pairs, contra-indicate any genetic influence on handedness. However, recent theories include chance postulates that allow MZ twins to differ for laterality, even in the presence of a genetic influence. Geschwind, Miller, DeCarli and Carmelli [17] have investigated the heritability of lobar brain volumes in twins in the light of such models. Some of the cerebral asymmetries that were present in the brains of twins from pairs of two right-handers (RR pairs) were greatly diminished in the brains of twins from pairs that included one or two left-handers (non-RR pairs). In the latter, the reduction was evident for both right-handers and left-handers. This supports the theory that the key genetic contrast is between people who carry a typical directional bias and those who lack this bias, and then lateralise at random.

The findings of Geschwind et al. challenge theories of handedness to be more specific about predictions for brain asymmetry. This paper explains the predictions of the right shift (RS) theory for genotype, brain asymmetry and handedness in healthy MZ and DZ twins. It shows how predictions differ between RR and non-RR pairs, over a range of incidences of left- and non-right-handedness. Predictions will be given

for sexes combined. Sex differences and certain types of non-healthy twins will be considered in discussion.

Outline of the right shift theory

The RS theory [3] was formulated after some 10 years work on questions about hand preference, hand skill, and related abilities. The theory depended on the discovery that several puzzles about handedness, including preferences in humans versus non humans, the normal distribution of asymmetry for hand skill versus the J-shaped distribution of preference, and the wide range of incidences of left-handedness, could be resolved in the light of a simple model. This was represented by two overlapping normal distributions of right minus left (R-L) hand skill, one with mean at zero difference between the sides for nonhumans, and one with mean to the right of zero for humans. A key discovery was that the thresholds drawn to distinguish mixed-handers from consistent left-handers (toward the left of the distribution) and mixed-handers from consistent right-handers (toward the right of the distribution) could be at the same locations for humans and nonhumans. The only difference between the two distributions was that the human one was displaced in a dextral direction. The question then was, 'What displaces the human distribution toward the right?' and the obvious first hypothesis, 'Whatever factor induces a brain asymmetry in favour of the left cerebral hemisphere.' From the beginning, the ‘RS factor’ was identified with the agent of left cerebral asymmetry, not with right-handedness. The process of exploring the implications of this model for the many questions that can be posed about human laterality has continued over many years [see reviews in 8, 13]. The present paper is a further step in that process.

The idea that the primary cause of lateral asymmetries in all species is random bias to either side, or fluctuating asymmetry, was fundamental. The special feature for humans was an agent of cerebral asymmetry that added value to the chance biases toward the left hemisphere and right hand. The possibility that RS might be absent in some humans and that in this case there would be no added value, but mean bias of zero, was supported by studies of the children of two left-handed parents [4, 7]. The idea that RS might be a factor for brain asymmetry was supported by findings for handedness and dysphasia [1, 5]. Annett and Alexander [14] showed how the model predicts quantitative relationships between handedness and cerebral speech laterality. The predictions were explained through hypothesised samples of patients with unilateral left or right sided cerebral lesions, 1,000 for each side, in order to avoid the use of decimals. The predictions were tested at two levels of incidence, 10 and 30 percent left-handedness. The present analysis describes individuals and twin pairs per 1,000, and also shows how relationships change over frequencies of left-handedness ranging from 5 to 40 percent.

The idea that the RS factor could be a single gene (RS +) followed the discovery that if the frequency of the RS - - genotype was estimated from the frequency of right hemisphere speech in population representative series of dysphasics, then handedness in families was predictable for almost all studies in the literature [6]. The gene frequencies derived from the dysphasia literature matched those estimated by Trankell [32] from an analysis of findings for family handedness. Trankell hypothesised a recessive gene for left-handedness, but one that was not penetrant in many cases. The RS theory does not expect RS - - genotypes to be left-

handed, but rather to develop left versus right cerebral advantage at random, and left- versus right-handedness independently at random. The theory of reduced penetrance is not required.

The derivation of gene frequencies from incidences of right hemisphere speech depended on the assumption that the RS + gene is dominant for left cerebral speech. That is, presence of the gene in single or double dose should induce the typical pattern of cerebral asymmetry, given normal development. Whether or not the gene is dominant for its effect on handedness is a separate question. Early applications of the model assumed the same shift for RS + + and RS + - genotypes, dominance for handedness. However, early estimates of shift were necessarily rough and they were subjected to further analysis [8, 13]. There was an important reason for arguing an additive effect for handedness. The genotype frequencies implied that the heterozygote (RS + -) is the most prevalent while both homozygotes are substantial. The genotype distribution suggested there could be a genetic balanced polymorphism with heterozygote advantage, and if true, the effect of the gene on some processes must be additive. Hence, the RS + gene is expected to be dominant for cerebral speech side but additive for other asymmetries associated with cerebral advantage.

Fig. 1 about here

Fig. 1 represents the main features of the RS theory graphically. Each feature needs to be considered with reference to twinning. First, there is the normal (Gaussian) distribution of R-L differences, due to fluctuating asymmetries likely to occur in the growth of bilaterally symmetrical creatures. The normal distribution depends on congenital variation in the course of foetal development in every

individual, whether singleborn or twin. It is the primary, universal and non-genetic cause of handedness in humans and nonhumans. The second feature of the model, a gene for human left hemisphere advantage (or more probably right hemisphere disadvantage), acts like a constant added to the random fall of chance asymmetries. The gene may be absent, or present in single or double dose. The R-L hand skill distributions represented in Fig. 1 are as expected for singleborn males, with shifts of 1z and 2z for the RS + - and RS + + genotypes respectively. Shifts of 1.2z and 2.4z respectively are expected for singleborn females, because the female distribution of hand skill asymmetry is shifted a little further to the right than that of males. The letter 'x' represents a possible threshold that classifies 10 percent of the population to the left as sinistral. Each of the three genotypes overlap 'x', showing that there may be right- and left-handers *within* genotypes and hence within MZ twin pairs. The gene and genotype frequencies of twins are expected to be the same as for the singleborn, and the same for both sexes.

From the first application of the RS genetic model to the distribution of handedness in twin pairs, it was clear that the shifts that successfully predicted handedness in families could not apply to twins. A smaller shift was required, with the same reduction for both MZ and DZ pairs. This implied that the expression of the RS + gene is reduced by some factor associated with twinning itself, independent of zygosity. For the dominant model for handedness, a reduction of shift of about 50 percent gave virtually perfect predictions for twin pairs [6]. For the later additive model, a reduction of 33 percent was sufficient [8]. For either model, the reduction of shift implies that twins are more often left-handed than the singleborn (by about 3 - 5

percent for left-handed writing). It had been suggested earlier that twins are more often left-handed, but the evidence was controversial and rejected [21]. There is now strong evidence for this difference [16, 25, 26]. Contrary to the argument that the need for a different shift in twins is a weakness for the RS theory [23], it has strengthened the theory in several ways. First, the theory predicted the higher frequency of left-handedness in twins than the singleborn, at a time when the evidence was uncertain. Second, it suggested that expression of the RS + gene is a function of size or maturity at birth, consistent with the higher frequency of right-handedness in females than males, and in full-term than premature and low birth weight infants. Third, it was consistent with the slower development of speech in twins than the singleborn.

The fifth element of the RS theory represented in Fig. 1 is the threshold. There is a continuum of asymmetry for hand skill, and a clear relationship between strength of preference for either hand and degree of R-L skill. Left-handedness can be defined in many ways, ranging from left preference for all significant unimanual actions (about 3 percent of the population) to left-hand preference for any one of these actions (some 30 - 35 percent of the population). When 35 percent are classified as non-right-handers, over 40 percent of twins are likely to be so classified. Therefore, predictions for brain asymmetry in twins must be examined at several levels of incidence for handedness. It is important to note that the threshold approach allows the RS theory to predict the available data for handedness in families and in twin pairs over the whole range of incidences found in different studies [12, 13]. This does not imply an elastic relationship between incidence and prediction. Thresholds along the asymmetry continuum are mapped precisely to the genotype distributions represented by the three

normal curves. Look-up tables relating thresholds to incidences and incidences to genotype distributions were given by Annett [13, Appendices III - VI]. The relevant table for twins, male, female and sexes together, is given here in Appendix I. Other theories of handedness have postulated a chance component but none other than the RS theory has used the threshold approach. Contrasts between theories will be considered in discussion.

The RS genotype distribution of MZ and DZ twins

The RS theory is a quantitative theory, underpinned at each stage of its development by regularities in empirical data. The hypothesis of an RS factor but no mirror left shift factor followed from analyses of findings for hand and paw preference in relation to areas under the normal curve, as explained above. From the postulate that the RS factor was for left hemisphere speech and that in the absence of this factor, cerebral speech would arise by chance, it followed that the proportion of RS - - genotypes was twice the frequency of atypical speakers. Right hemisphere speech was found in 9.27 percent of combined data from four samples, and this estimate was found to be reliable when checked against further data [6, 8, 13]. This implied that about 18.54 percent of the population lack RS +. If a single gene is involved, the square root of this proportion gives the frequency of RS - (.4306). The frequency of RS + is therefore .5694. The genotype frequencies follow:

RS + + = .3242: RS + - = .4904: RS - - = .1854

These proportions are represented in the relative sizes of the three normal curves in Figure 1. For the present analyses per 1,000 population, the proportions are rounded to 325, 490, and 185 for the RS + +, RS + -, and RS - - genotypes respectively. The

genotype distribution is constant for the population as whole, and for twins as individuals. However, the distribution of genotypes in pairs differs between MZ and DZ twins.

Table 1 about here

Table 1 gives the numbers per genotype for the general population, and for MZ and DZ pairs. For MZ twin pairs the genotype distribution is the same as for individuals, because there is no genetic variability within pairs. The gene is absent in 185 and present in 815 pairs. For DZ twins, all combinations of genotype occur. Some 724 DZ pairs are both gene carriers, in 181 pairs there is one carrier and one non-carrier, and in 95 pairs no carrier of the RS + gene. Thus, concordance for RS - - genotype is about twice as high in MZ pairs (18.5 percent) as DZ pairs (9.5 percent).

Typical and atypical brain asymmetry in MZ and DZ twin pairs.

Table 2 about here

How would the genotype distributions translate into distributions of brain asymmetry, on the hypothesis that RS - - genotypes develop cerebral speech on either side at random? Of course, there may be varying degrees of bilateral speech, but for the present purpose it must be assumed that a binary left versus right classification can be made. Table 2 sets out the probabilities for typical (T) and atypical (A) cerebral laterality in 1,000 individuals, 1,000 MZ pairs and 1,000 DZ pairs. For individuals, the rule is that 92.5 are atypical. This represents the observed frequency of right hemisphere speakers in the general population, from which the parameters of the model were derived. Other quantitative features of the model follow from this starting point.

For MZ twins, the 815 pairs that are both gene carriers are concordant for typical brain asymmetry (TT). If cerebral laterality develops at random in RS - - pairs, then the proportions must be 25, 50, 25 percent for TT, TA and AA respectively. This implies that the 185 pairs concordant for RS - - genotype will be 46, 93, 46 for TT, TA, AA respectively (rounding the decimals). Summing for MZ pairs, TT, TA and AA are 861, 93, and 46 (or 86.1, 9.3 and 4.6 percent) respectively.

For DZ twins, the 724 pairs with two gene-carriers are TT. Among the 95 pairs of non-gene-carriers there are 24, 47, and 24 TT, TA and AA respectively. DZ twins also include 181 pairs with one gene-carrier and one non-carrier. Half of these pairs are TT and half TA. Summing over pairs gives 838, 138, and 24 (or 83.8, 13.8, 2.4 percent) TT, TA and AA respectively. Compared with MZ pairs, concordant pairs are less frequent and discordant pairs more frequent, but the differences would be not be detectable unless samples were large and assessments of cerebral speech side highly reliable.

RS genotypes by handedness in MZ and DZ twins

The rules and proportions for genotype and brain asymmetry described above apply to all samples of MZ and DZ twins, but the relative proportions differ with classifications for handedness. A worked example for handedness is given in Table 3, for an incidence of 14 percent left-handers, sexes combined. This approximates the mean incidence for combined data from 12 studies of MZ and DZ twins [13, p. 141] and also for other combined studies, dating from 1960, compiled by Sicotte et al. [26].

Table 3 about here

Table 3 shows the relevant distributions of handedness for twins as individuals and as pairs when 140 per 1,000 are called left-handed. The numbers of right-handers and left-handers for each genotype follow directly from the areas under the three normal curves represented in Figure 1, but with adjustments for reduced shift in twins (see Appendix 1). The 140 left-handers include 10, 65 and 65 with RS + +, RS + -, and RS - - genotypes respectively.

In order to calculate pair concordance for handedness, the proportions of right- and left-handers in each genotype are required, as listed under 'handedness by genotype'. Combinations of RR, RL and LL handers are as expected for random binomial assortment within genotypes. (For example, in MZ twins of RS + + genotype the number of RR pairs is 305 (from (.968 x .968) x .325), the number of RL pairs is 20 (from (2(.968 x .032)) x .325), the number of LL pairs is 0 (strictly 0.3 per 1,000, from ((.032 x .032) x .325)). Table 3 (b) sets out the numbers of MZ pairs and Table 3 (c) the numbers of DZ pairs called RR, RL and LL, for each genotype pairing.

The distributions of handedness in MZ and DZ pairs are very similar. In terms of percentages the totals are almost indistinguishable, 75.2, 21.7, 3.1 percent for RR, RL and LL MZ pairs respectively and 74.6, 22.9 and 2.5 percent similarly for DZ pairs. This similarity is incompatible with strong genetic control of handedness, as mentioned above. But in the light of the RS model of a genetic *influence* on handedness, how do pairs classified for handedness differ for genotype? Table 3 (b) gives the proportions for genotype pairs by handedness pairs for MZ twins. For example, the 305 MZ RR pairs of dominant RS + + genotype represent .405 of the RR

total (752). There are few RS - - genotypes in MZ RR pairs (10.4 percent) but many more in LL pairs (74.2 percent). In view of the difficulty of assembling a reasonable sample of LL pairs, it is useful to combine RL and LL pairs as non-RR pairs (following Geschwind et al. [17]). In non-RR pairs there would be some 8.1 percent dominant homozygotes but 43.1 percent recessive homozygotes. There are about four times as many recessive homozygotes in non-RR as in RR pairs for MZ twins. For both RR and non-RR pairs, the most frequent type is the heterozygote (49 percent of both). Thus, contrasts between RR and non-RR pairs of MZ twins depend on the relative frequencies of the two homozygotes, not on heterozygotes.

Table 3 (c) sets out the numbers of RR, RL and LL pairs for each genotype pairing of DZ twins. The proportions for genotype pairs by handedness pairs are summarised for two gene-carriers, one gene-carrier, and no gene-carrier. (When comparing the MZ and DZ pairs it must be noted that proportions for 'both +' in DZ twins are equivalent to the sum of the proportions for '++ x + + ' and '+ - x + - ' for MZ twins. For example, 80.7 percent of RR DZ twins and 89.6 percent of RR MZ twins are both gene-carriers.) The chief differences between MZ and DZ pairs are first, that the latter may include only one gene-carrier, 13.9 percent of RR and 30.3 percent of non-RR pairs. Second, pairs of RS - - genotypes are about twice as frequent in MZ as DZ twins (10.4 and 43.1 percent for MZ twins and 5.4 and 21.7 percent for DZ twins in RR and non-RR pairs respectively).

One of the analyses of Geschwind et al. [17] concerned twins from RR and non-RR pairs as individuals. How do twins from these two types of pair differ for proportions of individuals who lack the RS + gene? For MZ twins the proportions are

the same for individuals as for pairs, because of the absence of genetic variability within MZ pairs (10.4 for RR and 43.1 for non-RR pairs as described above). In DZ pairs, half of the individuals from 'one +' pairs is a non-gene-carrier. The value required is the sum of 'neither +' and 50 percent of 'one +' (12.3 for RR and 36.8 for non-RR pairs).

Fig. 2 about here

Fig. 2 shows the proportion of non-gene-carriers among individuals from the four types of twin pair, when incidences of left-handedness range from 5 to 40 percent. The highest frequency of RS - - genotypes, the top line of the graph, is found in non-RR MZ pairs. For DZ non-RR pairs the frequencies are a little smaller. The proportions are considerably smaller for DZ RR pairs, and lowest for MZ RR pairs.

A striking feature of the graph is the similarity of predictions for MZ and DZ pairs of each handedness type. The separation between RR and non-RR pairs is slightly greater for MZ than DZ pairs reflecting, of course, the stronger concordance of MZ twins for genotype. The graph shows that the highest proportions of RS - - occur at the lowest frequency of left-handedness (5 percent). The proportions decline as incidences of left-handedness rise. As explained above, the number of non-gene carriers remains constant, 185 per 1,000, but these individuals are distributed differently over the various handedness classifications. Another feature of the data in Fig. 2 that might be of interest is the ratio of non-gene-carriers in non-RR to RR pairs. Although the actual frequencies are high at the left and decline toward the right, the ratios are lowest at the left (3.8 for MZ and 2.9 for DZ twins) and highest at the right (7.4 for MZ and 4.1 for DZ twins).

Concordance for brain asymmetry with levels of left-handedness

How does the above analysis for genotypes in RR versus non-RR pairs translate into proportions with typical (T) and atypical (A) brain asymmetry? Table 4 sets out the numbers of MZ and DZ twins, per 1,000 pairs for RR, RL and LL handedness and for TT, TA and AA brain asymmetry. The frequency of left-handedness is 14 percent, so that the numbers can be derived directly from Table 3.

Table 4 about here

For MZ twins of RS + + and RS + - genotypes all pairs should be concordant for typical brain asymmetry. Among RS - - pairs there should be 25, 50, 25 percent TT, AT, AA respectively. Thus, the 78 RR MZ pairs of RS - - genotype (see Table 3) are expected to be distributed as 19.5, 39, 19.5 for TT, TA and AA respectively. (It is possible, of course, that enquiry into several aspects of cerebral asymmetry would reveal that many RS - - individuals had unusual patterns of cerebral organisation, even if speech output was left lateralised. The present analysis concerns the single criterion of speech side, in order to show the logic of the argument.) Summing over all RR pairs (with rounding of decimals) gives 693, 39, 20 TT, TA, AA respectively.

Fig. 3 about here

Table 4 sets out the numbers per 1,000, for MZ and DZ twins, for each type of handedness pair. The totals for TT, TA and AA in MZ twins are 861, 93, and 46 respectively, and in DZ twins 838, 138, 24, respectively (matching Table 1). Proportions of brain asymmetry pairs within handedness pairs are also given in Table 4. This shows that 92.1 percent of RR and 67.7 percent of non-RR MZ pairs are expected to be TT. The corresponding calculations for DZ twins found 89.0 percent of

RR pairs and 68.5 percent of non-RR pairs TT. Fig. 3 shows TT concordance in RR and non-RR pairs for incidences of left-handedness from 5 to 40 percent. Note that percentage concordance rises for all types of pairs with increasing frequencies of left-handedness. The percentage of non-TT pairs may be obtained by subtraction. Intermediate values may be obtained by interpolation.

Concordance of atypical speech (AA) is about four times as frequent in non-RR pairs as in RR pairs (2.7 percent for RR and 10.5 percent for non-RR MZ pairs and 1.3 percent for RR and 5.5 percent for non-RR DZ pairs). The proportions are about twice as high in MZ as in DZ pairs.

Discussion

This paper has set out the predictions of the RS theory with respect to concordance for genotype, cerebral speech side and handedness in healthy twins. Relationships between genotype and cerebral asymmetry are straightforward. All normal carriers of the RS + gene have the typical pattern of cerebral dominance, and all non-carriers lateralise at random, for speech and for other functional asymmetries. Gene frequencies are hypothesised to be the same in twins as the singleborn, and in both sexes. All MZ pairs have identical genotype, about 81.5 percent gene-carriers and 18.5 percent non-carriers. DZ twins may differ for genotype, 72.4 percent both carriers, 18.1 percent one carrier and 9.5 percent both non-carriers of the RS + gene. When the gene is identified, the assumptions of the model and the contrasts between MZ and DZ pairs should be detectable in samples of reasonable size.

With respect to cerebral dominance, concordance for atypical speech side is expected for 4.6 percent of MZ and 2.4 percent of DZ pairs. Discordance of cerebral

speech laterality would be likely in some 9 percent of MZ pairs and 14 percent of DZ pairs. However, unusual patterns of cerebral laterality might be found in both members of some 18.5 percent of MZ pairs, and 9.5 percent of DZ pairs if several asymmetries were assessed in a large sample. Whether these contrasts are detectable will depend on sample size and the reliability of laterality assessments. The fundamental premise of the RS theory, that atypical asymmetries are independent, would be invalidated if MZ twins were more often concordant for atypical cerebral speech than predicted above.

What are the effects of classification for handedness? Right-handedness is not determined by the RS + gene, but it is more probable in its presence. It was shown first (in Table 3) how the assortment of pairs for handedness follows straightforward rules of binomial combination within genotypes, from the proportions classified as right and left-handed in each genotype. These proportions were derived from areas under the normal curves of the distributions for R-L hand skill (as in Fig.1 but with values for twins given in Appendix 1). When 14 percent of twins are left-handed, the distributions of RR, RL and LL pairs are expected to be 75.2, 21.7, 3.1 for MZ twins and 74.6, 22.9, 2.5 for DZ twins respectively. These predictions are well matched by findings for combined data for 2627 MZ and 2394 DZ pairs [13, p.140].

The similarity of the MZ and DZ distributions for handedness shows that *variability* for handedness is not fully determined by genes. It has long been argued that environmental effects are likely to be of major importance [15, 24, 31]. The RS theory agrees that random environmental influences are the main cause of asymmetry for hand skill (see Fig. 1). The theory does not postulate genes for handedness, but

rather a gene for left cerebral dominance. Further, there is very little genetic variability because some 81 percent of the twin population, like the general population, are gene-carriers. The gene shows its presence by raising the probability of right-handedness above 50 percent (chance) in both twins and the singleborn. Searches for laterality differences between MZ and DZ pairs are generally unfruitful because the typical bias is highly prevalent in both types of twin. To take an extreme example to make the point, 100 percent of normal MZ and DZ twins walk upright, but that does not imply that there is no genetic influence on upright walking. The assumption that there should be major differences between MZ and DZ pairs is valid only for traits where there is strong genetic variability, but not where there is strong genetic uniformity. The small genetic variability due to the presence or absence of the RS + gene is associated with differences between MZ and DZ pairs, as shown in Figs. 2 and 3. But these differences are small and not likely to be statistically significant unless samples are very large.

Differences for brain asymmetry between RR versus non-RR pairs [17] depend on the effect of handedness classification on probable genotype. Table 3 showed the predictions for a sample of twins with a frequency of left-handedness at 14 percent. For MZ twins the percentage of RS - - pairs is 10.4 percent in RR and 43.1 percent in non-RR pairs. For a smaller incidence, as for 7.2 percent in the Geschwind et al. sample, the corresponding percentages are about 13 and 50 percent. For both levels of handedness, the ratio of non-gene-carriers in non-RR to RR pairs is about 4:1. Would this be sufficient to account for differences in cerebral asymmetry for twins as observed by Geschwind et al.? It may be noted that the contrasts of mean

asymmetry coefficients, and also of intra-class correlations, between twins from non-RR and RR pairs described by Geschwind et al. [17, Tables 3 and 5] were smaller than a ratio of 4:1. Without further knowledge of the mechanisms, the relevance of these ratios cannot be clearly judged. However, as a first approximation, it seems likely that the differences predicted here would be compatible with the differences observed.

The twins studied by Geschwind et al. were males, whereas the predictions here are for sexes combined. How different would the predictions be if the sexes were distinguished? Sex differences for handedness in the general population are small, and were disputed except for very large samples. Few studies of normal twins have distinguished the sexes, but those that have done so found slightly higher incidences of left-handedness in males than females [review in 13, p. 142]. When 14 percent of twins are left-handed for sexes combined, the incidences are probably about 13 percent for females and 15 percent for males. It should be recalled that the predictions for genotype and cerebral asymmetry (in Tables 1 and 2) are expected to hold for both sexes. Differences would arise only when differences for handedness are taken into account, and these would be trivial unless truly enormous samples of twins distinguished for sex were available. If this question should be of interest, the genotype frequencies associated with observed incidences of left-handedness in each sex can be obtained from Appendix I and the predictions re-calculated. Suggestions in the literature that cerebral asymmetries are weaker in females than males run counter to the evidence for stronger expression of the RS + gene in females than males. The latter is seen in the higher frequency of right-handedness, more efficient speech

learning in infancy, and the relatively poorer spatial abilities of females than males. Differences between the sexes are not substantial enough, in my view, to require differences in the fundamental rules for cerebral dominance. This is point on which the RS model is open to test.

What evidence is available as to cerebral asymmetries in twins when pairs were distinguished for handedness? Steinmetz, Herzog, Schlaug et al. [30] described asymmetry of the planum temporale (PT) in 20 pairs of MZ twins, 10 pairs RR and 10 pairs RL for handedness, including both sexes. Correlations for PT asymmetry were low within both types of handedness pair, suggesting considerable non-genetic variability for PT size, as argued above for R-L hand skill asymmetry. Did RR and RL pairs differ for PT concordance? Making a binary division at 0.0 for PT asymmetry, 9 of the RR pairs and 6 of the RL pairs were concordant for typical direction of PT, consistent with the predictions of Fig. 3.

Mean asymmetries in favour of left PT larger, the typical direction, were found for right-handers, while the mean for left-handers was close to zero, as expected for chance bias to either side. How did the overall distribution of PT asymmetry differ between RR and RL pairs? Steinmetz et al did not address the question directly, but PT asymmetry was probably more variable in the RL pairs. Right-handed twins in RL pairs were not less biased to left PT than right-handers in RR pairs, in contrast to the observations of Geschwind et al. for certain cerebral asymmetries. However, it should be noted (in Table 3 above) that about 49 percent of RR pairs and 52 percent of RL pairs of MZ twins are expected to be heterozygote

carriers of the RS + gene. With Ns of 10 pairs of each type, marked differences between RR and RL pairs were not likely to be observed.

Functional brain asymmetry, as assessed by dichotic listening, was described for MZ and DZ twins of both sexes by Springer and Searleman in RR pairs [27] and in non-RR pairs [28, 29]. Dichotic listening should not be regarded as directly diagnostic of cerebral speech asymmetry but there is a positive relationship in typical cases [9]. In RR pairs, Springer and Searleman found concordance for typical right ear advantage (REA) slightly higher in MZ twins (88 percent in 50 pairs) than DZ twins (77 percent in 35 pairs), broadly consistent with predictions for concordance for typical brain asymmetry for RR pairs in Fig. 3 above. In RL pairs, left-handers resembled left-handed singletons in showing no significant ear effect. Right-handers in RL pairs resembled right-handed singletons for bias to REA. In 6 pairs of LL or ambidextrous (AA) twins, there were 6 individuals with and 6 without REA, fully consistent with random bias to either side. If all non-RR pairs had been considered together, a clear reduction in overall bias would be likely. However, the critical point in the Geschwind et al. data was that this reduction was present for right-handers as well as left-handers in non-RR pairs, and this was not clear for dichotic listening asymmetry.

Geschwind et al [17] referred to two other theories that adopt a chance postulate to account for left-handedness, those of McManus [22] and Klar [18]. These theories resemble the RS theory in proposing a typical directional bias and chance in the absence of that bias. In other respects the theories are very different [10, 13]. Both McManus and Klar propose that the directional gene is for right-handedness, while

the RS theory suggests that it is for left cerebral advantage. The McManus and Klar models of handedness follow that proposed by Layton [19] for *situs inversus* of the viscera, 'directional bias' *or* 'chance'. The RS model proposes that for handedness there is chance for every individual (including every individual twin) and an added weighting toward dextrality in the presence of the RS + gene. The RS model for handedness is 'chance for all' *plus* 'right weighting for some' (see Fig. 1).

Both McManus and Klar treat handedness as a binary variable, right or left, and because there is a single gene for right-handedness, there must be a fixed incidence for left-handedness. McManus [22] proposed that the 'true' incidence of left-handedness is 7.75 percent and that other values in the literature are in error. In fitting the theory to observations, genotypes are re-assigned to phenotypes to allow for supposed errors in the data, so making the model unfalsifiable over the typical range of incidences of left-handedness. Klar proposed that the true incidence of left-handedness is 9.0%, derived from the findings of Rife [25]. He argued that Rife was the only investigator to adopt the true criterion (any one left preference in several actions). Klar did not attempt to fit his model to any other data. However, Rife [25] reported incidences of 5.1 percent for mothers, 5.4 percent for fathers, 7.6 percent for daughters, 9.6 percent for sons, 11.4 percent for MZ twins and 15.4 for DZ twins. Other studies adopting Rife's criterion found incidences of 16.7 - 27.3 percent [20].

The RS theory was formulated after examining the puzzle of the wide range of incidences of left-handedness reported in the literature. The proposed solution was an essential foundation of the theory, namely that hand preferences are related to a continuum of R-L asymmetry for hand skill, and that different incidences depend on

different cut-points or thresholds along this continuum [23]. The threshold approach enables the RS theory to make successful predictions over the whole range of incidences of handedness and eyedness, which is not possible for McManus [10, 11] or for Klar. However, the 9 percent frequency of left-handedness assumed by Klar is very close to the 9.27 percent frequency for atypical cerebral speech estimated by Annett [6]. Therefore, some of the quantitative features of Klar's analysis bear a strong resemblance to those of the RS theory. The argument that the RS + gene is 'for' left cerebral speech allowed predictions to be made for genotype and cerebral speech in twins directly (in Tables 1 and 2), without reference to handedness. McManus and Klar need to invoke additional rules to account for cerebral laterality and for relationships between cerebral speech and handedness. How they might do so in relation to cerebral asymmetry in twins, it would be inappropriate to speculate here.

The present predictions are for healthy twins. They are not expected to hold for twins affected by a possible mutation of the RS + gene that I have called 'agnosic' (not 'agnostic' as in some literature sources). The agnosic gene is hypothesised to lose its directional coding and so impair the right or the left hemisphere at random [see 13, chapter 14]. When paired with a normal RS + gene, but not a normal RS - gene, the agnosic gene would lead to impairment of both sides of the brain by chance in 50 percent of cases. These cases are hypothesised to be at risk for schizophrenia. Twins affected by the agnosic mutation would lose normal cerebral dominance. The rules formulated above for healthy twins would not apply, but speculations about rules that might take their place is beyond the scope of this paper.

In conclusion, the RS theory makes clear and specific predictions about the genotype distribution and the cerebral asymmetry of healthy MZ and DZ twins. The predictions are constant for all samples of twins, but comparisons between RR and non-RR pairs vary with different criteria of left-handedness. Most studies of laterality in twins have sought differences between MZ and DZ pairs and failed to find any. This is expected because the predicted differences are small and would be undetectable except in enormous samples. Of greater interest is the question how twins differ between RR and RL or non-RR pairs. It was for this reason that the predictions of the RS theory have been set out here so that they can be tested when suitable data becomes available. Samples must be representative of the population. Ideally they will be classified for handedness using firm criteria that are both strict (left writing) and generous (any *left* hand preference from several unimanual actions, but *not either* hand preference as in some questionnaires). This will check that the model is equally successful at different thresholds of incidence.

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Table 1. The RS genotype distribution in the population and in MZ and DZ twins per 1,000 pairs

RS genotype	*N general*		*MZ twin pairs*			*DZ twin pairs*		
++	325		++ x ++	325		++ x ++	200	
+ -	490		++ x +-	0		++ x +-	219	
- -	185		+- x +-	490		+- x +-	305	
		both RS +			815			724
			++ x - -	0		++ x - -	30	
			+- x - -	0		+- x - -	151	
		one RS +			0			181
			-- x --	185		- - x - -	95	
		neither RS +			185			95

Table 2. Typical (T) and atypical (A) brain asymmetry in the population and in MZ and DZ twins per 1,000 pairs

RS genotype	*Population*		
	N	T	A
++	325	325	0
+ -	490	490	0
- -	185	92.5	92.5
total	1,000	907.5	92.5

	MZ twin pairs			
genotype	N	TT	TA	AA
++ x ++	325	325	0	0
+- x +-	490	490	0	0
-- x --	185	46	93	46
total	1,000	861	93	46

	DZ twin pairs			
	N	TT	TA	AA
both +	724	724	0	0
one +	181	90	91	0
neither +	95	24	47	24
total	1,000	838	138	24

Table 3. Genotype and handedness in twins as individuals and as MZ and DZ pairs when the incidence of left-handedness is 14 percent.

(a) Twins per 1,000 individuals

RS	*N*	*Handedness*		*Handedness by genotype*	
		R	L	R	L
+ +	325	315	10	.968	.032
+ -	490	425	65	.868	.132
- -	185	120	65	.650	.350
total			140		

(b) MZ per 1,000 pairs

	Handedness pairs				*Genotype pairs by handedness pairs*			
	N	RR	RL	LL	RR	RL	LL	RL + LL
++ x ++	325	305	20	0	.405	.092	0	.081
+ - x + -	490	369	113	8	.491	.521	.258	.488
- - x - -	185	78	84	23	.104	.387	.742	.431
total		752	217	31				

(c) DZ per 1,000 pairs

	N	RR	RL	LL		RR	RL	LL	RL + LL
++ x ++	200	188	12	0					
++ x + -	219	184	34	1					
+ - x + -	305	230	70	5					
					both +	.807	.506	.24	.480
++ x - -	30	19	11	0					
+ - x - -	151	85	59	7					
					one +	.139	.306	.280	.303
- - x - -	95	40	43	12	*neither* +	.054	.188	.480	.217
total		746	229	25					

Table 4. Typical (T) and atypical (A) brain asymmetry in twin pairs by handedness pairs, when the incidence of left-handedness is 14 percent.

(a) MZ twins

	Ns per 1,000 pairs			*Brain asymmetry pairs by handedness pairs*			
	RR	RL	LL	RR	RL	LL	non-RR
TT	693	154	14	.921	.710	.452	.677
TA	39	42	12	.052	.193	.387	.218
AA	20	21	5	.027	.097	.161	.105

(b) DZ twins

	RR	RL	LL	RR	RL	LL	non-RR
TT	664	162	12	.890	.707	.480	.685
TA	72	56	10	.097	.245	.400	.260
AA	10	11	3	.013	.048	.120	.055

Appendix I

The genotypes of left-handers per 1,000 twins for incidences of left-handedness 5 - 45 percent: RS + -, RS + + genotype means are 0.66z, 1.33z for males, 0.80z, 1.60z for females, and 0.73z, 1.47z for sexes combined respectively.*

	Males			*Females*			*Both sexes*		
	RS - -	RS + -	RS + +	RS - -	RS + -	RS + +	RS - -	RS + -	RS + +
Total population	185	490	325	185	490	325	185	490	325
Percent Left-handers									
5.0	26	21	3	30	18	2	28	20	2
7.5	37	33	5	42	30	3	40	31	4
10.0	47	46	7	53	42	5	50	44	6
12.5	56	59	10	63	55	7	60	57	9
15.0	64	72	14	72	68	10	68	70	12
20.0	80	99	21	88	96	16	84	97	19
25.0	93	126	30	102	124	23	98	125	27
30.0	106	154	40	115	153	32	111	153	36
35.0	116	182	52	126	182	42	121	182	47
40.0	126	210	64	136	211	53	132	210	58
45.0	135	237	78	144	240	66	140	238	72

* adapted from Annett [13, Appendix VI]

Figure Legends

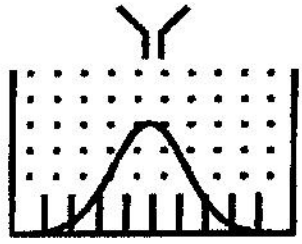
Fig. 1 A schematic representation of the right shift theory, see text [from 13].

Fig. 2 Percentage of non-gene-carriers (RS - - genotypes) in twins from MZ and DZ pairs that are RR or non-RR for handedness, when left-handedness ranges from 5 - 40 percent.

Fig. 3 Pair concordance for typical brain asymmetry in RR and non-RR handedness pairs of MZ and DZ twins, when left-handedness ranges from 5 - 40 percent.

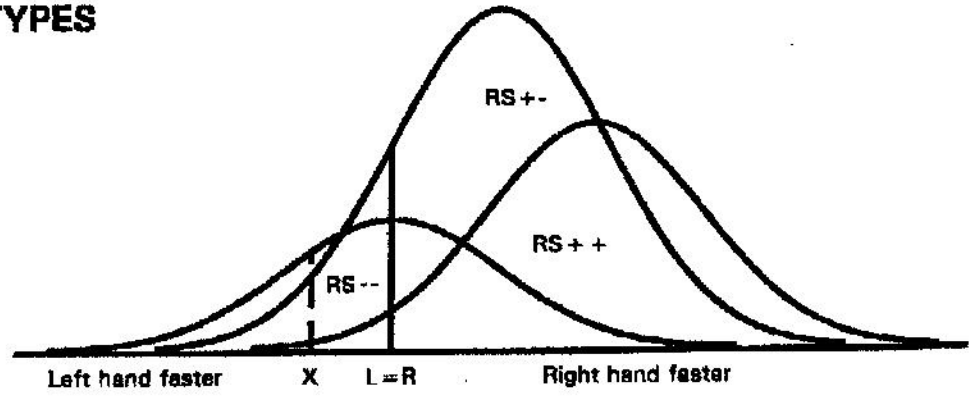
Fig.1

1. CHANCE



2. RS + GENE

3. GENOTYPES



4. SHIFT

5. THRESHOLDS

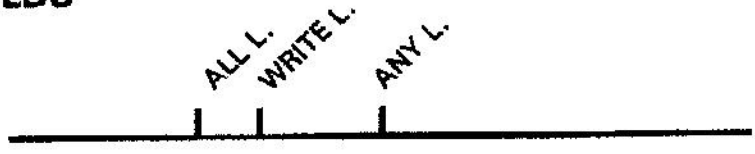


Fig. 2

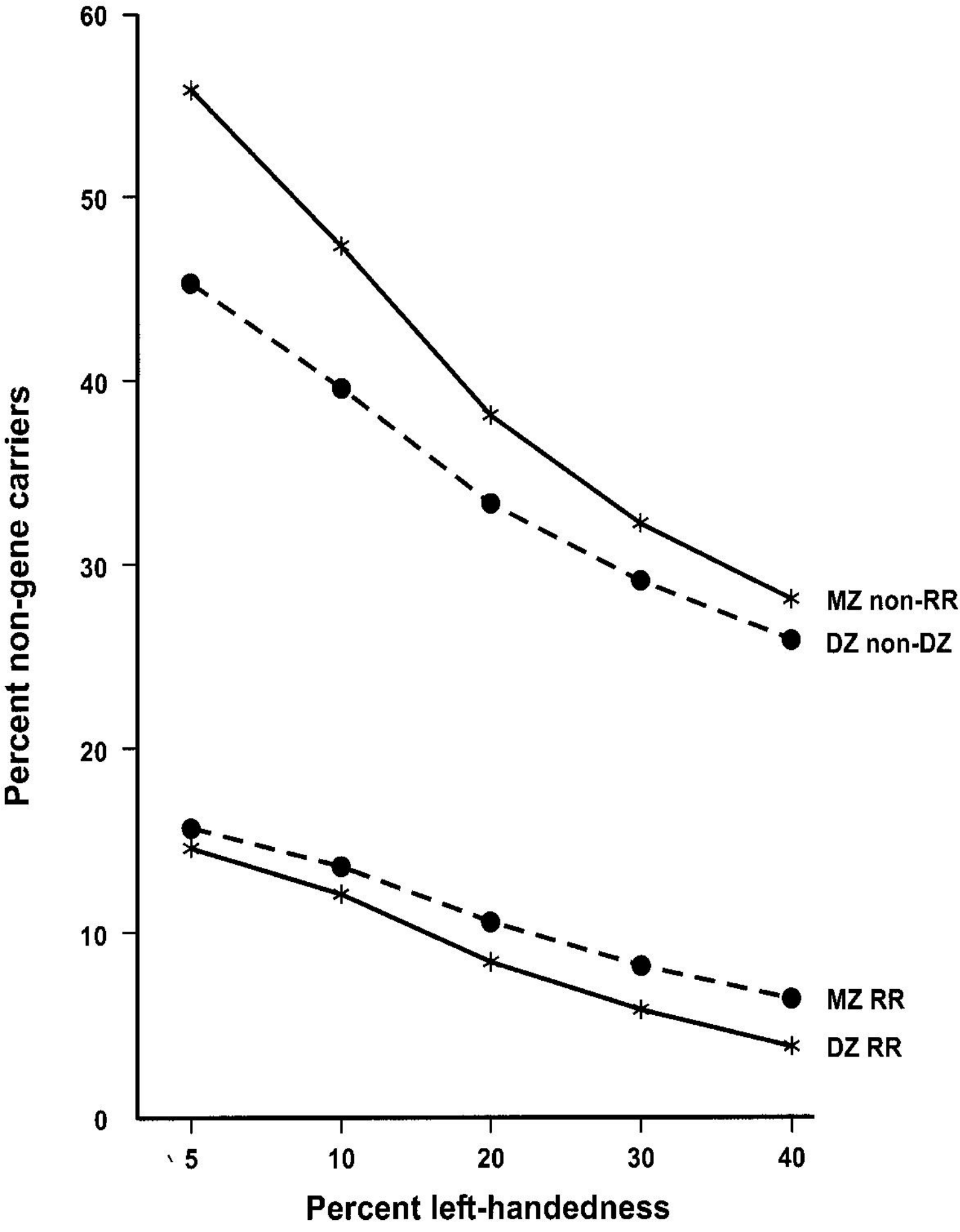
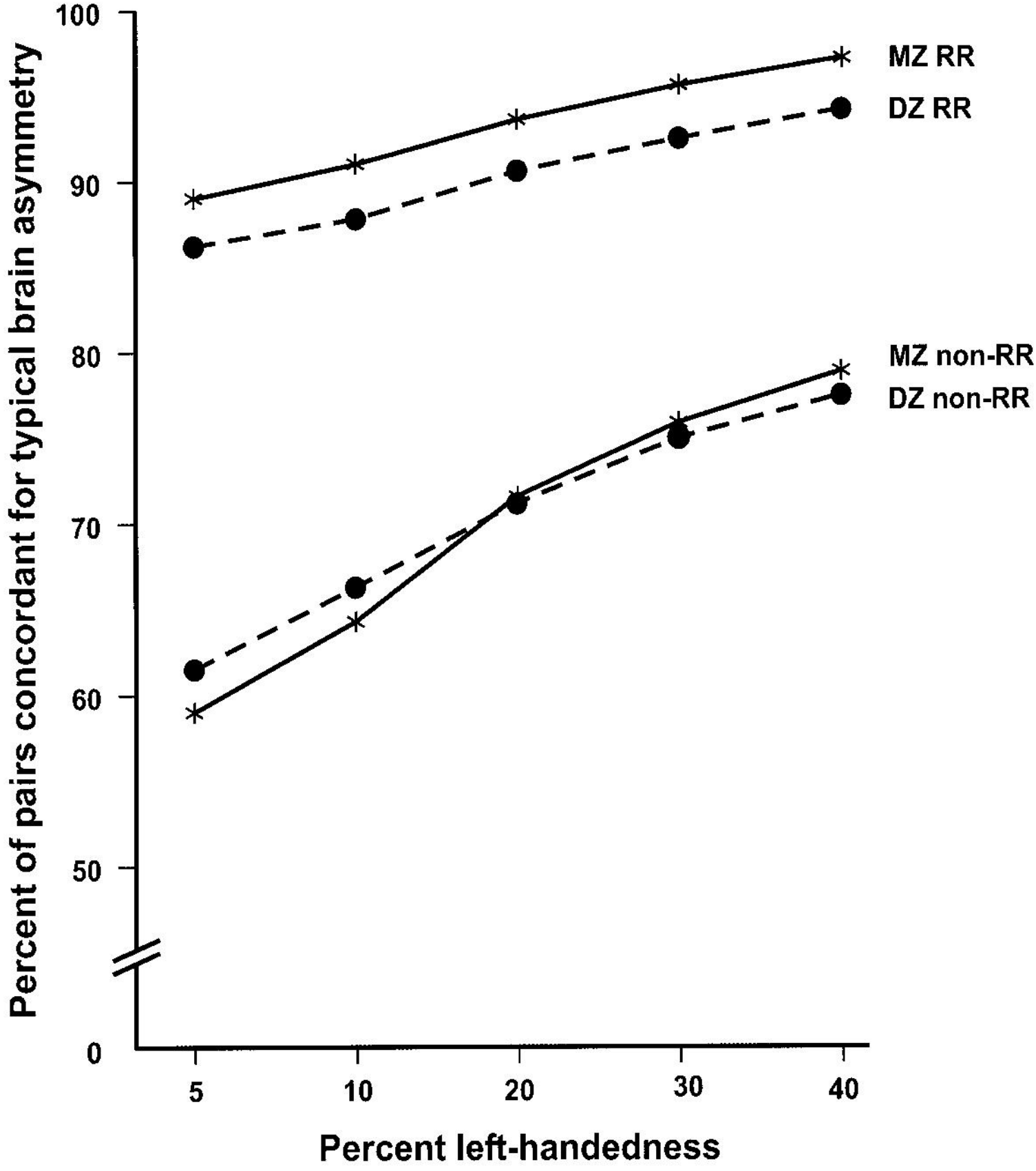

60
50
40
30
20
10
0
Percent non-gene carriers
5
10
20
30
40
Percent left-handedness
MZ non-RR
DZ non-DZ
MZ RR
DZ RR

Fig. 3


100
90
80
70
60
50
0
Percent of pairs concordant for typical brain asymmetry
5
10
20
30
40
Percent left-handedness
MZ RR
DZ RR
MZ non-RR
DZ non-RR