The Fruitless Search for Genes in Psychiatry and Psychology: Time to Re-examine a Paradigm?

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ABSTRACT

The past three decades have witnessed the failure of molecular genetic gene finding efforts in psychiatry and psychology. One rarely considered explanation for this failure is that the genes presumed to underlie psychiatric disorders and psychological traits do not exist. Although the search for genes is based on the results of previous studies of families, twins, and adoptees, the authors argue that these studies are subject to environmental biases which may have confounded researchers' conclusions in favor of genetics. They conclude by calling on the scientific community to embark on a serious reassessment of the validity of family, twin, and adoption studies in light of the dramatic failures of gene finding efforts.

The Fruitless Search for Genes in Psychiatry and Psychology

The June, 2009 edition of *The Journal of the American Medical Association* reported the results of a meta-analysis by Neil Risch and his colleagues (*1*). These researchers showed that a 2003 study by Caspi and colleagues (*2*), where the investigators believed they had found a genetic variation associated with depression when combined with stressful life events, did not stand up to replication attempts. Caspi and colleagues' original study had been widely reported in the media and elsewhere as constituting a major genetic discovery in psychiatry.

However, to the critical observers of genetic research in psychology and psychiatry, including those who had pointed to several glaring problems in Caspi and colleagues' study *(3)*, the failure to replicate these results came as no surprise at all. This study merely suffered the same fate as other gene-finding claims in psychiatry over the past thirty years, such as the much publicized yet subsequently non-replicated claims of nearly a generation ago for bipolar disorder (*4*), and for schizophrenia (*5*). Clearly, some type of systematic error is common to these subsequently unsubstantiated findings.

Previously, a group of leading psychiatric genetic researchers had recognized in 2008, "It is no secret that our field has published thousands of candidate gene association studies but few replicated findings" (*6*). And in the same year, behavior geneticists Robert Plomin and colleagues could not cite any substantiated gene findings for personality or IQ (*7*). Risch et al. (*1*) concluded that "few if any of the genes identified in candidate gene association studies of psychiatric disorders have withstood the test of replication":

> Despite progress in risk gene identification for several complex diseases, few disorders have proven as resistant to robust gene finding as psychiatric illnesses. The slow rate of progress in psychiatry and behavioral sciences partly reflects a still-evolving classification system, absence of valid pathognomonic diagnostic markers, and lack of well-defined etiologic pathways. Although these disorders have long been assumed to

> result from some combination of genetic vulnerability and environmental exposure, direct evidence from a specific example has not been forthcoming*(1)*.

Thus, the fields of behavior genetics and psychiatric genetics may be approaching a period of crisis and re-examination. The reason is straightforward: despite well-funded international efforts carried out over the past few decades, the genes believed to underlie the major psychiatric disorders, and variation in normal psychological traits, have not been found.

There are two broad explanations for the ongoing failure to discover genes in psychiatry and psychology. The first, which is favored by genetic researchers and their backers, is that genes for "complex disorders" exist (although each gene may be of small effect size) and will be discovered once researchers improve their methods and increase their sample sizes. The second explanation, though rarely if ever considered in mainstream works, is that genes for psychiatric disorders and for normal variation in psychological traits do not exist.

For the past two decades the popular and scientific literature has been filled with discussions of how improved methods in molecular genetic research will lead to gene discoveries. Although we cannot rule out such possibilities, our purpose here is to suggest that the misreading of previous kinship research has led the scientific community to the premature conclusion that genes for psychiatric disorders and psychological trait variation must exist.

The reason that scientists are certain that such genes exist is their belief that previous family, twin, and adoption studies have provided conclusive evidence in favor of genetics. Hence Risch and colleagues' statement that psychiatric and behavioral disorders have "long been assumed to result from some combination of genetic vulnerability and environmental exposure."

Kinship studies of this type are known collectively as "quantitative genetic research." While constituting a necessary first step, family studies are widely seen as being unable to disentangle the potential role of genetic and environmental factors. Because family members

share a common environment as well as common genes, the finding that a trait "runs in the family" can be explained on either genetic *or* environmental grounds. As Plomin and colleagues recognized, "Many behaviors 'run in families,' but family resemblance can be due to either nature or nurture." They concluded, correctly in our view, that "[f]amily studies by themselves cannot disentangle genetic and environmental influences" (*7*).

Twin Studies

Thus twin studies and adoption studies, which have been carried out since the 1920s, constitute the main quantitative genetic results cited in support of genetics. We will touch on some problem areas in adoption research later, but for now we focus on twin studies, which are the most frequently cited studies in support of important genetic influences on psychiatric disorders and variations in "normally distributed" traits such as IQ and personality. There are two main types of twin research methods: studies of twins reared-together, and studies of twins reared-apart.

Studies of twins reared-together, which use a technique called the "twin method," compare the trait resemblance of reared-together monozygotic (MZ) versus reared-together same-sex dizygotic (DZ) twin pairs. If monozygotic pairs resemble each other more than dizygotic pairs (on the basis of correlations or concordance rates), twin researchers conclude that the trait has a genetic component, and then go on to calculate heritability estimates based on the magnitude of the difference. They conclude in favor of genetics on the basis of several theoretical assumptions about twins, the most important and controversial of which is the assumption that MZ and same-sex DZ twin pairs experience roughly equal environments. This is known as the "equal environment assumption," or "EEA." The logic appears straightforward,

since MZ pairs share a 100% genetic similarity, whereas DZs share only 50% of their genes on average.

There is, however, a fatal flaw in this logic: The equal environment assumption of the twin method is obviously not correct, since most research in this area finds that MZ twin pairs experience much more similar environments than do DZ pairs (*8-10*). Moreover, MZ pairs resemble each other more anatomically than DZ pairs, and this clearly will elicit different treatment from the social environment. Therefore the greater psychological trait resemblance of MZ versus DZ twin pairs, a result found by most twin researchers, can be explained solely by non-genetic factors related to MZ pairs' greater environmental and treatment similarity. From the standpoint of environmental confounds, the twin method has precisely the same problem as family studies because in both, the comparison groups experience far different environments.

Interestingly, most contemporary twin researchers acknowledge that the environments experienced by MZ pairs are more similar than those experienced by DZs (*8-11*). However, on the basis of two main arguments, they continue to hold that the EEA is valid and that the twin method reliably measures genetic influences.

The first argument is that, although MZ and DZ environments are different, these environments must be shown to differ in aspects relevant to the trait in question. Furthermore, twin researchers often implicitly or explicitly suggest that twin method critics bear the burden of proof for demonstrating that these admittedly unequal environments differ on trait relevant dimensions (*12,13*).

The second argument twin researchers put forward in defense of EEA and the twin method is that MZ pairs tend to "create" more similar environments for themselves by virtue of their greater genetically-caused similarity of behavior (*7, 8*). For example, according to one

group of researchers, although MZ twins ‘‘may well be treated more similarly’’ than DZs, ‘‘this is far more a consequence of their genetic similarity in behaviour (and of ensuing responses by parents and others) than a cause of such similarity’’*(14)*.

Regarding the first argument, the proponents of a scientific theory or technique, rather than their critics, bear the burden of proof for showing that their theory or technique is correct (*15*). Although twin researchers have carried out a series of tests of the equal environment assumption (*8*), these studies have done little to uphold the validity of the twin method (*10*). Ironically, although EEA test researchers usually conclude that their findings support the EEA, most find that MZ twin pairs experience much more similar environments than do DZ pairs *(10)*. However, if differing environments automatically and without qualification invalidate genetic interpretations of family study data, as most behavior geneticists and psychiatric geneticists readily concede, then the differing environments of MZ vs. DZ twin pairs must invalidate genetic interpretations of twin method data as well.

We have seen that the second argument modern twin researchers put forward in defense of the twin method is that MZ twin pair environments are more similar than those of DZ pairs because MZs create more similar environments for themselves on the basis of their greater genetic similarity. However, this actually supports an environmental argument, for it is primarily the similar or dissimilar social treatments/experiences that organize children’s behaviors.

Moreover, researchers putting forward this “twins create their own environment” position use circular reasoning, in that they *assume* the very thing they need to *demonstrate*. Twin researchers’ claim that twins’ behavioral resemblance is caused by genetics is based implicitly on the results of previous twin studies. Thus, modern twin researchers circularly rely on the twin method to validate the twin method, and they circularly *assume* that twins’ behavioral

resemblance is caused by genetics, in order to *conclude* that twins' behavioral resemblance is caused by genetics *(16)*.

Thus the only relevant question in determining the validity of the EEA and the twin method is whether—not why—MZ pairs experience more similar environments (*9*).

Buried within the schizophrenia twin research literature, which is frequently cited in support of a genetic basis for the condition, is a finding that the pooled concordance rate for same-sex DZ twins is two-to-three times greater than that of opposite-sexed DZ twins (11.3% vs. 4.7%; *9,10*). Because the genetic relationship between same-sex and opposite-sex DZ twin pairs is the same, from the genetic perspective we should find no significant difference between these pooled rates (17). Moreover, the pooled schizophrenia concordance rate for DZ twins is almost double what it is for ordinary (non-twin) siblings (*18*), despite the fact that the genetic relationship between DZ twins and ordinary sibling pairs is the same. These findings are consistent with a purely environmental etiology of schizophrenia, since pairs experiencing more similar environments and a closer emotional bond are consistently more concordant for schizophrenia than are pairs experiencing less similar environments and a weaker emotional bond. These results provide additional evidence that—as we have seen with family studies—the twin method is unable to disentangle potential genetic and environmental causes of schizophrenia and other psychiatric disorders (*9*,*17,19*).

Thus, there are two main conclusions one can reach on the basis of twin method data:

> **(1) <u>Contemporary Twin Researchers' Conclusion</u>**: The greater resemblance of MZ vs. same-sex DZ twin pairs provides solid evidence that a sizable portion the population variance for psychiatric disorders and psychological traits can be explained by genetic factors, **or**

> **(2) <u>Twin Method Critics' Conclusion</u>**: The twin method is a faulty instrument for assessing the role of genetics, given the likelihood that MZ vs. same-sex DZ comparisons measure environmental rather than genetic influences. Therefore, all previous interpretations of the twin method's results in support of genetics are probably wrong.

We argue here that the available evidence calls for the acceptance of Conclusion #2, and we agree with three generations of critics who have argued that the twin method is no more able than a family study to assess the roles of nature and nurture. Because the equal environment assumption is not supported by the evidence, all conclusions in favor of genetics on the basis of twin method data are at best premature, and most likely are simply wrong.

Because many scientists and commentators have had doubts about the validity of the twin method, some have pointed to studies of twins reared-apart (TRA studies), such as the Minnesota TRA study published by Bouchard and colleagues in 1990 (*20*). However, problems with the methodology and underlying logic of these studies have been outlined by several reviewers (*9, 21-23*). Problem areas include: (1) it is doubtful that most MZ twins reared-apart (known as MZAs) deserve the status of having been "reared-apart," since most pairs had significant contact with each other for many years (*21-22*); (2) in several studies, there were biases favoring the recruitment of MZA pairs who resembled each other more for behavioral traits than MZA pairs as a population (22); (3) there is controversy about whether "intelligence" and "personality" are valid and quantifiable constructs; (4) the Minnesota researchers failed to publish life history information for the twins under study, and then denied independent reviewers access to raw data

and other unpublished information (*9*); and (5) there was likely researcher bias in favor of genetic explanations of the data.

Perhaps the most important problem is the original TRA researchers' failure to control for several critical environmental influences shared by MZA pairs, including even those extremely rare cases in which studied MZA pairs were separated at or near birth and grew up without knowing each other (*21*). Environmental influences shared by even perfectly separated MZA pairs include common age, common sex, common ethnicity, common physical appearance, common socioeconomic class, common culture, and common prenatal environment. Reared-apart twin pairs (as well as genetically unrelated people born at the same time) are subject to the social and historical influences of their birth cohort. As behavior genetic researcher Richard Rose once observed, "Were one to capitalize on cohort effects by sampling [genetically] unrelated but age-matched pairs, born, say, over a half-century period, the observed similarities in interests, habits, and attitudes might, indeed, be 'astonishing'"(*24*).

Thus, for reasons unrelated to heredity, we should expect to find a much higher "video game playing behavior" correlation in the United States among pairs of randomly selected 11-year-old middle-class Caucasian boys than we would expect to find among randomly selected pairs drawn from the entire 11-100-year-old male and female population of the United States *(16)*. This example illustrates one of the central fallacies of TRA studies. (Bouchard and colleagues (*25*) were the first TRA researchers to address age and sex confounds, but their adjustments were inadequate to deal with this problem.)

On purely environmental grounds, therefore, we would expect MZA pairs to correlate well above zero for psychological and behavioral traits. This means that the appropriate control group with which to compare MZA correlations would be a group consisting of *genetically*

unrelated pairs of strangers matched on the environmental influences experienced by MZA pairs (*9,16*). Most previous MZA studies, however, mistakenly used reared-together MZs as controls. Thus we see that, like the twin method, studies of twins reared-apart are subject to their own set of potentially invalidating environmental confounds.

Adoption Studies

Although twin research has been called the "'Rosetta Stone' of behavior genetics" (*26*), adoption studies are also used to assess the role of genetic influences on various traits and disorders. Adoption studies investigate people who receive the genes of their birthparents, but are reared in the family environment of people with whom they share no genetic relationship. Adoption research has focused on IQ and personality, and has been extended to psychiatric disorders such as schizophrenia, attention-deficit/hyperactivity disorder, and bipolar disorder. In particular, the Danish-American adoption studies (*27,28*) are widely cited as having established schizophrenia as a genetic disorder. Several commentators, however, have pointed to a number of crucial errors and biases in these studies (*9,10,29-32*).

Like family and twin studies, adoption studies are subject to their own set of environmental confounds and biases, casting doubt on their ability to separate the influences of nature and nurture (*9,10,16*). Included among these biases are late separation (and accompanying attachment disturbance), range restriction (*33*), whether adoptees and family members are representative of their respective populations (*7,34*), and the selective placement of adoptees.

Tienari and colleagues (*35*) investigated the adoptive families of Finnish index adoptees whose biological mothers were diagnosed with schizophrenia, and the adoptive families of control adoptees, whose biological mothers were not so diagnosed. Although 7% of the index

adoptees became psychotic in contrast to 1% of the control adoptees (which can be accounted for by selective placement factors, see below), Tienari and colleagues' analysis of the families of index adoptees diagnosed as psychotic reveals that 6 of 43 (14%) adoptees who were reared in "seriously disturbed adoptive families" were diagnosed psychotic. In striking contrast, none (0%) of the 48 index adoptees reared in "healthy or mildly disturbed adoptive families" was diagnosed psychotic (*35*). Moreover, 19 of the 32 adoptees (60%; index and control combined) raised in "severe disturbance" Finnish adoptive families developed a major psychological dysfunction (which included "character disorders," "borderline syndrome," and "psychotic"), whereas none of the 15 adoptees (0%) reared in Finnish "healthy" adoptive families developed such a dysfunction (*19,35*).

Looking more closely at the "no selective placement assumption" of adoption studies, psychiatric adoption researchers must assume that factors relating to the adoption process did not lead agencies to place certain groups of adoptees into environments contributing to a higher rate of the disorder in question. However, the evidence suggests that adoption studies of schizophrenia were confounded by environmental factors on the basis of the perceived "hereditary taint" of adoptees with a biological family history of mental disorders placed in early-to-mid 20th century Europe (*9,10,32*).

For example, Finland (like Denmark) had a long history of eugenics-inspired legislation aimed at curbing the reproduction of "hereditarily tainted" people (*9,36,37*). The Finnish government created a commission in 1926 to study the possibility of sterilizing people seen as "mentally retarded," "mentally ill," or epileptic. In 1935, the Finnish parliament passed the Sterilization Act, which allowed the compulsory eugenic sterilization of "idiots," "imbeciles," and the "insane," which included people diagnosed with schizophrenia and manic-depression. In

fact, compulsory eugenic sterilization was not abolished in Finland until 1970. The Finnish adoptees Tienari and colleagues studied were born between 1927 and 1979, and were therefore placed in an era in which the biological offspring of people diagnosed with a psychotic disorder were seen as undesirable "tainted" adoptees. Clearly, few prospective Finnish adoptive parents would have wanted to adopt such a child.

Selective placement has also been identified as a confounding factor in IQ adoption research, since adoption agencies frequently attempt to match adoptees and adoptive families for socioeconomic status, in addition matching on the basis of the assumed intelligence potential of the adoptee (*22,38*).

Thus, despite adoption studies' theoretical potential to disentangle genetic and environmental influences, it is likely that environmental factors have confounded the original researchers' conclusions in favor of genetics.

Conclusions

We have suggested that the body of quantitative genetic research in psychiatry and psychology is contaminated by environmental factors. In addition, these studies contain other types of biases *(9,10).* Although the relatives in these studies frequently manifest traits and disorders in patterns predicted by genetic theories, these patterns usually match the predictions made by theories of *non*-genetic causation as well *(16).* Thus, it is likely that family, twin, and adoption studies have been unable to disentangle the potential roles of genetic and environmental influences on traits and disorders, and that the researchers who typically perform this research have greatly underestimated the potential role of environmental confounds. It has been left to critics to focus on these problems, yet their voices have been lost in the vast literature produced in the past few decades in favor of important genetic influences on these traits.

We call on researchers in psychiatry and psychology, and other behavioral scientists, to embark on a serious reassessment of the validity of twin and adoption studies in light of the failure of gene finding efforts. In 1994, behavior geneticists Robert Plomin, Michael Owen, and Peter McGuffin wrote in *Science* of a genetic variant associated with Alzheimer's Disease, and continued, "We predict that QTL [quantitative trait loci, or genes of various effect sizes] associations will soon be found for other complex human behaviors" (*39*). However, this prediction has turned out to be wrong (*1*,*16*). Three genetically-oriented Nobel prize winning researchers and their colleagues, in a 2010 "Policy Forum" article also appearing in *Science*, recognized the "frustrating lack of progress" in understanding the genetics of mental disorders *(40).*

A final issue to consider is the nature of human psychology, including mental disorders, and its relation to biochemical mechanisms. We suggest that human psychology is a higher form of consciousness that is mediated by social mediations such as concepts, artifacts, and social institutions. This distinctive kind of phenomenon, or order of reality, is not a mechanical process akin to an animal instinct. It is therefore unlikely that it is directly governed by a biochemical mechanism such as a hormone, enzyme, or neurotransmitter. Psychological disturbances are meaningful reactions to stressful situations, even if disorientation is present. The reductionist explanation of psychology eliminates meaningfulness, intentionality, and higher consciousness, It construes psychology as turned on and off by a mechanism akin to a light switch. This is particularly faulty when one realizes that the biochemical mechanisms that are invoked as explanatory constructs have extremely general effects. They do not affect single behaviors. Serotonin, for example, transmits nerve impulses on all the 100 billion axons to the thousands of synapses associated with *each* one of them. How could this general function make one anti-

social or depressed in particular? There are no particular ions on particular axons that are directly connected to depression or conduct disorder, wherein serotonin can target and specifically transmit or blocks those ions.

A more realistic view of what human psychology is and how human biology affects it would help avoid the conundrums into which genetic research has fallen (*41*).

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