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# Subclinical Microcrania, Subclinical Macrocrania, and Fifth-Month Fetal Markers (of Growth Retardation or Edema) in Schizophrenia: A Co-twin Control Study of Discordant Monozygotic Twins

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**Summary:** *Objectives:* We tested the hypothesis that gestational injuries in some patients with schizophrenia would leave their mark as a subtle reduction in head circumference (subclinical microcrania). It had been previously shown that prenatal injuries can differentially affect members of an MZ pair. We therefore examined the relationship between head circumference and a marker of prenatal injury (i.e., an in-utero, nonshared environmental effect) in monozygotic (MZ) twin pairs discordant for schizophrenia. *Method:* Twenty-two probands with DSM-III-R schizophrenia were compared to their unaffected MZ co-twins. Fetal-size discrepancy between MZ twins is a marker of differential-intrauterine injury to one of the two MZ members. Fingertip dermal cells migrate to form ridges during the fifth month of gestation. Finger-ridge count is lower in the MZ twin which was *physically smaller* during this fifth-month cell migration period. The intrapair-MZ-unsigned-percent difference in ridge count (MZu%dRC) is thus an index of fifth-month fetal injury. The variables of a priori focus in this study were two within-pair physical measures: MZu%dRC and "MZ percent difference in head circumference" (MZ%dHC). *Results:* There was no overall head-circumference-group difference in the 22 pairs between the affected and unaffected twins; however, we were able to draw some conclusions because of our access to genetically identical controls, which serve as an indicator of what each patient's head circumference and dermal-ridge count *would have been if he or she were not afflicted with schizophrenia:* among the 12 affected twins with subclinical *macro*crania, none had markers of second-trimester injury, but of the 10 affected MZ twins with subclinical *micro*crania, five had such injury markers (three had ridge-count markers of second-trimester edema and another two had ridge-count markers of second-trimester-growth retardation, $p = .0228$). Overall, in the 22 MZ twin pairs, a significant relationship was found between MZ%dHC and MZu%dRC (Spearman's $r_s = -0.45$; $p < .036$). Of the variance in head circumference, 20.2% were predicted by within-pair discrepancy in ridge counts. *Conclusions:* The head circumferences of all subjects were in the normal range. Decreased head circumference in affected MZ co-twins (relative to unaffected MZ co-twin) characterizes discordant MZ pairs with larger finger-ridge-count differences (i.e., second-trimester fetal-size differences). This study using ideal genetic controls suggests that, while present only in some patients with schizophrenia, the decrease in head circumference is most likely a consequence of in-utero nonshared environmental

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deleterious events manifesting as growth retardation or as fetal edema and occurring around the fifth prenatal month. **Key Words:** Schizophrenia—Etiology—Embryology—Neurodevelopment—Dysmorphology—Dermatoglyphics—Twins—Monozygotic—Nonshared environment. **NNBN 8:44–52, 1995**

Head circumference is a part of the neuropsychiatric and pediatric examinations and serves as a rough, but highly cost effective, estimate of normal and abnormal brain development. Specifically, smaller head circumference is considered a clinically useful marker of neurodevelopmental brain disease. While underutilized by psychiatrists, head circumference is widely used in pediatrics and child neurology (1). The magnetic resonance imaging (MRI) (2–5) data in schizophrenia indicate smaller brains. The question of whether patients with schizophrenia have a slightly smaller (6–8), larger (9), or unchanged (10, 11), mean-head circumference has been controversial.

Here we report on 22 pairs of monozygotic (MZ) twins discordant for schizophrenia. Twin data are unique because an individual can serve as his or her co-twin's "built-in" control. This built-in control allows one to draw more powerful conclusions from small samples. Discordant MZ twin studies thus provide a powerful method to test for environmental effects, because twin genotypes are controlled, although phenotypes may differ (12–15).

Recent studies also indicate that some prenatal injuries may not affect both MZ twins to the same extent (16–21). Thus, discordant MZ twins may be used to look for clues that the observed within-pair phenotypic differences exist because of within-pair variations in prenatal-environmental injuries.

Fetal-size discrepancy between MZ twins is a marker of differential-intrauterine injury to one of the MZ members. Fingertip-dermal ridges are known to develop during the early fifth month of gestation. For example, Babler (22) has examined 105 fetuses and concluded that fingertip dermal ridges develop between weeks 17 and 25 of gestation. Ridge count is lower in a fetus who was physically smaller during distal-upper-limb ridge development (23). In this study, we hypothesized a priori that in-utero, nonshared environmental events (e.g., ischemic or other intrauterine injury), that can differentially affect members of MZ pairs, may in part be responsible for the smaller head circumference occasionally reported in patients with schizophrenia. Moreover, what we know of neural development suggests that the second trimester is a particularly critical time period for such nonshared events to have an effect on brain growth (including head circumference). If this timetable is accurate, then we would expect a reduction in head circumference in the schizophrenic member of discordant MZ pairs to be associated with markers of second-trimester, intrauterine pathology. As stated earlier, it is noteworthy that many prenatal injuries, especially ischemias, frequently do not affect both MZ twins to the same extent (16–21).

Once formed in the fifth month of gestation, dermal ridges are indelible anatomical features. Thus, ridge count is not permanently disrupted by delivery-room or postnatal insults to the brain or body of the subject, such as postnatal psychotropic medication, alcohol or other drug abuse, dehydration, trauma, or aging (16, 21, 23, 24, 25). For this reason, ridge count remains the mainstay of person-identification techniques (24). The main reason that ridge count has long been replaced by newer methods in *zygosity* determination is that it is disrupted by various intrauterine insults. The *only* environmental conditions that can change ridge count are intrauterine ones (22, 25–27).

Prenatal-injury research (22, 23) suggested to us that fingertip *ridge-count should be lower in the MZ twin, which was physically smaller during early fifth-month fetal development* (16). High heritability of the head circumference and total-finger ridge count in MZ twins (28, 29) make them the unique measures for investigating the neurodevelopmental disorders. In the present study, we examined the relationship between reductions in head circumference in MZ pairs discordant for schizophrenia and ridge-count discrepancies. Using this technique, this study is able to test carefully one possible hypothesis regarding the etiology of the head-circumference reductions reported in some studies (6, 7) of patients with schizophrenia. Each healthy MZ co-twin served as an indicator of what the proband's head circumference and dermal-ridge count would have been if he or she were not afflicted with schizophrenia.

## METHODS

### Subjects

The original sample included 26 pairs of MZ twins, discordant for schizophrenia (52 individuals), recruited with the help of patients' families groups from the United States and Canada by the Twin-Studies Unit at the National Institutes of Mental Health

**TABLE 1.** *Within-pair data for monozygotic twins*

| | | Head circumference | | Total finger ridge count | |
|---|---|---|---|---|---|
| Twin pair | Sex | Raw difference (cm) | % Difference (MZ%dHC) | Raw difference (cm) | % Difference (MZ%dRC) |
| | | *A. Discordant for schizophrenia* | | | |
| 1 | F | −0.1 | −0.18 | 17 | 12.4 |
| 2 | F | 0.2 | 0.38 | −10 | −5.0 |
| 3 | M | 1.0 | 1.79 | 5 | 2.3 |
| 4 | M | 1.2 | 2.15 | 10 | 7.6 |
| 5 | M | 0.5 | 0.88 | 8 | 5.6 |
| 6 | M | −1.5 | −2.59 | 12 | −21.8 |
| 7 | F | 1.0 | 1.8 | 6 | 3.4 |
| 8 | M | 0.8 | 1.4 | 3 | 2.1 |
| 9 | F | −0.5 | −0.93 | 19 | 19.8 |
| 10 | M | 1.0 | 1.79 | −6 | −7.1 |
| 11 | F | −0.5 | −0.92 | 20 | 14.0 |
| 12 | M | 0.3 | 0.52 | 10 | 8.2 |
| 13 | F | 1.0 | 1.72 | 8 | 3.9 |
| 14 | F | −1.2 | −2.16 | −2 | −2.0 |
| 15 | M | 0.3 | 0.5 | 5 | 3.8 |
| 16 | M | −0.5 | −0.81 | −23 | −13.0 |
| 17 | M | −1.2 | −2.18 | −13 | −10.8 |
| 18 | M | 0.8 | 1.42 | −16 | −7.9 |
| 19 | F | 0.5 | 0.88 | 6 | 4.6 |
| 20 | M | −1.2 | −2.03 | 2 | 2.0 |
| 21 | F | −0.2 | −3.25 | −10 | −25.6 |
| 22 | M | −0.7 | −1.13 | −47 | 52.2 |
| | | *B. Control twins* | | | |
| 1 | F | 0.5 | 0.93 | 14 | 7.8 |
| 2 | F | 1.0 | 1.90 | 3 | 2.7 |
| 3 | F | 0.2 | 0.36 | 0 | 0.0 |
| 4 | M | 1.5 | 2.60 | 1 | 0.8 |
| 5 | M | 1.0 | 1.70 | 2 | 1.0 |
| 6 | F | 0.7 | 1.3 | 18 | 11.8 |

(NIMH). This sample, in which all twins were MZ, has been exhaustively studied and described elsewhere (12, 16, 30–32). Recent molecular-genetic studies using this sample continue to confirm the current consensus that the discordant MZ twins are genetically identical (30). Each of the 52 individuals was interviewed by two senior NIMH research neuropsychiatrists (L.B.B. and E.F.T.) with the complete Structured Clinical Interview for DSM-III-R (SCID I and II), and all psychiatric diagnoses were made according to DSM-III-R criteria (33, 34). It is noteworthy that this sample of MZ twins is largely upper-middle class, relatively functional. Thus, this study is less susceptible to the selection biases toward severity that may have existed in some of the prior work in this area. As of July 1994, the average length of discordance for all pairs was 14.4 years (range: 6 to 27 years). In discordant twins, conversion to concordance almost always occurs in the first 4-year period of discordance (13).

Of the original 26 NIMH pairs, 25 MZ pairs had ridge-count data, and only 23 of these had head-circumference data. Of these 23 pairs the discordant status of one pair was questionable (i.e., at the time of this writing, the apparently well co-twin of this pair was beginning to exhibit symptoms suggestive of the onset of some psychotic disorder). Thus, we performed our main analyses on 22 of the original 25 NIMH MZ pairs. The data on the 22 pairs were examined for the presence of outliers. There existed one outlier defined as a value greater than two standard deviations from the MZu%dRC or MZ%dHC means. The data were analyzed both with and without this outlier. All analyses were based on a priori hypotheses. The raw data in Table 1 are included to allow additional analyses by interested readers. The demographic data on the MZ twins is shown in Table 2. Their ages ranged from 25 to 44 years. The details on the diagnostic description of the MZ twins discordant for schizophrenia have been previously reported (32). For our sample the mean age of on-set and global assessment of functioning (Axis V) is shown in Table 2. Because of the generally nonnormal distribution of the data, nonparametric tests were used (35, 36).

## Additional Controls

An NIMH sample of eight pairs, in which *neither* MZ twin had schizophrenia, (per SCID NP) was also available. These subjects have been described elsewhere (12, 16, 37). Out of these eight MZ pairs, six MZ pairs had both head-circumference and ridge count data. These six pairs served as additional controls. Older studies of ridge-count in "normal" twins (e.g., 37) are not usable for our purpose, since common disorders now known to affect ridge count, for example, dyslexia (25), were not excluded. Note that psychiatric screening of "healthy" MZ volunteers is essential—as we have suggested elsewhere (16),

**TABLE 2.** *Composition of the twin sample: mean ages (years)*

| Sample | *n* | Mean (S.D.) |
|---|---|---|
| MZ pairs discordant for schizophrenia | | |
| Age of onset | 22 | 21.1 (4.90) range: 11–30 |
| Global assessment of functioning (axis V) | 22 | 39.0 (12.10) range: 15–63 |
| Male | 13 | 30.6 (5.16) |
| Female | 9 | 31.3 (4.98) |
| Control MZ twin pairs (both MZ twins healthy) | | |
| Male | 2 | 40.5 (4.95) |
| Female | 4 | 28.7 (2.63) |

MZ, monozygotic.

"genes which predispose to schizophrenia may act by making individuals more vulnerable to the brain-disrupting effects of commonplace prenatal insults." Consequently, nonschizophrenic genotypes which suffer a fifth-month fetal injury may manifest ridge-count anomalies, neurological symptoms, cognitive deficits, and decreased head circumference without manifesting schizophrenia (16, 23, 25). Also note, that this study's strength derives from the built-in genetically identical controls.

The following a priori definitions were used:

1. *Subclinical microcrania:* Head circumference is smaller in the affected than in the unaffected MZ co-twin.
2. *Subclinical Macrocrania:* Head circumference is larger in the affected than in the unaffected MZ co-twin.
3. *Fifth Month Fetal Growth Retardation Markers:* Ridge count in the affected MZ twin is at least 13.5% (2 SD) smaller than in the unaffected co-twin.
4. *Fifth Month Fetal Edema Markers:* Ridge count in the affected MZ twin is at least 13.5% (2 SD) larger than in the unaffected co-twin.

### Measures

We studied the head circumference and total-finger-ridge count which show a very high heritability in MZ twins (28, 29). Head circumference was measured in the standard fashion by a research pediatrician (P.O.Q.) using anthropometric metal tape (38, 39, 40, 41). Metal-tape measurements of circumference were taken as the greatest head diameter frontal to occipital, that is, "anteriorly the tape is placed just superior to the eyebrows and posteriorly it is placed so that the maximum circumference is measured" (42). This metal-tape method is unaffected by variations in hair style. Also, no obvious hair-style differences were noted within pairs. The pediatrician who took the head measurements was blind to the ridge-count data and twin diagnosis. Similarly, the technician performing the ridge counts was blind to the head-circumference data and twin diagnosis.

Finger-ridge prints were obtained as described elsewhere (16, 24). All ridge counts were made blind to the subject's diagnosis and to twin-pair membership. The sum of the ridge count for all 10 fingers yielded a standard total-finger-ridge count for each subject (24, 26, 43). These sums were then used to obtain the MZu%dRC as described below.

### Interrater Reliability for Ridge-Count and Head-Circumference Data

To establish the reliability of the ridge-count data, ridges were independently recounted by a trained physical anthropologist (Dr. Przybyla) for all the twins studied. The intraclass-correlation-coefficient for the two raters was 0.98, indicating a high degree of inter-rater reliability for the ridge-count data. The reliability of head circumference was not specifically addressed in this sample. However, for another study and sample conducted by the research pediatrician who collected the head-measurement data, we report here (P.O.Q.), head circumference interrater reliability was 0.93 (44), and the interrater reliability for the Waldrop minor physical-anomaly scale, which includes head circumference as a variable, was 0.70 to 0.96 (38, 40).

## Data Analysis

### *The Two Major Variables of Interest*

**The Signed Within-Pair MZ Percent Difference in Head Circumference (MZ%dHC).** MZ%dHC for discordant twins remains signed since the direction of within-pair differences in head circumference is important: a negative value of the MZ%dHC indicates that the twin with schizophrenia has a subclinical microcrania when compared to his or her MZ co-twin, while a positive value indicates a subclinical macrocrania in the affected MZ twin. Note that, unlike microcrania, subtle *macrocrania is rarely of second-trimester origin and is more likely to be an indication of other pathology such as intranatal (delivery room) intracranial bleeding, or meningitis during infancy* (1).

**Our Fifth-Month Fetal-Injury Index is the Within-Pair, MZ Unsigned Percent-Difference in Ridge Count (MZu%dRC).** Unlike our measure of within-pair differences in head circumference, the unsigned (absolute) value is taken when finger-ridge counts are examined in Fig. 3, because any within-pair discordance in finger-ridge count *regardless of direction* is likely to be indicative of fifth-month fetal injury—and thus associated with microcrania (also see definitions above). As we pointed out elsewhere (16), studies by Bouchard and colleagues (45) and other researchers (14, 43, 46) demonstrate that the expected MZu%dRC in MZ twins free of prenatal injury approaches zero. *Prenatal ischemic and nutritional injuries and other causes of intrauterine growth retardation result in lower ridge count, while infection and edema result in higher ridge count* (see ref. 16 for a review). In other words, a discrepancy in ridge count in *either* direction in MZ twins can be viewed as a second-trimester fetal-size marker, that is, result of injuries that caused either intrauterine growth retardation (and lower ridge count) or edema (and higher ridge count) in the affected MZ twin during the fifth month of gestation (see Fig. 3).

### *Usage of Percent Difference*

We routinely chose to analyze the MZ within-pair *percent difference* scores for our two independent measures, because in pairs with genetically high finger-ridge counts or head circumferences, even a large within-pair discrepancy on these dimensions can translate into a relatively small percent difference (16). Such analysis controls for between-pair differences in body size (e.g., height, which was not available on any of the subjects). Both the MZu%dRC and MZ%dHC were calculated by the general formula: $(X_1 - X_2)/X_2$ where $X_1$ is the total-finger-ridge count or head circumference of the affected twin, and $X_2$ represents the analogous measure in the unaffected co-twin.

### *Analysis of Additional Controls*

For the small sample of six MZ control pairs (both healthy), there was no obvious reason to place one of the twins in the denominator, so the smaller HC of the two was used (e.g., [Twin HC minus Co-twin HC/ Smaller Co-twin HC] × 100). This conservative approach maximized the size of the difference in the control group, and this maximization of the normal range moved in the direction of the null hypothesis. Since the direction of within-pair differences in head circumference is uninformative—MZ%dHC values were arbitrarily plotted above zero (Figs. 2 and 3).

## Hypothesis

We hypothesized a priori that the twin pairs with the larger values of MZu%dRC (MZ-intrapair-ridge differences) would tend to have more negative values of MZ%dHC. This hypothesis would indicate that the intrauterine disturbance resulting in larger MZu%-dRC may have also caused the head circumference of the affected twin to be smaller than that of his or her co-twin (see Fig. 1).

## RESULTS

There was no overall tendency for the affected members of the MZ pairs to have smaller heads in general. The mean head circumference of the affected twins ($n$ = 22) was 56.732 cm (SD = 2.45) and the unaffected co-twin was 56.759 cm (SD = 2.35). When the outlier is excluded from the analysis ($n$ = 21), the mean head circumference was 56.514 cm (SD = 2.28) and 56.509 cm (SD = 2.08) in affected twins and unaffected co-twins, respectively. We can, also, rule out intelligence as an important covariate in our data, in that IQ was not correlated with MZu%dRC, MZ%dHC, or raw-score head circumference (data not shown).

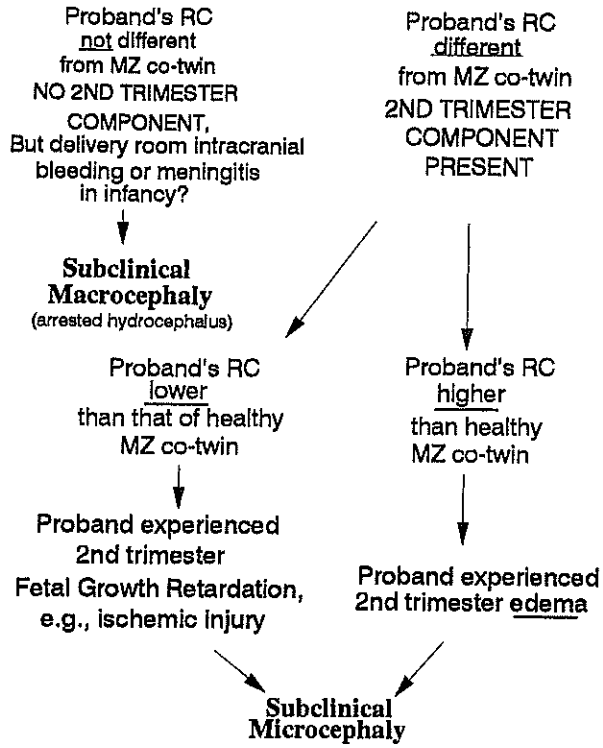


FIG. 1. Our working hypothesis.

The distribution of the raw data is presented in Fig. 2. Inspection of Fig. 2 shows that of the 10 probands with subclinical microcrania, fifth-month fetal-edema markers, as defined above, were found in three probands and fifth-month fetal-growth-retardation markers were found in two other probands. This distribution points to the kind of deleterious events contributing to the penetrance of the disorder. For instance, in the pairs in which the affected members had subclinical microcrania (smaller heads than their genetically identical controls), second-trimester events may have been important; whereas, in the 12 pairs where the affected MZ twin shows subclinical macrocrania, delivery-room intracranial bleeding or postnatal events leading to arrested hydrocephalus may have contributed to the liability.

Figure 3 displays a scatterplot between MZ%dHC and MZu%dRC (i.e., our Fifth-Month Fetal-Injury Index). The data were analyzed by Spearman rank correlation coefficient ($r_s$). The correlation of MZ%dHC and MZu%dRC between proband and co-twin control ($n$ = 22) was −0.45 ($p < .036$). When the

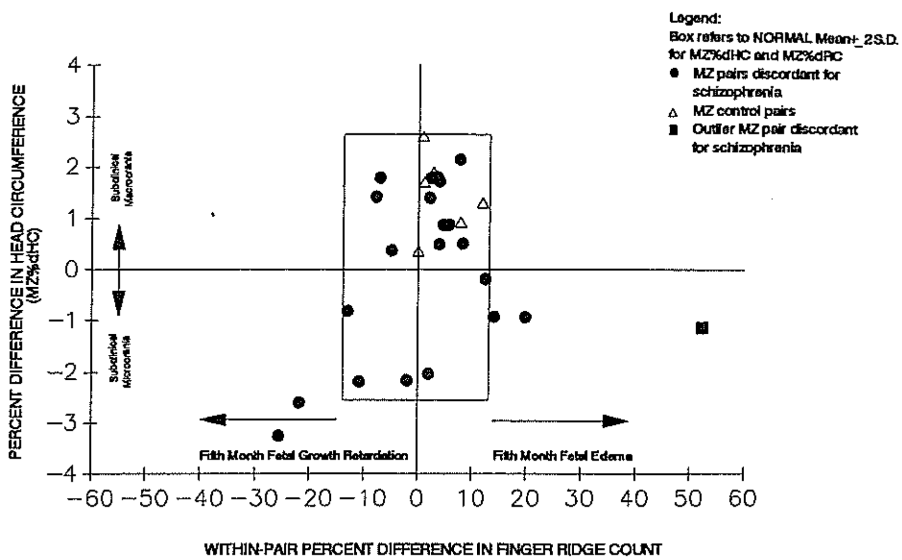


**FIG. 2.** Scatterplot of the distribution for within-pair percent differences in head circumference (MZ%dHC) and finger ridge count.

outlier was excluded ($n$ = 21) from the analysis, the correlation was still significant (−0.43; $p < .049$). In other words, there is a significant tendency for the affected twins to have smaller head circumference than their unaffected co-twins, as members of the twin pairs vary increasingly in finger-ridge counts (i.e., there are increasing differences in nonshared, second-trimester effects on members of the same twin pair). Approximately 20.2% of the variability in within-pair differences in head circumference is shared with within-pair discrepancies in finger-ridge counts (Fig. 3). We a priori divided our sample into two groups of twin pairs: Those showing greater evidence of differential-second-trimester-deleterious effects, and those showing little evidence of differential-second-trimester events. Our control group of MZ pairs had a mean MZu%dRC of 4.0% with a SD of 4.7%. Taking this figure as our normative basis, we identified twin pairs with MZu%dRCs greater than 2 SDs above this mean (i.e., 13.5%) as our "high" second-trimester-injury group ($n = 5$), and the remaining pairs as the "low" second-trimester injury group ($n = 17$). The resulting 2 × 2 matrix is presented in Table 3. As shown in Table 3 and Fig. 3, among the 12 affected twins with subclinical macrocrania, none were in the "high" second-trimester-injury group. Whereas, among the 10 affected MZ twins with subclinical microcrania, five were in the "high" (greater than 2 SD above mean) second-trimester injury group. These five subjects included three showing ridge-count markers of second-trimester edema and another two showing ridge-count markers of second-trimester growth retardation. The results from the Yates' correction for continuity $\chi^2$ test statistics indi-

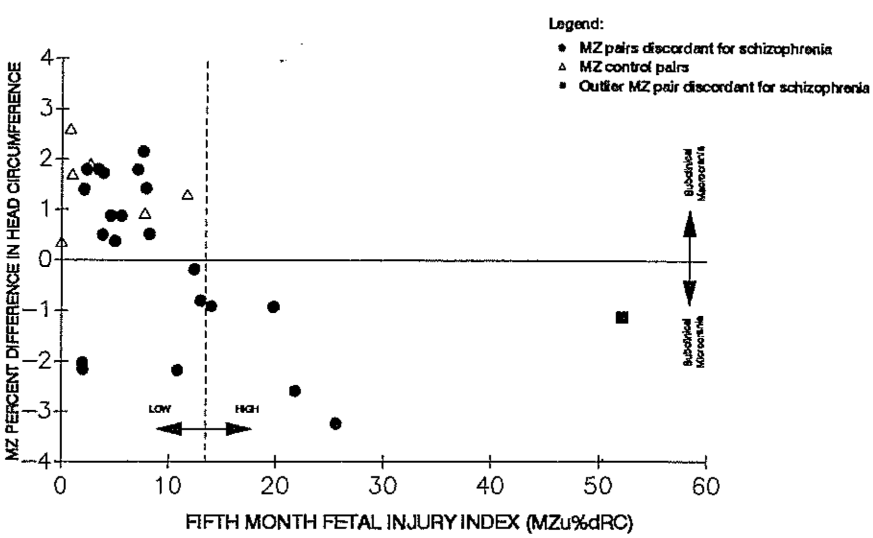


**FIG. 3.** Scatterplot for head circumference (MZ%dHC) and MZ % differences in finger ridge-count (MZu%dRC) and in MZ twins discordant for schizophrenia and MZ controls. MZu%dRC is our Fifth-Month Fetal Injury Index. Spearman's Rank Order Tests: $r_s = -.45$; $p < .036$ ($n = 22$); $r_s = -.43$; $p < .049$ ($n = 21$).

**TABLE 3.** *The frequencies of discordant MZ twin pairs with schizophrenic members having small head circumferences and significant within-pair finger ridge discrepancies*

| | | Significant (high) 2nd trimester injury as evidenced by within-pair fingertip ridge-count discrepancy 2 SD or more above normal mean value | |
|---|---|---|---|
| | | No | Yes |
| Affected MZ twin has subclinical microcrania (a smaller head circumference than the unaffected MZ co-twin) | No | 12 | 0 |
| | Yes | 5 | 5* |

$\chi^2 = 5.178$; $df = 1$; $p = .0228$.
* $p = .0449$ excluding outlier.

cated a significant group difference ($\chi^2 = 5.178$; $df = 1$; $p = .0228$). These results suggest that decreased head circumference in an affected MZ co-twin (relative to unaffected MZ co-twin) characterizes pairs with larger finger-ridge-count differences.

## DISCUSSION

There is renewed interest throughout medicine, in the role of environment/gene interaction during gestation (47). Discordant MZ twins may be ideal for exploring nonshared environmental risk factors contributing to the etiology of disorders. This study is the first to use discordant MZ twins to control fully for the substantial genetic effects on head circumference. It is also the first to correlate head circumference in schizophrenia with a physical marker that does not change after it is formed during the mid-second trimester. The findings of this study are consistent with substantial, carefully conducted, recent research reporting on the role of intrauterine environmental effects in the etiology of some cases of schizophrenia (8, 9, 31, 48–50).

The results of this study are in line with our hypothesis: Decreased head circumference in affected MZ co-twins (relative to unaffected MZ co-twins) characterizes a subgroup of pairs with larger finger-ridge-count differences. In other words, a consistent pattern of affected MZ twins having smaller head circumference than their respective unaffected genetically identical controls is present only in those MZ twin pairs in which there is evidence of differential second-trimester (nonshared) effects on members of the same twin pair. This study suggests that the decreased head circumference seen in some patients with schizophrenia is neither widespread nor genetic in origin—but rather, a consequence of in-utero, nonshared, environmental deleterious events (possibly fetal-growth retardation or edema) occurring around the fifth prenatal month (16, 50, 51). These results may suggest that head circumference should be routinely measured in all future twin studies in psychiatry. Head circumference is closely related to brain size (52) and is an important variable in infant anthropometry. Head circumference shows high heritability—and thus even subtle deviations in MZ twins may be instructive. Also, these results suggest that, as we have pointed out elsewhere (16, 21, 31), twin studies can be enhanced by the incorporation of embryological paradigms.

We should, however, stress that the head circumferences of all subjects were in the normal range—thus the term *subclinical.* Our ability to draw any conclusions is wholly due to our access to genetically identical controls, which serve as an indicator of what the patients' head size and ridge count would have been if he or she were not afflicted with schizophrenia.

### Subclinical microcrania

Overall, only 45.5% (10/22) of the affected discordant MZ twins had smaller head circumferences than their unaffected MZ twins. Smaller head size in our patient sample was associated with dermatoglyphic markers of mid-second-trimester intrauterine injury (i.e., high MZu%dRC in five of ten patients). This finding is consistent with the growing consensus that the non-genetic non-shared environmental "second-strike" is often an intrauterine pathology (e.g., 16, 50).

### Subclinical macrocrania

While we expected *normo*crania in many patients, a suggestion of subclinical macrocrania was found in 12 out of the 22 affected twins. This is consistent with an earlier study of nontwins (9). None of these 12 had fifth-month-fetal-injury markers. Macrocrania is a much more benign finding in neurology, especially when subtle (1). While extreme macrocrania is often a cause of delivery-room complications, two known etiologies of *subtle* macrocrania (arrested hydrocephalus) are minor delivery-room-intracranial bleeding and meningitis in infancy (1). Future research should examine the possible connection of macrocrania to delivery-room and early postnatal-risk factors which may contribute to the expression of the genetic predisposition to schizophrenia.

The following list addresses some of the limitations of this study:

1. Most importantly, some major recently discovered prenatal risk factors, such as malnutrition (48), toxicological teratogenicity, and viral teratogenicity (50) are likely to play a role in etiology of some patients with schizophrenia, but are not likely to be demonstrated in our MZ twin design—as they are liable to affect both twins (and presumably result in concordance for schizophrenia when a pregnancy involves MZ twins genetically predisposed to schizophrenia). However, the obstetric literature is somewhat unclear (18–20).

2. Another obvious limitation is that, while cost effective and widely used in pediatrics and child neurology, a change in head circumference is a very crude estimate of brain size (1). There is a great need to examine the correlation between this fifth-month fetal injury marker with more accurate measures of brain volume (e.g., MRI) in these discordant twins. Such studies are currently beginning in our neurodevelopmental laboratory. Studies of markers of the third, fourth, sixth, and seventh month are also beginning in our laboratory. While head circumference is vastly inferior compared to MRI for most purposes, it has one clear advantage for our purpose: it is an indelible marker of very early brain maldevelopment and not affected by postnatal factors such as hydration and traumatic brain injury. The results of this study are not inconsistent with MRI findings in this sample (12) and other samples of MZ twins discordant for schizophrenia (53).

3. We were surprised not to find usable normative head-circumference data on healthy monozygotic twins in the published literature. The findings of this study may also be limited by the absence of head-circumference measures of a larger number of psychiatrically healthy MZ twin-pairs, and this issue should be addressed by further research.

4. Clinical and other possible differences between the subclinical macrocrania and subclinical microcrania groups also need to be addressed by future research. However, while both members of the MZ twin pairs (especially the ill twin) in this study perform slightly lower than matched samples of control twins on a variety of neuropsychological measures, most of the variance in head size which was observed is probably not a reflection of etiologic factors related to IQ (32).

5. As with other twin-study reports, these findings should be cautiously generalized. Although some recent studies indicate that *the etiology of schizophrenia in twins is probably not different from the etiology of schizophrenia in singletons* (15).

In summary, the present study, using an embryological paradigm and "ideal genetic controls," provides the first strong evidence to suggest that, when present, decreased head circumference in schizophrenia is associated with measurable anthropometric markers of fifth-month in-utero environmental injury.

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## REFERENCES

1. Volpe JJ. *Neurology of the Newborn.* Philadelphia: WB Saunders, 1987.
2. Pakkenberg B. Post-mortem study of chronic schizophrenic brains. *Br J Psychiatry* 1987;151:744–52.
3. Harvey I, Ron MA, DuBoulay G, et al. Reduction of Cortical volume in schizophrenia on magnetic resonance imaging. *Psychol Med* 1993;23:591–604.
4. Schwarzkopf SB, Nasrallah HA, Olson SC, et al. Family history and brain morphology in schizophrenia: an MRI study. *Psychiatry Res* 1991;40:49–60.
5. Brunton CJ, Crow TJ, Frith CD, et al. Schizophrenia and the brain: a prospective clinico-neuropathological study. *Psychol Med* 1990;20:285–304.
6. Andreasen N, Nasrallah HA, Dunn V, et al. Structural abnormalities in the frontal system in schizophrenia. *Arch Gen Psychiatry* 1986;43:136–144.
7. Pearlson GD, Kim WS, Kubos KL, et al. Ventricle-brain ratio, computed tomographic density and brain area in 50 schizophrenics. *Arch Gen Psychiatry* 1989;46:690–7.
8. McNeil TF, Cantor-Graale E, Nordtsrom LG, Roselund T. Head circumference in 'preschizophrenic' and control neonates. *Br J Psychiatry* 1993;162:517–23.
9. Green M, Satz P, Gaier DJ, et al. Minor physical anomalies in schizophrenia. *Schiz Bull* 1989;15:91–9.
10. Grove WM, Lebow BS, Medus C. Head size in relation to schizophrenia and schizotypy. *Schiz Bull* 1991;17:157–61.
11. Jones GH, Lewis JE. Head circumference in elderly long-stay patients with schizophrenia. *Br J Psychiatry* 1991;159:435–8.
12. Suddath RL, Cristison GW, Torrey EF, et al. Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia: *N Engl J Med* 1990;322:789–94.
13. Belmaker R, Pollin W, Wyatt RJ, Cohen S. A follow-up of monozygotic twins discordant for schizophrenia. *Arch Gen Psychiatry* 1974;30:219–22.
14. Slater E. Psychotic and neurotic illnesses in twins. London, Her Majesty's Stationary Office, 1953.
15. Gottesman II. Confirming unexpressed genotypes for schizophrenia: risks in the offspring of Fischer's Danish identical and fraternal discordant twins. *Arch Gen Psychiatry* 1989;46:867–72.
16. Bracha HS, Torrey EF, Gottesman II, et al. Second-trimester

markers of fetal size in schizophrenia: A study of monozygotic twins. *Am J Psychiatry* 1992;149:1355–61.
17. Hamilton WJ, Boyd JD, Mossman HW. Human embryology: prenatal development of form and function. Cambridge, UK: Heffer and Son, 1972.
18. Spellecy WN. Antepartum complications in twin pregnancies. *Clin Perinatol* 1988;15:79–86.
19. Penrose LS. Congenital syphilis in monovular twins. *Lancet* 1937;1:322.
20. Menez-Bautista R, Fikrig SM, Pahwa S, et al. Monozygotic twins discordant for the acquired immunodeficiency syndrome. *Am J Dis Child* 1986;140:678–9.
21. Lohr JB, Bracha HS. A monozygotic mirror-image twin-pair with discordant psychiatric illnesses; a neuropsychiatric and neurodevelopmental evaluation. *Am J Psychiatry* 1992;149: 1091–4.
22. Babler WJ. Prenatal communalities in epidermal ridge development. In: Durham NM, Plato CC, eds. *Trends in dermatoglyphic research.* Dordrecht: Kluwer-Academic Publishers; 1990;54–68.
23. Netley C, Rovet J. Relations between a dermatoglyphic measure, hemispheric specialization, and intellectual abilities in 47 XXY males. *Brain Cogn* 1987;6:153–60.
24. Federal Bureau of Investigation. The science of fingerprints: classification and uses. Washington DC, US Government Printing Office, 1984.
25. Jamison CS. Dermatoglyphics and the Geschwind hypothesis: I. Theoretical background and palmar results of dyslexia. In: Durham NW, Plato CC, eds. *Trends in dermatoglyphic research.* Kluwer-Academic Publishers, 1990:99–113.
26. Markow TA, Gottesman II. Fluctuating dermatoglyphic asymmetry in psychotic twins. *Psychol Res* 1989;29:37–43.
27. Newell-Morris LL, Fahrenbruch CE, Sackett GP. Prenatal psychological stress, dermatoglyphic asymmetry and pregnancy outcome in the pigtailed macaque (Macaca nemestrina). *Biol Neonate* 1989;56:61–75.
28. Holt SB. The genetics of dermal ridges. Charles C Thomas, Springfield, IL; 1968:63.
29. Sharma K, Byard PJ, Russell JM, Rao DC. A family study of anthropometric traits in a Punjabi community. I. Introduction and familial correlation. *Am J Phys Anthropol* 1984;63:389–95.
30. Polymeropoulos MH, Xiao H, Torrey EF, et al. Search for a genetic event in monozygotic twins discordant for schizophrenia. *Psychol Res* 1993;48:27–36.
31. Bracha HS, Torrey EF, Bigelow LB, Linington BB. Subtle signs of prenatal maldevelopment of the upper limb ectoderm in schizophrenia: a monozygotic twin study of prenatal markers in psychosis. *Biol Psychol* 1991;30:719–25.
32. Torrey EF, Bowler AE, Taylor EH, Gottesman II. *Schizophrenia and manic depressive disorder: the biological roots of mental illness as revealed by the landmark study of identical twins.* New York: BasicBooks, 1994.
33. Spitzer RL, Williams JBW. *Structured clinical interview for DSMIII-R, patient version (SCID-P).* New York: New York State Psychiatric Institute, Biometrics Research, 1986.
34. American Psychiatric Association. DSMIII-R: Diagnostic and statistical manual of mental disorders, Washington, DC: American Psychiatric Association, 1982.
35. Thomas DH. *Refiguring anthropology: first principles of probability and statistics.* Prospect Heights, IL: Waveland Press, 1986.
36. Kleinbaum DG, Kupper LL, Muller KE. *Applied Regression and Other Multivariable Methods* 2nd Ed. Boston: PWS-Kent Publishing Company, 1988.
37. Smith JJ, Penrose LS. Monozygotic and dizygotic twin diagnosis. *Ann Hum Genetics.* 1955;19:273–89.
38. Waldrop M, Pedersen F, Bell R. Minor physical anomalies and behavior in preschool children. *Child Dev* 1968;39:391–400.
39. Nelhaus G. Head circumference from birth to eighteen years: practical composite international and interracial graphs. *Pediatrics* 1968;41:106–114.
40. Waldrop M, Halverson CF. Minor physical anomalies and hyperactive behavior in young children. In: Hellmuth J, ed. *Exceptional Infant (V. II): studies of abnormalities.* New York: Bruner/Mazel, 1971.
41. Kaufman DM, Solomon GE, Pfeffer CR. Child and adolescent neurology for psychiatrists. Baltimore: Williams & Wilkins, 1992.
42. Lohman TG, Roche AF, Martorell R. *Anthropometric standardization reference manual.* Champaign, IL: Human Kinetics Books; 1988:41.
43. Holt SB. Quantitative genetics of finger-print patterns. *Br Med Bull* 1961;17:247–50.
44. Quinn PO, Renfield M, Burg C, Rapoport JL. Minor physical anomalies: a newborn screening and 1-year follow-up. *Am J Acad Child Adolesc Psychol* 1977;16:662–9.
45. Bouchard TJ, Lykken DT, McGue M, et al. Sources of human psychological differences: the Minnesota study of twins reared apart. *Science* 1990;250:223–8.
46. Nylander PPS. Fingerprints and the determination of zygosity in twins. *Am J Phys Anthropol* 1971;35:101–8.
47. Lie RT, Wilcox AJ, Skjerven R. A population-based study of the risk of recurrence of birth defects, *N Engl J Med* 1994;331:1–4.
48. Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch hunger winter of 1944–1945. *Arch Gen Psychiatry* 1992;49:983–8.
49. Torrey EF, Taylor EH, Bracha HS, et al. Evidence for a prenatal origin of schizophrenia in a subgroup of discordant monozygotic twins. *Schiz Bull* 1994;20:423–32.
50. Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1988;45:189–92.
51. Bracha HS. Etiology of structural brain asymmetry in schizophrenia, an alternative hypothesis. *Schiz Bull* 1991;17:551–3.
52. Cooke RW, Lucas A, Yudkin PL, Pryse-Davies J. Head circumference as an index of brain weight in the fetus and newborn. *Early Hum Dev* 1977;1:145–9.
53. Reveley MA, Reveley AM, Baldy R. Left cerebral hemisphere hypodensity in discordant schizophrenic twins. *Arch Gen Psychiatry* 1987;44:625–32.