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Levels of explanation in psychiatric and substance use disorders: implications for the development of an etiologically based nosology

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Abstract

The soft medical model for psychiatric illness, which was operationalized in DSM-III, defines psychiatric disorders as syndromes with shared symptoms, signs, course of illness and response to treatment. Many in our field want to move to a hard medical model based on etiological mechanisms. This essay explores the feasibility of this move and asks whether psychiatric disorders have the needed single clear level of explanation for an etiologically based nosology. I propose seven criteria for a good explanation: (i) strength, (ii) causal confidence, (iii) generalizability, (iv) specificity, (v) manipulability, (vi) proximity and (vii) generativity. Applying them to cystic fibrosis, a gene-level approach to etiology performs well across the board. By contrast, a detailed review of alcohol dependence and a briefer review of major depression suggests that psychiatric disorders have multiple explanatory perspectives no one of which can be privileged over others using scientific data alone. Therefore, a move toward an etiologically based diagnostic system cannot assume that one level of explanation will stand out as the obvious candidate on which to base the nosology. This leaves two options. Either a hard medical model will be implemented that will require a consensus about a preferred level of explanation which must reflect value judgments as well as science. To take this approach, we need to agree on what we most want from our explanations. Alternatively, we will need to move away from the traditional hard medical model that requires that we ground our diagnoses in single biological essences, and focus instead on fuzzy, cross-level mechanisms, which may more realistically capture the true nature of psychiatric disorders.

Keywords

diagnosis; philosophy; psychiatric nosology

Introduction

"It is appropriate under these circumstances to ask whether new aims and methods will open up more promising vistas in the field of clinical research. We naturally will then turn our attention from merely classifying and categorizing diseases to a more exalted and satisfying

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exercise—understanding disease processes and how they inter-relate."[1] Kraepelin, 1920, p. 509.

"I have nothing particularly original to say about how one identifies *the* cause of something from among the many events and conditions on which it depends. It seems fairly clear that this selection is often a response to the purpose and interests of the one doing the describing."[2] Dretske, 1991, p. 24.

In DSM-III, DSM-III-R and DSM-IV psychiatric disorders are conceptualized as syndromes with shared symptoms and signs, and a similar disease course and response to treatment. Ideally, such syndromes should have other evidence for diagnostic validity such as running in families and having distinguishing biological, environmental and psychological correlates[3] (although for many disorders such information is not yet available). This approach to psychiatric illness reflects a *soft* medical model[4] as it makes no explanatory claims. Indeed, in their goal of producing an atheoretical diagnostic manual, the developers of DSM-III eschewed explanatory approaches to psychiatric illness.

By contrast, the *hard* interpretation of the medical model, toward which Kraepelin was striving in the above quote, is committed to specific causal hypotheses as a defining feature of a disorder. That is, if you cannot explain a distinct and unambiguous etiology for a syndrome, preferably in biological terms, then you do not have a *real* disorder.

Many in our field want to move from a soft to a hard medical model for psychiatric illness.[5,6] This essay explores one important conceptual and empirical issue in such a move —the need to choose a privileged level of explanation.

A hard medical model works best when applied to disorders that have a single clear cause. The best paradigms for this model are diseases resulting from Mendelian genetic defects, vitamin deficiencies, and infectious or parasitic diseases.[7] That is, for infectious and parasitic diseases, the disorder is etiologically defined by the nature of the invading organism and sometimes location of the infection. In Mendelian medical disorders, the disease is etiologically defined by the gene whose function is disrupted. These privileged levels of explanation provide critical information about the disorder (for example, etiology, predicted symptoms, course of illness and response to treatment).

At what level of explanation should psychiatric disorders be etiologically defined? In addition to older claims that psychiatric disorders should be defined on the basis of neuropathology,[8,9] intra-psychic mechanisms,[10] neurochemistry[11] or environmental stressors,[12] the recent psychiatric literature contains further proposed answers to this question including molecular genetics,[13] molecular neuroscience,[6] systems neuroscience (that is, 'circuits'),[14] cognitive neuroscience,[15] latent genetic factors[16] and temperament.[17,18]

In the first part of this essay, I review the etiology of alcohol dependence (AD), a paradigmatic complex neuropsychiatric syndrome, which has been well studied from many perspectives. Second, I propose and review seven pragmatic criteria for a good explanation: (i) strength, (ii) causal confidence, (iii) generalizability, (iv) specificity, (v) manipulability, (vi) proximity and (vii) generativity.

Third, I apply these seven criteria to cystic fibrosis (CF) and AD. Although the gene-level of explanation does very well for CF on all seven criteria, no single explanatory level for AD performs well across the board. I briefly review what is known about the etiology of major depression (MD), the results suggesting a pattern similar to that seen for AD.

Finally, I explore the conceptual problem of the choice of level of explanation for the multifactorial disorders that we have in psychiatry. Unless unexpected scientific developments point to single clear explanations for psychiatric illness, there are only two viable approaches available. Either we develop a consensus about the levels of explanation we want to utilize as a basis for nosology, with the recognition that such a judgment must result from a mixture of scientific findings and values; or, we move away from our effort to base our nosology on single levels of explanation toward the use of complex and fuzzy multi-level causal networks.

Part I: the etiology of AD

We organize the empirically supported risk factors for AD (here defined broadly to include the biomedical syndromes of alcohol abuse and dependence as well as the major adverse consequences of alcohol use) in four levels, each of which has its own sub-categories: biological, psychological, social and cultural. Although biomedicine has traditionally focused on biological explanations of illness, for completeness and potential relevance for psychiatric illness, I also review non-biological etiological factors.

Biological risk factors

Aggregate genetic effects—Twin and adoption studies provide convincing evidence that aggregate genetic risk factors impact strongly on liability to AD with an estimated heritability of 50–60% (for example, see refs 19–22). However, these aggregate risk factors are not highly specific, reflecting in part a broad liability to the abuse of all psychoactive drugs[23] and an even broader disposition toward externalizing behaviors.[24,25] Similar heritability for AD have been found across both sexes and in all populations examined to date. However, the impact of these genetic risk factors on AD can be modified by environmental exposures including religious beliefs,[26] marital status[27,28] and aspects of the social environment.[29,30]

Molecular genetic variants—Molecular genetic variants that influence risk for AD can act primarily in the liver on ethanol metabolism, the tongue on taste or the brain—directly or indirectly mediating the wide range of behavioral response to ethanol including hedonic effects, tolerance and dependence. The strongest replicated molecular effect, because of a variant that inactivates the aldehyde dehydrogenase gene, is strongly protective against risk for AD.[31,32] For example, one study from Taiwan found that for each normal allele at the ALDH2*1 locus, the OR for AD was 6.89.[33] However, this variant is found only in East Asian populations.[31] In these populations, the protective effect of this variant on risk for AD is declining in recent historical cohorts, perhaps because of greater social pressures to consume alcohol.[34] Variants in the alcohol dehydrogenase gene are also related to risk for AD and are more widely dispersed across human ethnic groups.[31] Functional variants in bitter-taste receptors that reduce the sensitivity to bitter stimuli are associated with risk for AD[35] and/or heavy drinking.[36]

Of the range of other replicated molecular variants, the most robust are probably in the GABA system—in particular in GABA2 subunit genes.[37] However, the effects of these variants on risk for AD are individually very small. A recent genome-wide association analysis detected odds ratios for single-nucleotide polymorphisms in the GABRA2 gene and AD of between 1.11 and 1.15.[38] Many other risk genes have some supporting evidence for involvement in the etiology of AD (for a review, see Kalsi *et al*.[39]) including several glutamate receptors, neuropeptide Y, brain-derived neurotrophic factor (BDNF) and several genes from the dopamine system. None of these genes have been shown to consistently have an effect on the risk for AD approaching that seen for the ALDH2 locus.

Interestingly, recent evidence suggests that some of the molecular variants that increase risk for AD also, in children, increase vulnerability to conduct disorder.[40] Some studies show that the impact of one molecular genetic variant for AD on risk of illness is modified by the presence of other molecular risk factors (for example, Chen *et al*.[41]).

Alcohol sensitivity—A large literature has examined the inter-relationship between the objective and subjective response to alcohol administration and (i) the presence vs. absence of a family history of AD and (ii) future risk for AD. The evidence generally suggests that (i) individuals with a positive family history for AD have lower levels of response to the aversive effects of alcohol and (ii) low levels of response to alcohol predicts future risk for AD even after controlling for family history.[42–44]

Dysfunctional neural systems—A range of studies has suggested that dysfunctional neural systems predispose to AD. One large body of research suggests that individuals at increased risk for AD demonstrate electrophysiological abnormalities manifest both in resting electroencephalography and in several event-related potential paradigms, particularly a low P300 response.[45] In neuropsychological and imaging studies, frontal executive deficits have been noted in individual at high risk for the development of AD and other externalizing disorders,[46,47] particularly those involving attentional and visuospatial tasks.[48–50]

The pattern of observed functional deficits (executive function, visuospatial ability, gait and balance) has implicated at least two independent neural systems that both involve the frontal cortex: the cerebellar-frontal system and cortico-cortical system between prefrontal and parietal cortices.[51–54] Porjesz *et al*.[45] summarizes these findings as follows

> These imaging studies strongly suggest that the frontal lobes and their connections with limbic and other cortical regions are compromised even in the subjects who are at risk for developing alcoholism and it is possible that these may be the structural bases of the electrophysiological indices of predisposition to alcoholism.

These neural systems reported to be disturbed in AD are also associated with a range of other substance abuse problems and disinhibitory traits more broadly.[45]

Psychological risk factors

Personality—A range of personality traits predispose to AD.[55,56] Most of these traits fall into two broad clusters—those that reflect negative emotionality (for example, neuroticism) and those that reflect externalizing tendencies (for example, impulsivity, novelty seeking and sensation seeking).[55–59] These traits have been shown in longitudinal samples beginning in childhood or adolescence (for example, Dubow *et al*.[58] and Englund *et al*.[59]) to predict heavy alcohol intake or AD suggesting that these associations are likely causal.

Attitudes/expectancies—Two broad sets of beliefs influence drinking behavior generally and risk for AD specifically. The first of these is alcohol expectancies.[60–62] One major approach identified three higher-order expectancy factors identified as ‘sedating,’ ‘positive’ and ‘negative’ that all predicted future alcohol use.[63] Manipulating expectancies in some, but not all, studies impacts on subsequent drinking and risk for AD.[64] The other major set of beliefs is ‘reasons for drinking’ where, for example, Cooper[65] developed four dimensions: (i) social (for example, to be sociable), (ii) enhancement (for example, to get high), iii) coping (for example, to forget your worries) and (iv) conformity (for example to fit in.). Reasons for drinking also impact on risk for heavy alcohol consumption and AD (for example, Abbey *et al*.[66] and Farber *et al*.[67]).

Social risk factors

Sher *et al*.[55] suggest that social environmental influences on AD can be usefully divided into two groups—severe stressors (typically experienced early in life) that produce relatively durable changes in risk, and more proximal environmental exposures that either 'represent situational goals or constraints' (p 203)—that is that either encourage or discourage heavy and problematic alcohol consumption.

Several early childhood adversities have been associated with risk for AD including parental loss,[68,69] poor parent–child relationships[70,71] and childhood sexual abuse (CSA).[72] A twin-family design showed that the association of parental loss on AD was likely causal, and not a result of genetic risks for AD leading to premature parental death or divorce.[68] CSA is strongly associated with risk for subsequent AD.[72] In a population-based twin study of women,[73] severe CSA had a robust association with risk for AD (odds ratio = 4.01) that did not attenuate when detailed measures of family functioning and parental psychopathology were added, and remained strong when examined in twin pairs discordant for CSA. These findings were confirmed in an independent twin cohort.[74]

The experience of being parented by an individual with AD can have complex effects on risk for AD, increasing risk in most subjects[75,76] but decreasing it in others.[77]

As confirmed by twin studies (which show adolescent alcohol use to be strongly influenced by environmental effects[78,79]), alcohol consumption and risk for AD are robustly predicted by social factors such as peer substance use, drug availability and social class.[55,80] Confirming these observations are ecological studies of college populations that show very strong correlations between heavy drinking and drinking-related problems, and the density of near-by alcohol outlets (for example, Weitzman *et al*.[81]).

The impact of social norms on excess drinking has been subject to a number of controlled trials and a Cochrane review.[82] In college students, those receiving feedback via the web or computer about normative levels of alcohol consumption had significant reductions in alcohol-related problems and binge drinking.

Cultural risk factors

A wide diversity of cultural, religious and economic factors impacts on risk for AD. Cultural, historical and geographical factors substantially influence the preferred form of ethanol (for example, beer, wine and spirits).[83] The acceptability of public drunkenness,[84] and the appropriateness of drinking by men versus women (which strongly influences gender-specific risk for AD)[85] also varies widely across cultures. In migrant and native populations, rates of AD often rise with the breakdown of traditional cultural practices and beliefs.[56,86]

In a detailed meta-analysis of the impact of beverage alcohol price on drinking behavior,[87] Wagenaar concludes that 'a large literature establishes that beverage alcohol prices and taxes are related inversely to drinking. Effects are large compared with other prevention policies and programs. Public policies that raise prices of alcohol are an effective means to reduce drinking.' In an earlier review that includes the impact of pricing on alcohol-related problems, Chaloupka *et al*.,[88] although well aware of the problems of causal inference, conclude that the reduction in alcohol consumption related to increased price is probably causal, impacts across the spectrum of light and heavy drinkers, and leads to a reduction in 'many of the consequences of heavy drinking, including alcohol-related violence and crime.'

In the United States, religious beliefs influence both alcohol consumption and the risk for progression to AD.[80] The size of alcohol beverages that are permitted for sale impacts on the

frequency of alcohol-related problems.[89] Extended hours of alcohol availability in pubs and bars has been shown, in Europe, Iceland, Australia and North America, to typically result in an increase in a range of alcohol-related problems as reported by police and health authorities.[90] A detailed literature review of the geographical distribution of retail outlets where alcohol can be purchased show that increased outlet density 'is associated with increased alcohol consumption and related harms, including medical harms, injury, crime and violence'[91] (p 566). These results were confirmed by another recent review of outlet density, which also showed a similar impact of the hours and days that alcohol was available for purchase.[92]

Part II: the choice of levels of explanation

In both philosophy of science and epidemiology, a large literature examines the characteristics of a 'good' scientific explanation. Instead of reviewing this literature here, I take a more pragmatic approach and focus on seven plausible criteria particularly germane for psychiatric research by which to judge how much weight should be given to a particular explanatory perspective. I make no claim for the novelty of these individual criteria as they can all be found in the previous epidemiological[93] and/or philosophical literature.[94,95]

Strength reflects the magnitude of the association between the explanatory variable and disease risk. This concept is captured by a range of 'effect size' statistics used in biomedicine such as an odds ratio, risk ratio or the proportion of variance accounted for.

Causal role reflects the degree to which the risk factors identified in the explanatory process truly alters the probability of disease as opposed to being associated through non-causal mechanisms. Given the frequent inability—for practical or ethical reasons—to conduct controlled experiments with human populations, this is often a question.

Generalizability reflects the degree to which an explanation applies across a wide range of differing background conditions.[96] A highly generalizable risk factor will increase risk of illness in all environments—that is, its effects are independent of other background factors. By contrast, the impact of a risk factor with low generalizability will be highly dependent on the particular constellation of background factors.

Specificity refers to the degree to which that explanation applies only to the disorder under consideration versus other disorders. Specificity is relevant if you want to know what causes X, and not Y and Z (two other potentially related psychiatric disorders).

Manipulability of an explanation reflects the degree to which (i) the identified risk factors can be altered through intervention and (ii) this intervention impacts on risk of illness.[95]

Proximity reflects the location of the risk factor in the causal chain to the disease. An explanation with high proximity sits close to the disease process in a causal chain. If, by contrast, many steps intervene between the explanation and the disease, then that explanation would have low proximity. Low proximity in no way implies that such distal risk factors reflect 'ultimate' causes.

Generativity reflects the probability that the explanatory variables identified would have the potential to lead to further fruitful etiologic understanding of the disease.[94,97]

These criteria are not unrelated as three examples illustrate. First, strength and generalizability are likely correlated because across a diverse subject pool exposed to a wide variety of background conditions, a strong risk factor will probably be generalizable. If it were strong in only a small subset of the sample, its average effect would per force be

modest. Second, manipulability depends on causal confidence. If the explanatory factors do not actually cause the disease, then altering them will not influence risk of illness. Third, specificity and proximity will tend to be inter-related as causal processes tend to 'fan out' in their effects so explanations with low proximity are likely to have low specificity.

Part III: evaluation of selected explanations by our seven criteria

I 'field test' these criteria by applying them to a classical medical disorder, CF, which arises from mutations in the protein CF transmembrane conductance regulator gene (CFTR) (Table 1). The association is extremely strong as all individuals with two dysfunctional CFTR genes get CF, and no individual with at least one functioning gene develops CF. We have absolute causal confidence that they cause illness. The mutation will cause the disease in any environmental background so it is highly general-izable. The mutation is specific—it does not cause other kinds of disorders (although there are some variations in the clinical phenotype of different mutations). CFTR mutations are theoretically highly manipulable because they are most critically expressed in the lung which can be directly accessed with various gene transfer technologies. CFTR mutations are proximate to the disease mechanism as they directly initiate the pathophysiological cascade leading to illness. Finally, CFTR mutations are potentially highly generative in that by following up the biological effects of the mutation, the pathophysiology of CF can be directly dissected.

Let us now apply these seven criteria to selected risk factors for AD (Table 1). Latent genetic risk factors strongly influence liability to AD (high strength). As genes can influence phenotypes but not the other way around, we have high confidence in their causal effects. Studies across a variety of European populations are consistent but we know little about other human populations and we have identified a series of factors which modify these genetic influences—so generalizability is intermediate. These risk factors are not very specific and, being statistical and not biological concepts, provide no hope for directly changing risk (very low manipulability). Generativity is intermediate as these latent constructs cannot stimulate biological research but have stimulated extensive studies using genetic epidemiological methods to advance our understanding of causal pathways to AD.

Variants in the aldehyde dehydrogenase (ALDH) gene strongly influence risk for AD, are highly specific and we can be confident in their causal effects. They are indirectly manipulable as the effects of the variant can be simulated pharmacologically by the drug disulfiram. However, their effects are not generalizable, being seen only in East Asian populations and, being expressed in the liver, are quite distal to the primary disease process in the brain in AD. Further understanding of the effect of these variants is not likely to provide further deep insights into the etiology of AD, so generativity is low.

Variants in the GABA system appear to have a quite weak overall effect on risk for AD, are only somewhat specific to AD, are likely causal and probably relatively broadly generalizable. They may be relatively proximal to a set of brain mechanisms important in the etiology of AD and could provide important insights into the illness including possible treatments, so generativity is high. Direct manipulability is very low as gene therapy for any psychiatric disorder is a distant possibility at best but indirect modification through drugs is potentially feasible so an intermediate score is given.

CSA strongly contributes to risk for AD and the limited evidence suggests much of the effect is causal, and probably generalizes across most conditions. However, it is highly nonspecific, increasing risk for nearly all psychiatric and substance use conditions. It is very distal in the causal chain of effects leading to AD. It is unclear the degree to which a further understanding of the impact of CSA will yield critical insights into the etiology of AD.

Impulsivity is strongly associated with risk for AD across nearly all studied populations. However, it is quite nonspecific as it predicts a wide range of other outcomes including antisocial behavior and use of other substances. We are currently not very effective at changing personality so manipulability is low. However, understanding how impulsivity leads to AD could open up important etiologic insights, so generativity is at least moderate.

Deviant peer groups are strongly associated with risk for AD across many samples but are nonspecific as they predispose to a range of deviant behaviors.[98,99] However, manipulability is considerably higher as several studies have shown how communities can alter the acceptability of deviant behaviors[100] and recent twin modeling suggests that changing shared environmental effects on deviance can feed back to reduce individual deviance.[101]

The causal efficacy of changing social norm expectations on pathological drinking behavior has been rigorously proven by controlled trials. These trials also demonstrate its manipulability. However, its effects are quite distal and while it will clarify social modification of drinking behavior, would likely provide limited insight into the nature of AD itself.

Taxation is highly manipulable and generalizable and probably has a direct and rather simple causal effect. However, it is very distant from any disease process and its mode of action is not likely to generate important further insights into the nature of AD. Very similar conclusions would be reached for the hours of alcohol availability in pubs and bars.

Table 1 reveals a single clear privileged level of explanation for CF and a hodge-podge for AD. What might be seen for other psychiatric disorders? Let me sketch what we might find for MD. Single gene effects for MD are even smaller and less well established than for AD.[102,103] Aggregate genetic effects are also somewhat weaker[104] and are modified by a range of environmental exposures.[105,106] Structural and functional magnetic resonance imaging studies have suggested a range of central nervous system abnormalities that correlate with MD[107–109] but the specificity and strength of these associations, as well as their causal status, remain uncertain. A number of physiological abnormalities including endocrine and immune function have been reported in cases of MD but again, sensitivity and specificity have typically remained modest. Several aspects of personality are strongly correlated with risk for MD—especially neuroticism. This association is almost certainly causal[110] but is nonspecific as high levels of neuroticism predispose to many internalizing disorders. Some cognitive processes may be more specific and here their causal role has been clearly demonstrated by many randomized controlled trials of cognitive behavior therapy.[111] A range of early environmental risk factors have been well established for MD (for example, poor parenting and sexual abuse)[112,113] and are generalizable across cultures[114] but are quite nonspecific. Stressful life events can be quite strongly associated with risk for MD.[115,116] Much, but not all, of this association is likely causal[117] and some classes of events are moderately specific for MD.[116,118] However, stressful life events are likely to be quite distal influences on risk pathways to MD and many such events predispose to other psychiatric disorders. Economic factors can impact on risk for MD via levels of unemployment[119] and cultural factors can shape the expression and help-seeking behavior of those with depressive syndromes.[120]

Part IV: choosing a privileged level of explanation

The previous expectation that one kind of explanatory variable for AD would perform well by all of our criteria and emerge as an obvious candidate for the privileged level that could be used for a nosology was not fulfilled. If a detailed exercise were performed for MD, our sketch suggests a similar pattern of findings would emerge. Nature does not appear to have provided us one critical level of explanation for psychiatric illness that stands out from the

background. For CF, explanatory power is highly concentrated in the level of DNA base-pair variation. For psychiatric disorders, explanatory power is dispersed and diffuse.

These findings have important implications for the long desired move for psychiatry to the hard medical model. The current status of our science, and, most probably, the nature of psychiatric disorders them-selves, does not yield up unambiguous choices for the best level at which to define psychiatric illness etiologically. A number of levels of explanation (for example, neuropathology, neurochemistry, molecular genetics, molecular neuroscience, systems neuroscience, cognitive neuroscience, latent genetic factors, temperament and environmental stressors) have been proposed and have their advocates. But science alone with not adjudicate definitively between their conflicting claims.

Before proceeding, two important issue needs consideration. First, given the heterogeneity in the nature and causes of psychiatric disorders, the ideal etiological mechanisms for all these disorders are unlikely to lie on the same level. So the problem outlined in this essay—which for simplicity treated psychiatric disorders as a unity—will actually break apart into a series of smaller but similarly difficult problems about explanatory variables and the ideal level of etiologic theories for a range of groups of psychiatric disorders. We have recently seen the early phases of this process in a proposal for a meta-structure of DSM-5.[121]

Second, a rejection of the hard medical model for psychiatric disorders should not be misunderstood as setting up a deep divide between etiologic models for psychiatric and medical disorders. The hard medical model, while historically critical in the evolution of disease conceptualization,[7] is in fact an idealization which fully applies to only a small group of Mendelian, nutritional, infectious and parasitic disorders. Although not a focus on this essay, if we examined complex medical disorders such as hypertension, type 2 diabetes or asthma, the picture would more closely resemble that seen for AD than for CF. Thus, the real dividing line, I suggest, is between those few medical disorders where essentialist models really apply, and the large majority of medical and psychiatric disorders that can be much more accurately understood as reflecting disorders of complex multi-level systems.

So if we as a field want to move from the soft to the hard medical model, what options are open to us? We could wait for another Treponema pallidum-like discovery for a major psychiatric disorder—a strong, basic, single etiologic agent. We will then be in a position, like we are for CF, where the science will robustly point to one level of explanation and we can unambivalently base nosology thereon. I doubt that such findings will emerge. Alternatively, we might hope that we could detect a process of emergent simplification. That is, the etiological pathways of numerous basic etiologic processes would pass through a single bottle-neck—perhaps at the level of systems neuroscience or neuropsychology—on their way to causing a psychiatric disorder. We could then use that bottleneck—the place where the diverse etiologic pathways come together—to define our disorders. Note, however, that this approach would not define disorders etiologically in traditional terms. Behind the bottleneck, on which we would base our diagnoses, a range of different etiologic mechanisms would be operative.

Or, we could try to move to the hard medical model based on developments in our current research programs. One obvious approach would be to select a smaller list of criteria for a good explanation with the hope that this will lead to one level of explanation standing out in its performance. However, the value attached to individual criteria for a good explanation differs depending on what is wanted from the explanation. A basic biobehavioral researcher will be interested in etiology and would value explanations with high levels of causal confidence, strength and proximity. For a clinical researcher, specificity and manipulability will likely be important as she would want to know how treatment of condition X should

differ from that of Y or Z. Those from a public health perspective who are focused on prevention will be interested in causal confidence, strength, generalizability and manipulability. They want to find true strong causes that apply across most conditions and which they can alter thereby reducing risk. Low specificity might even be a virtue as you might reduce risks for a broad area of disorders. For someone identifying a high-risk population, strength will be important but not causal confidence. As long as the risk factors reflect liability to illness, it will not be critical that the association be causal. If you were running a research program or a pharmaceutical company, generativity would be critical as a particular explanation need not be strong, as long as it leads to etiologic pathways from which treatments might arise. My position here is analogous to that taken by Kuhn in a famous essay on theory choice in science.[94] There he argues that no precise algorithm can be constructed for scientists to choose the best theory. Rather, a series of criteria can be proposed.

> Individually, the criteria are imprecise: individuals may legitimately differ about their application to concrete cases. In addition, when deployed together, they repeatedly prove to conflict with one another (Kuhn[94] p 322).

As emphasized in our opening quote, Dretske says, 'It seems fairly clear that this selection (of the best causes/explanation) is often a response to the purpose and interests of the one doing the describing.'[2]

If, as our review of the data suggest, there is no *a priori* way to pick a single level of explanation on which to base an etiological nosology, we could try to argue it out on pragmatic grounds. What do we most want as a field from our explanations? Although science will not be irrelevant, important issues of value will have to be involved. Without science to unambiguously lead us, we will be on less certain and more value-laden ground.

This approach will raise issues similar to those confronted in the choice of validators for the weak medical model concept of psychiatric disorders.[122] If you want a disorder that maximally runs in families, forecasts poor outcome or predicts treatment response, then science could deliver but it could not chose which validator should be most important.

However, we have a major alternative and this is to stop trying to mimic the hard medical model of Mendelian and infectious diseases. This approach, which assumes that diseases have single clear essences, is probably inappropriate for psychiatry (and much of chronic disease medicine). Rather, our disorders can be more realistically defined in terms of complex, mutually reinforcing networks of causal mechanisms.[123] Such a viewpoint has been developed to explain what kinds of things biological species are—fuzzy sets defined by mechanisms at multiple levels that act and interact to produce the key features of the kind.[124] As previously outlined,[125] this shift from a focus on single etiological agents to disordered multi-level mechanisms has been advocated by a number of thoughtful philosophers of biology and neuroscience (for example, see refs 126–130) and is particularly appropriate for psychiatric illnesses.

Although this approach probably represents a more realistic concept of the nature of psychiatric disorders,[123] it will not yield a single clear level of explanation on which to ground our nosology. Rather, our disorders would need to be defined as higher-order disturbances in multi-level mechanisms. One important consequence of the adoption of this perspective would be to turn our field away from seeking for overly simplistic single-cause etiological models with which we have been too enamored such as the 'dopamine hypothesis of schizophrenia'[131] or the 'serotonin hypothesis of depression.'[132] A further beneficial consequence might be that we would value more than we now do the difficult but critical research that stitches together the cross-level etiological insights we are obtaining in

psychiatric and substance use disorders. Although we might mourn, as a loss of innocence, our abandonment of the hard medical model for psychiatric illness, this messier picture—where we need to base our nosologic categories on fuzzy sets of cross-level mechanisms varyingly instantiated in individual patients—presents a much most realistic picture of what an etiologically based psychiatric nosology would really look like.

Conclusion

Many in our field are dissatisfied with the soft medical model for psychiatric illness that was operationalized in DSM-III. Instead, they want to move to a hard medical model based on etiological mechanisms. Although this move is easy for the relatively rare diseases with a single clear level of explanation, this might prove more difficult for psychiatric illness. I develop a series of criteria for a good explanation. Applying them to CF, we find that a gene-level approach to etiology performs well across the board. However, a detailed review of AD and a more cursory look at MD suggests that psychiatric disorders are likely to have multiple valid explanatory perspectives. It will not be possible to *a priori* privilege one perspective over using scientific data alone. When moving toward an etiologically based diagnostic system, it cannot be assumed that the level of explanation would be obvious or broadly agreed upon. Rather, a consensus that reflects value judgments as well as science will be needed to identify the goals. This effort may have to be repeated multiple times across different disorder groups, resulting in a patchwork of etiological levels used to define disorders where the choice of level reflects a mixture of scientific evidence and value judgments about what we want from our explanations of psychiatric illness. Alternatively, we can move away from trying to ground our diagnoses in single biological essences, and focus instead on fuzzy, cross-level mechanisms that may do a better job of capturing the true nature of psychiatric illness.

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Table 1

An evaluation of selected explanations for cystic fibrosis and alcohol dependence by seven specified criteria

Disorder/level	Strength	Causal role	Generalizability	Specificity	Manipulability	Proximity	Generativity
Cystic fibrosis							
CFTR mutations	++	++	++	++	+	++	++
Alcohol dependence							
Latent genetic risk	++	++	+	-	--	--	0
ALDH variants	++	++	--	++	++	0	-
GABA receptor variants	--	++	+	+	0	+	++
Childhood sexual abuse	++	+	+	--	--	--	0
Frontal lobe dysfunction	+	+	0	--	-	-	+
Impulsivity	++	+	+	--	-	-	+
Peer deviance	++	0	+	--	+	+	+
Social norm expectations	+	+	0	+	++	-	-
Taxation	+	+	++	+	++	--	--

Abbreviation: CFTR, cystic fibrosis transmembrane conductance regulator gene.

Scores: ++ high; + moderate; 0 intermediate or unknown; - low; -- very low.