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Essay Review

The Fallacy of the 50% Concordance Rate for Schizophrenia in Identical Twins

By

Jonathan Leo

A Review of *The Gene Illusion* by Jay Joseph.
2003, PCCS Books, Ross-on-Wye.

The common practice of treating psychiatric conditions with medications is justified by the belief that mental illnesses are the result of underlying biological deficits. Genetic research is one avenue of research that is frequently cited as proof in support of this belief; and, in turn, one of the most commonly cited pieces of genetic evidence is the concordance rate for identical twins diagnosed with schizophrenia. When discussing schizophrenia twin studies psychiatrists often report a 45%-50% concordance rate for identical twins, compared to only a 15% concordance rate for fraternal twins. These numbers which are often cited in psychiatry textbooks, peer reviewed papers, magazine articles, speeches and even newspaper articles are generally considered the most important piece of evidence supporting the biological theory of schizophrenia—and even as evidence that mental illnesses in general are biologically based. Concerning the genetic theory of schizophrenia, the most recent edition of the neuroscience textbook *Fundamental Neuroscience* by Squire et al. (2003) states, "The most compelling evidence is the 50% concordance rate for monozygotic twins relative to the 15% concordance for dizygotic twins" (Rapp and Bachevalier, 2003, p. 1193). A new book *The Gene Illusion*, by Jay Joseph shatters the validity of this statement and leaves the most commonly mentioned statistic in psychiatry in tatters. Joseph's book is an analysis of psychiatric genetic research and covers topics such as the heritability concept, the genetics of IQ, the genetics of criminality, the schizophrenia adoption studies—but his most devastating criticism is of the schizophrenia twin studies (Joseph, 2003).

It is hard to find any defense of biological psychiatry that does not mention the schizophrenia twin research. As just one example, Steven Hyman, the former-chairman of NIMH, appeared before President George Bush's *Commission on Bioethics* for the purpose of defending the meteoric rise in the use of Ritalin

and other psychotropic drugs in young children. In his opening monologue he did *not* cite a study documenting the biological basis of Attention Deficit Hyperactivity Disorder (ADHD); he did *not* cite a study showing the benefits of Ritalin; instead he cited the "50% schizophrenia twin concordance rate" (see www.bioethics.org). His comments, which are not uncommon, are simply an echo of a commonly held belief in psychiatry that if schizophrenia is "genetic" then other psychiatric conditions such as ADHD must also be "genetic." But in another sense when a psychiatrist defends the biological basis of mental illness and starts the discussion by citing genetic evidence, and not biological evidence such as pathological markers or blood tests, this is a tacit acknowledgement that in fact there is no biological evidence. If there was good biological evidence then why not mention it?

Over the past fifty years the history of psychiatry has been nothing more than the absolute triumph of "nature" over "nurture" —at least in the way the medical community looks at human distress. In the world of biological psychiatry "genes" have won the gold medal and completely pushed "the environment" right off the stage, and no historical analysis of this victory would be complete without a discussion of the schizophrenia twin studies. For instance, if the genetic theory of anorexia never pans out this would have no bearing on the way psychiatrists approach other mental illnesses, but if the most compelling evidence that mental illnesses are genetic is flawed—and that the major cornerstone of the profession is false—then the psychiatry profession has a problem.

Twin studies are important to psychiatric genetic researchers because scientists can compare two different types of twins. Identical twins have the same genotype, while fraternal twins share on average only 50% of the same genes. If the development of a certain disease is due to heredity, then genetic researchers would expect more of the identical twins to share the disease as compared to the same-sex fraternal twins. If the identical twin concordance rate for schizophrenia is 50% and the non-identical twin concordance rate is only 15% then schizophrenia must be genetic—so the thinking goes. If the identical twin concordance rate for schizophrenia is not 50% then what is it? The answer depends on how in-depth you investigate these studies.

How about 40%?

"The 50% concordance rate" comes from pooling numerous schizophrenia twin studies. Joseph presents a table showing all fifteen schizophrenia twin studies conducted from 1928 to 1998 with a range of pairwise identical twin concordance rates from a low of 11% to a high of 69%. Joseph pools the data, does his own calculation and reports that the pooled concordance rate reported with the pairwise method is 40.1%. Thus right at the start the 50% concordance rate is called into question. But why the discrepancy between Joseph's 40% and the more commonly reported 50%? One reason is due to differences in the way results are reported.

There are two ways that schizophrenia twin researchers report their results. One is the pairwise method, the other is the proband method. Most readers who are not intimately familiar with these studies probably interpret concordance rate findings as the percentage of twin pairs who are both diagnosed with schizophrenia within a sample in which one twin of each pair is known to be schizophrenic. For instance if schizophrenia is diagnosed in both members of 50 twin pairs out of a total sample of 100 then most people would think that the concordance rate is 50%, but it is not that simple. Schizophrenia researchers refer to this type of reporting as the pairwise concordance, yet some prominent researchers prefer to use the proband method of reporting. In the proband method, the *proband* is the member of a twin pair who was used initially to qualify the pair for inclusion in the sample. It is possible for both members of a twin pair to be probands, in which case that pair would appear twice in the

sample. The proband method will always produce higher numbers. As an example, if there is a sample of 3 pairs of twins and in 1 of those pairs both members are diagnosed with schizophrenia then according to the pairwise method the concordance rate would be 1/3 or 33%, but according to the proband-wise method the rate would be 2/4 or 50%.

Of course, certainly some people would say that 40% is still significant, but, Joseph does not stop here; in fact he is just getting started.

How about 20%?

Joseph's table also highlights another problem with the way the schizophrenia twin research is commonly discussed. From looking at his table it is clear that the more recent studies, which are generally considered more methodologically sound, have lower concordance rates then the older studies. One of the earliest studies was published in 1946 by Franz Kallmann who reported a 69% concordance rate for identical twins. He increased this to 86% after factoring in an age-correction (Kallmann, 1946). Kallmann's pairwise concordance rate is at odds with many of the more recent studies. Given the fact that Kallmann's numbers are not in line with the newer studies and that his diagnoses were not blind there seems to be ample reason for not including Kallmann's data in the pooled calculations. For some people, the fact that Kallmann also believed in compulsory sterilization for people diagnosed with schizophrenia—and their relatives—creates a bit of a problem.

Kallmann's study was one of the largest twin studies so his study also has a significant effect on the final pooled numbers. But if one pools the nine most recent studies, as Joseph does, starting with Tienari's 1963 study then the concordance rates are 22.4% for monozygotic twins and 4.6% for fraternal twins.

In the past two decades there have been three schizophrenia studies that found low concordance rates for monozygotic twins; but rather than change the way psychiatrists think about the genetics of mental illness, as Joseph shows, the psychiatry profession would not let the results of these three studies stand for very long.[1]

Tienari, 1936; 1968; 1971;1975

In 1963 Tienari published a twin study which according to Joseph "took the schizophrenia twin-studying world by storm." Tienari reported that none of the sixteen identical twin pairs in his study were concordant for schizophrenia and that only one fraternal pair out of 21 was concordant. The difference between Kallman's 85% and Tienari's 0% identical twin concordance rates could not have been more dramatic, yet only seventeen years separated the two studies. Tienari updated his study several times and in his final 1975 paper Tienari reported an identical twin pairwise figure of 3/20 (15%) and a non-identical twin concordance rate of 3/42 (7.1%).

Gottesman and Shields were the first psychiatric genetic researchers to tackle these numbers and in 1982 wrote that the Tienari's low concordance rate could be due to the small sample size and the lack of an age-correction factor (Gottesman and Shields, 1982). Some schizophrenia researchers have applied an age-correction factor to their samples to take into account the fact that the subjects might not have passed thru the period in their lives when people are most likely to develop schizophrenia. However, it is unclear why Gottesman thinks that Tienari should have applied an age-correction factor when Tienari's twins were all over 40 years old and had passed the risk period for schizophrenia. Joseph (and Boyle before him) points out that four other twin studies also had a small sample size and that even Gottesman and Shields own study only had 24 twins. Regardless of these arguments, in his book *Schizophrenia Genesis*, Gottesman states that Tienari reported a final pairwise concordance rate of 36% for identical twins (Gottesman, 1991, p. 111) when it was actually 15% (3/20) (Tienari, 1975, p. 33).

Tienari's study also illustrates the problem with reporting findings via the proband method.

By 1987 the psychiatric geneticist Kenneth Kendler had converted Tienari's 3/20 (15%) identical twin pairwise concordance rate into the proband method and reported that Tienari's concordance rate was 7/21 or 33% (Kendler, 1987). Anyone other than an expert in this field would most likely think that 7 out of 21 pairs were concordant when actually only 3 out 20 pairs or 15% were concordant. [2]

The NAS-NRC Study (Hoffer and Pollin, 1970)

In 1970 Hoffer and Pollin analyzed a large sample of twins from the NAS-NRC veterans sample and reported a pairwise concordance rate for identical twins as 13.8% and for fraternal as 4.1%.

Only two years later Allen and colleagues reanalyzed the study which now included additional twin pairs that had been identified in the meantime. The new identical twin concordance rate was reported as 27% and fraternal 4.8% (Allen, Cohen, and Pollin, 1972). However these figures were obtained by widening the diagnostic criteria. In 1982 Gottesman and Shields converted the 27% identical twin pairwise concordance to a probandwise rate of 43%. Somehow mainstream psychiatry researchers had transformed an initially reported rate of 13.8% to 43%. [3].

Koskenvuo, Langinvainio, Kaprio, Lonnqvist, and Tienari, 1984

This study had one of the largest samples of twins, yet is almost never acknowledged by schizophrenia twin researchers in their reviews; interestingly, they have not explained why it has been left out of their reviews. In the Koskenvuo study the concordance rate was 11% for identical twins and 1.8% for fraternals.

So even before getting into any real analysis or much controversy, for that matter, it is clear that there is very little justification for saying that there is 50% concordance rate for monozygotic twins, and little justification for textbooks authors and review authors to pool the older studies with the more carefully designed newer studies. At the very least, these authors should be pointing out the discrepancies between the more recent studies and the older studies. Going one step further, textbook authors should probably point out that the newer studies have actually revealed the fallacy of the "50% concordance rate."

If you think I am being extreme here ask yourself this question: If the chronological order of these studies were reversed and the older biased studies had, say, a 20% concordance rate and the newer less biased studies had a 86% concordance rate would psychiatry and genetic researchers still be pooling the data or would they be citing a concordance rate closer to 86%?

Like much of the psychiatry literature, the more one examines the initial claims of psychiatry researchers the more the validity of those claims is called into question. In the case of schizophrenia twin research it does not take much more than scratching below the surface to see that textbooks would be more correct to write about a 20% concordance rate for schizophrenia in identical twins - and that is simply based on a more accurate reporting of the original authors' research.

Certainly the proponents of the genetic theory of schizophrenia will take issue with some of Joseph's analysis—such as using the pairwise rather than probandwise reporting method, or the validity of Kallmann's data. But as Joseph points out, staring these critics directly in the face is a very telling statistic: In three modern schizophrenia twin studies *84% of the identical twins were judged discordant for schizophrenia.*

Even an acknowledgement by the main stream psychiatry profession that the schizophrenia concordance rate was closer to 20% would necessitate a rewording of many of their core tenets. There are twin studies of diseases with well-known biological factors that some psychiatrists have equated with schizophrenia, but the language used to discuss these diseases is very different from the language used to discuss psychological trauma. Take the conclusions in a paper that used the classical twin

method to investigate the role of genetics in a disease with a known biological marker. Based on a concordance rate of 30.8% for identical twins and 4.7% for non-identical twins the authors concluded that there was a genetic component to the disease, but they also had this to say about the environment:

> -The data from this twin study also have important implications for the nature of environmental or non-heritable effects on the development.
> -This unambiguously demonstrates the powerful effect of nonheritable factors.
> -Taken in sum, these observations are entirely consistent with a broader concept of the role of the environment (Sadovnick, Armstrong, Rice et al., 1993, p. 285)

The disease these researchers are talking about is multiple sclerosis (MS) and even though they attribute a portion of the etiology of MS to genetics, they go out of their way to point out that the environment is just as, if not more, important than genetics. [4] A handout for the general public, from the *Multiple Sclerosis Genetics Research Group* tells people that "in some combinations these normal genes appear to predispose some individuals to develop MS *after exposure to an undefined environmental factor or factors" (italics added)*. It's hard to imagine a patient handout on psychological distress saying "normal genes appear to predispose some individuals to develop depression after exposure to an undefined environmental factor" or a neurology textbook saying that the strongest evidence for the biological basis of MS comes from twin studies.

However if one digs a little deeper, then even the idea that there is a 20% concordance rate is highly suspect. For Joseph, even a 20% concordance rate means little because the twin methodology is based on a fundamentally flawed assumption. [5] But before reading further ask yourself this common sense question: Do you think that families, teachers, friends, and society in general treat identical twins more alike than non-identical twins?

Is the Twin Method Valid?

The validity of the twin method is based on answering "No" to this question. The classical twin method assumes that identical twins do not have more similar environments than fraternal twins. This equal environment assumption, or EEA, is critical for the twin method because if identical twins are treated more alike than fraternal twins then any difference in the concordance rates between the two types of twins could be attributed to their environment. Psychiatric geneticists will have a much more difficult time with this part of the book because Joseph is not just saying that this flawed assumption might cause a slight overemphasis on the side of genetics, rather he is saying that because the EEA is false it is impossible to draw any meaningful conclusions from twin studies. In his words, " the entire theoretical basis for twin studies that look at genetic components of human behavior and psychiatric conditions *stands or falls on the veracity of this assumption" (Joseph, 1998, p. 329)*.

One way of testing the equal environment assumption is to compare fraternal twins to other siblings because in terms of their genetic makeup fraternal twins are no more alike than non-twin siblings so any difference in the rate of schizophrenia between fraternal twins and siblings must be due to something other then genes. Six of the schizophrenia twin studies also compared the concordance rates between fraternal twins and non-twin siblings and five of these studies found that fraternal twins had a higher concordance rate compared to non-twin siblings, and in two of these studies the differences were significant (Leo and Joseph, 2002). The only study that found a similar rate was by Kallmann. There are several other ways of evaluating the EEA in schizophrenia, and Joseph devotes a considerable amount of text to this discussion. As just one example, Joseph

pools the data from those twin studies that report both the same-sex fraternal and opposite-sex fraternal twin concordance rates. The same-sex fraternal concordance rate is 11.3% and the opposite-sex fraternal rate is 4.7%. This difference is hard to explain based on genetics, but most twin researchers simply ignore the data. [6] Even if you do not agree completely with Joseph's view that the twin studies are invalidated by the flawed EEA, it is clear from his book that the majority of the secondary sources, like the textbook cited at the beginning of this review, that discuss the schizophrenia twin studies are seriously flawed.

Susceptibility Genes

An interesting twist to this discussion concerns the recent paper in *Science* about the discovery that individuals with at least one copy of the short allele of the 5-HTT promoter polymorphism were more susceptible to depression *if they were also exposed to a series of traumatic events (Caspi, Sugden, Moffitt et al., 2003)*. Some researchers have said that this study will aid in identifying people prone to depression even though in the group of clinically depressed patients exposed to four traumatic events 86% of them carried at least one copy of the short allele, or susceptibility gene, while in the group exposed to four traumatic events who did not become depressed, 72% were also carriers of the short allele. It is unclear how this information would aid in identifying who is susceptible to depression or, even more controversial, what type of treatment would be provided. Imagine the interaction between a doctor and a clinically depressed patient who had experienced four traumatic events; it would seem that the most important element in this interaction would be the traumatic events, and not whether the person had the short allele. The person's genetic makeup is entirely unnecessary for any explanation of the depression and the "genetics" in no way implies that drugs are needed. But most importantly, and not mentioned in many of the newspaper accounts of this study, is that 68% of the population carries at least one copy of this allele. [7] These investigators have not discovered anything unique about people diagnosed with depression, rather they have discovered something very general about human nature—more then 2/3rds of us carry an allele that makes us susceptible to depression after suffering a series of traumatic events. In addition, even people without the short form became depressed; serotonin processing has been implicated in numerous DSM-IV conditions; and this allele is most likely involved in many other traits—some of which might be considered beneficial.

If the majority of us are susceptible to depression after a series of traumatic events this certainly calls into question the "line" that psychiatrists have drawn between normal and abnormal. Is depression following traumatic events part of our humanity? Is it possible that someone who is "normal" can be labeled as "abnormal?" Is the drug treating a "disease" or covering up a normal reaction to stress? The study seems to raise more questions about the wisdom of the widespread use of psychotropic drugs than it answers. The authors of the study stated: "Until this study's findings are replicated, speculation about clinical implications is premature" (p. 389). Yet have they really thought through this comment? If this study is replicated tomorrow what clinical plan are these scientists even *remotely* entertaining?

Perhaps one of the more confusing statements from psychiatric genetic researchers appears in a recent issue of *Science.* In a discussion of "ADHD genes" Steven Faraone stated: "My hope is that once we've discovered those genes, we'll be able to do a prospective study of kids at high versus low genetic risk. That's when you'll see environmental factors at work." But certainly one can still see environmental factors at work in children without knowing their genotype; Maria Montessori saw the importance of environmental factors 60 years ago. Yet, even more confusing is Faraone's next comment. According to the re-

porter, "Eventually, he (Faraone) adds, environmental changes could play an important role in treating some ADHD patients" (Brown, 2003, p. 160). Eventually? What are we waiting for? Why not implement the changes right now? Changing the environment is exactly what many people opposed to Ritalin have been saying for years. Faraone seems to be falling right in line with Thom Hartmann who believes that children with ADHD are not dysfunctional but have different genes—hunter gatherer genes—and that what is needed is a different environment (Hartmann, 1996). Apparently Faraone cannot give credence to a role for the environment in the etiology of ADHD without knowing the genotype. He should probably elaborate on what environmental changes he has in mind for a child who does not want to sit still in school, why these changes could not implemented right now, and how knowing the genotype will aid in developing a plan. Faraone has certainly put a very unique twist on the whole discussion by saying that once we know genotypes we can alter the environment, but in one sense his discussion can't really be taken too seriously; because allowing for a dose of reality, anyone remotely familiar with the topic of genetic susceptibility is all too aware that right around the corner is the real pitch—the medication tie-in. An earlier statement by Faraone is much more representative of how genetic research is more often used: "Many parents are reluctant for their children to take psychotropic medication and others find it difficult to maintain the prescribed regimes. These problems are mitigated by discussing the genetic etiology of ADHD…" (Faraone, 1996, p. 598).

Quite simply, main-stream psychiatry is in a position where, for political and economic reasons, they could never acknowledge that the conditions they treat have more to do with environmental causes then genetic predispositions. Take ADHD for example, the problem for the Ritalin proponents is that they could never publicly admit that treating so many children with psychotropic drugs has anything *at all* to do with the environment. If they admitted that something like smaller classrooms could lead to a decrease in psychotropic drug use the façade of treating a medical condition would be revealed. All of sudden Ritalin would go from being advertised as something to treat a medical condition, to a drug that is "quick, easy and cheap"—at least compared to changing the environment. In the world of American pop culture, the current view of mental illness is that someone is walking down the street, everything is going fine, life is good and then out of the blue, there is a chemical shortage. At the route of every twisted thought is a twisted molecule and at the route of every twisted molecule is a twisted gene so the theory goes. This portrayal of mental illness has certainly served its purpose as a marketing tool, yet it is becoming increasingly harder to justify this view based on a realistic appraisal of the science.

Besides having profound implications for the science of biological psychiatry, a debunking of the "50% concordance rate" also has implications for the clinical side of biological psychiatry. Patients diagnosed with a mental illness are often told that their condition is due to a problematic gene which is causing a biochemical imbalance. Because there are no neuropathological markers for psychiatric disorders a psychiatric diagnosis is based on a careful patient history that includes questions about mental illnesses in other family members. The idea being that when a psychiatrist is examining a patient and deciding what psychiatric diagnosis to make, or even whether to make a psychiatric diagnosis at all, a family history of mental illness can sway the decision one way or another. Thus, the diagnosis of an individual patient is based, in part, on a previous diagnosis in another family member. Some psychiatry researchers have taken this to the extreme and claim that they can identify people who are "at-risk" of developing schizophrenia. Not surprisingly, one of the risk factors these researchers use to identify candidates for pre-psychotic

treatment is a family history of schizophrenia. But as Joseph's book documents, making a diagnosis of schizophrenia, or predicting who will get schizophrenia, based on a family history has little scientific rationale.

Conclusions

I have only touched on one aspect of Joseph's book, but his book covers much more than the identical twin schizophrenia concordance rate. In fact, the section on the schizophrenia twin data is only 20 pages out of a 334-page book. For those psychiatrists who point out that the famous schizophrenia adoption studies have confirmed the genetic theory of schizophrenia Joseph has a whole chapter. As just a teaser, how many psychiatrists are aware *that the most often cited schizophrenia adoption study rests its case on the basis of counting spectrum disorders among index and control paternal half-siblings?*

Many of the recent popular books on nature vs. nurture have taken at face value what behavioral geneticists have previously written in review articles and textbooks. Take Steven Pinker's recent book *The Blank Slate* about the importance of genetics in the molding of human traits (Pinker, 2002). For Pinker, the twin studies are one of the most important supporting pieces of evidence for his argument, yet regarding the EEA—an assumption on which the twin method succeeds or fails—he devotes about two sentences plus a citation to a twin expert. Like Pinker, there are many authors who attempt to take the existing body of knowledge on nature and nurture and work out where on the continuum between the two extremes the truth falls. But these authors bring to the table a set of assumptions like "the 50% concordance rate" that they have primarily taken from secondhand sources. Joseph's book is not about trying to work out a happy medium on the nature-nurture continuum by analyzing secondary sources. Instead he has gone right to the original studies, analyzed them, pointed out the problems with these studies, and in the process has revealed that the "grand synthesizers" of the nature versus nurture debate have based their work on a set of questionable assumptions.

It will be interesting to see how, or even if, the psychiatry profession responds to Joseph's book, because for the most part the profession has ignored him. As of this point no American publisher has picked up his book; and many of his previously published papers which formed the basis for the book did *not* come from mainstream psychiatry journals, but instead came from less well known journals. The profession that has written and published thousands of pages about the schizophrenia twin and adoption studies but few papers pointing out the simple fact that the newer more methodologically sound schizophrenia twin studies have found only a 22.4% identical twin concordance rate. Or that the most-often cited schizophrenia adoption study is based on the diagnosis of spectrum disorders in half-siblings? Of course people will be arguing about the nuances of individual twin studies for years, and you might not agree with all of Joseph's critique; but after reading his book, the next time you see an announcement in the paper about the discovery of a gene for emotional distress you will be a little more skeptical. The problem for the psychiatry profession is that Joseph's readers will likely take his debunking of the "50% concordance rate" one step further and question the entire scientific basis for biological psychiatry.

National Public Radio recently aired a piece describing how in the future we can swab our cheeks, send the sample off to a company, and conveniently find out all the genes we carry for various diseases such as schizophrenia. I talked to the author of the piece and pointed out to him that no one has discovered a gene for schizophrenia. He referred me to his source which was a company involved in the enthusiastic race to find a gene, or genes, for schizophrenia. No doubt the search for genes for schizophrenia and other DSM-IV conditions will continue at a frantic pace, and it is certainly this company's prerogative to spend millions of their dollars in the hunt for these genes. However, if Joseph is

correct they would probably be better off trying the slot machines.

Jonathan Leo, Ph.D., Department of Anatomy, Western University of Health Sciences, 309 East Second Street, Pomona CA, 91767. Email: jleo@westernu.edu.

Notes

1. Joseph's discussion builds on Mary Boyle's discussion in her 1990 book *Schizophrenia: A Scientific Delusion (Boyle, 1990).*
2. The basis for Kendler reporting 7/21 even with the proband method is unclear.
3. In 1983 Kendler and Robinette created a wider diagnostic category and reanalyzed the original sample and still only found a pairwise identical twin concordance rate for schizophrenia of 18.3% (30/164) (Kendler and Robinette, 1983).
4. This study also found no difference between the non-identical twins and other siblings which is confirmatory evidence for the validity of the EEA regarding multiple sclerosis. This is not the case for the schizophrenia twin studies.
5. There are other scientists that have written that the true concordance rate is closer to 25% (Torrey, 1992).
6. In 1982 Gottesman and Shields claimed that there is no difference between same sex and opposite sex fraternals in recent studies. But by recent studies they were referring to one study—Kringlen's 1967 investigation (see Joseph 2002, p. 150).
7. 68% of the New Zealanders in this study had at least one copy of the short allele. It is possible that this allele could vary between different groups, or races, of people.

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