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Genetic Relatedness and the Lifetime Risk for Being Diagnosed with Schizophrenia: Gottesman's 1991 Figure 10 Reconsidered

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This paper performs a critical analysis of Irving Gottesman's 1991 "Figure 10," which lists the lifetime risks of developing schizophrenia among the relatives of people diagnosed with schizophrenia. Figure 10, which has been cited in numerous psychiatry and abnormal psychology textbooks, is almost always discussed in support of important genetic influences on schizophrenia. However, the pooled results in Figure 10 can also be explained by environmental factors. Moreover, the risk percentages Gottesman reported are derived from biased research designs, some of which are based on implausible theoretical assumptions, while some results are not included. It is concluded that a closer look at the studies used to compile Figure 10 might lead psychiatrists, psychologists, and genetic researchers to decide that, in addition to problems in schizophrenia adoption research and the ongoing failure to find postulated "schizophrenia genes," the evidence supporting a genetic basis for schizophrenia is far weaker than is currently believed.

Figure 10 from Irving I. Gottesman's 1991 *Schizophrenia Genesis: The Origins of Madness* has played an important role in support of genetic and biological theories of schizophrenia within psychology and psychiatry. Although Figure 10 appeared in a book primarily intended for a general audience, the authors of textbooks and scientific papers (e.g., Barondes, 1999; Comer, 1998; Kirov, O'Donovan, and Owen, 2005; Nolen-Hoeksema, 1998)

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frequently cite or reproduce Figure 10's pooled data of the schizophrenia "grand average risk" percentages of various relatives, classified in terms of these relatives' degree of genetic relatedness to a person diagnosed with schizophrenia (Gottesman, 1991, p. 96). Figure 10 is an easily understandable bar chart which suggests that the more closely someone is genetically related to a person diagnosed with schizophrenia, the greater risk that person has of being diagnosed with schizophrenia. In Gottesman's words "the degree of risk correlates highly with the degree of genetic relatedness" (p. 96).

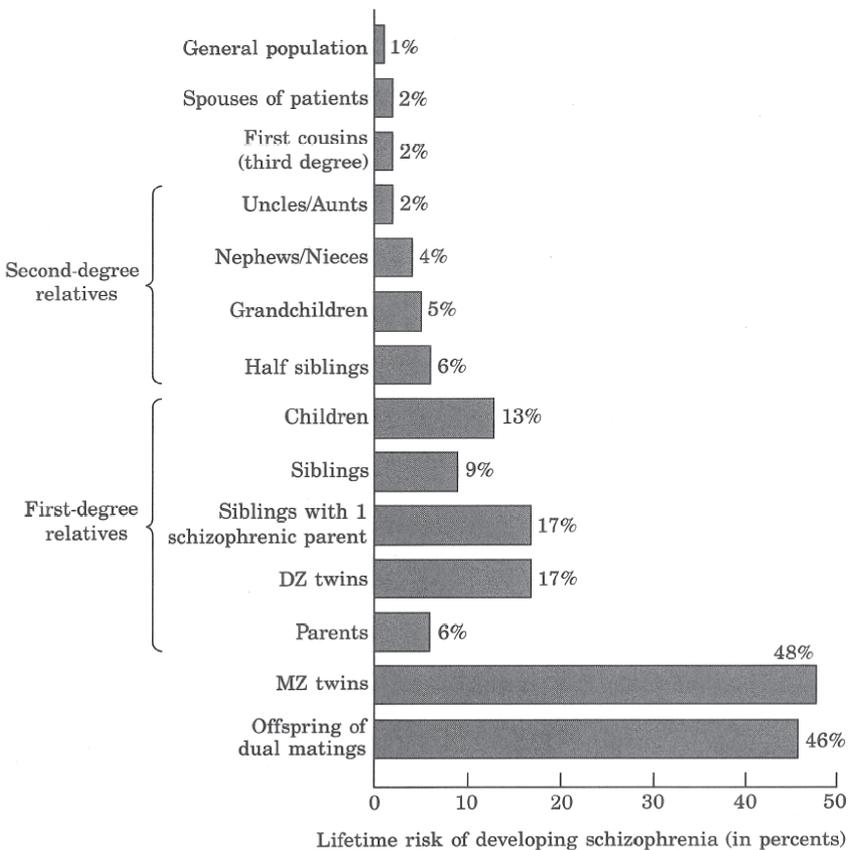


Figure 1: Gottesman's 1991 Figure 10 of the "Grand Average Risks for Developing Schizophrenia Compiled from the Family and Twin Studies Conducted in European Populations Between 1920 and 1987." From *Schizophrenia Genesis: The Origins of Madness* (Gottesman, 1991, p. 96), New York, W.H. Freeman and Company. Copyright © 1991 by I.I. Gottesman. Reprinted with permission.

Gottesman's estimation of the lifetime risk for developing schizophrenia among various types of relatives of people diagnosed with schizophrenia is seen in our Figure 1. Gottesman calculated the risk percentages in his Figure 10 (our Figure 1) by pooling the results of selected schizophrenia family, twin, and dual mating studies. Like all pooled results, we must pay attention to various methodological issues, such as the inclusion of one data set that can skew the results. The authors of secondary sources typically take Figure 10 at face value, and accept Gottesman's conclusion that the data from Figure 10 support genetic theories of schizophrenia. In fact, we are aware of no publication that has performed a critical analysis of the data and conclusions generated from Figure 10. Thus, we pay particular attention to the family and twin studies that form the basis for Figure 10, and offer alternative explanations of these studies' results.

We will argue that the risk factors presented in Figure 10 (a) appear to be influenced by methodologically unsound and biased research, (b) are not reflective of all the data available at the time the figure was published, (c) are inflated by the use of the probandwise twin concordance rate calculation, and (d) are consistent with environmental causes of schizophrenia. Family and twin studies published after the appearance of *Schizophrenia Genesis* are not relevant to (and do not detract from) our argument, since our purpose is to examine the evidence available at the time Figure 10 was produced.

We do not address schizophrenia adoption research in this review because its findings were not included in Figure 10. Although the results of these studies (e.g., Heston, 1966; Kety, Rosenthal, Wender, and Schulsinger, 1968; Kety, Rosenthal, Wender, Schulsinger, and Jacobsen, 1975; Kety, Wender, Jacobsen, Ingraham, Jansson, Faber, and Kinney, 1994; Rosenthal, Wender, Kety, Welner, and Schulsinger, 1971; Tienari, Sorri, Lahti, Naarala, Wahlberg, Moring, Pohjola, and Wynne, 1987; Tienari, Wynne, Läksy, Moring, Nieminen, Sorri, Lahti, and Wahlberg, 2003) are seen by some researchers as constituting conclusive evidence in favor of genetic influences on schizophrenia, we believe that this body of research is greatly flawed by poor methodology, bias, and a violation of adoption studies' "No selective placement assumption" (Joseph, 2004b, 2004c, 2006; Lewontin, Rose, and Kamin, 1984). Moreover, although some researchers have claimed that schizophrenia genes were discovered in 2002–2004 (e.g., Cloninger, 2002; Elkin, Kalidindi, and McGuffin, 2004), there is good reason to doubt these claims (Joseph, 2004a, 2004b, 2006; Kendler, 2005; Propping, 2005). Clearly, there would be little reason to analyze Figure 10 if we accepted the current consensus position in psychiatry and psychology that the genetic basis of schizophrenia is virtually a proven fact. We certainly do challenge this position, and our analysis should be seen in this context.

Family Data

The studies pooled in Figure 10 are not listed in *Schizophrenia Genesis*, nor is there any indication of the weighting that each individual study's sample had in relation to the overall pooled data. This creates a problem, since many older studies were biased because they were performed non-blinded by investigators strongly devoted to genetic theories, who often advocated eugenic sterilization programs for people diagnosed with schizophrenia (Joseph, 2004b; Lewontin, Rose, and Kamin, 1984), and who used vague and nonstandardized definitions of schizophrenia. The classic example is Franz Kallmann's massive 1938 schizophrenia family study of 1,087 German schizophrenia patients and their 13,851 relatives. In describing his study, Kallmann called for directing eugenic measures not only at people diagnosed with schizophrenia, but towards their "heterozygotic taint-carrier" biological relatives as well (1938, p. 3). For Kallmann, these relatives were "eugenically undesirable" people whose numbers should be "kept at the lowest possible number" (p. 47). Because Kallmann viewed his "schizophrenia probands" as carriers of the "hereditary taint of schizophrenia," and because he made non-blind diagnoses, his objectivity has been called into question by several authors (e.g., Lewontin et al., 1984). Kallmann also failed to adequately describe how he defined schizophrenia.

In Chapter 2 of *Schizophrenia Genesis*, Gottesman recognized that "each diagnosis within a schizophrenic's family should be made 'blindly' (completely without knowledge of relatedness to other family members) lest that knowledge contaminate impartial decisions about diagnosis," and that researchers making non-blinded diagnoses constitutes "poor practice" (p. 18). Yet, since blind diagnostic procedures in psychiatric genetics were not introduced until the 1960s (and only in a limited number of studies), Figure 10 appears to be influenced by data produced by researchers such as Kallmann, who employed the "poor practice" of non-blinded diagnosis, and made diagnoses on the basis of a vaguely defined notion of what constituted "schizophrenia." Gottesman noted that Kallmann's "militant, hereditarian point of view has prevented a full appreciation of [Kallmann's] data" (p. 107), but why should diagnostic data produced by the non-blinded and "militantly hereditarian" Kallmann be accepted? Truly, each and every diagnosis Kallmann made in his family and twin studies was "tainted" by his views on the genetics of schizophrenia.

The impression given in Figure 10 is that (excluding DZ twins) the average first-degree relative schizophrenia rate is 11–12%. These pooled data, however, do not include a series of schizophrenia family studies published between 1980 and 1985 (see Table 1), from which the pooled first-degree relative schizophrenia rate is only about 4%.

Table 1
Results of Modern Schizophrenia Family Studies Published Through
1987 Using Blind Diagnoses and Structured Interviews

Diagnoses of Definite Schizophrenia Among the First-Degree Biological Relatives
of People Diagnosed with Definite Schizophrenia

<i>Author(s)</i>	<i>Year</i>	<i>Country</i>	<i>First-Degree Biological Relatives</i>	<i>First-Degree Biological Relatives Diagnosed with Schizophrenia</i>	<i>Percentage</i>
Scharfetter and Nüsperli	1980	Switzerland	726	45	6.2%
Tsuang et al.	1980	USA	729	31	4.3%
Pope et al.	1982	USA	199	0	0.0%
Abrams and Taylor	1983	USA	70	2	2.9%
Guze et al.	1983	USA	111	4	3.6%
Baron et al.	1985	USA	376	19	5.1%
Kendler et al.	1985	USA	723	26	3.6%
Frangos et al.	1985	Greece	572	19	3.3%
POOLED			3,536	146	4.1%

Age correction not used.

Figure 10 did not include the studies from Table 1 (or at least not those performed in the United States), because the results were derived from “family and twin studies conducted in *European* [emphasis added] populations between 1920 and 1987” (Gottesman, 1991, p. 96). Limiting the analysis to European studies resulted in the omission of at least six American schizophrenia family studies, whose pooled first-degree relative schizophrenia rate was only 3.7% (as opposed to 11–12% from Figure 10). According to Gottesman (1991, p. 97), “pooling after judicious removal of the poorest data gives a clear and stable summary pattern not obtainable from any one or two studies.” Unfortunately, the better-designed American studies were omitted while the potentially more biased early European investigations were included, which impacted the results of the pooled rates. In the case of Figure 10, we ask: Was the correct decision made about which data to include and which data to exclude?

Gottesman emphasized the European data in Figure 10 because the Europeans had better access to “relatively stable populations,” were sometimes able to use national psychiatric registers, and sampled from homogeneous populations having a “high degree of cooperativeness from relatives . . .” (p. 97). Yet, most of these studies were performed by investigators who were not blind when it came to making a diagnosis.

Regardless of which family studies one counts or fails to count, however, increased schizophrenia rates that might exist among the spouses, cousins, aunt/uncles, nieces/nephews, grandchildren, half-siblings, full-siblings, par-

ents, and children of people diagnosed with schizophrenia can be explained by the more similar physical and psychological environments these relatives share when compared with randomly selected members of the population (who have a 1% lifetime risk). Most genetic researchers concede this point, as exemplified by Faraone, Tsuang, and Tsuang, who point out that “‘familial’

Table 2
Pairwise Concordance Rates in Schizophrenia Twin Studies
Published Between 1920 and 1987

“Classical Studies”								
<i>Author(s)</i>	<i>Year</i>	<i>Country</i>	<i>MZ Pairs</i>	<i>Number Concordant</i>	<i>%</i>	<i>Same-Sex DZ Pairs</i>	<i>Number Concordant</i>	<i>%</i>
Luxenburger [a]	1928	Germany	17	10	59%	13	0	0%
Rosanoff et al.	1934	USA	41	25	61%	53	7	13%
Essen-Möller [b]	1941/1970	Sweden	7	2	29%	24	2	8%
Kallmann	1946	USA	174	120	69%	296	34	11%
Slater	1953	UK	41	28	68%	61	11	18%
Inouye	1961	Japan	55	20	36%	17	1	6%
“Contemporary Studies”								
Tienari	1963/1975	Finland	20	3	15%	42	3	7%
Gottesman and Shields	1966b	UK	24	10	42%	33	3	9%
Kringlen [c]	1967	Norway	45	12	27%	69	3	4%
NAS-NRC [d]	1969/1983	USA	164	30	18%	268	9	3%
Fischer [e]	1973	Denmark	25	9	36%	45	8	18%
Koskenvuo et al.	1984	Finland	73	8	11%	225	4	2%
Pooled Rates								
“Classical”			335	205	61%	464	55	12%
“Contemporary”			351	72	21%	682	30	4%
TOTAL			686	277	40%	1,146	85	7%

Concordance rates based on researchers’ narrow or “strict” definition of schizophrenia; age correction factors not included. Unless otherwise noted, when two dates are stated, the first indicates the year results were first published, and the second indicates the final report, whose figures are reported in the table.

[a] Based on results reported by Gottesman and Shields (1966a). Hospitalized co-twins only.

[b] MZ twin results from Essen-Möller (1970). He did not report DZ twin results in his 1970 paper. DZ twin concordance rate based on (1941) definite cases among co-twins, as reported by Gottesman and Shields (1966a, p. 28).

[c] Based on a strict diagnosis of schizophrenia; hospitalized and registered cases.

[d] National Academy of Sciences-National Research Council. Original report by Pollin et al. (1969); final report by Kendler and Robinette (1983).

[e] Final report of an expanded sample originally collected by Harvald and Haugue (1965).

and ‘genetic’ are not synonymous,” because “disorders can run in families for many reasons: genes, cultural transmission, shared environmental adversity, and so forth” (1999, p. 11). We agree with this assessment.

Twin Studies

Given the widespread recognition that family data can be explained on environmental grounds, the concordance rates of monozygotic (MZ) versus dizygotic (DZ) twins, listed in Figure 10 as 48% and 17% respectively, are generally viewed, albeit incorrectly as we will soon argue, as solid evidence in support of genetic influences on schizophrenia. However, these concordance rates do not represent the best picture of these studies’ results. Table 2 contains our compilation of schizophrenia twin studies published between 1920 and 1987, covering the same period surveyed in Figure 10.

The concordance rates listed in our Table 2 are based on pairwise calculations and use the investigators’ “strict” definition of schizophrenia when differing diagnostic standards were used in the same study. Figure 10’s concordance rates are based on the “proband” concordance method, which always produces higher concordance rates than the pairwise method. For example, suppose we have 10 pairs of MZ twins, where in three pairs both members are diagnosed with schizophrenia, whereas in the remaining seven pairs only one member is diagnosed with schizophrenia. In this case, the pairwise concordance rate would be $3/10 = 30\%$. Using the proband method, which doubles the numerator and adds the original numerator to the denominator, the concordance rate is calculated as $6/13 = 46\%$. As seen in Table 2, the pooled MZ pairwise concordance rate for the methodologically superior “contemporary” studies (see the discussion below) published since 1963 is only 21%. Thus, in about 80% of pairs sharing an identical genetic makeup, where one twin is diagnosed with schizophrenia, his or her co-twin is *not* diagnosed.

Nevertheless, psychiatric geneticists argue that the contemporary results continue to support the genetic position on the basis of a 4–5 times greater MZ versus DZ concordance rate difference. However, this conclusion is based on the acceptance of the MZ–DZ equal environment assumption of the twin method (Kendler, 1983), which is not discussed in *Schizophrenia Genesis* (see below).

Classical and Contemporary Studies

Most twin researchers now agree that the schizophrenia twin studies published since 1963 (Tienari and after) are methodologically superior to the

older studies published between 1928 and 1962. Twin researchers made methodological changes following the publication of critiques in the early 1960s by David Rosenthal and Don Jackson, who highlighted several important problems in the studies published to that point (Jackson, 1960; Rosenthal, 1960, 1961, 1962a, 1962b). Most “contemporary studies” published since 1963 have drawn their samples from consecutive hospital admissions or from twin registers. A majority of the older “classical” studies published before 1963 used resident hospital samples, which twin researchers now agree can introduce biases resulting in inflated concordance rates (Rosenthal, 1962b). Moreover, the contemporary studies used more precise diagnostic criteria (some had access to national psychiatric registers), and employed more accurate methods of zygosity determination (whether twins are MZ or DZ). Although we say that the modern studies used “more precise” diagnostic criteria, it would be more accurate to say that their authors *stated* their diagnostic criteria. For example, in a table listing schizophrenia twin studies used in their meta-analysis, Sullivan and Kendler (2003, p. 1188), in a column designating the “diagnostic criteria” used in each study, wrote “unstated” for the studies of Essen-Möller, Inouye, Kallmann, Rosanoff et al., Slater, and Tienari. The modern view is captured in Neal and Oltmanns’s 1980 schizophrenia textbook, where they praised the contemporary twin studies for “using a variety of improved sampling procedures, more accurate means of determining zygosity, and blind diagnostic evaluations . . .” (1980, p. 192).

The general theme of Gottesman’s (1991) discussion was that although the contemporary studies are methodologically superior to the classical, both are valid tests of the genetics of schizophrenia. As Gottesman and Shields wrote in their 1982 work *Schizophrenia: The Epigenetic Puzzle*, “We feel quite comfortable in concluding that the twin studies of schizophrenia as a whole represent variations on the same theme and are, in effect, sound replications of the same experiment” (p. 115). But upon examination of the data in our Table 2, this does not appear to be the case. Our numbers differ from Figure 10 because Gottesman included age-correction factors, used the probandwise concordance method, and relied on the original investigators’ liberal definition of schizophrenia. In addition, the pooled percentages in Figure 10 apparently did not include the results of Koskenvuo and colleagues’ (1984) low concordance rate study, which are missing from virtually all textbooks and reviews of schizophrenia twin research published through 2004. Koskenvuo et al. actually found a *zero percent* concordance rate [0/24] for the 24 older pairs in their “Born before 1935” group (Koskenvuo, Langinvainio, Kaprio, Lönnqvist, and Tienari, 1984, p. 327). Furthermore, a table in *Schizophrenia Genesis* listing “Concordance Rates for Schizophrenia in Newer Twin Studies,” upon which Figure 10’s pooled probandwise rates of 48% MZ, 17% DZ are based (Gottesman, 1991, p. 110), omitted the large NAS–NRC study

from this calculation, and failed to include the Koskenvuo et al. data. As we see in Table 2, both studies reported low concordance rates.

It is apparent from the data presented in Table 2 that there is a large concordance rate difference between the “classical” and “contemporary” studies published during the period surveyed by Gottesman. Pooled pairwise MZ concordance in the classical studies is 61%, whereas for the contemporary studies it is only 21%; the classical pooled pairwise DZ rate is 12%, whereas it is only 4% in the contemporary studies. Clearly, the reduced bias and more careful methods used in the newer investigations suggest that they constitute a more accurate assessment of true MZ and DZ twin schizophrenia concordance rates. The 48% probandwise rate seen in Figure 10 more closely matches, and serves as a major source of, the potentially misleading 50% concordance rate figure found in most psychiatry and psychology textbooks. Some biologically-oriented investigators, such as E. Fuller Torrey (1992), have argued that Gottesman’s figures are too high. And according to Walker and colleagues, a more accurate assessment (again, without Koskenvuo and colleagues’ 1984 data) finds average pairwise schizophrenia concordance rates of 25% MZ, 7% DZ in the more methodologically sound studies (Walker, Downey, and Caspi, 1991).

Equal Environment Assumption

The presentation of schizophrenia twin data in Figure 10 also overlooks the critics’ main objection to the twin method, which is that the MZ–DZ “equal environment assumption” is false. To conclude that concordance rate differences between MZ and DZ twins are due to genetics, one must assume that MZs do not experience more similar environments than DZs. However, the evidence suggests that MZ twins experience much more similar environments than DZ twins (Joseph, 1998, 2004b, 2006). In his discussion of Figure 10, Gottesman did not mention that drawing conclusions in favor of genetics is dependent on the validity of the equal environment assumption. Instead, he wrote, “Undeniably, when twins are reared together, the identical twin of a schizophrenic is much more likely to be schizophrenic than is the fraternal twin of a schizophrenic” (Gottesman, 1991, p. 116), implying that genes are the best explanation for concordance rate differences.

The equal environment assumption is so counterintuitive, in fact, that few people both in and out of science really believe that DZs’ environments are as similar as MZs’ (Kendler, 1983; Rowe, 1994). Ironically, twin researchers themselves were the main proponents of the idea that these environments are equal, but only until the mid-1960s, as has been shown elsewhere (Joseph, 1998, 2004b). Moreover, most schizophrenia twin researchers concluded that concordance rate differences were at least partly the result of

environmental influences (Joseph, 2004b), and Gottesman, in the 1960s, wrote that “a psychological hypothesis such as identification might be used to explain differential concordance rates in MZ and DZ twins . . .” (Gottesman and Shields, 1966a, p. 55).

The equal environment assumption is even more implausible for conditions such as schizophrenia, where psychiatry has long recognized that one member of a closely related pair (whether twin or non-twin) can become psychotic due to the influence of the other member of the pair. *Folie à deux* (shared psychotic disorder) has been defined as “a psychiatric entity characterized by the transference of delusional ideas and/or abnormal behavior from one person to one or more others who have been in close association with the primarily affected person” (Gralnick, 1942, p. 232). The relationship between *folie à deux* and concordance for schizophrenia among MZ twins was addressed by Jackson in his (1960) critique of genetic studies of schizophrenia (Joseph, 2001b). Jackson pointed out that long-standing association and social isolation were common factors linking *folie à deux* and the case histories of concordant MZ twins (which were supplied in some of the classical studies). He stressed that, although the twin relationship was not necessarily positive, “every twin report I have discussed mentions the strength of attachment between the pair, either in positive terms or in terms of mutual antagonism and jealousy. There are no indifferent cases” (1960, p. 68). Jackson noted that in Kallmann’s 1946 twin study, MZ twins (average age, 33 years) who had lived apart for five years or more were listed as having a 77.6% concordance rate, while “nonseparated” pairs were listed at 91.5%. He observed that “a separation even past the formative years was apparently very effective in reducing the concordance rate” (1960, p. 69). Thus, the results of schizophrenia twin studies might have recorded little more than MZ twin pairs’ greater likelihood of developing *folie à deux* when compared with DZ twin pairs.

In Figure 10, the higher MZ versus DZ schizophrenia concordance rates are assumed to be the result of the more similar *genetic* resemblance of MZ versus DZ twins. However, a plausible alternative hypothesis to genetic interpretations of MZ–DZ comparisons holds that higher MZ versus DZ schizophrenia concordance rates are completely explained by the more similar treatment and environments of MZ versus DZ twins, and by MZs’ stronger emotional bond and “ego fusion.” Although Gottesman has never written a detailed theoretical defense of the equal environment assumption, other twin researchers (e.g., Kendler, 1983) have attempted to do so while at the same time recognizing that MZs experience more similar environments than DZs. (For critical examinations of the EEA, see Joseph, 1998, 2002, 2004b, 2006; Pam, Kemker, Ross, and Golden, 1996.)

Failure to Include Opposite-Sex DZ Concordance Rates

Figure 10 also omits the pooled concordance rates of *opposite-sex* DZ twins. This omission is unfortunate because, due to much lower DZ opposite-sex versus same-sex schizophrenia concordance in several studies reporting such rates, one might draw a different set of conclusions from Figure 10 had these results been included.

Although the twin method compares the concordance rates of MZ versus same-sex DZ twins, several studies reported rates for opposite-sex DZ twins as well. As Jackson observed long ago, according to genetic theory there should be no difference between same-sex DZ and opposite-sex DZ twin concordance rates in disorders such as schizophrenia, for which the lifetime diagnosis risk does not differ significantly by sex (Gottesman, 1991, p. 68). "On the other hand," Jackson wrote, "if the hypothesis is correct that identical twins are more concordant for schizophrenia because of their 'twinness,' one would expect a higher incidence of concordance for schizophrenia in same-sexed fraternal twins because they are more alike from the identity standpoint than different-sexed fraternal twins" (1960, p. 65).

We see in Table 3 that the pooled same-sex DZ concordance rate in studies published between 1920 and 1987 is 2.7 times greater than the pooled opposite-sex DZ rate (11.3% vs. 4.7%). Yet, to our knowledge no proponent of

Table 3

Same-Sex and Opposite-Sex Dizygotic (DZ) Twin Pairwise Concordance Rates in Schizophrenia Twin Studies Published Between 1920 and 1987 Reporting Both Rates

Author(s)	Year	Same-Sex		Opposite-Sex		Probability*
		DZ Concordance	%	DZ Concordance	%	
Rosanoff et al. [a]	1934	5/53	9%	0/48	0%	.036
Kallmann	1946	34/296	11%	13/221	6%	.019
Slater	1953	11/61	18%	2/54	4%	.014
Inouye [b]	1961	2/11	18%	0/6	0%	(ns)
Harvald and Haugue [c]	1965	4/33	12%	2/29	7%	(ns)
Kringlen [d]	1967	3/69	4%	3/64	5%	(ns)
POOLED RATES		59/523	11.3%	20/422	4.7%	
(Pooled excluding Kringlen)		(56/454)	(12.3%)	(17/358)	(4.7%)	

* Fisher's Exact Test, one-tailed. (ns) = statistically non-significant at the .05 level.

[a] Based on twins sharing "similar affections" in Rosanoff et al.'s Table 3 (1934, p. 269).

[b] Based on results reported by Gottesman and Shields (1966a, p. 50). Includes "schizophrenia and schizophrenia-like disorders," which were the only figures provided.

[c] Preliminary report of the Danish sample. The final results from this sample are provided in Fischer's (1973) study, which did not report opposite-sex DZ twin concordance rates.

[d] Based on Kringlen's strict definition of schizophrenia; hospitalized and registered cases.

the twin method has ever tried to explain this difference on genetic grounds (Joseph, 2004b).

The figures from Kallmann's large 1946 twin study illustrate this point. Although this investigation has been the subject of criticism, twin researchers, while pointing to several methodological errors, have since the mid-1960s (e.g., Shields, Gottesman, and Slater, 1967) defended Kallmann's data. Indeed, in *Schizophrenia Genesis* Gottesman wrote that although "sadly lacking in details," Kallmann's investigation "is basically sound" (Gottesman, 1991, p. 107). However, in addition to finding a large MZ–DZ schizophrenia concordance rate difference, Kallmann (1946, p. 317) found a same-sex DZ rate of 34/296 (11.5%), but an opposite-sex DZ rate of only 13/221 (5.9%). Unable to explain this difference in terms of genetics, Kallmann (1946, p. 321) stated that the "morbidity rates for opposite-sexed and same-sexed two-egg [DZ] twin partners vary only from 10.3 to 17.6%."¹ While stressing that the rates vary "only" from 10.3 to 17.6%, Kallmann apparently failed to understand that this difference runs counter to the assumptions of the twin method and suggests that MZ–DZ differences could also be explained by non-genetic factors. One could argue that the statistically significant concordance rate difference between his same-sex and opposite-sex DZ twins invalidates the equal environment assumption, upon which Kallmann based his genetic interpretation of MZ–DZ concordance rate differences.

Gottesman discussed concordance rate differences between the two types of DZ twins in a 1966 article co-authored by James Shields. "One significant and consistent difference that emerged from our analyses," they wrote, "was a lower concordance rate for opposite-sex fraternal pairs than same-sex fraternal pairs for studies giving information on this point" (Gottesman and Shields, 1966a, p. 76). In the same article they produced a table presenting Kallmann's same-sex DZ and opposite-sex DZ findings, listing the rates as 11% and 6% respectively (p. 35). Because only one study (by Kringlen) reporting opposite-sex DZ schizophrenia rates appeared between 1966 and 1987, Gottesman's 1966 and 1991 pooled data were very similar (see the pooled rates in Table 3, both with and without Kringlen's data). The difference is that Figure 10 did not include this "significant and consistent" data, which might have led readers to conclude that concordance rate differences in general can be explained by environmental factors.

DZ Twins versus Siblings

Further evidence that environmental factors influence or completely explain MZ–DZ concordance rate differences is the comparison between DZ

¹These percentages reflect Kallmann's age-adjustment of the raw figures.

twins versus the ordinary (non-twin) siblings of people diagnosed with schizophrenia. In Figure 10, for example, the DZ twin risk is given as 17%, but as only 9% for siblings. However, genetic theory cannot account for this difference, since both sibling sets have the same genetic relationship to each other. Theories emphasizing DZ twins' stronger psychological bond, more similar treatment, and greater physical proximity would predict a greater DZ twin versus sibling risk, and this is what we find in Figure 10 (Leo and Joseph, 2002). Gottesman did not offer an explanation for these differences in his discussion of the patterns of familial risk, even though previous critics had pointed to DZ-sibling differences in their analyses. For example, in 1960 Jackson discussed the "very striking finding that same-sexed fraternal twins, especially sisters, have a much higher concordance rate than ordinary sibs" (p. 60). And more recently, Lewontin et al. (1984, p. 218) observed that "from an environmental viewpoint — and only from such a viewpoint — we would expect concordance among DZs to be higher than among ordinary sibs."

Dual Mating Studies

The final representation in Figure 10 is a 46% schizophrenia risk among the offspring of two parents diagnosed with schizophrenia, obtained from "dual mating studies." The percentage Gottesman actually found among the five studies he surveyed, from which he pooled 134 "risk lives," was closer to 33%. He increased the risk percentage to 46% because he decided to use an age correction formula (Gottesman, 1991, p. 101). While it is true that many offspring in these types of studies have not passed through the "schizophrenia risk period" (typically 15–45 years of age), age correction can be misleading because it adjusts rates upwards on the basis of offspring *possibly* being diagnosed with schizophrenia in the future. A solution to this problem would be to count only those offspring (or twins in schizophrenia twin studies) over 45-years-old. But due to their reluctance to reduce sample sizes and thus decrease statistical power, several researchers have preferred to use age correction formulas. Regarding Gottesman's dual mating figures, 33% represents a finding; 46% represents an educated guess.

Gottesman did not identify the five studies he used to arrive at a 46% risk, and in his own 1989 dual mating study he listed eight previous investigations studying the "offspring of two schizophrenic parents" (Gottesman and Bertelsen, 1989, p. 288). Half were published before 1953, and there is no indication that diagnoses in these studies were made blind. Thus, genetically-oriented researchers diagnosed the offspring of two people they viewed as carrying the "hereditary taint" (a common term in that era) of schizophrenia. It is not difficult to imagine that they would tend to see more "schizophrenia" among these offspring than among the offspring of people

they knew did not carry a psychiatric diagnosis. In Gottesman's own study based on Danish registers, he found a "morbid risk" of only 10% (1/14 before age-correction) among the offspring of "reactive psychosis" dual matings (Gottesman and Bertelsen, 1989).

Another problem with dual mating studies is that it is unusual to find two biological parents diagnosed with schizophrenia who also rear their child. It is important to know at what point in a child's development each parent is diagnosed, as well as the circumstances of the child's upbringing. More than any other type of genetic study, detailed case histories are essential in dual mating studies. Simple numbers or "morbidity rates" will not do. Moreover, like the other risk factors outlined in Figure 10, dual mating results can be explained by environmental factors, since these offspring were reared by two people diagnosed with schizophrenia. Consistent with having experienced emotional deprivation and abuse, Gottesman reported that the offspring of schizophrenia dual matings were at "considerably higher risk for other psychiatric abnormalities" (1991, p. 101). Suppose that a dual mating study of pellagra (a disease caused by malnutrition) finds high rates of pellagra among the offspring of two parents diagnosed with pellagra. This finding would be the result of their parents' diets, not their genes. Thus, like other types of studies, potential genetic and environmental influences are not easily disentangled in dual mating studies.

Conclusion

As we have seen, there are several problems with the schizophrenia lifetime risk percentages compiled in Figure 10. The most important is that, although it is almost always reproduced or discussed in terms of providing evidence in favor of genetics, the various risk percentages are plausibly explained by factors such as differential exposure to deviant familial rearing patterns, modeling the behavior of relatives, common exposure to environmental agents, the more similar environments experienced by MZ versus DZ twins, and bias. Textbook authors using Figure 10 as a secondary source pay little attention to plausible alternative explanations. Although molecular genetic researchers have failed to identify presumed schizophrenia genes (Joseph, 2004a, 2004c, 2006; Kendler, 2005; Propping, 2005), they remain convinced that schizophrenia has a strong genetic component on the basis of data such as those reported in Figure 10, in addition to the results of severely flawed adoption studies (Joseph, 2004b). We suggest that a critical analysis of the studies reporting these data might lead molecular genetic researchers to conclude that the basic premise of their work — that the genetic basis of schizophrenia has been decisively established — is not as solid as they originally believed.

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