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Psychiatric "diseases" versus behavioral disorders and degree of genetic influence

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Abstract

Background: Psychiatric conditions in which symptoms arise involuntarily ("diseases") might be assumed to be more heritable than those in which *choices* are essential (behavioral disorders). We sought to determine whether psychiatric "diseases" (Alzheimer's Disease, schizophrenia, and mood and anxiety disorders) are more heritable than behavioral disorders (substance use disorders and anorexia nervosa).

Methods: We reviewed the literature for recent quantitative summaries of heritabilities. When these were unavailable, we calculated weighted mean heritabilities from twin studies meeting modern methological standards.

Results: Heritability summary estimates were as follows: bipolar disorder (85%), schizophrenia (81%), Alzheimer's Disease (75%), cocaine use disorder (72%), anorexia nervosa (60%), alcohol dependence (56%), sedative use disorder (51%), cannabis use disorder (48%), panic disorder (43%), stimulant use disorder (40%), major depressive disorder (37%), and generalized anxiety disorder (28%).

Conclusions: No systematic relationship exists between the disease-like character of a psychiatric disorder and its heritability; many behavioral disorders appear more heritable than conditions commonly construed as diseases. These results suggest an error in "common-sense" assumptions about the etiology of psychiatric disorders. That is, among psychiatric disorders, there is no close relationship between the strength of genetic influences and the etiologic importance of volitional processes.

Introduction

Psychiatric patients present with a variety of kinds of difficulties. One way to coherently address this diversity is to recognize and use distinct methods of psychiatric reasoning for

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particular kinds of difficulties (Ghaemi, 2003, McHugh, 2005, McHugh and Slavney, 1998). One of the most intuitive distinctions in reasoning is between that for psychiatric conditions that manifest primarily with involuntary symptoms and that for conditions that manifest primarily as dysfunctional behaviors.

"Disease" reasoning in psychiatry generally assumes some primary disruption in brain functioning; thus, as noted by McHugh and Slavney, a disease is something a patient *has* (McHugh and Slavney, 1998). Some diseases with prominent psychiatric symptoms have a known histopathology (e.g., Alzheimer's Disease), and some even a known etiology (e.g., Huntington's Disease), while in other putative psychiatric diseases these characteristics are less clear. For example, psychiatrists routinely employ disease reasoning in conceptualizing problems of patients with schizophrenia or mania; the spontaneous nature of the symptoms and their discontinuity from normal human experience suggest a primary disruption in brain functioning (McHugh and Slavney, 1998). Disease logic is also often used in conceptualizing the emergence of depressive or anxiety syndromes (McHugh and Slavney, 1998, Sheehan, 1983).

In contrast, "behavioral" reasoning assumes that patients are ill because of what they are *doing* (McHugh and Slavney, 1998); thus, behavioral reasoning is strongly tied to individual choices, their antecedents, and their consequences. Some behavioral disorders, e.g., alcohol and drug use disorders, are usually construed as out-of-control motivated behaviors. Other behavioral disorders, like anorexia nervosa, are usually construed as being shaped by culture and social learning (McHugh and Slavney, 1998). Clinicians typically treat behavioral disorders by attempting to persuade patients to choose to alter their behaviors (with help in disrupting the physiologic drives and other factors that provoke and sustain the behaviors). Thus, behavioral reasoning, in particular, invokes learning principles.

A key distinction between these methods of reasoning is the role of volition. That is, symptoms of psychiatric diseases – memory disturbance, hallucinations, and emotional disturbance – are typically understood as arising involuntarily. In contrast, behavioral disorders centrally involve voluntary control (though undoubtedly persons do not choose behavioral *disorders*). "Common sense" might suggest that neurobiological and genetic factors should be especially influential in the genesis of psychiatric syndromes that are disease-like in their manifestations, while other forces might have greater impact on the genesis of syndromes that manifest with disturbed behaviors. That is, common sense might suggest that any syndromes that centrally involve human decision making (Do I take this next drink? Do I eat this donut?) should be less genetically influenced than syndromes in which symptoms appear unbidden. Such reasoning is consistent with the public's notion that behavioral disorders like alcoholism are more "self-inflicted" than schizophrenia, depression, or Alzheimer's Disease (Schomerus et al., 2006).

In recent years, genetic epidemiological studies of psychiatric syndromes have expanded to a sufficient degree to empirically examine this issue. We have reviewed the extant twin study literature to produce the best available estimates of the heritabilities of well-studied adult psychiatric syndromes, with the goal of answering the following simple question: are genetic

influences consistently greater in disease-like psychiatric disorders than in syndromes of which the major manifestation is disordered behavior?

Method

For the purposes of this review, we drew upon recent quantitative summaries of the heritabilities of the disorders of interest, if available. To identify relevant studies of phenotypes not previously summarized, we performed PubMed searches (e.g., “Alzheimer Disease [MeSH Terms] AND twins [MeSH Terms]”), and we searched reference lists of source and review articles. We selected reports that met modern methodological standards for twin studies; i.e., they used systematic ascertainment, data collection, and diagnostic procedures, as well as blinding to co-twin diagnostic status (and/or zygosity). In addition, we limited our focus to categorical phenotypes for which heritability had been estimated in at least three separate samples. If more than one study reported on identical participants, we only included the most informative with regard to heritability. We calculated mean heritability estimates, weighted by the number of pairs in which at least one twin was affected, for the tables below. If the number of pairs with an affected twin was not reported, we calculated mean heritability estimates weighted by the total number of affected twins in each study. As used in this study, heritability is the proportion of individual differences in liability to an illness (in a particular population) that results from genetic differences between individuals.

Results

Diseases

We know of no previous quantitative summary of the heritability of Alzheimer’s Disease. Table 1 lists the five studies that met our inclusion criteria (Bergem et al., 1997, Breitner et al., 1995, Gatz et al., 2005, Gatz et al., 1997, Gatz et al., 2006, Meyer and Breitner, 1998, Raiha et al., 1996). The most comprehensive investigation, with the largest number of affected twins, is the recent study by Gatz *et al.* based on the Swedish Twin Registry (Gatz et al., 2005, Gatz et al., 2006). There was some overlap, in terms of affected subjects, with a smaller previous study based on that registry (Gatz et al., 1997). The weighted mean heritability estimate was 75%, whether or not we included the earlier study (Gatz et al., 1997).

Sullivan *et al.* recently performed a meta-analysis of published twin studies of schizophrenia, incorporating ascertainment corrections (Sullivan et al., 2003). Though only four of the twelve twin studies met modern methodologic standards, results did not vary significantly between studies that did and did not meet these standards. The point estimate of heritability was 81%.

We know of no previous quantitative summary of the heritability of bipolar disorder employing twin studies that meet modern methological standards. Table 2 lists the three studies that met our inclusion criteria (Kendler et al., 1993, Kendler et al., 1995, Kieseppa et al., 2004, McGuffin et al., 2003). Note that the affected subjects in the Maudsley study

by Cardno *et al* (Cardno et al., 1999) were included in the later study by McGuffin *et al.* (McGuffin et al., 2003). The weighted mean heritability estimate was 85%.

Sullivan *et al.* conducted a meta-analysis of published twin studies of major depressive disorder in 2000; five studies met inclusion criteria (Sullivan et al., 2000). The point estimate of heritability was 37%. Kendler *et al.*, in a more recent large Swedish twin study, reported a similar heritability estimate for lifetime major depressive disorder (38%) (Kendler et al., 2006b).

Hettema *et al.* conducted a meta-analysis of published twin studies of panic disorder; three studies met inclusion criteria. The point estimate of heritability was 43% (Hettema et al., 2001a).

Though Hettema *et al.* meta-analyzed two published twin studies of generalized anxiety disorder (Hettema et al., 2001a), the authors excluded one eligible study because of its complex ascertainment scheme (Roy et al., 1995), and an additional eligible study was published since the meta-analysis (Mackintosh et al., 2006). Table 3 lists the four studies that met our inclusion criteria (Hettema et al., 2001b, Mackintosh et al., 2006, Roy et al., 1995, Scherrer et al., 2000); one study only included males (Scherrer et al., 2000). The weighted mean heritability estimate was 28%.

Behavioral Disorders

Goldman *et al.* recently reviewed large unselected twin studies of substance use disorders (Goldman et al., 2005). Weighted mean heritability estimates were as follows: cannabis use disorder (abuse or dependence), 43% (five studies); sedative use disorder, 51% (three studies); stimulant use disorder, 40% (three studies); cocaine use disorder, 72% (three studies); and alcohol dependence, 56% (five studies). We identified one more recent eligible study of cannabis use disorder (Kendler et al., 2006a), and, in this study, the heritability estimate was higher than most previous studies (77%); including it (total of 6 studies), the weighted mean heritability estimate was 48%.

We know of no previous quantitative summary of the heritability of anorexia nervosa. Table 4 lists the three studies that met our inclusion criteria (Bulik et al., 2006, Klump et al., 2001, Wade et al., 2000); these studies only included women. The weighted mean heritability estimate was 60%.

Summary

Figure 1 shows heritability summary estimates for psychiatric diseases/disease-like conditions and behavioral disorders. Bipolar disorder, schizophrenia, Alzheimer's Disease, and cocaine use disorder had the highest heritabilities of the phenotypes addressed in this report – all 70% or higher. The phenotypes with the next highest heritabilities (40 – 60%) were anorexia nervosa, alcohol dependence, sedative use disorder, cannabis use disorder, panic disorder, and stimulant use disorder. The least heritable phenotypes (heritabilities < 40%) were major depressive disorder and generalized anxiety disorder.

Discussion

Our results do not strongly support the prediction that psychiatric "diseases" are more heritable than behavioral disorders. On the one hand, Alzheimer's Disease and two disease-like conditions, schizophrenia and bipolar disorder, have very high heritabilities. On the other hand, panic, major depressive, and generalized anxiety disorders have substantially lower heritabilities, lower than those of most of the behavioral disorders examined. Thus, there does not appear to be a systematic relationship between the disease-like character of a psychiatric disorder and its heritability. Indeed, idiopathic Parkinson's Disease, another neuropsychiatric condition with a known histopathology, does not appear particularly heritable (Wirdefeldt et al., 2004).

It might be argued that major depression and anxiety disorders should not be considered "disease-like," as these conditions are frequently accompanied by long-standing personality vulnerabilities (Bienvenu et al., 2004, Bienvenu et al., 2009, Roth et al., 1972). Major depression is likely a heterogeneous condition, including a more disease-like "endogenous" form and a less disease-like "neurotic" form (Roth, 2001, Shorter, 2009). Though some studies suggest that endogenous features are associated with higher heritability (Leckman et al., 1984a, Leckman et al., 1984b, McGuffin et al., 1996), aspects of depressive illness that appear particularly salient for heritability include the related features recurrence, early onset, and perhaps short duration (Kendler *et al.*, 2007). When adjusted for the latter features, endogenous symptoms do not appear to uniquely predict heritability (Kendler et al., 1994, McGuffin et al., 1996, Weissman et al., 1986). In addition, the presence of comorbid anxiety disorders appears to increase, rather than decrease, the heritability of depressive illness (Kendler et al., 1994, Weissman et al., 1986).

Our results are inconsistent with the notion that psychiatric problems can be divided accurately into those which are "biologically" caused and involuntary versus those which involve choices. That is, our findings support the proposition that biological/genetic factors influence volitional behavior, though it seems unlikely that genes simply evoke particular problem behaviors. The mechanisms through which genetic factors influence behavior are probably numerous. For example, genes can alter the hedonic and/or adverse effects of cannabis (Lyons et al., 1997) and alcohol (Thomasson and Li, 1993), making it more or less pleasant to consume these substances. Genes can also influence levels of sensation-seeking (Agrawal et al., 2004), making some individuals more prone to behaviors like drug use that are rewarding in the short term but harmful in the long term. Other heritable temperamental traits may similarly influence the development of eating disorders (Wade et al., 2008). While personal decisions are no doubt important in behavioral disorders, genes clearly influence their development. Thus, genes apparently do not respect the boundary between "free will" and "determinism."

One final implication of our findings is noteworthy. When we think about diseases in psychiatry, we often think not only about high heritability but also about low levels of personal responsibility and blame-worthiness. By contrast, when we consider behavioral disorders (especially substance use disorders), we sometimes think not only of reduced genetic influences, but also of higher levels of personal responsibility and blame-worthiness.

After all, since behavior is under at least partial voluntary control, it seems natural to assume that a behavioral disorder is "the patient's fault." Indirectly, our findings challenge this assumption. Given the apparent lack of a consistent relationship between heritability and disease versus disturbed behavior, should we also re-examine our conception about the relationship between disease and disturbed behavior on the one hand and moral responsibility and blame-worthiness on the other? Our results emphasize the important distinction between stigmatizing destructive behaviors, in a treatment context, and stigmatizing patients in a social (especially medical) context. Unfortunately, persons with behavioral disorders like alcoholism *are* stigmatized, and not just by the general public (Farrell and Lewis, 1990, Schomerus et al., 2006, To and Vega, 2006). Given that vulnerability to behavioral disorders is under substantial genetic control, our results emphasize the inappropriateness of libertarian attitudes towards these devastating conditions. That is, we humans do not appear equally *free* in our decisions.

Limitations

Three limitations deserve comment. First, it is important to recognize that the genetic influence on a phenotype (heritability) is not immutable; it is dependent upon the environment. Indeed, it is most accurate to characterize heritability of an illness in terms of a specific population at a particular point in time (Kendler, 2005). Since different environmental factors may be relevant for different psychiatric illnesses in particular populations, it is difficult to address this limitation effectively. Nevertheless, within cohorts, the pattern of results in Figure 1 appears consistent. For example, in studies using Swedish Twin Registry data with the same or overlapping birth cohorts, heritability estimates were as follows: bipolar disorder, 79%; Alzheimer's Disease, 78-79%; anorexia nervosa, 56%; major depressive disorder, 38%; and generalized anxiety disorder, 27% (Bulik et al., 2006, Gatz et al., 1997, Gatz et al., 2006, Kendler et al., 2006b, Kendler et al., 1995, Mackintosh et al., 2006). Also, in studies using adult Virginia Twin Registry data, heritability estimates were as follows: drug use disorder, 66%; alcohol dependence, 49%; major depressive disorder, 39%; panic disorder, 37%; and generalized anxiety disorder, 22% (Hettema et al., 2001b, Kendler et al., 2001, Kendler and Prescott, 1999, Kendler et al., 2003).

Second, unreliability – a form of measurement error – is confounded with unique environmental effects in twin models, and some diagnoses appear more reliable than others in unselected samples. For example, in studies of adults employing the Virginia Twin Registry, the reliabilities of lifetime diagnoses of panic, major depressive, and generalized anxiety disorders tended to be lower (κ = 0.34-0.56) than those of cocaine, sedative, cannabis, and stimulant use disorders (κ = 0.47-0.68) (Foley et al., 1998, Hettema et al., 2001b, Kendler et al., 2001, Kendler et al., 2000). Since no psychiatric diagnosis is made with 100% reliability, heritability estimates tend to be underestimates, but the heritabilities of the disease-like conditions above would be expected to be slightly more underestimated than those of the substance use disorders. Nevertheless, it is unlikely that correcting heritability estimates for unreliability would substantially reorder the results in Figure 1. In fact, the reliability of cocaine dependence (κ = 0.47) was slightly lower than that of panic disorder (κ = 0.56) in the studies cited above, yet the heritability estimates from these studies were 0.79 and 0.37, respectively, for these diagnoses.

Third, etiologic heterogeneity is likely in psychiatric disorders, so our heritability estimates inevitability reflect an averaging across potentially different etiologies. For example, as noted above, certain clinical aspects of major depressive disorder appear associated with higher heritability, including recurrence and early age-at-onset (Levinson et al., 2003, Sullivan et al., 2000). However, it is not clear that problems of etiologic heterogeneity would impact heritability estimates differentially for disease-like versus behavioral conditions.

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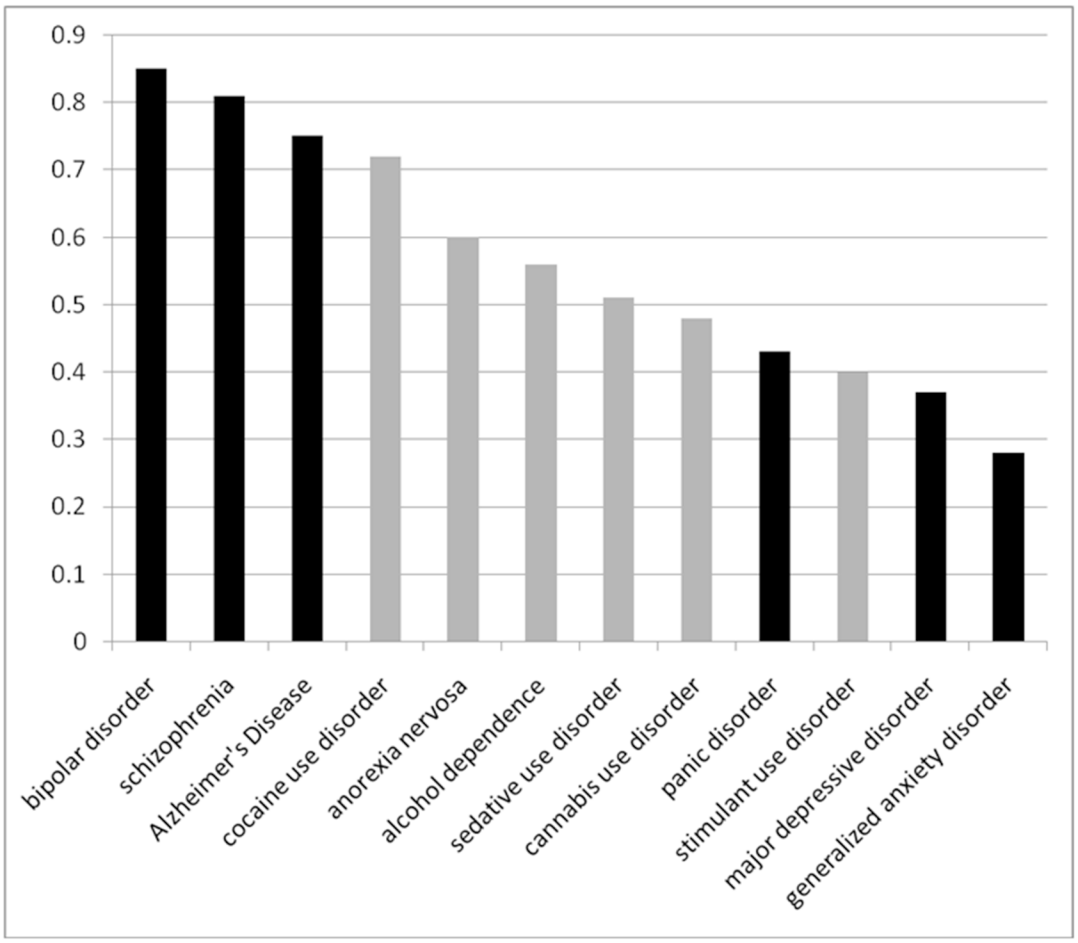

Figure 1.
Heritability summary estimates for psychiatric diseases/disease-like conditions (black) and behavioral disorders (grey)

Table 1.

Twin studies of Alzheimer's Disease

Study	Country	Age (years)	Basis for Diagnosis	Diagnostic Criteria	Number of Pairs [a]	Heritability
Breitner et al., 1995 Meyer and Breitner, 1998	U.S.A.	62-73	Nurse/physician examination, neuropsychological testing, and laboratory tests	NINCDS-ADRDA,[b] DSM-III-R, or CERAD and NIA criteria for post-mortem diagnosis	36	74% [c]
Raiha et al., 1996 Pedersen et al., 2001	Finland	≥ 18	Hospital discharge medical record review	NINCDS-ADRDA, DSM-III-R	84	63% [d]
Bergem et al., 1997 Pedersen et al., 2001	Norway	≥ 65	Physician examination, laboratory tests	NINCDS-ADRDA, DSM-III-R	32	58% [d]
Gatz et al., 1997 Pedersen et al., 2001	Sweden	≥ 54	Physician examination, neuropsychological testing, and laboratory tests	NINCDS-ADRDA, DSM-III-R	40	78% [d]
Gatz et al., 2005 and 2006	Sweden	≥ 65	Physician examination, neuropsychological testing, and laboratory tests	NINCDS-ADRDA, DSM-IV	392	79%
Summary						75%

[a] at least one twin affected

[b] National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association

[c] Best-fitting multiple-threshold (age at onset) model by Akaike Information Criteria (note: the fit of models with no additive genetic component, only a shared environmental component, or a smaller additive genetic component plus a shared environmental component, fit almost as well). Models assumed that all subjects would develop Alzheimer's Disease if subjects lived long enough.

[d] Estimated using a single-threshold model, not accounting for age (potentially inflates the estimate of a shared environmental component) (Pedersen et al., 2001).

Table 2.

Twin studies of bipolar disorder

Study	Country	Age (years)	Basis for Diagnosis	Diagnostic Criteria	Number of Pairs [a]	Heritability
Kendler et al., 1993 and 1995	Sweden	37-57	Questionnaire	DSM-III-R	35	79%
McGuffin et al., 2003	U.K.	≥ 15	Medical record review,+/− research interview, outside informants	DSM-IV	67	85%
Kiesseppa et al., 2004	Finland	53 (±13) [b]	Medical record review, diagnostic interview, +/− outside informants	DSM-IV	25	93%
Summary						85%

[a] at least one twin affected

[b] mean ± standard deviation

Table 3.

Twin studies of generalized anxiety disorder

Study	Country	Age (years)	Basis for Diagnosis	Diagnostic Criteria	Number Affected [a]	Heritability
Roy et al., 1995	Sweden	53 (±13) [b]	Questionnaire	DSM-III-R, broadened	128	49%
Scherrer et al., 2000	U.S.A.	≥ 37	Diagnostic interview	DSM-III-R, broadened	827	37%
Hettema et al., 2001	U.S.A.	≥ 20	Diagnostic interview	DSM-III-R, broadened	1,173	22%
Mackintosh et al., 2006	Sweden	≥ 55	Diagnostic interview	DSM-III-R, broadened	1,415	27%
Summary						28%

[a] among subjects in complete pairs, estimated

[b] mean ± standard deviation

Table 4.

Twin studies of anorexia nervosa

Study	Country	Age (years)	Basis for Diagnosis	Diagnostic Criteria	Number of Pairs [a]	Heritability
Wade et al., 2000	USA	≥ 17	Diagnostic interview	DSM-III-R, broadened	71	58% [b]
Klump et al., 2001	USA	16-18	Diagnostic interview, questionnaire	DSM-IV, broadened	23	74%
Bulik et al., 2006	Sweden	≥ 40	Diagnostic interview, medical record review, questionnaire	DSM-IV	49	56%
Summary						60%

[a] at least one twin affected

[b] estimated in best-fitting bivariate model with major depressive disorder