

## A Monozygotic Mirror-Image Twin Pair With Discordant Psychiatric Illnesses: A Neuropsychiatric and Neurodevelopmental Evaluation

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*One piece of genetic evidence for the biological distinctness of schizophrenia and bipolar illness is the rarity of monozygotic twin pairs in which one twin suffers from schizophrenia and the other from bipolar disorder. The authors describe a pair of monozygotic mirror-image twins with discordant diagnoses, schizophrenia in one twin and bipolar or schizoaffective disorder in the other.*

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Since Kraepelin first clearly divided the major mental illnesses into the broad categories of "dementia praecox" and "manic-depressive illness," researchers have puzzled over the relationship of these two conditions. Until 1982 there were no reports of twin pairs in which one twin suffered from schizophrenia and the other from bipolar disorder (1). In 1982 McGuffin et al. (2) reported identical male triplets, two of whom were diagnosed as having schizophrenia and the third of whom had bipolar illness. More recently, Dalby et al. (3) reported identical male twins, one of whom was reliably diagnosed as having schizophrenia and the other of whom had a diagnosis of mania. Studies of monozygotic twins have revealed very few pairs discor-

dant for schizophrenia and bipolar disorder, which supports the biological distinctness of schizophrenia and bipolar illness. Most of the other available genetic evidence also supports the distinctness of the two conditions (1, 4, 5), although there is some disagreement (6, 7).

The present paper is a neuropsychiatric study of one pair of monozygotic twins who appear to be discordant for schizophrenia and either bipolar illness or schizoaffective disorder. An interesting and unusual feature of these twins is that they are mirror images of one another.

### CASE REPORTS

Both twins received physical examinations, CT scans, EEGs, and medical workups including thyroid function tests, CBC, electrolyte measurements, and urinalysis. All the results were within normal limits. Apart from a brief history of mild cannabis abuse, there was no history of substance abuse in either twin and no other evidence that the mental disorder was secondary to organic factors. Their prenatal and birth histories were unremarkable. There was no known family history of major mental illness.

*Twin 1.* This twin was first hospitalized at the age of 22 after several months of severe auditory and visual hallucinations and delusions. She was withdrawn, would make bizarre

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comments such as "I'm an airplane," and would talk to people who were not present. While in church she would suddenly start laughing, stating that people were telling her jokes. She would often stare into space while mumbling to herself, and her thoughts were fragmented or loosely associated.

Over the next 3 years she was hospitalized several times and treated with high-potency neuroleptics with minimal or no effect. After nearly 4 years of severe psychosis, haloperidol treatment eventually resulted in improvement. She first came under our care when she was 27 years old, and the haloperidol treatment was discontinued during the course of a research study. She became very psychotic and experienced auditory and visual hallucinations, talking to herself and claiming to be in heaven with angels surrounding her and talking to her. When she was again treated with haloperidol, 20 mg/day, her symptoms almost completely resolved and she was able to work as a secretary for several years. The haloperidol dose was gradually reduced, but at 5 mg/day she suffered a severe psychotic decompensation and was rehospitalized. She was restabilized with haloperidol decanoate injections, 100 mg every 2 weeks. Although not yet able to return to work, she is able to function independently at this time. This patient has been given diagnoses only of chronic paranoid or chronic undifferentiated schizophrenia on the basis of both the Schedule for Affective Disorders and Schizophrenia (SADS) and *DSM-III*.

*Twin 2.* This twin was prone to rapid mood swings and angry outbursts since childhood, and at age 19 she developed severe depression and anxiety. She also described a vague sensation that people were staring at her and manipulating her and stated that her vision would become very acute and vivid, although for only very short periods. She once said she felt as though "a force like a boyfriend of mine grabbed me and took me into the bedroom, although no one else was around." She also felt at one point as though her father's emotions would "come through" her but was vague about exactly what this meant. She consistently denied hallucinations, and there was no loosening of associations.

Later in the course of her illness, she described episodes in which she had to go "faster and faster." At one point she wished to give up everything and become an artist, stating that she could be "the greatest artist in the world." She was grandiose, irritable, very talkative, and easily distracted, and she slept poorly. During the course of her illness she was treated with lithium, perphenazine-amitriptyline, haloperidol, thioridazine, desipramine, amitriptyline, fluphenazine, and carbamazepine. None of these medications was clearly effective.

At age 27 she was admitted to a private hospital because she was having severe mood changes, including depression and anger, and suicidal thoughts. Her self-esteem was poor and she felt inferior to others. Her speech was pressured and she fidgeted continually. She was treated with trifluoperazine, although there was no evidence of psychosis. Her mood partially stabilized, and she was discharged on a regimen of trifluoperazine with the diagnosis of schizoaffective disorder.

Later that year she began feeling very depressed and stayed in bed for 4 months. She slept 14 to 18 hours a night, gained 13 lb, and experienced fatigue and loss of energy. She lost interest in many of her hobbies, withdrew socially, and developed feelings of worthlessness and occasional thoughts of suicide. She was noted to spend a lot of time in front of the mirror, and she commented negatively on her appearance, stating she had developed a "cow neck" and severe acne—neither of which was true. Her memory and concentration were poor. She claimed her family was unfair to her, but she could give

no specific examples. She denied having hallucinations or delusions. A SADS interview provided a diagnosis of manic-depressive illness.

Over the following year she had numerous irritable outbursts, depressive episodes, and suicidal thoughts. She never had frank delusions or hallucinations and never manifested the bizarre behavior or fragmentation of thought seen in her twin sister. Occasionally she would have racing thoughts and would strike people without provocation. She was treated with lithium for several months without effect. Over the past several years her mood has stabilized and she has been functioning productively in a secretarial position. Her only medications have been small doses of haloperidol (usually 1 mg/day) for agitation or fluoxetine for depression.

#### LABORATORY AND INVESTIGATIVE PROCEDURES

Zygoty was determined by blood group analysis at the Immunogenetics Laboratory of Johns Hopkins Hospital, by using the method of Wilson (8). Blood typing is the most reliable method for assigning zygoty to twins (9). The probability of monozygoty was determined to be 0.9999941 (the probability of dizygoty was 0.0000591).

Handedness was determined by using the Edinburgh Inventory (10) and the Annett Handedness Preference Questionnaire (11). Additional tests were used to determine footedness and eyedness. Twin 1 was determined to be fully right-handed, right-footed, and right-eyed, and twin 2 was determined to be fully left-handed, left-footed, and left-eyed.

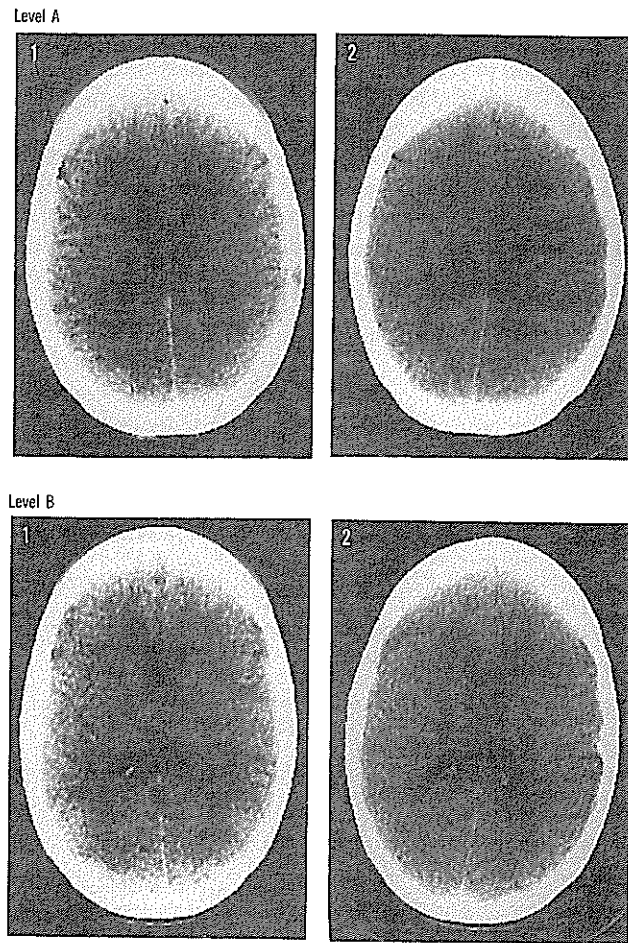
Both twins had 12 years of education. According to the Wechsler Adult Intelligence Scale, their full-scale IQs were 85 and 86, respectively. Twin 1 had a verbal IQ of 89 and a performance IQ of 84, and twin 2 had a verbal IQ of 86 and a performance IQ of 92.

Two slices from the CT scans of the twins, taken at similar levels, are presented in figure 1. The ventricle-brain ratios (VBRs) of twin 1 and twin 2 were 11.6 and 7.9 for the slices at level A and 11.0 and 10.9 for the slices at level B. The occipital regions of the twins appear to be mirror image; twin 1 demonstrates a wider right occipital lobe, and twin 2 has a wider left occipital lobe. When the method of Luchins et al. (12) was applied, the ratios of the left occipital width to the right occipital width for twin 1 were 1.05 (slice A) and 1.11 (slice B), whereas for twin 2 they were 0.94 (slice A) and 0.90 (slice B).

Photographs of the faces of the twins were made and measured according to the method of Sackeim et al. (13). Although several asymmetries were seen, the most interesting asymmetries occurred when the patients smiled. In the measurement of the lateral point of the nostril to the corner of the mouth, twin 1 showed a more pronounced and elevated smile on the right side, whereas twin 2 had a more pronounced smile on the left side.

We performed a standard ridge count and fingerprint pattern examination of the two twins (14). With standard ink techniques hand prints were obtained on both

**FIGURE 1. CT Scans of Monozygotic Mirror-Image Twins With Discordant Psychiatric Disorders<sup>a</sup>**



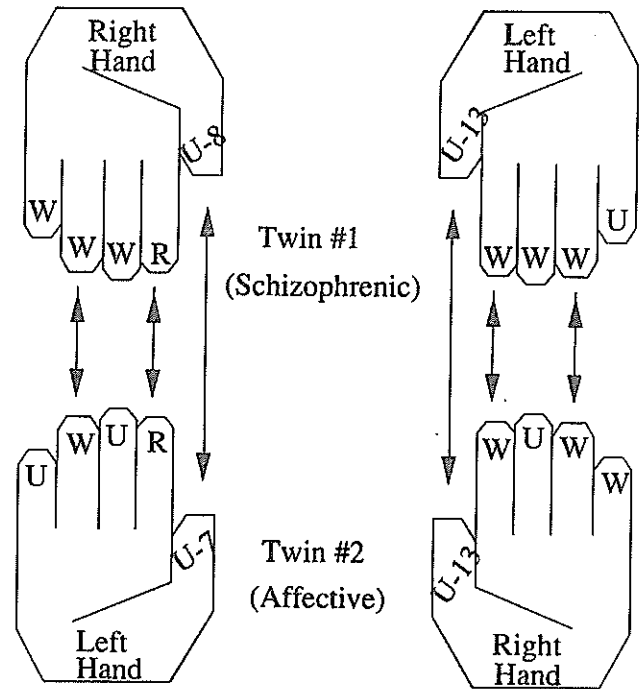
<sup>a</sup>Twin 1 (left) had schizophrenia, and twin 2 (right) received diagnoses of bipolar or schizoaffective disorder. The respective scans for the two twins were taken at approximately similar levels. Right and left orientation is the same for all slices, and the right hemisphere is on the reader's left.

hands for both twins. The quality of the fingerprints allowed pattern identification but only incomplete identification of ridge counts. The results available are presented in figure 2. Two facts are evident from examination of the twins' dermatoglyphics: 1) the similarity is greater in the mirror (heterolateral) comparison than in the standard (homolateral) comparison, and this similarity suggests again that these are mirror-image twins; 2) the degree of similarity is low, and the fingerprints do not appear "twin-like," especially in the standard comparison. These monozygotic twins likely would have been misclassified as fraternal in older studies, e.g., the study by Slater (15).

**DISCUSSION**

Over the 6 years that we have followed these twins, the diagnosis of twin 1 has never been in doubt. Twin 2

**FIGURE 2. Dermatoglyphics of Monozygotic Mirror-Image Twins With Discordant Psychiatric Disorders<sup>a</sup>**



<sup>a</sup>The standard (homolateral) similarity score was 4, whereas the mirror (heterolateral) similarity score was 6 (i.e., higher). U=ulnar loop, W=whorl, R=radial loop.

has had a more confusing clinical picture, initially having symptoms suggestive of schizophrenia but later having symptoms of depression and mania and receiving diagnoses of bipolar or schizoaffective disorder. Although we are not yet prepared to give a definite diagnosis of bipolar illness to twin 2, it is clear that she has had much greater mood instability and much less psychosis than her sister.

Before we discuss the differences in clinical symptoms in these twins, the dermatoglyphic findings deserve comment. Dermatoglyphics have been used in twin studies to help determine zygosity (most such studies were before 1970). The assumption in many of these studies (15, 16) that dermatoglyphics are purely "genetic" markers has since proved to be false. Research since 1970 has shown that dermatoglyphics may be affected substantially by second-trimester prenatal insults, such as rubella, cytomegalovirus, and other viral infections (17). These considerations may have special relevance for monozygotic twin studies of schizophrenia (17, 18). The low dermatoglyphic similarity in this pair of monozygotic twins, whose zygosity was verified by human lymphocyte antigen testing, is consistent with a prenatal insult.

It is not clear why these monozygotic twins have such different presentations. Because twin 1 clearly has schizophrenia, we considered whether twin 2 has an atypical presentation of the same process—perhaps related to a milder prenatal insult, as just discussed. If this

is the case, then two of the possibilities that might account for the different symptoms are that 1) the twins have suffered the same disease process but with different degrees of severity, and 2) the mirroring is in some way related to the symptoms.

#### *Differences in Severity*

It is possible that twin 2 simply has a milder case of the same condition afflicting twin 1. This may be reflected in the ventricular size, because twin 1 has larger ventricles than twin 2, which is in keeping with reports of larger ventricles in the schizophrenic members of twin sets discordant for schizophrenia (19, 20) (although patients with mood disorders have also been reported to have large ventricles; see reference 21). Nevertheless, the notion that severity alone can account for the clinical differences strikes us as unlikely. We have observed both twins at different levels of severity throughout their respective illnesses, and they are consistently very different psychiatrically. Twin 1 manifests much more psychosis, and twin 2 demonstrates greater mood lability at all levels of severity.

#### *Differences Related to Mirroring*

It is tempting to speculate that the clinical differences may relate to the twins' being mirror images. Whether monozygotic twins become identical or mirror image is believed to be associated with the timing of the egg's splitting. If the egg splits earlier (the rule), both twins will be either right- or left-handed. If it splits later (which is uncommon), they will be opposite handed (22).

We have documented that these twins have opposite handedness, footedness, eyedness, facial asymmetry, fingerprint patterns, and emotional gesturing (asymmetric facial expression when smiling). The twins also have opposite occipital lobe asymmetry. The more commonly observed occipital asymmetry (in which the left occipital lobe is larger than the right) was reversed in the schizophrenic twin but was preserved in the affectively ill twin, a finding that supports previous reports in the literature (12, 23, 24).

If the differences in clinical presentation are in some way related to mirroring, what could be the nature of this relationship? It is possible that the same process affected both twins but the differences in brain organization, related to the mirroring process itself, contributed to the differences in clinical symptoms. For example, one of us (25) has proposed that the left hemisphere may be more susceptible to damage because it lags behind the right hemisphere during certain phases of prenatal development, thus placing it at greater risk for prenatal damage. It is possible that, because of mirroring, in twin 2 it was the right hemisphere that lagged behind and thus suffered more damage. Another possibility is that an asymmetrical insult affected the left hemispheres of both twins. In twin 1, who is right-handed, the damage occurred in a "typi-

cal" left hemisphere, but in twin 2, because of the mirroring, the left hemisphere might actually function more like a right hemisphere. Either of these two possibilities would imply that similar damage might cause either more psychosis or more mood disorder, depending on whether the left hemisphere or the right hemisphere is more affected.

Of course, these are only a few of many speculations that could be made regarding these cases. We believed the cases would be of interest to investigators and clinicians concerned with schizophrenia and mood disorders and to those interested in the importance of neurodevelopment and laterality of brain function.

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