# EMBRYONIC DETERMINATION OF BRAIN PROGRAMMING ASYMMETRY

## A Neglected Element in Twin-Study Genetics of Human Mental Development

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*Departures from the usual human brain asymmetry, manifested in unusual laterality of motor dominance and/or speech representation, seem to have some genetic basis, and have been found associated with: schizophrenia, epilepsy, alcoholism, dyslexia, dysphasia, autism, and mental retardation. This can also derive from embryonic disturbances, as evidenced by excessive association with: first births, late births, birth difficulties, and twinning. MZ twins develop from embryos which have often split after at least some commitments to the cellular development of bilateral symmetry have been made. The effects of such a split are visibly recorded in mirror-imaging, in tooth emergence patterns, in shapes of mouth, nostrils, eyes, and ears, in hairwhorl placement and pattern. Brainfunction laterality is also found to be subject to mirror-imaging.*

*Data from the 1972 publication of the Gottesman and Shields genetic twin study of schizophrenia serve to illustrate the power of the neglected embryonic discriminator: Fully one-third of their MZ schizophrenic sample (nearly ten times the best population estimate) were characterized as lefthanded or ambidextrous. If the sample is divided between pairs with and without any sign of laterality disturbance, the results are very strikingly altered. The pairs with no sign of laterality disturbance are 88% concordant, whereas unusual laterality pairs are 24% concordant. Several severity indicators are in excess, by ratios of 2 to 10-fold, among the RH pairs. Nuclear subtypes are (2.5) times as frequent, and schizoid premorbid personalities are twice as frequent, among the RH pairs.*

Much of the functioning of the human mind depends on the asymmetrically specialized programming of the basically very symmetrical brain hemispheres. Intelligence, speech, reading, writing, the basic stability of ongoing brain function, and personality integration, are all subject to variations which correlate with variations in the asymmetry of brain programming. The simplest of many clues to these relationships is the fact that lefthanders are found in statistical excess among retardates; among people with speech, reading, and learning problems; and among epileptics, alcoholics, schizophrenic adults, and schizophrenic children (Boklage 1974).

The basic symmetry of the human body, including the brain, is determined by cellular differentiations which occur very early in embryogenesis. When the prochordal plate appears at one edge of the germinal disc (Hamilton and Mossman 1972), anterior, posterior, left, and right are irreversibly determined. Viable MZ twinning events then become approximately impossible. But 70% of MZ twinning events occur while the inner cell mass is arranging itself into the germinal disc and making the cellular developments responsible for that first visible demonstration of symmetry specialization (Bulmer 1970). From a morphogenetic point of view, the primordia of left-side and right-side structures are composed of similar cells which differ importantly in that they are programmed to build structures with completely different orientations in space. Often, as is true of the limbs, the mirror-image structures have similar function. In the special case of the human brain, it is a feature of basic importance that the symmetrical halves are very differently programmed.

Much of what we are accustomed to calling environmental differences between MZ twins, especially in mental development variables, may in fact be embryonic differences. Since twin studies have been

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such an important source of information on human mental development, the differences between MZ twins are enormously important in determining our opinions about etiology. " Environmental " is used to mean everything not coded in nuclear genes, and is in fact usually taken to mean things that parents do to children (witness the prevalence of fostering studies and twins-raised-apart studies). If, as I suspect, these meanings are nowhere near identical, our interpretations of the results of twin studies may err seriously. I suggest that many important differences within pairs of MZ twins are in fact embryonic in origin; that the asymmetric cellular specialization of the brain hemispheres begins early enough in embryogenesis that MZ twinning events frequently disturb the results of early commitments.

MZ twins sometimes mirror-image in the skin structures of the mouth, face, and head. The embryonic precursors of those structures surround immediately on three sides the neural ectoderm from which the brain will develop. It is not surprising, then, that MZ twins also, and quite frequently, mirror-image in the assignment of functions to the brain hemispheres Among 40 pairs of MZ twins tested by Satz et al. (1968) for handedness and speech laterality, 9 pairs included lefthanders, and 15 pairs had one or both twins with right-brain speech. On a per-zygote basis proper to questions of possible genetic action, both characteristics are in considerable excess among the twins in this sample. The twins were between 12 and 18 years of age, identical in 24 blood antigens, students in pulic schools, and available for testing; no other selective criteria seem to have been applied (Table 1).

Table 1. *Distribution of handedness and speech laterality in MZ twins*

| Handedness | Right-Right | | | Left-Left | | | Right-Left | | |
|---|---|---|---|---|---|---|---|---|---|
| Speach hemisphere | Model I | Data | Model II | Model I | Data | Model II | Model I | Data | Model II |
| Left-Left | 31 | 24 | 23 | 1 | 0 | 0 | 2 | 3 | 2 |
| Right-Right | 4 | 2 | 2 | 1 | 0 | 0 | 1 | 0 | 0 |
| Right-Left | 0 | 10 | 12 | 0 | 0 | 0 | 0 | 1 | 2 |

None of 9 pairs including a lefthander were concordant for lefthandedness. Only 2 of 15 pairs were concordant for right-brain speech. Thus a minimum of 35%, or 14 pairs, mirror-image in speech laterality, strictly defined left-handedness, or both. The observations will not fit a model based on general population frequencies. They will not fit any model requiring concordance in either characteristic, nor requiring any interaction between the two. These are the features of Model I in the table. The data best fit the hypothesis of Model II that handedness and speech laterality are independently determined, each by a single factor in two possible states, with the cellular expression of both factors randomly assorted between the members of the twin pairs.

Yet there is an undeniable genetic component: 57% of the pairs discordant in (unusual) laterality come from families which include lefthanders; 30% of the laterality-concordant (primarily normal) pairs come from such families; 40% for the whole group. There is an overall excess of lefthanders among the families of these MZ twins; concentrated in, but not limited to, the families of twins with unusual laterality.

The simplest explanation is that the determinants of unusual laterality, present in genetic form at the conceptions of these twin pairs, are brought to expression by cellular embryonic processes which are randomized either by the twinning split or by yet unknown factors which contribute to causing the split.

Lefthandedness and other laterality disturbances are statistically excessive among the relatives of lefthanders and the relatives of MZ twins, among schizophrenics, epileptics, alcoholics, dyslexics,

dysphasics, and retardates. And the factors determining at least some aspects of brain laterality are expressed throungh mechanisms which can be disturbed in MZ twinning. The excellent twin study data of Gottesman and Shields (1972) include handedness data for most of the twins; this allows an examination of the embryonic aspects of the known relationship between schizophrenia and brain laterality disturbance.

The first thing one notices about handedness among these twins is that 62% of the MZ pairs show unusual laterality in one or both members. There is no excess among the DZ twins. The MZ pairs which include 2 righthanders are 8 in number, exactly as expected from a binomial distribution based on frequencies of left- and righthandedness within the sample. Seven of those 8 pairs are concordant for schizophrenia, 6 concordant even in subtype. Thirteen pairs include at least 1 lefthander; 3 both-lefthanded and 10 mirror-imaged; again exactly in accord with binomial distribution. Only 3 of those 13 pairs are concordant for schizophrenia, none of them concordant in subtype. The members of righthanded pairs have the more severe illnesses by every indicator, including condition ot the close of the study, length of time spent in hospital (2.4 times as long on the average), and Average Global Psychopathology Rating. The lefthanded members of the mixed-laterality pairs have more severe illnesses than their righthanded cotwins, but still much less severe than, the illnesses of members of righthanded pairs. These data are summarized in Table 2.

The members of mixed-laterality pairs are less likely to be schizophrenic at all, with lefthanders representing the majority of cases. The members of mixed-laterality pairs only half as often had schizoid personalities before breakdown; less than half as often were diagnosed as respresenting a nuclear

Table 2

| | Righthanded pairs (2 RH) | Lefthanded pairs (1-2 LH) |
|---|---|---|
| | 8 pairs RH-RH | 3 pairs LH-LH<br>10 pairs LH-RH |
| Concordance | 7 pairs concordant, 88% | 3 pairs concordant, 23% |
| Subtype concordance | 6 pairs concordant in subtype, 86% | 0 pairs concordant in subtype, 0% |
| Severity I,<br>Not working now | 9/16 members, 56% | 6/26 members, 23%<br>5/16 LH, 31%<br>1/10 RH, 10% |
| Severity II, over<br>1 year in hospital | 12/16 members, 75% | 9/26 members, 35%<br>9/16 LH, 56%<br>0/10 RH, 0% |
| Severity III, over<br>2 year in hospital | 10/16 members, 63% | 4/26 members, 15%<br>4/16 LH, 25%<br>0/10 RH, 0% |
| Severity IV, Mean<br>Global Psychopathology Rating | 5.42 overall<br>(7/16 over 6.0) | 4.1 overall<br>4.2 LH<br>3.8 RH (1/26 over 6.0) |

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Table 3

| | Righthanded pairs (2 RH) | | | Lefthanded pairs (1-2 LH) | |
|---|---|---|---|---|---|
| Consensus diagnosis | 15/16 members, 94% | | | 16/26 members, 62%<br>12/16 LH, 75%<br>4/10 RH, 40% | |
| Prebreakdown personality | 9/16 schizoid, 56%<br>2/16 other abnormal, 13%<br>5/16 normal, 31% | | | 7/26 schizoid, 27%<br>10/26 other abnormal, 38%<br>9/26 normal, 35% | |
| Nuclear subtypes | 9 | hebephrenic | 1 | 1 LH | |
| | 2 | catatonic | 0 | | |
| | 8 | typical or true | 4 | 2 LH | 2 RH |
| | 6 | process or chronic | 5 | 5 LH | |
| Neutral ? | 5 | paranoid | 6 | 2 LH | 4 RH |
| | 4 | undifferentiated | 5 | 5 LH | |
| | 2 | atypical | 2 | 2 LH | |
| Non-nuclear subtypes | 1 | depression | 4 | | 4 RH |
| | 0 | schizoaffective | 5 | 5 LH | |
| | 0 | pseudoneurotic | 5 | 2 LH | 3 RH |
| | 0 | reactive | 5 | | 5 RH |

subtype; much more often diagnosed as representing a definitely non-nuclear subtype (Table 3). The differences in concordance between righthanded and mixed-laterality MZ pairs are nearly as great by proportion, as the differences between all MZ and the DZ in the series. Among the DZ twins in this study, there is no statistical relationship of lefthandedness to the diagnosis of schizophrenia, concordance, severity or subtype.

Among these MZ twins, lefthandedness is strongly associated with atypical, relatively mild schizophrenia, strongly antithetical to severe nuclear schizophrenia and to concordance in MZ twin pairs. These data suggest the existence of two different fully biological mechanisms in the etiology of schizophrenia, which are considered in detail elsewhere (Boklage 1974). They also suggest a previously unsuspected source of discordance in MZ twin pairs in mental development variables, and therefore an important caution to twin studies concerned with such variables.

One can argue, on the basis of these data — regardless of their particular relationship to schizophrenia, that MZ pairs including lefthanders (a loose definition seems preferable) must either be excluded or analyzed as a separate class in any study of human mental development. The difference due to applying this discrimination to the twin sample in the Gottesman and Shields study is adequate illustration: casewise concordance, all MZ, 64%, casewise concordance, RH-RH MZ only, 93%.

It may also have important implications for understanding the biology of the twinning process itself. This is not the first suggestion of cellular developmental mechanisms wherein a MZ twinning event separates the genetic determination of a characteristic from its embryonic expression. Nance (1969) and Davies et al. (1971), working from the semantically different, but embryologically congruent, perspective of " cytoplasmic inheritance ", have reviewed a considerable literature concerning symmelia, and — of special interest here — anencephaly, spina bifida, and midline neurological deformations. This latter group of anomalies frequently occur together or in close relatives. Their rates are highly correlated, in spite of wide variations across populations and secularly within populations.

There is a 4 to 5% risk of recurrence in a sibship, in the absence of any evidence of increased parental consanguinity. Twins are considerably over-represented, but almost never concordant.

Matrilineal transmission seems very likely to be involved in these anomalies, and is suggested in the transmission of unusual laterality as well by the fact that lefthanded children have a greater excess of lefthanded mothers than of lefthanded fathers (Falek 1959). Situations in which a given genotype is expressed only, or disproportionately, in the progeny of affected females have been called cytoplasmic inheritance. This is a reasonable outgrowth of the knowledge that the female gamete supplies most of the cytoplasm of the zygote. This would presumably include any organizational factors in the egg cortex which might be distributed nonrandomly in the membranes of dividing embryonic cells. Since the language of cell biology ordinarily separates "membrane" and "cytoplasm" at least phenomenologically, and since variations in uterine biochemistry might also be involved in mammalian development, I suggest that the less definitive term "maternal effects" is presently the more accurate. This nomenclature would appear to have not only greater semantic accuracy, but also greater heuristic value for human research, in that "maternal effects" are within the range of available statistical methods. The biochemical approaches required to define separately the effects of variations in egg cytoplasm, membrane organizational factors, and uterine biochemistry are not presently available to researchers in human reproduction.

These data, especially in the light of some other comments made at this meeting, seem to call for the re-examination of the dogma that MZ twinning is independent of important biological variation and therefore of genetic control. The association of twinning with unusual brain programming symmetry and with neural tube closure anomalies, both of which groups of dysfunctions have some genetic basis, is very suggestive. The high frequency of birth defects and early mortality attests to the embryonic dangers involved. Could it be, for example, that brain-symmetry anomalies and MZ twins have the highest viabilities of numerous possible outcomes of a class of high-frequency-low-viability embryogenic disorders? The vast majority of affected embryos might be expected to abort without notice before the next menstruation. If maternal or genetic factors which might increase the likelihood of these effects should also decrease the likelihood of survival, their detection might be very difficult. Symmetry effects, especially with regard to their manifestations in mental development, may be among the best variables for study, since the timing of their developmental expression seems to coincide well with the time span during which most MZ twinning events occur.

Further twin studies, testing the involvement of other aspects of brain laterality and their hereditary origins, should aid in determining the brain foci involved in schizophrenia, as well as several other major disorders of human mental development. An important bonus may be an increased understanding of twinning and of more usual human embryogenesis.

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