Twins With Schizophrenia: Genes or Germs?

by James O. Davis and Jeanne A. Phelps

Abstract

High concordance for schizophrenia in monozygotic (MZ) twins is often cited as evidence for the etiological influence of genetics; however, even if twins are separated at birth, MZ twin concordance is influenced by the shared prenatal environment. Study of the placentation status of MZ twins provides a way to investigate some prenatal influences, including the possible role of viral infections. The probability of shared infections is likely to be greater in monochorionic MZ twin pairs than in dichorionic pairs because of shared fetal circulation in the monochorionic pairs. We drew from published twin studies and used reported concordance for handedness as a retrospective marker of placentation status. We found that MZ twin pairs with opposite-hand preferences were concordant for psychosis in 9 of 15 cases (60%), while only 18 of 56 twin pairs (32%) with same-hand preferences were concordant for psychosis. These results suggest that shared prenatal viral infection may account for much of the high concordance for schizophrenia in identical twins.


The high concordance for schizophrenia in monozygotic (MZ) twins is usually interpreted as evidence of genetic influence. Some who study twins through pedigree or population strategies have maintained that MZ twins reared apart (MZA) "share essentially no environmental influences, and the MZA correlation is a direct estimate of heritability" (Waller et al. 1990, p. 139). This widely cited position is untenable, however, because it discounts the influence of the shared prenatal environment of all twins. Smotherman and Robinson (1990) recently noted an unfortunate tendency for researchers to ignore the importance of the prenatal period: "[T]he behavioral literature is replete with examples of experimental design, reasoning, and conclusions that convey the implicit assumption that the prenatal period is irrelevant to the postnatal expression, function, or development of behavior" (p. 97).

Few researchers, particularly those concentrating on schizophrenia, have taken advantage of the fact that MZ twins offer a special opportunity to study prenatal influences. The placenta is a critically important determinant of the prenatal environment: "It is a physical and physiological link between mother and child, and it exhibits variations with regard to membrane type, size, shape, and circulation which may be important in themselves or may affect the nutrition of the embryo or the transport of drugs, toxins, and other agents which can influence brain development" (Melnick et al. 1978, p. 426). Because MZ twinning produces a variety of placentation arrangements or chorion types, different types of MZ twins may experience very different intrauterine environments. We contend that these variations in placentation, described below, are especially relevant to investigations of the intriguing viral hypothesis of schizophrenia.

Reprint requests should be sent to Dr. J.O. Davis, Dept. of Psychology, Southwest Missouri State University, Springfield, MO 65804-0027.
In approximately 40 percent of MZ twins, twinning occurs early, and so separate blastocysts arrive in the uterus independently, attach separately, and develop their own separate placentas, chorion, and amnions. These twins are dichorionic monzygotic (DC-MZ). The fetal circulation of DC-MZ twins is almost never connected (Bulmer 1970). On the other hand, approximately 60 percent of MZ twinning occurs in the early blastocyst stage, with the inner cell mass splitting into two separate cell masses within the same blastocyst cavity, resulting in a shared placenta and chorion (and occasionally one amnion). These twins are monochorionic monzygotic (MC-MZ). In about 90 percent of MC-MZ twins, there is shared fetal circulation (Bulmer 1970).

The placenta acts as a barrier to infection, but it is an imperfect barrier. Because MC twins share blood circulation while DC twins generally do not, MC-MZ twins would be likely to share any infection that crosses their single shared placenta. On the other hand, an infection might cross the placenta of one member of a DC-MZ twin pair (or a dizygotic pair, all of whom are dichorionic), but not the placenta of the cotwin. If it can be shown that MC-MZ twins are more concordant for schizophrenia than DC-MZ twins, this finding would be consistent with the growing evidence that the mother’s exposure to infectious disease, especially during the second trimester of pregnancy, increases the risk of later schizophrenia in her child (Torrey et al. 1988; Bracha et al. 1992; Pulver et al. 1992; Sham et al. 1992; Adams et al. 1993).

It is important to note that shared circulation can lead to problems for some MC twins. From 15 to 30 percent develop “twin-transfusion syndrome” (Bulmer 1970), a condition that can cause mild to marked differences in weight and appearance between the twins at birth (Tan et al. 1979; Scerbo et al. 1986). Twin-transfusion syndrome occurs when there is a significant degree of arteriovenous anastomosis between the placental circulations of the twins, such that the twin on the arterial limb infuses blood into the circulation of the cotwin, leaving the infused twin plethoric and the donor twin anemic (Fananoff and Martin 1987). The infused twin may be larger (up to 1,000 grams) and jaundiced and may suffer cardiac atrophy or polycythemia, among other health problems, while the donor twin may appear very pale and may suffer from hypoglycemia, decreased muscle mass, and cardiac atrophy, as well as other problems (Scerbo et al. 1986).

Despite these intrapair differences in the 15 to 30 percent of MC-MZ twins who suffer from twin-transfusion syndrome, more intrapair similarity in MC twins than in DC twins has been found on measures of plasma cholesterol (Corey et al. 1976) and on measures of behavioral characteristics. Reed et al. (1991), using dermatoglyphics to estimate placentalation retrospectively, found that MC-MZ pairs were more similar than DC-MZ pairs on measures of type A characteristics but not on measures of cognitive function and hostility. Munsinger (1977), using birthweight differences to estimate placentalation retrospectively, claimed that twin-transfusion syndrome decreased the intrapair similarity of IQ in MC twins, but Kamin (1978) reanalyzed Munsinger’s own data and found the opposite effect. In perhaps the strongest study in terms of methodology, Melnick et al. (1978), who worked with twin pairs of known placentaion, found that with respect to IQ, members of DC-MZ pairs were significantly more discordant than members of MC-MZ pairs. Their findings led them to discount the influence of twin-transfusion syndrome on intrapair variation in IQ: “Apparentl, either the frequency or the degrees of severity of the consequences of the transference syndrome or both have been overestimated” (Melnick et al. 1978, p. 430).

We found no schizophrenia studies that considered placentaion in twins. While it would be desirable to contrast the schizophrenia concordance rates of MZ twins of known placentaion, the data for this type of investigation are not yet available. So we adopted an interim strategy for assessing placentaion status retrospectively to determine whether there is any evidence of differences in MC-MZ/DC-MZ concordance for schizophrenia. For this study, we based our strategy on hand preference in MZ twins. The logic underlying our use of handedness as a marker and our findings are reported below, followed by recommendations for future research.

A variety of placentaion arrangements are produced by MZ twinning. DC placentaion is generally associated with twinning that occurs up to the 4th day after fertilization; MC placentaion develops in twinning that occurs from the 4th day on. Finally, even later twinning results in mirror imaging (Macgillivray et al. 1975; Springer and Deutsch 1981; Lohr and Bracha 1992; Torrey et al. 1993), and if twinning is very late (e.g., after the 13th day), conjoined
twins can occur (Scerbo et al. 1986). Approximately one-fourth of MZ twins are mirrored (Springer and Deutsch 1981). Although it is clear that mirroring is the result of late twinning, the embryological mechanisms are not completely understood. Springer and Deutsch (1981) offer this speculation:

At some point early in development, chemical gradients that establish an axis of bilateral symmetry are established in the embryo. If the division that forms two individuals occurs after that point (and in the proper plane), one embryo will develop from what was to be the left half of the original embryo, and one will develop from what was to be the right half. [p. 112]

Mirroring is usually confined to the ectodermal layer and only rarely involves internal organs. MC twins can mirror for hand preferences, birthmarks, hair swirls, and dermal ridge patterns on hands and feet (Springer and Deutsch 1981). Because both mirroring and sharing a single placenta occur as a result of late twinning, mirroring is a special case of MC placentation.

Mirrored handedness is undoubtedly an imperfect marker of placentation status, and we realize there may be a number of problems associated with its use. First, although there is a logical basis for positing an association between mirrored handedness and MC placentation (i.e., both are the result of late splitting), no one has tested the accuracy of this marker with samples of twins of known placentation.

Second, statistical power would be compromised if left-handedness is caused by other factors. Genetics, brain pathology (especially that caused by prenatal and perinatal stressors), and learning all have been proposed as other factors that could lead to the emergence of left-handedness (Halpern and Coren 1990). However, Halpern and Coren (1990) conclude that genetic theories fail to explain handedness patterns in twins, and Torrey (1994) points out that, although insult to the brain is widely cited as a cause of left-handedness, there are remarkably few research data to support this claim. Further, if learning reduces the incidence of left-handedness, then twins who were originally mirrored for handedness would be misclassified, once again decreasing our statistical power.

A third problem with using handedness as a marker is that only MC twins who split very late are mirror imaged, so mirroring for handedness will fail to correctly identify the placentation status of nonmirrored MC twins. Thus, handedness is a very conservative marker in the sense that it reduces the number of twin pairs that can be used, which makes statistical significance harder to achieve. Although we can be reasonably certain that mirrored MZ twins are indeed MC, not all MC-MZ twins are mirrored, and nonmirrored twins will be classified into the DC group by this marker.

In summary, studies of placentation status in MZ twins provide a way to assess the possible effects of prenatal influences and particularly the role of infections. While other retrospective strategies for estimating placentation have been used (Munsinger 1977; Reed et al. 1978, 1991), we are fortunate that MC placentation and mirroring for handedness are both explained by late division in the early blastocyst stage, so that hand preferences provide a readily accessible, albeit imperfect, marker for placentation.

We reanalyzed information on handedness from three recent studies on samples of twins in which one or both twins had schizophrenia (Lewis et al. 1989; Lohr and Bracha 1992; Torrey et al. 1993). Lewis et al. (1989) reported on 30 pairs drawn from the Maudsley Hospital Twin Register collected since 1967, after the older Maudsley series used by Boklage (1977), which was collected before 1967. Torrey et al. (1993) provided 40 more pairs of twins for this study with their data from the National Institute of Mental Health (NIMH) Twin Study Unit. Lohr and Bracha (1992) were able to report one more pair that had been recruited for the Maudsley project but had been unable to travel in order to participate. Together, the three studies provided 71 pairs of MZ twins.

We did not include twin samples from older studies that relied on fingerprints or subjective judgments of appearance to determine zygosity. Lohr and Bracha (1992) contend that such studies of twins were conducted before researchers had knowledge about the effects of mirroring and viral infections on skin patterns, which likely resulted in MC-MZ twins’ being incorrectly assigned to the DZ group. Twin-transfusion syndrome is another factor that can lead to misclassification of MZ twins as DZ, because this syndrome leads to marked differences in weight and appearance between the members of the pair (Tan et al. 1979). These and other concerns led us to exclude one of the better known and more controversial studies of handedness in twins with schizophrenia conducted by Boklage (1977). First, Boklage relied on the older Maudsley Hospital twin series reported by Gottes-
man and Shields (1972). In their 57 pairs, zygosity was determined only by fingerprinting in 5 cases and by appearance alone in 21 pairs. Second, there were problems with the determination of handedness. Boklage decided that any left-foot preferences or ambidexterity would qualify as "not right handed." This is a decision not followed by subsequent researchers, who have relied instead on writing preferences and standardized tests. Third, and perhaps most disturbing, were the comments of Lewis et al. (1989), who found evidence that fewer than half of the proband cases in the Maudsley series who received consensus diagnoses of schizophrenia would match current criteria for schizophrenia. Finally, a number of attempts to replicate Boklage's findings have failed (Luchins et al. 1980; Lewis et al. 1989; Torrey et al. 1993).

Based on the 71 cases reviewed, twin pairs who preferred opposite hands were more often concordant for schizophrenia or psychosis. Of 15 pairs that included a left-handed and a right-handed twin, 9 (60%) were concordant for schizophrenia or psychosis, while only 18 of 56 (32.1%) twin pairs with same-hand preferences were concordant ($\chi^2 = 3.90, p < 0.025, df = 1$, one-tailed test). Because only 21 percent (15 of 71) of our cases were opposite-handed, and because the expected rate of MC twinning is 60 percent, we can assume that many of those in the same-hand-preference condition must be MC. In that case, the 32.1 percent concordance rate for same-hand-preference pairs would be too high an estimate of the schizophrenia concordance rate for DC-MZ twins, as it would likely be inflated by the presence of hand-concordant MC-MZ twins.

Additional data from the NIMH twins provided convergent validation for handedness as an indicator of mirror imaging and/or placentation. First, following Munsinger (1977), who used weight differences to retrospectively assess placentation, we analyzed all NIMH twins' birth weights to determine whether discordance for handedness would be associated with larger within-pair birthweight differences and greater between-pair variance, which would be expected in cases of twin-transfusion syndrome in MC placentation (Munsinger 1977). The birthweight difference of hand-discordant twin pairs averaged 14.9 percent, compared with 9.4 percent for same-hand-preference pairs ($t = 2.10, p = 0.05, df = 59$). There was also greater variance in birth-weight differences in the hand-discordant twins ($F = 2.75; df = 9.45, p = 0.05$), which is consistent with reports on twin transfusion (Tan et al. 1979). Skre et al. (1992) also reported similar birth-weight differences for concordant and discordant twins with schizophrenia.

Second, we also inquired whether hand-discordant twins in the NIMH series showed any additional signs of mirroring. Dr. Torrey (personal communication October 1993) reported that 10 of the 15 twin pairs with opposite-hand preferences reported in Torrey et al. (1993) showed additional signs of mirror imaging for appearance. Because mirror imaging is expected in 25 percent of MZ twins (Springer and Deutsch 1981), the 67 percent of hand-discordant twins who were mirror-imaged in Torrey et al.'s study contrasts significantly ($z = 3.723, p < 0.001$) with the overall expected rate.

Based on these suggestive findings, we intend to employ dermatoglyphics analysis as a more refined way to estimate placentation retrospectively. This strategy (Lohr and Bracha 1992) also relies on the relationship between mirroring and placentation and avoids some of the problems discussed above. We hope dermatoglyphics will provide confirmation of these findings and spur further research on placentation effects.

Of course, the best method of determining placentation is direct examination of the placenta in twin births, an avenue of investigation that we strongly recommend. Research on placentation takes on greater significance in light of the increasing support for the influence of viral infections on schizophrenia (Torrey et al. 1988; Pulver et al. 1992; Sham et al. 1992; Adams et al. 1993).

In the National Advisory Mental Health Council's Report to Congress on the Decade of the Brain entitled Approaching the 21st Century: Opportunities for NIMH Neuroscience Research (National Institute of Mental Health 1988), the Council posed "a challenge for neuroscience: 50 important questions to answer in the decade ahead." We feel research on placentation effects in schizophrenia can shed light on these questions:

1. What role do viruses play in mental illness? (p. vi)
2. What factors account for the lack of complete concordance in identical twins? (p. vii)
3. How do physical illnesses cause psychopathology? (p. viii)

References

Adams, W.; Kendell, R.; Hare, E.; and Munk-Jorgensen, P. Epidemi...


Acknowledgment

This article is based in part on a presentation at the Fifth Annual Convention of the American Psychological Society, Chicago, IL, June 1993.

The Authors

James O. Davis, Ph.D., is Professor, Department of Psychology, and Jeanne A. Phelps, Ph.D., is Assistant Professor, Department of Psychology, Southwest Missouri State University, Springfield, MO.

Announcement

Nominations are being sought for the 1995 *Psychological Foundation/Gralnick Award* for schizophrenia research. Candidates for this award of $2,000 must demonstrate an exceptional contribution to schizophrenia research with emphasis on the discovery and/or treatment of the earliest signs of schizophrenia, emphasizing the psychological aspects of the disease process. Preference will be given to individuals working in a psychiatric facility.

Individuals must submit applications to the American Psychological Foundation by April 1, 1995. To request an application or additional information, please contact:

Cynthia Garber
The American Psychological Foundation
750 First St., NE.
Washington, DC 20002
Telephone: (202) 336-5814