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The "Missing Heritability" of Psychiatric Disorders: Elusive Genes or Non-Existent Genes?

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The psychiatric genetics field is currently undergoing a crisis due to the decades-long failure to uncover the genes believed to cause the major psychiatric disorders. Since 2009, leading researchers have explained these negative results on the basis of the "missing heritability" argument, which holds that more effective research methods must be developed to uncover presumed missing genes. According to the author, problems with the missing heritability argument include genetic determinist beliefs, a reliance on twin research, the use of heritability estimates, and the failure to seriously consider the possibility that presumed genes do not exist. The author concludes that decades of negative results support a finding that genes for the major psychiatric disorders do not appear to exist, and that research attention should be directed away from attempts to uncover "missing heritability" and toward environmental factors and a reassessment of previous genetic interpretations of psychiatric family, twin, and adoption studies.

> Scientific attention always comes at a certain cost: the decision to investigate one area is simultaneously a decision to ignore another...
>
> —Robert Proctor,
> *The Cancer Wars* (Proctor, 1995, p. 243)

> Why is it that the molecular genetics of schizophrenia has seemingly been forever poised on the brink of great breakthroughs?
>
> —Molecular genetic researcher
> David Goldman in the August 2011 edition of the
> *American Journal of Psychiatry* (Goldman, 2011, p. 880)

THE MISSING HERITABILITY ARGUMENT

At the dawn of the 21st century, genetic researcher Neil Risch (2000, p. 847) expressed concern that "human genetics is now at a critical juncture" because the methods used in molecular genetics to identify the genes "underlying rare Mendelian syndromes are failing to find the numerous genes causing more common, familial, non-Mendelian diseases." At that time the Human Genome Project (HGP) was nearing completion, and Risch saw "new opportunities... for unraveling the complex genetic basis of non-Mendelian disorders based on large-scale genome-wide studies" (Risch, 2000, p. 847). Other researchers (e.g., Hyman, 2000) expected the completion of the HGP to speed up the identification of genes for major psychiatric disorders such as schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), depression, borderline personality disorder, autism, obsessive-compulsive disorder, and anxiety disorders. Around the same time, psychiatric genetic researcher Lynn DeLisi (2000) wrote that her field "appears to be at a crossroads or crisis" (p. 190). Psychiatric molecular genetic researchers view most psychiatric conditions as "multifactorial complex disorders," meaning that they view them as being caused by a complex interacting admixture of multiple genes and multiple environmental risk factors.

Over a decade later, human genetic research into "complex disorders"—and "multifactorial complex psychiatric disorders," in particular—finds itself at an even more critical juncture. A generation of psychiatric genetic researchers have tried, yet have failed, to identify

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the genes that they believe underlie the major psychiatric disorders (Collins et al., 2102; Gershon, Alliey-Rodriguez, & Liu, 2011; Joseph, 2011; Turkheimer, 2011a), even though many expected to discover these presumed genes by the end of the 1980s. Indeed, behavioral geneticist Robert Plomin and his colleagues (Plomin, DeFries, McClearn, & McGuffin, 2008) described the "euphoria of the 1980s," which led to disappointment after some initial claims "could not be replicated" (p. 206). A generation later, and despite great technological progress, the story remains pretty much the same (Haworth & Plomin, 2010; Nisbett et al., 2012; Turkheimer, 2011a, 2011b). At the same time, some psychiatric genetic researchers argue that replicated gene discoveries have been made for some disorders (e.g., Craddock & Owen, 2010). Flint, Greenspan, and Kendler, in their 2010 book on genetic research in psychiatry, mentioned the *ALDH*2 gene, which appears to influence the risk for alcoholism. They cited this example to counter the possibility that their readers had heard "that 'science has not yet found a gene that conclusively influences risk for psychiatric disorder'" (Flint, Greenspan, & Kendler, 2010, p. 58).

Nevertheless, the 100-year-old field of psychiatric genetics finds itself in a crisis due to the continuing failure to find the genes that the field has said along must be there. Molecular genetic research into psychiatric disorders dates back to at least 1969, which saw the publication of a study of "manic-depressive disease" (now known as bipolar disorder; Reich, Clayton, & Winokur, 1969). Thus, psychiatric molecular genetic research has a 43-year history. It also has a 43-year history of subsequently unsubstantiated gene finding claims for psychiatric disorders, as Reich and colleagues concluded, "Affective disorder in which mania occurs is probably linked on the X chromosome. . . .This finding clarifies some aspects of transmission. It also *proves* a genetic factor in manic-depressive disease" (Reich et al., 1969, p. 1367, emphasis added).

The "missing heritability" interpretation of negative results has been developed in the context of the ongoing failure to uncover most of the genes presumed to underlie common non-Mendelian medical conditions, and, with possible rare exceptions, all of the genes presumed to underlie the major psychiatric disorders. In the words of Francis Collins, current Director of the U.S. National Institutes of Health, and former Director of the National Center for Human Genome Research, missing heritability "is the big topic in the genetics of common disease right now" (quoted in Maher, 2008, p. 18). As I write this, the topic had grown even bigger (Nisbett et al., 2012; Plomin, 2011; Turkheimer, 2011a; Zuk et al., 2012).

According to one group of prominent researchers, heritability is "missing" due to the finding that genome-wide association (GWA) studies "have explained relatively little of the heritability of most complex traits, and the variants identified through these studies have small effects" (Eichler et al., 2010, p. 446). Genome-wide association studies, which have been used extensively since 2005, involve rapidly scanning markers across the genomes of many people to find common genetic variants associated with particular diseases or traits. In the popular literature the word "gene" is shorthand for genetic variant, which refers to differing variations of a gene found among individuals or populations. GWA studies focus on common variants, which refer to variants found in 5% or more of the population. The dominant view in human genetics, and the rationale for GWA studies, has been that common variants underlie common diseases, which is known as the "common disease, common variant hypothesis." Given the lack of findings from GWA studies, some now propose that research attention should focus on identifying *rare* variants which might underlie medical and psychiatric disorders. Rare variants are defined as variants found in less than 0.5% of the population (Manolio et al., 2009). It is important to remember that even if a variant is associated with a trait or disease, it does not necessarily mean that the variant *causes* the trait or disease. "Association" and "correlation" are synonymous concepts in this context, and it is axiomatic that correlation does not equal cause.

A large group of genetic researchers in medicine, including Francis Collins and many other prominent investigators, published a 2009 article in *Nature* entitled, "Finding the Missing Heritability" (Manolio et al., 2009). This article has since served as a reference point for molecular genetic researchers, including those in psychiatry, who have attempted to come to terms with years of negative results. Manolio and colleagues recognized that "the identification of genetic variants contributing to . . . 'complex diseases' has been slow and arduous" (p. 747), and they saw the few positive findings of variants for non-psychiatric medical conditions as explaining "only a small proportion of the estimated heritability" (p. 748). Turning to psychiatric disorders, the authors recognized "the lack of variants detected so far for some neuropsychiatric conditions" (p. 748). They had no doubt that the problem is missing heritability, as opposed to non-existent heritability, because "a substantial proportion of individual differences in disease susceptibility is known to be due to genetic factors" (p. 748). Finding missing heritability is important, they wrote, in order to aid in "better prevention, diagnosis, and treatment of disease" (p. 748). Manolio et al. saw missing heritability as the " 'dark matter' of genome-wide association in the sense that one is sure it exists, can detect its influence, but simply cannot 'see' it (yet)" (p. 748).

Manolio and colleagues' (2009) position that they are "sure" that genes exist and await discovery was based on the results of family studies, which, at least as they pertain to psychiatric disorders and variation in psychological

traits such as IQ and personality, are widely recognized as being unable to disentangle the potential roles of genes and environment (Bouchard & McGue, 2003; Faraone, Tsuang, & Tsuang, 1999; Plomin et al., 2008). Strikingly, the authors did not mention twin studies, which human genetic researchers believe *are* able to disentangle these influences (see below for an analysis of this claim). Manolio and colleagues believed that current heritability estimates are roughly accurate, and suggested several research strategies to uncover the genetic "dark matter" they are sure exists. They saw this as an important task that will "illuminate the genetics of complex diseases and enhance its potential to enable effective disease prevention or treatment" (p. 747). From the "missing heritability" standpoint, genetic variants that cause disorders have found good hiding places that require better methods and larger sample sizes to flush them out.

Challenging the Missing Heritability Position

The missing heritability interpretation of GWA results was challenged by Jonathan Latham and Allison Wilson (2010, para. 4), who concluded that the "genetics revolution . . . is in big trouble" due to the inability of GWA studies, with a few notable exceptions, to find important disease genes. "Instead of invoking missing genes," wrote Latham and Wilson, if "we take the GWA studies at face value, then apart from the exceptions . . . genetic predispositions as significant factors in the prevalence of common diseases are refuted" (2010, para. 8). They concluded, "The dearth of disease-causing genes is without question a scientific discovery of tremendous significance" (Latham & Wilson, 2010, para. 17).

Latham and Wilson (2010) pointed to the "plentiful evidence" that environmental factors cause many common diseases, even as the popular press and science journals continue to focus on genetics and the need to keep looking for genes. Manolio and colleagues' (2009) position, as Latham and Wilson described it, was that "since heritability measurements suggest that genes for disease must exist, they must be hiding under some as-yet-unturned genetic rock" (Latham & Wilson, 2010, para. 25).

Addressing the larger picture, Latham and Wilson (2010) wrote that although the "evidence for genetic causation has always been weak" because it is based mainly on "disputed" studies of twins and other relatives, it is "necessary to understand the role that genetic determinism plays in consolidating the social order" (para. 37). Writing mainly about genetic research in medicine, but with much relevance to psychiatry, they identified groups in society with an interest in promoting genetic determinist theories of disease causation. Among these they included politicians and corporations "because it substantially reduces their responsibility for people's ill health," and medical researchers, who in turn "can raise research dollars with relative ease" with the help of these politicians and corporations (Latham & Wilson, 2010, para. 37).

"The history of scientific refutation," wrote Latham and Wilson (2010), "is that adherents of established theories construct ever more elaborate or unlikely explanations to fend off their critics" (para. 41). We will soon see how this has been carried out in the area of twin research.

Currently, the missing heritability position has provided psychiatric and behavioral genetic researchers with a ready-made explanation for their continuing failure to discover genes. To cite one example, a group of researchers looking for the genes that they believe underlie human personality traits explained their negative results on the basis of "missing heritability," as opposed to concluding that their findings might indicate that no such genes exist. Downplaying their negative findings, the researchers predicted that genes will be found in the future on the basis of "newer technologies . . . and novel statistical approaches combined with larger samples and meta-analyses . . . " (Verweij et al., 2010, p. 314).

Moving Toward the Status of a "Null Field"?

Future historians will assess the current "missing heritability" stage of psychiatric genetic research in one of three main ways. The first would be that researchers were able to improve their methods and uncover genes playing an important role in causing mental disorders. The second would be that some genes are eventually identified, but society did not consider this an important discovery and chose to focus on improving social, family, and other environmental conditions. The third outcome would be that no genes are ever found, most likely because they do not exist, and psychiatric genetics was declared a "null field" and was disbanded.

As John Ioannidis (2005) defined it, a null field is an area of research "with absolutely no yield of true scientific information" (p. 700). For example, a branch of psychological research dedicated to studying parenting techniques that cause Huntington's Disease would eventually turn out to be a null field.

If we view psychiatric genetics as a potential null field, we would expect, as Ioannidis (2005) put it, "all observed effects sizes to vary by chance around the null in the absence of bias" (p. 700). The claimed effect sizes of a null field are "in fact the most accurate estimate of the net bias" existing in that field. Ioannidis recognized that researchers working in such a discipline "are likely to resist accepting that the whole field in which they have spent their careers is a 'null field.' " However, additional

evidence or lack of evidence "may lead eventually to the dismantling of a scientific field" (p. 700). In what may turn out to be a stage in this process, an open letter endorsed by 96 leading psychiatric genetic researchers urged potential funding sources not to "give up" on genome-wide association (GWA) studies of "psychiatric diseases" (Sullivan et al., 2012, p. 2).

The main purpose of the present review is to argue that the combination of negative gene finding attempts plus previously documented problems with "quantitative genetic" studies of families, twins, and adoptees should lead to a different set of conclusions than those currently put forward by psychiatric molecular genetic researchers and their supporters. A detailed critical evaluation of this body of research is beyond the scope of this review. (For those interested in such an evaluation, see Joseph, 2004, 2006, 2010a, and the references therein.)

In the following pages I discuss four key problems with the missing heritability position, and in the process provide evidence that psychiatric genetics may indeed be heading toward an eventual designation as a null field in science.

FOUR KEY PROBLEMS WITH THE MISSING HERITABILITY ARGUMENT

Four major problem areas in psychiatric molecular genetic research in general—and with the missing heritability concept in particular—are as follows:

1. It is based on the genetic determinist belief that we must identify genes in order to understand, treat (as opposed to simply removing symptoms), and prevent psychiatric disorders;
2. Although the claim that psychiatric disorders have an important genetic component is based mainly on twin studies (and to a lesser degree, family and adoption studies), obvious and invalidating environmental confounds in twin research are usually denied or overlooked;
3. It is based on the misused and frequently misunderstood concept of heritability. Heritability estimates were designed to predict the outcome of selective breeding programs. They are *not* an indicator of the relative influences of genes and environment. Moreover, most heritability calculations are derived from environmentally confounded (and otherwise biased) research methods; and
4. Researchers rarely give serious consideration to the possibility that years of negative gene finding results indicate that genes for psychiatric disorders do not exist.

Let us now examine each of these four problem areas.

Genetic Determinism

Evolutionary biologist Richard Lewontin (2009) has described genetic determinism as the "assumption that all-important variations in basic physiological and developmental processes are the direct result of genetic variation . . . " (para. 2). In its extreme form, genetic determinists claim that our personalities are pretty much set for us at birth. "The older one gets," wrote Nobel Laureate James D. Watson (2003), "the more most of us conclude that children come into the world with fixed personalities that are hard to ascribe to specific home or school environmental influences" (p. xxii). According to genetic researchers Hamer and Copeland (1998), "people are different because they have different genes that created different brains that formed different personalities" (p. 25).

Most genetic researchers believe that both genetic and environmental factors are necessary for the development of psychiatric disorders, and many believe that environmental factors are important. However, they usually emphasize the presumed genetic component while claiming that environmental factors are not well understood. At the same time, they tend to ignore or downplay research showing that adverse life experiences and events play a major role in the development of psychiatric disorders (for a review of some of this research, see Bentall, 2003; Read, Mosher, & Bentall, 2004). In the words of Michael Rutter (2006), a leading psychologist and behavioral geneticist who believes strongly in the importance of genetics and genetic research, "It is quite striking that behavioral genetics reviews usually totally ignore the findings on environmental influences. It is almost as if research by non-geneticists is irrelevant" (pp. 11–12). We could extend this observation to cover the allied and overlapping field of psychiatric genetics.

Because genetic determinism asserts the primacy of genetics and downplays or ignores the evidence implicating environmental factors, its adherents place great importance on heritability calculations and gene searches. In 2000, for example, National Institute of Mental Health chief Steven Hyman stressed the primary role of genetics, writing that "it is absolutely critical that we succeed in identifying and cloning genes that produce vulnerability to schizophrenia" (Hyman, 2000, p. 2).

However, it is not "critical" or even necessary to identify genes in order to fully understand, prevent, or treat psychiatric disorders. If we are able to identify and mitigate the environmental factors contributing to these disorders, many of which are known and documented, they would not show up regardless of any possible genetic predisposition. To cite two examples from medicine, polio has been largely eradicated by a vaccine developed without any knowledge of possible variations in people's genetic susceptibility to be stricken with polio, and pellagra is prevented by enriching foods with

the proper nutrients. As I write this, a Google search for the term "genetics of polio" yields 77 results, and I obtained only two results for the term "genetics of pellagra." On the other hand, a search for the term "genetics of schizophrenia" yields 158,000 results, "genetics of autism" yields 295,000, "genetics of bipolar disorder" yields 112,000, "genetics of depression" yields 67,000, and "genetics of ADHD" yields 37,000 results.

Reliance on Twin Research

Turning to problem area number two, it is a troubling development in science, particularly in light of decades of negative findings, that molecular genetic researchers do not appear to have made a serious critical evaluation of twin research. Instead, they tend to rely on the authoritative authors of secondary sources who usually attempt to validate twin research both theoretically and empirically. In most cases, these authors of secondary sources have staked a large part of their professional careers on the validity of twin research (examples of such authors include Gottesman, 1991; Kendler, 1983; Plomin et al., 2008). Yet, most psychiatric molecular genetic study publications begin with a statement to the effect that the genetic basis of the disorder has been firmly established on the basis of family, twin, and (sometimes) adoption studies, thus providing the rationale of their investigations.

Because family studies are widely recognized as being unable to disentangle the potential role of genetic and environmental factors, and because adoption studies are problematic and relatively few have been performed (Joseph 2004, 2006, 2010a),[1] studies of reared-together twins constitute the main evidence cited in support of a genetic basis for the major psychiatric disorders and many non-psychiatric medical conditions.

The chief psychiatric research method using twins is the *twin method*, which compares the trait resemblance of reared-together MZ twin pairs (also known as monozygotic, or identical, who share 100% genetic similarity), versus the trait resemblance of reared-together same-sex DZ twin pairs (also known as dizygotic, or fraternal, who average a 50% genetic similarity). For psychiatric disorders, trait resemblance is measured with correlations or concordance rates. Researchers count twin pairs as *concordant* when both members are diagnosed with the same disorder and *discordant* when they diagnose only one member of the pair. Based on the assumption that the childhood and adult environments of MZ and DZ pairs are comparable, known as the *equal environment assumption* (or "EEA"), twin researchers conclude that genetic factors explain the usual finding that MZ pairs are significantly more concordant than DZ pairs for the disorder in question.

However, critics have argued that the equal environment assumption is not correct, and that genetic interpretations of twin method data are confounded by the finding that MZ pairs experience much more similar environments than DZ pairs. These commentators have also highlighted many other theoretical and methodological twin method problem areas (critical analyses of the twin method and the EEA include, Boyle, 2002; Charney, 2008a, 2008b; Jackson, 1960; Joseph, 1998, 2000, 2004, 2006, 2010a; Kamin, 1974; Lewontin, Rose, & Kamin, 1984). Problem areas in psychiatric twin studies, which have been carried out since the 1920s, have included the acceptance of unsupported theoretical assumptions, the lack of an adequate and consistent definition of the trait or disorder under study, the questionable reliability and validity of the psychiatric disorder under study, the use of non-blinded diagnoses, the use of diagnoses that were made on the basis of inadequate information, the use of unreliable methods of zygosity determination (whether a pair is MZ or DZ), that hospital psychiatrists might have given MZ twins similar diagnoses because they were influenced by their knowledge of the twins' common genetic heritage, the unnecessary use of age-correction formulas, the use of non-representative sample populations, small sample sizes, the lack of an adequate description of the methods, and investigator bias in favor of genetic conclusions. More recently, Evan Charney has shown that many of the biological and genetic assumptions underlying twin research may not be true (Charney, in press).

MZ pairs also experience a much closer emotional bond than DZ pairs, and sometimes experience "identity confusion" (Jackson, 1960). In his 1967 schizophrenia twin study, Einar Kringlen found that over 90% of the MZ pairs had experienced "identity confusion" in childhood, compared to only 10% of the DZ pairs. A full 72% of MZs were "brought up as a unit," but only 19% of the DZs had been brought up this way. In his "global evaluation of twin closeness," Kringlen found that 65% of the MZs pairs had experienced an "extremely strong" level of closeness, which was true for only 19% of the DZ pairs (Kringlen, 1967, Table 46, p. 115). He concluded that these results showed "the same differences as

[1]Psychiatric genetic adoption studies of schizophrenia, bipolar disorder, ADHD, and other diagnoses have their own set of potentially invalidating problems. Among these are included questionable methods of defining diagnoses and counting and comparing relative groups, a lack of case history information on adoptees and their families, the use of inappropriate statistical procedures, the use of late-separated adoptees and the failure to give sufficient consideration to the psychologically harmful impact of the rupture of attachment bonds, the failure to assess the role of important environmental variables, non-blinded diagnostic procedures, reaching conclusions in favor of genetics on the basis of statistically non-significant findings, and the potentially confounding effect of agencies' selective placement of adoptees on the basis of their birthparents' socioeconomic and perceived genetic status. (Critical analyses of psychiatric adoption research can be found in Boyle, 2002; Joseph, 2004, 2006; Pam, 1995; Lidz, 1976; Lidz & Blatt, 1983.)

previous authors have shown'' and that ''monozygotic pairs are closer . . . than dizygotic pairs and that monozygotics receive a more similar social influence than dizygotics'' (pp. 114–116). To the best of my knowledge, Kringlen's 1967 findings have never been discussed in any publication produced by the fields of psychiatric genetics or behavioral genetics.

Most contemporary twin researchers recognize that MZ pairs experience much more similar environments than those experienced by DZ pairs (e.g., Bouchard & McGue, 2003; Faraone et al., 1999; Flint et al., 2010; Rutter, 2006; Smith et al., 2012). However, instead of concluding that the twin method is confounded by these environmental differences, they continue to uphold the validity of the twin method and EEA on the basis of several studies in which researchers ''tested'' the equal environment assumption and concluded that it is supported (for example, Kendler, 1983; Flint et al., 2010; see Joseph, 2006, chapter 9 for a critique of the ''EEA test'' literature, as well as some additional comments on the EEA test studies cited by Flint et al. in the following sections).

The Achilles' Heel of the Twin Method

For the most part, twin researchers' defense of the validly of the equal environment assumption and the twin method *comes down to one main argument*. This argument states that, although it is true that MZ pairs experience much more similar environments than DZ pairs (which would seem to invalidate the EEA), the twin method and the EEA are valid on the basis of MZs having ''created'' or ''elicited'' more similar environments for themselves because they are more genetically similar than DZ pairs. This has been called the ''twins create their own environment theory'' (Joseph, 1998).[2]

[2]Another argument twin researchers put forward in defense of the twin method is that, although MZ and DZ pairs do indeed experience different environments, critics must show that these environments differ on ''trait-relevant'' dimensions (for example, see Evans & Martin, 2000; Flint et al., 2010; Medland & Hatemi, 2009; Rowe, 1994; Smith et al., 2012). Even if this were shown, however, supporters of the ''twins create their own environment'' position could still argue in favor of the twin method's validity on the basis of MZ pairs having ''created'' more similar ''trait relevant'' environments for themselves (see Joseph, 2006, 2010a). Still another argument twin researchers and their supporters make is that, although there are problems with the twin method, the conclusion that it measures genetic influences is validated in the context of the larger picture of genetic research using other methods (such as family and adoption studies). For example, ''Because each method has its limitations, we cannot rely on either a single study or class of studies to draw conclusions about the effects of genes and environment on mental illness. Instead, from an examination of many studies we seek a pattern of converging evidence that consistently confirms genetic and/or environmental hypotheses about the familial transmission of a disorder'' (Faraone et al., 1999, p. 45). However, the validity of the twin method (and other research strategies) can only be determined by evaluating its merits when standing alone (Joseph, 2006; Lilienfeld, Lynn, & Lohr, 2003).

For example, twin researchers Scarr and Carter-Saltzman (1979) recognized that although the EEA is a ''critical assumption,'' the twin method is ''tenable'' because, ''Although MZ twins generally experience more similar environments, this fact seems to result from their genetic similarities and not to be a cause of exaggerated phenotypic resemblance'' (p. 541). Thus, for these authors the validity of the EEA and the twin method rests on the claim that MZ pairs create more similar environments for themselves on the basis of their greater genetic similarity.

Kenneth Kendler (1983) was one of the first twin researchers to attempt a detailed theoretical and empirical justification of the equal environment assumption, sixty years after the twin method was developed. In this 1983 article he, like others before him (as shown in the following sections), defended the validity of the EEA and the twin method on the basis of the ''twins create their own environment'' position. As Kendler (1983) argued, ''the available evidence suggests that the similarity of the social environment of monozygotic twins is the result of the behavioral similarity of the twins'' (p. 1416), and that the EEA and the twin method are valid because ''the similar phenotypes in monozygotic twins are caused by their genetic similarity'' (p. 1414). Nearly three decades later, Kendler's position remained pretty much the same (see Flint et al., 2010, pp. 25–33).

The centrality of the ''twins create their own environment'' position is seen in the following list of quotations from leading twin researchers and their supporters. These quotations span almost six decades, and establish how twin researchers' conclusions in favor of genetics flow from this position. Afterwards, I will show that this argument rests on the logical fallacy of circular reasoning. Although I have made this argument briefly elsewhere (Joseph, 2006, 2010a, 2010b), this is the first presentation of a large number of quotations demonstrating the longstanding and central nature of twin researchers' ''twins create their own environment'' argument.

According to the *Penguin Dictionary of Psychology*, circular reasoning is ''Empty reasoning in which the conclusion rests on an assumption whose validity is dependent on the conclusion'' (Reber, 1985, p. 123). Rips (2002) observed that in one form of the ''fallacy'' of circular reasoning, ''the arguer illicitly uses the conclusion itself . . . as a crucial piece of support, instead of justifying the conclusion on the basis of agreed-upon facts and reasonable inferences.'' Rips concluded, ''A convincing argument for conclusion c can't rest on the prior assumption that c, so something has gone seriously wrong with such an argument'' (Rips, 2002, p. 767). Figure 1 illustrates the circular reasoning we will see in the following passages from leading twin researchers and their supporters.

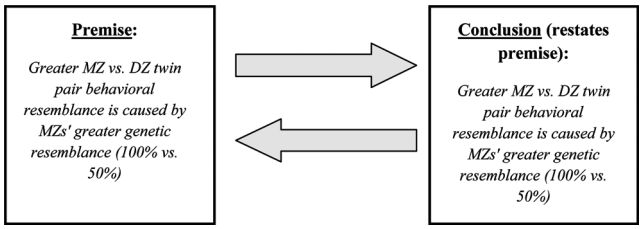

FIGURE 1 Circular reasoning used by twin researchers since the 1950s in support of the twin method.

The first example of a twin researcher invoking the circular "twins create their own environment" argument in defense of the twin method that I am aware of is psychiatric genetic researcher James Shields (1954). As we are about to see, this argument has been the main theoretical defense of genetic interpretations of twin method data ever since:

> In so far as binovular [DZ] twins are treated differently from one another and more differently than uniovular [MZ] twins, this is likely to be due, not so much to causes outside the twins as to innate differences in the needs of the binovular twins themselves, manifested by different patterns of behavior. (Shields, 1954, p. 240)

> The popular notion that the behavior patterns of one-egg [MZ] twins are alike chiefly because of unusual similarity in their early environments has yet to be substantiated. If confirmed, the argument would only strengthen rather than weaken any correctly formulated genetic theory. Psychodynamic concepts, too, are built on the premise that man is selective in respect to important aspects of his life experiences and so can be thought of as 'creating his own environment.' (Kallmann, 1958, p. 543)

> The assumption [has been] confirmed that the environment in which twins are brought up is generally much more alike for monozygotic than for dizygotic twins. . . . This similarity in the environment of monozygotic twins must naturally ultimately be due to their identical genotype . . . (Juel-Nielsen, 1965/1980, p. 26)

> Greater early differences in fraternal twins than in identical pairs due to hereditary factors will usually elicit more differential behavior toward each individual on the part of the parents, sibs, and friends. (Vandenberg, 1966, p. 330)

> The large difference between the concordance figures for MZ and DZ twins cannot be explained exclusively by the more similar environment of MZ twins. If MZ twins create a similar environment through their greater similarity, they do so because of the greater inherited similarity in their appearance and response modes. Thus, in a roundabout way, we still come back to the importance of heredity. (Zerbin-Rüdin, 1972, p. 48)

> Most probably, identical twins are treated more alike because they look and act more alike. (Loehlin & Nichols, 1976, p. 87)

> Although the similarity in environment might make MZ twins more similar, the similarity in behavior of MZ twins might *create* for themselves more similar environments. As recently reviewed . . . these two alternative hypotheses have been subject to empirical test in at least nine different studies. Consistently, these studies suggest that the environmental similarity of MZ twins is the *result* and not the cause of their behavioral similarity. (Kendler, 1987, p. 706, emphasis in original)

> Twins tend to elicit, select, seek out, or create very similar effective environments and, to that extent, the impact of these experiences is counted as genetic influence. (Bouchard, Lykken, McGue, Segal, & Tellegen, 1990, pp. 227–228)

> Do parental treatments mold twins' traits alike? Or do twins' similar genetic traits provoke a search for similar, mutually reinforcing environmental opportunities? In the tendency of MZ twins to receive similar treatments, or to seek them out, the arrow of causality is certainly bidirectional. (Rowe, 1994, p. 45)

> It appears that the more similar parental treatment of MZ vs. DZ twins occurs *in response to* the greater similarity of actions initiated by MZ pairs. . . . It seems . . . likely that the increased similarity in treatment of MZ twins is a consequence of their genetic identity and the more similar responses this elicits from the environment. (Evans & Martin, 2000, p. 78, emphasis in original)

> Two children who have similar genes are more likely to be similar in behavior, as the behavioral genetic studies showed. Therefore, they are more likely to be treated similarly by their parents. (Harris, 2006, p. 42)

> The EEA will not be violated if that [MZs eliciting more similar environments] is all that is occurring. That is because if the environments are being entirely driven by genes, it is reasonable to attribute the effects to genes provided, and only provided, that the environments that differ between MZ and DZ pairs do not have an effect on the trait being studied. (Rutter, 2006, pp. 41–42)

> Negative parenting is typically assumed to be the cause of children's antisocial behavior but in point of fact children play an important role in shaping their own environment, in this case by influencing the behavior of their parents. (Alford, Funk, & Hibbing, 2008, p. 322)

> A subtle, but important, issue is that identical twins might have more similar experiences than fraternal twins because identical twins are more similar genetically.

> Such differences between identical and fraternal twins in experience are not a violation of the equal environments assumption because the differences are not caused environmentally. (Plomin et al., 2008, p. 79)

> There is little argument that MZ twins are treated more similarly than DZ twins in certain aspects. . . . However, the central questions of the equal environment assumption (EEA) are whether these differences influence the specific trait under analysis and if these environmental differences are manifestations of the genetic similarity of MZ twins. (Medland & Hatemi, 2009, pp. 198–199)

> It is important to note that if MZ twins are treated more alike than DZ twins, it is most likely associated with their genetically based behavioral similarities. (Segal & Johnson, 2009, p. 82)

> In measuring similarity of treatment or social environments in twin studies, it is important to consider that MZ twins, because of their more similar behavior, can elicit more similar treatment. (Flint et al., 2010, p. 31)

> MZ environments are more similar than DZ environments . . . *because of the initial difference in genetic predispositions*. (Sturgis et al., 2010, p. 222, emphasis in original)

As previously mentioned, the first problem with the ''twins create their own environment'' position, as it has been articulated by twin researchers since the 1950s, is that it is a circular argument. We have seen Kendler (1983) put forward this position on the basis of the assumption that ''the similar phenotypes in monozygotic twins are caused by their genetic similarity'' (p. 1414). But this is precisely what twin researchers *conclude* from MZ-DZ comparisons. Thus, twin researchers' conclusion that MZ-DZ differences are explained by genetics is based on circularly assuming the very same thing, and as seen in Figure 1, Kendler and the twin researchers cited above simultaneously and circularly *assume and conclude* that ''the similar phenotypes in monozygotic twins are caused by their genetic similarity'' (Joseph, 2010a). In the aforementioned, we saw Zerbin-Rüdin (1972, p. 48) invoking the ''twins create their own environment'' argument, after which she concluded, ''in a roundabout way, we still come back to the importance of heredity.'' Apparently, she did not see the ironic circularity of the ''roundabout'' method she and other twin researchers have used for over five decades to argue that MZ-DZ correlational or concordance rate difference are caused by genetic factors.

The *Penguin Dictionary of Psychology* provides an example of the ''futility'' of circular reasoning. An instinct theorist was asked why all the sheep in an open field clustered together, and he answered, ''because all sheep have a gregarious instinct'' (Reber, 1985, p. 123). When he was asked how he knew that sheep had such an instinct, he replied, ''It's obvious, just look at them all clustered together in that open field'' (Reber, 1985, p. 123). In a similar fashion, when we ask twin researchers why we should accept their claim that the greater behavioral resemblance of MZ versus DZ pairs is caused by genetics they reply, in effect, ''It's obvious, just look at the way that MZ pairs are more similar genetically.''

A circular argument consists of ''using as evidence a fact which is authenticated by the very conclusion it supports,'' which ''gives us two unknowns so busy chasing each others' tails that neither has time to attach itself to reality'' (Pirie, 2006, p. 27). Yet twin researchers have centered their theoretical defense of the twin method on reasoning of this type.

On what basis, one might ask, do twin researchers assume that genetic factors cause the behavioral resemblance of MZ twins leading them to supposedly ''elicit'' more similar treatment? For the most part they base this claim, explicitly or implicitly, on their interpretations of the results of *previous twin studies* (Joseph, 2006). In other words, ''in a roundabout way'' genetic interpretations of previous twin studies are circularly used to validate genetic interpretations of subsequent twin studies. This is like arguing that a study whose authors conclude that phrenology is a legitimate science is valid because previous studies, also performed by phrenologists, found phrenology to be a legitimate science.

Other Sources of Evidence

Supporters of the ''twins create their own environment'' position might nevertheless argue that the genetic basis of twins' personalities and behavior has been established by other types of research, such as adoption studies, twins reared-apart (TRA) studies, and molecular genetic studies. TRA studies, however, which include the well-known Minnesota investigations (Bouchard et al., 1990), contain their own set of methodological problems, biases, and environmental confounds (Joseph, 2001, 2004, 2010a; Kamin, 1974; Lewontin et al., 1984). According to the psychologist Robert Sternberg (2007), due to the role of ''confounding variables'' in ''the method of separated identical twins . . . effects that may appear to be a result of genetic factors may, in fact, not be a result of such factors'' (p. 292).

Adoption studies of personality. Adoption research into personality presents a more interesting situation. The few studies that have been carried out suffer from a host of problems that could lead to spurious correlations supporting genetic theories of personality. These problems include range restriction, selective placement, late separation, attachment disturbance, the representativeness of

the parents, and the questionable nature of "personality" as a measureable and quantifiable construct (Joseph, 2010a). Leading behavioral genetic researchers have themselves highlighted and discussed some of these problems (see Bouchard & McGue, 2003; Plomin et al., 2008; Rutter, 2006).

Nevertheless, in a carefully designed 1998 Colorado Adoption Project longitudinal adoption study of personality (Plomin, Corley, Caspi, Fulker, & DeFries, 1998), the investigators found that the mean personality scale correlation between birthparents and their 245 adopted-away biological offspring—a relationship that they considered "the most powerful adoption design for estimating genetic influence," which "directly indexes genetic influence" (p. 211)—was *zero* (a non-significant .01 correlation). Thus, on the basis of this study we could conclude that genetic factors play no role in personality formation (which completely overturns the claims made by the Minnesota TRA researchers and their supporters). Interestingly, the results of this adoption study, which was performed by some of the world's leading behavioral genetic researchers, are rarely mentioned by the proponents of the missing heritability position, by psychiatric geneticists, by behavioral geneticists, by the authors of scholarly reviews, by journalists, by psychology textbook authors, or by the authors of books appearing since 1998 popularizing genetic research (examples of the latter include, Harris, 2006; Pinker, 2002; Rutter, 2006).

Molecular genetic research of personality. Turning to the molecular genetics arena, studies searching for genes underlying personality dimensions and traits have come up empty (Munafo & Flint, 2011), which we can interpret as additional evidence that twins' personalities are not determined by genetic factors. In a 2010 GWA study, the investigators recognized their "failure to find common genetic variants underlying Cloninger's psychobiological temperament scales," which "accords with previous studies that have failed to find common variants underlying Eysenck's Neuroticism and the Big Five personality scales" (Verweij et al., 2010, p. 315). A year earlier, a pair of investigators wrote that molecular genetic research into personality traits "has evidently not escaped the conundrum of non-replication that continues to plague the genetics of complex human phenotypes" (Ebstein & Israel, 2009, p. 240).

Environmental Factors Could Still Be the Only Cause of Psychiatric Disorders

A second problem with the "twins create their own environment" argument is that, even if twins do indeed create more similar environments for themselves because of their greater genetic similarity, MZ pairs could still show much higher concordance for psychiatric disorders than DZ pairs for purely environmental reasons. As political scientist Evan Charney (2008b) pointed out, in one of countless such possible scenarios, cranky children are more likely to be beaten and otherwise mistreated by their parents compared with non-cranky children. Clearly, abuse of this type could, for example, make it more likely that a child or adult will be subsequently diagnosed with depression. Yet apparently, twin researchers would count these cases of depression as genetically caused because the child's crankiness is genetic. Charney also suggested that according to twin researchers' logic, the effects on black slaves during slavery were "genetic" because the genetic trait of black skin color "created" or "elicited" their enslavement (Charney, 2008a, p. 337).

An Implausible Implied Family Environment

Still a third problem with the "twins create their own environment" argument is that it portrays children (twins) as behaving according to a genetic behavioral blueprint, yet somehow parents and other adults have themselves tossed aside the blueprint and are able to flexibly change their behavior and treatment of others on the basis of the twins' behavior and personalities (Joseph, 1998). In fact, adults' behavior should be far more unchangeable than children's because adults have experienced additional decades of behavior-molding family, peer, religious, and other socialization influences.

Thus, although the "twins create their own environment" argument should lead us to expect parents, teachers, and all other adults to be, behaviorally speaking, inflexible robots, twin researchers and their supporters portray them as being able to flexibly *change their behavior* on the basis of the twins' genetically-programmed behaviors and personalities. The prototypical "twins create their own environment" family environment is a strange and implausible one indeed: Genetically-programmed human children, meet your ever-so-flexible human parents.

Conclusions About the Twin Method

Few molecular genetic researchers or their supporters have written about the obvious pitfalls I have just outlined, other than some occasional statements that twin studies may have "overestimated heritability." Few have also noticed that twin researchers have based the validity of the twin method on the "futility" of circular arguments. Clearly, genetic interpretations of twin method data are confounded by environmental influences in much the same way as family studies are confounded by these influences.

Psychiatric genetic researchers and other proponents of "missing heritability" often ignore or misrepresent the arguments of twin method critics who express serious doubts about the equal environment assumption.

A recent example is found in a chapter on schizophrenia in *How Genes Influence Behavior* (Flint et al., 2010, pp. 26–30). Here, Jonathan Flint, head of the Psychiatric Genetics Group at the Wellcome Trust Centre for Human Genetics, Ralph Greenspan, and Kenneth Kendler (2010) ignored the numerous publications of critics of psychiatric twin research which include, for example, two books I have published on the topic (Joseph, 2004, 2006) and Don Jackson's seminal and never-refuted (1960) description of the numerous environmental confounds in schizophrenia twin research. Instead, they chose to focus on Leon Kamin's (1974) critique of I.Q. twin studies. Flint and colleagues (2010, p. 26) described Kamin as someone "who thinks that twin studies are not worth the paper they are printed on," who argues "in full blood" and "lambasts" twin researchers with his "diatribe," while aiming his "barbs" at the I.Q. test themselves. (Kamin's landmark critique finds additional support by the fact no genes for I.Q. or "general intelligence" have been found despite nearly two decades of sustained research; see Deary, 2012; Nisbett et al., 2012.)

As Flint et al. (2010, p. 26) saw it, the main problem with people like Kamin and his "scorn" for the twin method and the EEA is the "mixing of politics with science that always seems to accompany these studies." Thus, although psychiatric twin researchers more often choose to ignore all of the critics (Joseph, 2010a), Flint, Greenspan, and Kendler (2010) ignored most of them while launching an *ad hominem* attack against the author of a 36-year-old critique of *I.Q.* twin studies. The message and tone of their work is that anyone who dares to criticize twin research must be a hot-headed politically motivated outsider. This has been a common theme of such writings for decades and has served as a convenient method to ignore or dismiss the arguments of critics without having to answer their arguments directly. Flint and colleagues thereby continued the long running practice, described over 30 years ago by Stephen Jay Gould (1981) in *The Mismeasure of Man*, where genetic determinists "have often invoked the traditional prestige of science as objective knowledge, free from social and political taint. They portray themselves as purveyors of harsh truth and their opponents as sentimentalists, ideologues, and wishful thinkers" (p. 20).

Like other twin researchers, Flint and colleagues cited the body of equal environment assumption (EEA) test studies in support of the twin method (also discussed by Kendler, 1983). Most authors of the studies they referred to (but did not name), however, concluded in favor of the EEA on the basis of the circular "twins create their own environment" argument, or the "trait relevant" argument (discussed briefly in Footnote 2; see Joseph, 2006, chapter 9 for an in-depth critical review of the EEA test literature). The only EEA test study Flint and colleagues referred to by name was a 1977 investigation by Hugh Lytton, who observed parents and twins interacting in their homes. Flint et al. designated this "influential and sophisticated" study as a "Key Paper" evaluating the EEA (p. 30). The authors approvingly cited Lytton's conclusion that "parents respond to, rather than create, differences between the twins. . . ," after which they concluded, in a similarly circular fashion, "In measuring similarity of treatment or social environments in twin studies, it is important to consider that MZ twins, because of their more similar behavior, can elicit more similar treatment" (Flint et al., 2010, p. 31).[3] Contrary to the position of Flint et al. and most twin researchers, however, the only relevant question EEA test studies can answer is *whether*, not why, MZ pairs experience more similar environments than those experienced by DZ pairs.

Given the major problems in twin research, psychiatric molecular genetic researchers have made an enormous mistake in assuming that the twin method has provided convincing evidence that psychiatric disorders have a genetic basis. Latham and Wilson (2010) concluded that a reasonable interpretation of the failure to identify genes is that "heritability studies of twins are inherently mistaken or misinterpreted" (para. 32), and that the "dark matter" of missing heritability "becomes simply an artifact arising from overinterpretation of twin studies" (para. 35).

As the Nobel Prize winning chemist Wilhelm Ostwald wisely lectured his students in the early 20th century, "Among scientific articles there are to be found not a few wherein the logic and mathematics are faultless but which are for all that worthless, because the assumptions and hypotheses upon which the faultless logic and mathematics rest do not correspond to actuality" (Quoted in Hogben, 1933, p. 121).

I will end this brief critique of twin research with the words of psychologist Gerald McClearn, a longtime leading behavioral genetic researcher and co-author of the popular multi-edition textbook *Behavioral Genetics* (Plomin et al., 2008). After outlining several potential environmental biases in twin research, McClearn wrote

[3]Other problem areas in Lytton's (1977) study include (a) the small and very young twin sample, (b) potential bias because the raters were not blind to the status of the families, (c) poor inter-rater reliability, and (d) the unsupported claim that one can make a distinction between "child-initiated parental responses" and "parent-initiated actions." The raters observed twins and parents interacting in their homes, and in a comparable study Lytton referenced as a description of this method, he wrote, "It is obvious that the introduction of an observer in a home must affect relationships to some extent and produce some distortion of the 'normal' interaction" (Lytton, 1973, p. 8). Lytton also recognized that some parental behavior "may have been staged" (p. 8). For more details on problems in Lytton's frequently cited EEA test study, see Joseph, 2006, pp. 183–185.

the following in 1964, in an era when twin researchers wrote much more cautiously about their discipline:

> With these complicating features of the role of environment, the apparent ease of weighing the relative effects of nature and nurture by twin study *vanishes*. The greater disparity observed between fraternals than between identicals may be interpreted as due to heredity or environment or to some indeterminable combination of the two, depending on the predilections of the person making the interpretation. (McClearn, 1964, p. 196, emphasis added)

It is indeed the "predilection" of critics to interpret twin method results solely in terms of the environmental differences distinguishing the two types of twin pairs. Thus, advocates of a purely environmental (non-genetic) understanding of psychiatric disorders predict that psychiatric genetic research will find (1) familial clustering of the disorder, (2) higher MZ versus same-sex DZ concordance for the disorder, and (3) no replicated gene discoveries for the disorder (Joseph, 2005, 2006). The past 43 years of psychiatric genetic research has decisively confirmed these predictions.

The Heritability Problem

The third major problem with the missing heritability concept is the concept of heritability itself—missing or otherwise. According to Manolio and colleagues (2009), restating the common definition, heritability is "the portion of phenotypic variance in a population attributable to additive genetic factors" (p. 747). Researchers sometimes estimate heritability by doubling MZ-DZ twin correlational or concordance rate differences (Plomin et al., 2008). For example, if the MZ concordance rate for schizophrenia is 35%, and the DZ rate is 5%, researchers would estimate the heritability of schizophrenia as .60 (60%). Some researchers use more elaborate models and statistical procedures (using family, twin, and adoption data) which they believe are better able to assess the presumed genetic and environmental variances of psychiatric disorders, and heritability estimates are produced by these methods as well (Medland & Hatemi, 2009).

Although heritability estimates are widely used in psychiatry and psychology, the validity of the concept as used in these fields has been debated for decades. Critics have argued that heritability estimates (coefficients) *do not* approximate "how much" genes influence a trait or disorder. As behavioral geneticist Jerry Hirsch (e.g., Hirsch, 1997) repeatedly pointed out, a heritability estimate is not a "nature/nurture ratio" of the relative contributions of genes and environment.

Lewontin has shown that a "trait can have a heritability of 1.0 in a population at some time, yet could be completely altered in the future by a simple environmental change" (Lewontin, 1974, p. 400). An example is phenylketonuria (PKU), a genetic disorder of metabolism that causes mental retardation. Although PKU is a "highly heritable" single gene disorder, the administration of a low phenylalanine diet to the at-risk infant during a critical developmental period prevents PKU from causing mental retardation. Interestingly, in a society performing universal screening for the PKU gene, the heritability of the disorder would be *0.0*, because 100% of the *variation* of PKU in the population would be explained by infants' diets. Thus, heritability estimates can dramatically change even though susceptibility for the trait continues to be transmitted genetically (Joseph, 2004).

Because heritability coefficients were developed for animal breeders and tell us nothing about how much genes influence human behavior, heritability critic Douglas Wahlsten (1990) has written, "The only practical application of a heritability coefficient is to predict the results of a program of selective breeding" (p. 119). Wahlsten also pointed out that heritability calculations are based on the implausible assumption that heredity and environment do not interact.

Heritability Estimates in Psychiatry and the Behavioral Sciences Are Meaningless and Misleading

According to the biologist Steven Rose, the "heritability measure . . . except in the very specific context for which it was originally devised (agricultural breeding experiments) [is] rarely applicable, widely misunderstood and in most cases meaningless" (Rose, 1997, p. 293).

At least one leading researcher appears to have come around to the understanding that heritability estimates have little if any meaning. Behavioral geneticist Eric Turkheimer (2011a) wrote that "the relative magnitudes of the various components were supposed to tell us something about the importance of genetic and environmental causes underlying a trait, but they do not" (p. 598). He continued, "In the real world of humans, in a given context everything is heritable to some extent and environmental to some other extent, but the magnitudes of the proportions are variable from situation to situation, and have nothing whatsoever to do with the causal properties of genes and environment for the trait in question" (p. 598). Thus, heritability statistics tell us nothing about the potential magnitudes of genetic and environmental influences, and have "nothing whatsoever to do with the causal properties of genes" for a given trait. Elsewhere, Turkheimer (2011b) wrote that "Heritability is a distraction" (p. 239).

The irrelevance of heritability is seen in the example of autism. For many years, based mainly on the results

of three or four small twin studies, leading researchers variously described autism as showing "strong genetic determination" (Folstein & Rutter, 1977, p. 728), as being "under a high degree of genetic control" (Bailey et al., 1995, p. 63), as a "strongly genetic disorder" (Volkmar & Pauls, 2003, p. 1133), as having "very high heritability" (Rutter, 2006, p. 52), as being "one of the most heritable mental disorders" (Plomin et al., 2008, p. 227), and as a "highly heritable" syndrome (Kendler, 2010, p. 1293). Reviewers commonly estimate autism heritability at roughly .90, which is based on the estimate calculated by Bailey, Rutter, Gottesman and colleagues (Bailey et al., 1995) in their 1995 twin study, unambiguously titled "Autism as a Strongly Genetic Disorder: Evidence from a British Twin Study." Heritability estimates aside, however, the results of autism twin studies, like most other twin studies, can be explained completely by non-genetic factors, which in this case could be related to the more similar post- and *pre*-natal environments shared by MZ versus DZ pairs (Joseph, 2006, ch. 7). Like other major psychiatric disorders, researchers have been unable to discover any genes that cause autism (Miles, 2011).

In 2011, Joachim Hallmayer, Neil Risch, and their colleagues published a twin study and concluded that, although "genetic factors" continue to play "an important role," heritability is only 37%. They wrote that "a large proportion of the variance in liability can be explained by shared environmental factors" (Hallmayer et al., 2011, p. 1101). The online edition of this study, and its authors' conclusions, were widely reported in the American media in the summer of 2011.

But, even if heritability were a valid concept, in the context of human behavior and psychiatric disorders a heritability estimate is meaningless regardless of whether it is .99, .90, .37, .60, .02 or any other figure between 0.0 and 1.0. One reason is that, regardless of the presumed "strength" of the genetic component, identifying and eliminating the environmental trigger means that the disorder will disappear in the population. PKU is a good example of this.

Suppose a team of researchers conclusively proves that all children who eventually develop autism had eaten "Baby Delight Apricot Baby Food" between the ages of six and eight months, and that further investigation had shown that the ingestion of a rare chemical found only in this brand of apricot baby food by genetically predisposed children, during this sensitive developmental period, caused autism. The government immediately removes Baby Delight Apricot Baby Food from the market, confiscates existing inventories of the product, and issues warnings to parents. What would happen to the rate of new autism diagnoses a few years later? The answer is that it would be reduced to virtually zero. Thus, like PKU, presumed genetic factors appear to be "strong" (and difficult to change) only in the absence of (or denial of) identified environmental triggers. Paradoxically, heritability statistics and the genetic predisposition concept speak much more to what we *don't* know (or are unable or unwilling to change) about the environment than to what we *do* know about genetics (Joseph, 2004).

For most supporters of the "missing heritability" position, however, the validity of the heritability concept and the importance of precise heritability estimates are axiomatic (although at times they question whether particular estimates are accurate; see Zuk et al., 2012). Thus, the heritability estimates they rely on are an additional factor leading them astray and prevent them from giving more weight to the possibility that the genes they continue to look for do not in fact exist.

What Conclusions Can We Reach on the Basis of Gene Finding Failures?

The fourth and final "missing heritability" problem area is that few molecular genetic researchers in psychiatry appear willing to entertain the possibility that genes for the major psychiatric disorders do not exist, and have thus created this concept to explain negative results. However, the decades-long failure to discover causative genetic variants, coupled with the problems of family, twin, and adoption studies, means that the non-existence of genes for the major psychiatric disorders is a very real possibility.

Looking at the larger picture of molecular genetic research in all of medicine, we have seen Latham and Wilson (2010, para. 8) conclude that, apart from a handful of non-psychiatric medical disorders where some true associated gene variants may have been identified, "genetic predispositions as significant factors in the prevalence of common diseases are refuted." Although it is difficult to disprove a negative, one could reasonably conclude on the basis of 43 years of negative results that genetic predispositions for most or all of the major psychiatric disorders *appear* to be refuted. Given the track record of psychiatric molecular genetic research, all studies finding a significant association between a gene variant and a disorder should be considered false positive until proven otherwise.

While a few prominent researchers have stated publically, as have Elliot Gershon and colleagues (2011, p. 253), that "there is a sense of disappointment in the air," the majority of psychiatric genetic investigators continue to tell us in glowing terms that discoveries are coming soon (see my upcoming discussion of the Hudziak & Faraone paper). For example, Plomin and colleagues (2008) wrote of the "breathtaking pace of molecular genetics," and that "the behavioral sciences are at the dawn of a new era in which molecular genetic

techniques will revolutionize genetic research by identifying specific genes that contribute to genetic variance for complex dimensions and disorders" (p. 355). Currently, however, the failure to identify causative genetic variants is a defining feature of "multifactorial complex" psychiatric disorders (Joseph, 2006, 2010a).

Although most proponents of the missing heritability position fail to recognize it, a very plausible interpretation of the current state of affairs is that genes for the major psychiatric disorders have not been found because they do not exist. As we have seen Latham and Wilson (2010, para. 17) conclude, "The dearth of disease-causing genes is without question a scientific discovery of tremendous significance."

AN IMPLICIT ASSUMPTION OF GENETIC DETERMINISM IN PSYCHIATRY

An assumption of genetic determinism and psychiatric molecular genetic research is that the society in which it is undertaken is basically healthy and does not systematically cause great numbers of people to suffer psychological distress or manifest psychiatric disorders. In other words, the implicit assumption is: Healthy society—possibly containing some unhealthy family environments—unhealthy genes and brains.

But what if psychological theories are correct in pointing to the childhood family environment as playing a major role in a person's potential for healthy or unhealthy psychological functioning? There is also the larger sociological perspective, impacting these family environments both directly and indirectly, which emphasizes the psychologically harmful effects of racism, chronic stress, living in poverty, the oppression of women, social class status, discrimination against sexual minorities, diminished social networks (which may be a product of the culture and economic system), social inequality, corporate greed, advertising industry marketing campaigns, unemployment, and the consumer-driven individualist culture promoted in advanced industrial societies. As the psychologist Philip Cushman (1995) put it, the quest for corporate profit in the post-World War II era transformed the predominant American self into an "empty self," which is "striving for self-liberation through the compulsive purchase and consumption of goods, experiences, and celebrities" (p. 211). Clearly, an empty self is not an emotionally healthy self.

From these perspectives, in the words of sociologist Allan Horwitz (2002), "many of the fifty million Americans who meet the criteria for a mental disorder [each year] in community studies do not have valid disorders but suffer from distress that is rooted in stressful social arrangements and that will disappear when these situations improve" (p. 222).

Thus, an alternative to genetic determinists' implied "Healthy society—possibly containing some unhealthy family environments—unhealthy genes and brains" position could be characterized as "Unhealthy society—unhealthy families impacted by the unhealthy society—healthy genes and brains." From this perspective any possible genetic predisposition would be of little if any interest, and most of society's focus would be on improving social and family conditions, creating free universal healthcare, promoting equality, eradicating racism and other forms of oppression, greatly improving education, creating full employment, and so on.

If psychologically unhealthy family, social, and political arrangements are indeed the main factors underlying emotional problems and psychiatric disorders, then focusing on genetics and the brain are monumental diversions, in much the same way as the tobacco industry has preferred to focus on an alleged genetic predisposition to develop lung cancer and not on the carcinogenic effects of using tobacco (Chaufan, 2007; Proctor, 1995). Just like the tobacco industry, corporations and politicians that help create the social and environmental conditions causing an increase in mental health disorders and socially disapproved behavior (such as crime) have an interest in focusing attention away from the environment and towards people's bodies and brains. And, for the most part, it is they who fund research and dictate the research agenda.

Steven Rose (1997) spoke of the "urgent pressure to find explanations for the scale of social and personal distress in advanced industrial societies . . . explanations which shift the 'blame' for the problem away from the political realm an onto the individual" (p. 296). Indeed, genetic explanations of social and personal distress are one of the major ways that this shift has been accomplished.

AN ARTICLE EMBLEMATIC OF THE FAILURES OF PSYCHIATRIC GENETICS

Here I will focus on a single article that encapsulates the problems, biases, and fallacies of contemporary psychiatric molecular genetic research. The article was written by leading and widely published psychiatric genetic researchers James Hudziak and Stephen Faraone, and appeared in a 2010 edition of the prestigious *Journal of the American Academy of Child and Adolescent Psychiatry* (Hudziak & Faraone, 2010). It was written as an introduction to the papers and studies on genetic research of childhood psychiatric disorders that followed in the August, 2010 edition of the *Journal*.

Although Hudziak and Faraone's (2010) article was written in the context of 15 or so years of gene finding failures in the field of child and adolescent psychiatry,

this did not prevent the authors from describing their field in the most positive ways possible. They began with the opinion that "The Human Genome Project delivered much of what it promised" (p. 729). This point, however, is debatable (Latham & Wilson, 2010; Lewontin, 2009).

Hudziak and Faraone (2010) wrote that "advances in genomic medicine" have helped "debunk and demystify damaging misconceptions about why some children suffer with emotional behavioral illnesses and others do not" (p. 729). The unnamed "damaging misconceptions" apparently refer to ideas that childhood and adolescent psychiatric disorders are caused mainly by environmental conditions such as sexual, physical, or emotional abuse, mistreatment, abandonment, living in poverty, family violence, parental death, underfunded and unimaginative schools, and so on. But how has genomic medicine "debunked" this idea? By over 15 years of gene-finding failures? It would be more accurate to say that gene finding failures have *supported* these "misconceptions." And, even in the unlikely event that some predisposing genes are eventually discovered, psychologically harmful familial and social conditions would still comprise a major—and changeable—part of the environmental component of childhood and adolescent psychiatric disorders. As a group of mainstream psychiatric researchers found, in a carefully conducted study spanning 21 countries, "childhood adversities have strong associations with all classes of [psychiatric] disorders at all life-course stages in all groups of" the countries under study (Kessler et al., 2010, p. 378).

Child and adolescent psychiatrists, according to Hudziak and Faraone (2010), must be able to grasp the " 'new genetics' of complex disorders," which are "influenced by multiple or even thousands of genes interacting with environmental factors." They continued, "almost daily in newspapers, general magazines, and online, new genetic discoveries are announced" (p. 730). But why speculate about "thousands of genes" when the reality is that virtually *zero* genes have been discovered after 15 years of sustained research? And why refer positively to media reports of "new genetic discoveries" that almost always turn out to be false positive findings. As Faraone and colleagues recognized in 2008, "It is no secret that our field has published thousands of candidate gene association studies but few replicated findings" (Faraone, Smoller, Pato, Sullivan, & Tsuang, 2008, p. 1). The newspaper, magazine, and online accounts of these thousands of subsequently non-replicated "gene association studies" have served mainly to mislead the public and even the scientific community to believe that genes have been discovered. This clearly is not a positive development, as the authors seem to imply.

Leading psychiatric genetic researchers remain certain that genes await discovery because, from "twin, family, and adoption studies, we can learn whether or not an illness or trait is 'inherited' " (p.730). Yet, it has been shown here and elsewhere that family, twin, and adoption studies contain several potentially invalidating false assumptions and other biases (e.g., Joseph, 2000, 2004, 2006, 2010a).

Hudziak and Faraone (2010) wrote that "twin studies report that ADHD is influenced 60% to 90% by genes . . . " (p. 731). In fact, twin studies report nothing of the kind—twin *researchers* report that ADHD (attention-deficit/hyperactivity disorder) is influenced 60% to 90% by genes. This merely reflects their interpretations based on the validity of the equal environment assumption of the twin method and the heritability concept. Studies do not find and estimate heritability; *people* find and estimate heritability. Other people have interpreted these studies very differently.

A major problem is that genetic researchers, and even entire fields of science, repeat the same error of interpreting twin method results as evidence of genetics, every single time. As the eugenics critic Lancelot Hogben (1933) warned long ago, "there is a danger of concealing assumptions which have no factual basis behind an impressive façade of flawless algebra" (p. 121). An alternative interpretation of twin data holds that in most cases the twin method measures nothing other than the more similar environments MZ twin pairs experience when compared with DZ pairs, and decades of fruitless gene searches lend support to this position.

Hudziak and Faraone (2010) discussed previous successes in finding the genes that cause true genetic medical conditions such as Huntington's disease, and wrote that "it was hoped that similar discoveries . . . might be found for the child psychopathologies. Unfortunately, to date that has not been the case" (p. 731). But why is this result "unfortunate"? It is true that it is unfortunate for people making their living conducting gene searches, and for people whose careers are based on promoting genetic theories of psychiatric disorders. But for humanity in general, the failure to find genes is a welcome discovery and even a cause for celebration. If genetic factors play little or no role in the development of psychiatric disorders, we can then turn our full attention to the environmental conditions that cause them.

A conclusive finding that humans do not carry genes predisposing them to the major psychiatric disorders—and we appear to be approaching this point—would be one of the most positive recent developments in medical research.

For Hudziak and Faraone (2010), although "no causal DNA variant has been discovered using" genetic linkage analysis, "This has led to the important discovery that, if common variants exist, their genetic effect sizes must be very small" (p. 731). Thus, in rhetoric but not in reality, a gene finding *failure* is transformed into an "important discovery." An alternative interpretation,

unmentioned by the authors, is that researchers have discovered that no such genes exist.

The authors went on to discuss candidate gene studies that have helped us understand "the role of the environment in a child's outcome" (Hudziak & Faraone, 2010, p. 731). As evidence, they cited a study whose authors claimed to have shown that, when victimized by bullies, children with a particular gene variant, when compared with children who do not have the variant, "were at greater risk to have emotional problems at age 12 years" (p. 732). Hudziak and Faraone argued that candidate gene studies such as this one "could lead to public health interventions," such as "greater efforts to decrease bullying" (p. 732).

But didn't we already know, long before candidate gene studies, that bullying harmed children and that interventions aimed at reducing or preventing bullying would help alleviate the suffering of the victims and help prevent "childhood psychopathology"? Taking Hudziak and Faraone's (2010) example to its logical conclusion, we would need to perform a candidate gene study to know that hitting our heads with a ball peen hammer is harmful, because we must first determine whether genetically thinner skulls are more susceptible to hammer damage.

Simply put, we do not need molecular genetic research to teach us that bullying harms children any more than we need it to demonstrate the harmful psychological effects of, for example, sexual assault, war, unemployment, poverty, hunger, abandonment, domestic violence, alcoholism, racism, witnessing your spouse being murdered, and so on. But focusing on genes does serve as a diversion from noticing the harmful psychological effects of these and countless other adverse environmental conditions and events. It actually helps these harmful conditions to persist, which is the exact opposite result that Hudziak and Faraone (2010) claimed for molecular genetic research.

Although Hudziak and Faraone (2010) recognized the "failure of candidate gene studies to easily explain the heritability of childhood-onset disorders" (p. 732), we have seen them argue that these studies did provide useful information on where to focus public health interventions, such as an anti-bullying program. Thus paradoxically, it seems that the main finding of childhood and adolescent psychiatric molecular genetic research has been the identification of the environmental conditions—but not the presumed genes—that cause emotional damage and the appearance of psychiatric disorders.

By way of introducing the three ADHD GWA papers that followed, Hudziak and Faraone (2010) recognized that these studies "do not report genome-wide significant findings." However, they concluded that they "teach us a great deal about the promise and limitations of GWAS . . . " (p. 732). From another perspective, we could plausibly conclude that these studies "teach us" that it is very possible that genes for ADHD do not exist. "The discriminating reader might point out that none of the papers appearing in this issue of the *Journal* report positive GWAS findings," continued Hudziak and Faraone. "However, these negative findings send a valuable message: If common DNA variants cause child psychiatric disorders, their individual effects must be very small" (p. 732). Once again, the important and celebratory message these negative results send, when combined with 43 years of negative results in psychiatric genetic molecular genetic research, is that genes for the major psychiatric disorders are unlikely to exist.

After citing some claimed positive GWA results for true medical disorders, and a few positive findings for psychiatric disorders such as bipolar disorder and schizophrenia (which are likely to suffer the same fate as other such "findings" in the field over the past 43 years), Hudziak and Faraone (2010) speculated that positive results will emerge for child and adolescent psychiatric disorders once larger sample sizes are obtained: "We can only hope that funding agencies will provide similar funding levels to the investigation of child disorders so that similar sample sizes can be obtained" (p. 733). This helps explain the strenuous efforts of the authors, as well as of their colleagues, to present years of negative results and frustration in the most positive light possible. Clearly, as the world's leading psychiatric genetic investigators are well aware (Sullivan et al., 2012), funding agencies do not want to pour millions of dollars into projects that are unlikely to produce results.

After discussing whether future studies should focus more on rare as opposed to common genetic variants, Hudziak and Faraone (2010) wrote about their desire to study children's brain tissue to help better understand the causes of their psychiatric conditions: "Although there are brain tissue resource centers for adult-onset disorders, child psychiatric studies rarely have access to brain tissue" (p. 734). But there is nothing wrong with the brains of children diagnosed with psychiatric disorders such as ADHD, so there is no reason to study their brain tissue (Cohen & Leo, 2004). Moreover, in an extremely relevant question Thomas Szasz (1987) once posed in relation to schizophrenia, if it "is a brain disease, why do the scientists at the National Institute of *Mental Health*, rather than those at the National Institute of *Neurological Diseases*, tell us that?" (p. 50, emphasis in original).

Instead of studying brains and genes, societal and research attention should instead focus on the familial, social, political, and physical circumstances that cause children to act out, harm themselves and others, suffer low self-esteem, and experience sadness, loss, fear, heartache, loneliness, insecurity, and other negative emotions. Most genetic researchers pay little attention to these circumstances, and then lump together their differing "clinical manifestations" using the medical designation "child psychopathology."

Hudziak and Faraone (2010) ended their report as follows:

> Only 10 years ago, the first draft of the human genome was reported. In the intervening period, genetic research on developmental psychopathology has grown exponentially, as reflected not only in the number of published papers but also in the power of molecular genetic and statistical technologies. Although we are only in the infancy of our field, the pathway to discovery is clear. One can only imagine the incredible progress that will be made in the next decades. (p. 734)

Rather than emphasize the failure to uncover the genes that they believe underlie childhood psychiatric disorders such as ADHD and autism, and to recognize the possibility that they were wrong in believing that these genes exist, Hudziak and Faraone (2010) wrote of the "exponential" growth of genetic research and the "power" of their technologies. They implied that the "number of published papers" constitutes scientific progress, instead of emphasizing that the findings of these published papers—literally thousands of them as Faraone and colleagues had written in 2008—were not replicated. They also implied that failures are to be expected because "developmental psychopathology" molecular genetic research is only in its "infancy." Ten years earlier, Faraone and Biederman (2000), in a reply to my publication on genetics and ADHD (Joseph, 2000), had characterized ADHD molecular genetic research as being in its "infancy" while claiming, wrongly as it turned out, that "molecular genetic studies have already implicated several genes as mediating the susceptibility to ADHD" (Faraone & Biederman, 2000, p. 572).

Finally, Hudziak and Faraone (2010), again choosing to de-emphasize years of failure, claimed that the "pathway to discovery is clear," and that "incredible progress . . . will be made in the next decades" (p. 734). However, psychiatric geneticists have been saying this for over four decades. Rather than being in its infancy, 15 or so years of molecular genetic studies of childhood and adolescent psychiatric disorders has produced an important finding: The genetic basis of these disorders appears to have been refuted, and it is imperative that the scientific community re-examine genetic interpretations of the twin and adoption studies that compelled researchers to look for genes in the first place.

SUMMARY AND CONCLUSIONS

I have argued that the four main problem areas in the current "missing heritability" stage of psychiatric molecular genetic research are (1) the ideology of genetic determinism; (2) a reliance on twin studies, which are unable to disentangle the potential roles of genes and environment; (3) a reliance on heritability statistics; and (4) the failure to recognize that decades of failure may well indicate that genes do not exist. As stated previously, the purpose of the present review has been to question the missing heritability interpretation of failed gene finding attempts in the context of the problem areas of quantitative genetic research such as twin studies, and not to provide a comprehensive critical review of this body of research.

The issue researchers are grappling with is not missing heritability, but missing *genes* (Joseph, 2006; see also Crow, 2011), and there is good reason to believe that these "missing" genes are actually "non-existent" genes. "Where are the genes?" asked Richard Lewontin in 2009, and this question remains even more relevant today.

The historical crimes committed by the decidedly non-apolitical "racial hygienist" founders of psychiatric genetics in Nazi Germany have been documented (Baron, 1998; Gütt, Rüdin, & Ruttke, 1934; Joseph, 2004, 2006; Lerner, 1992; Müller-Hill, 1998; Ploetz & Rüdin, 1938a, 1938b; Ritter & Roelcke, 2005; Weiss, 2010), as well as the massively flawed research the field has produced (Boyle, 2002; Jackson, 1960; Joseph, 2004, 2006, 2010a; Lewontin et al., 1984; Pam, 1995), which leads to the following question: Has the field of psychiatric genetics contributed anything positive to the human condition in its roughly 100 years of existence? A leading group of psychiatric genetic researchers has supplied at least a partial answer. According to Glatt, Faraone, and Tsuang (2008), although they believe that their field possesses "a powerful toolbox of methods," the "major contributions of psychiatric genetic research to the diagnoses, treatment, prediction, and prevention of psychiatric disorders have yet to be realized" (pp. 24–25).

Paradoxically, it is becoming clearer every day that *the only positive contribution that the field of psychiatric genetics has ever made to the human condition is its apparent finding that genes for the major psychiatric disorders do not exist*. Future historians may well view the missing heritability stage of the psychiatric genetics field as a station on the road to its eventual destination alongside other "null fields" in the history of science.

In a widely cited 2000 article, Turkheimer concluded, mainly on the basis of twin studies, that "all human behavioral traits are heritable" (p. 160). As we have seen, at that time behavioral genetic and psychiatric genetic researchers were pinning their hopes on the completion of the Human Genome Project. So was Turkheimer, writing that "Behavior geneticists anticipate vindication" by the discovery of genes causing behavioral variation. On the other hand, wrote Turkheimer:

> Critics of behavior genetics expect the opposite, pointing to the repeated failures to replicate associations between

> genes and behavior as evidence of the shaky theoretical underpinnings of which they have so long complained. (p. 163)

That was an accurate description of environmentalist critics' expectations circa 2000 and earlier. A dozen years later, it appears that the critics have indeed been vindicated. As Turkheimer wrote in 2011, "to the great surprise of almost everyone, the molecular genetic project has foundered on the . . . shoals of developmental complexity . . . " (2011a, p. 600). Going further, he proposed the creation of a "new paradigm" (p. 600). It appears that the real problem is, as Turkheimer described it in 2000, the "shaky theoretical underpinnings" provided by twin research.

I began with a passage from Neil Risch, a leading and highly respected genetic researcher in medicine and psychiatry. I will close with a passage from a 1996 article he published with Kathleen Merikangas in *Science* (Risch & Merikangas, 1996). The authors discussed the "limited power" of linkage studies to identify variant genes, and argued that "the future of the genetics of complex diseases is likely to require large-scale testing by association analysis" that utilize "candidate genes" (p. 1516). As it turned out, candidate gene studies (and later, GWA studies) also failed to bear fruit, despite an investment of over $250 million (Visscher, Brown, McCarthy, & Yang, 2012). I cite this 1996 article mainly as a reminder that then, as now, researchers downplay the implications of negative findings at the same time that they claim that some new technology or technique will finally deliver the promised genes. Currently, the focus on rare variants or the "1000 Genomes Project" plays a similar role.

We may indeed be, as researchers in genetics sometimes write, "at the dawn of a new era." But the new era will be very different from the one they imagine. It will be an era in which it is recognized that genes for psychiatric disorders are either non-existent or irrelevant, and the attention of society and science will be focused mainly on the social, cultural, familial, economic, and political environments leading to, as Rose (1997, p. 296) put it, the "social and personal distress in advanced industrial societies." At the present time, psychiatry and some areas of psychology choose to locate this distress within the bodies, brains, and genes of individuals, and then assign them the status of being "mentally ill."

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