Explanation in Contexts of Causal Complexity: Lessons from Psychiatric Genetics

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Over the past decade there have been increasingly common claims that psychiatry is in a "crisis"(Hyman, 2013; Morgan, 2015; Poland and Tekin, 2017). These claims often target the lack of known or identifiable causal etiologies for psychiatric diseases, suggesting that they are "among the most intractable enigmas in medicine" (Sullivan et al., 2012, 537). While the intractable nature of these disorders is often associated with their "causal complexity" (Poland and Tekin, 2017, 5), it is not always clear exactly what is meant by this. How should we understand causal complexity in this domain? How does it challenge scientific efforts to understand and explain these diseases? This paper addresses these questions by examining two main types of causal complexity in psychiatry. My analysis clarifies what these types of causal complexity are, how they challenge efforts to understand and explain these disorders, and how scientists are working to overcome these challenges.

1 Introduction. Over the past decade there have been increasingly common claims that psychiatry is in a "crisis"(Hyman, 2013; Morgan, 2015; Poland and Tekin, 2017)–that it is an "embryonic" and "immature" science that remains in its "early stages" (Hyman, 2010, 155,171) (Hyman, 2013). According to these views, psychiatry is stuck within a disease framework that is "seriously flawed" (Poland and Tekin, 2017, 1) and marked by "incredible insecurity" and "nosologic instability" that are "beyond a full resolution" (Kendler and Zachar, 2008, 370-1). Many of these criticisms target the lack of known or identifiable causal etiologies for psychiatric disorders. This, of course, is compared to the relative success that has been enjoyed in identifying such etiologies for various non-psychiatric or "physical medicine" diseases. It has been suggested that "[p]sychiatric disorders are among the most intractable enigmas in medicine" and that they are "have been intractable to approaches that were fruitful in other areas" of medical science (Sullivan et al., 2012, 537). The intractable nature of these disorders is often associated with their "causal complexity" (Poland and Tekin, 2017, 5), where this is interpreted in a variety of ways. On one interpretation, causal complexity is connected with views that the human brain is "the most complex object in the known universe" due to its large number of neurons and synaptic connections (Hoffecker, 2011, ix). A second interpretation suggests that psychiatric disorders are complicated at the level of etiology or in terms of the causal processes that produce them (Uher and Zwicker, 2017). A third interpretation suggests that the genetic bases and heritability of mental disorders is complex is ways that we might not see with other conditions (Lemoine, 2016; Tsuang et al., 2006; Mitchell, 2012).

Despite efforts to provide clarity, it is not always clear exactly what is meant by "causal complexity" and how it leads to the "intractable" nature of these disorders. These points raise a number of questions. First, how should we understand causal complexity in this domain? Second, if causal complexity makes sense of the "intractable" and "enigmatic" nature of psychiatric disease, how exactly does it challenge our scientific efforts to understand and explain them?

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This paper addresses these questions by analyzing two types of causal complexity that are common in psychiatry and that challenge efforts to understand and explain these disorders. My analysis clarifies what these types of causal complexity are, how they challenge efforts to understand and explain psychiatric disease, and how scientists are working to overcome these challenges. This analysis examines work in psychiatric genetics where genome-wide association studies (GWAS) have been used to search for genetic causes of disease. I do not claim that genetic factors are the only relevant (or even the main) causes of these diseases. Instead, I suggest that examining scientific efforts to identify such causes reveals important types of causal complexity that emerge in this domain. As will become clear, one main suggestion of this analysis is that while these types of complexity are particularly common and troubling in psychiatry, they are actually found throughout many areas of medicine. The rest of this paper is structured as follows. In section two, I provide some background on disease causation, including particular causal standards that ideal diseases are often expected to meet. In section three and four I examine two different types of causal complexity, which I refer to as multicausality and causal heterogeneity. These sections discuss how these types of causal complexity should be understood, how they challenge disease explanation, and how scientists are working to overcome these challenges. In the fifth section, I examine a further challenge for disease explanation that is relatively unique to biomedicine and that has received little to no attention in the philosophical literature. The sixth section concludes.

2 A causal framework for disease: Some background. At a basic level, disease explanation involves a disease phenotype (D) and its causes or causal etiology (C). This set up helps clarify a common two-step process for discovering new diseases that has been employed from Hippocratic to modern times. In the first step, a disease phenotype (D) is associated with some symptomology that reoccurs, with variation, across patients.[1] A second step in this process involves identifying the causal factors (C) or the causal etiology that produces this disease phenotype.[2] While various "physical" or "somatic" diseases have known causal etiologies, most if not all psychiatric conditions are of unknown etiology. In this sense, most psychiatric disorders are stuck at this first stage of discovery. Researchers have identified the symptomology that they think characterizes these conditions, but they do not yet know what causes them. This causal information is essential for ensuring that a disease category is valid–it guides how researchers and physicians classify, explain, and discover "bona fide" disease traits (Hyman, 2010). Identifying etiology is valuable because it can be targeted to explain, predict, and control disease occurrence. While symptomology can suggest palliative treatments that comfort and mask symptoms, it usually cannot suggest curative measures or inform disease explanation, as both require targeting the root cause of disease.

In this sense, causal etiology serves as a gold standard for many interrelated projects in medicine, including disease classification, explanation, discovery, and treatment. Unsurprisingly, psychiatric conditions can face significant scrutiny when their etiologies are unknown. In particular, if the causal etiology of a purported psychiatric disease is unknown, the "legitimacy" and "validity" of the disease is often questioned. This is captured by the modern medical view that "if you cannot explain a distinct and unambiguous etiology for a syndrome, preferably in biological terms, then you do not have a *real* disorder" (Kendler, 2012, 1, emphasis original). This is not to say that the medical community questions whether patients actually experience these symptoms. Instead, they question whether the disease category associated with these symptoms will remain stable and

[1] I follow the custom of referring to both signs and symptoms as "symptomology."

[2] For further discussion of this disease discovery process see: (Hucklenbroich, 2014; Ross, 2018).

unchanged as more is uncovered about its causal etiology (Kendler and Zachar, 2008). Why this worry? One lesson that diseases have repeatedly taught us is that symptomology is a rough and unpredictable guide to causal etiology (Hyman, 2010, 161). The repeated presentation of clear-cut symptom clusters across various patients is simply no guarantee that these symptoms all arise from the same causal process. We see this in cases where the same etiology produces different symptoms and where different etiologies produce the same symptoms (Ross, forthcoming).[3]

A main goal of psychiatry is to get to this second step of disease discovery and identify the causal etiologies of these conditions (Sullivan et al., 2012, 537). One strategy that is used to achieve this goal involves collecting patients with the same diagnosis and searching among them for the factors that they have in common and that might be causally responsible for their disease. This involves starting with some phenotype of interest (D) and then searching backward or causally upstream to identify its causes (C).[4] This basic strategy has been implemented in genome-wide association studies (GWAS). These studies analyze the genomes of patients with particular psychiatric disorders in order to identify those gene variants that they all share and that potentially cause these diseases. Expectations about the type of results these studies should provide have been influenced by an "ideal" model of disease causation that continues to figure in modern medicine. This ideal model–sometimes referred to as the "hard" medical model or the "biomedical" model (Kendler, 2012; Engel, 1977)–originated with nineteenth century germ theory and it contains two main causal standards (Ross, 2018). First, this model involves a (1a) single cause standard, which maintains that a particular instance of some disease has one main causal factor. Second, this model also involves a (2a) shared cause standard, which maintains that all instances of a particular disease have the same (or some similar) causal process. This model captures the expectation that diseases should have single, shared causal etiologies.

Although some diseases meet the strict standards captured in this "ideal" model, most do not. GWAS have provided further evidence for the claim that psychiatric disorders often fail to fit this model. In particular, these studies have identified two types of causal complexity that capture ways in which this ideal model breaks down. First, these studies indicate that some psychiatric disorders are characterized by (1b) *multicausality* in the sense that each instance of the disease is caused by many gene variants that work together in aggregate to produce the condition. This finding conflicts with the single cause standard or monocausal-type picture. Second, these results also suggest that some psychiatric disorders are (2b) *causally heterogeneous* in the sense that distinct instances of the same disease are caused by different combinations of gene variants. This conflicts with the shared cause standard, as different overlapping combinations of causes are capable of producing the same disease.

This breakdown provides a helpful way to understand four distinct causal architectures (1a, 1b, 2a, 2b) and two types of causal complexity–(1b) multicausality and (2b) causal heterogeneity–as outlined in figure 1. In this figure, each causal architecture has to do with how "simple" or "com-

[3]As Insel et al. state, "[h]istory shows that predictable problems arise with early, descriptive diagnostic systems designed without an accurate understanding of pathophysiology. Throughout medicine, disorders once considered unitary based on clinical presentation have been shown to be heterogeneous...Conversely, history also shows that syndromes appearing clinically distinct may result from the same etiology" (Insel et al., 2010).

[4]This mirrors a strategy that originated with classical genetics, which involves starting from a phenotype and searching for its genetic causes ("forward genetics"), as opposed to starting from gene variants and searching for their effects ("reverse genetics") (Lawson and Wolfe, 2011).

plex" causal factors are with respect to some specified effect of interest.[5] This figure shows how each of these four architectures are related to each other and how they come apart. As monocausality and multicausality have to do with the number of causes for a single instance of disease, they operate at the token-level. They represent two sides of the spectrum for token causal etiology–one more complex (1b) and the other less so (1a). As causal homogeneity and causal heterogeneity have to do with whether causes are similar or different across cases of disease, they operate at the type or population level. These also represent two sides of a spectrum, but in this case for type causal etiology–one more complex (2b) and the other less so (2a). These token (1a, 1b) and type (2a, 2b) level causal architectures are not mutually exclusive. Knowing that a type-level disease trait is causally heterogeneous or homogeneous provides no information about whether its instances are multicausal or monocausal, and vice versa.[6] The category that a disease falls into on the left side of figure 1 does not dictate or influence which category it falls into on the right side (and vice versa). Diseases that meet the less complex causal architectures (1a, 2a) come with particular advantages, while diseases that meet the more complex ones (1b, 2b) involve various challenges for understanding, explanation, classification, and control. I discuss these types of causal complexity in more detail, the various challenges that they present, and how scientists work to overcome these challenges.

3 Multicausality. As briefly described above, multicausality can be thought of as contrasting with monocausality or the well-known "monocausal model" of disease. The former involves a disease instance that has many causes, while the latter involves a disease instance that has one main cause. Various conditions are thought to fit this monocausal picture, such as scurvy, tuberculosis, chicken pox, giardiasis, and Huntington's disease, among others. Genetic conditions that fit this monocausal model are often referred to as "single-gene," "monogenic," or "Mendelian" diseases, as opposed to diseases that are "polygenic" or "complex" (Cooper et al., 2013; Kendler, 2005; Torkamani et al., 2018; Mitchell, 2012). What does it mean to say that these diseases each have single main causes? How could any disease have a single main cause? Addressing these questions requires specifying what is meant by "causation" and how one factor could be privileged as the

[5] In other words, they have to do with simplicity and complexity at the level of causes (given some effect) and not at the level of an effect (given some cause).

[6] In other words, knowing that a *single instance* of some disease is multicausal or monocausal provides no information about whether *all instances* of the disease are causally heterogeneous or homogeneous. A disease that is monocausal and causally homogeneous is a disease that has a single main cause, where this cause produces all cases of the population-wide disease. These diseases fit the standard "hard" medical model and they include examples such as scurvy, tuberculosis, Huntington's disease, and chicken pox, to name a few. A disease that is monocausal and causally heterogeneous is one in which a single main cause produces each instance of the disease (moncausality), but different single causes produces distinct cases of the same disease (causal heterogeneity). A disease can be multicausal and causally homogeneous if each instance of the disease is caused by multiple factors (multicausality), but the same combination of factors cause every instance of the disease (causal homogeneity). Phenylketouria (PKU) is an example of this, because two factors cause each instance of the disease (multicausality) and the same two factors cause all cases of the disease (causal homogeneity). Finally, a disease can be multicausal and causally heterogeneous if each instance of the disease is caused by many factors (multicausality), but their are different combinations of causal factors that produce distinct instances of the disease (causal heterogeneity). These points are discussed in more detail throughout the paper.

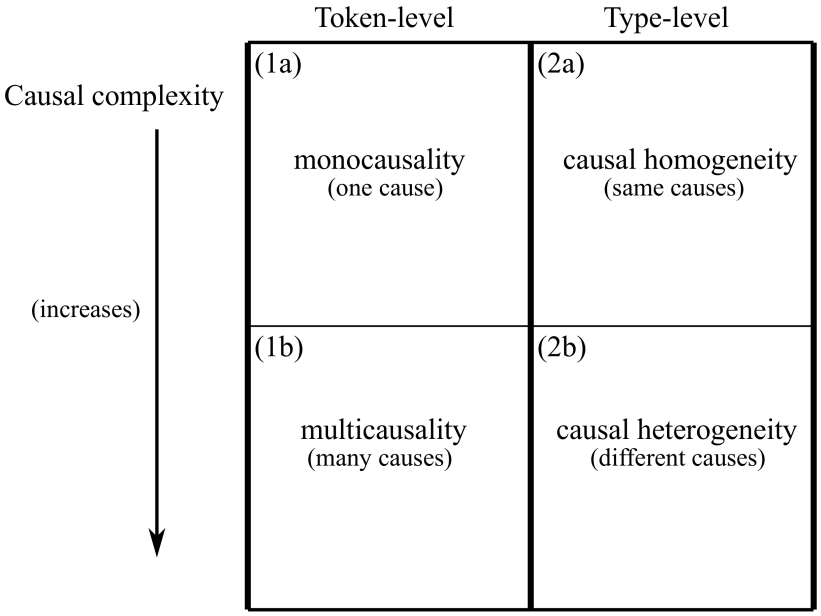

Figure 1: Four different causal architectures (1a, 2a, 1b, 2b) and two different types of causal complexity (1b, 2b).

main or most important cause of some outcome. In this paper, I rely on an interventionist account of causation, in which a causal factor "makes a difference" to its effect in the sense of providing control over it.(Woodward, 2003). On this account, to say that C is a cause of D means that an intervention that changes the values of C, and no other variables in background circumstances B, produces changes in the values of D. In other words, causes are factors that operate like handles or switches in the sense that they can be potentially manipulated to provide control over their effects. Manipulating these factors produces changes in the effects they are related to. Importantly, this account does not require that such an intervention is currently or technologically available, but just that *if* such an intervention were performed, the ensuing change in the effect variable *would* occur (Woodward, 2003, 11). Notice that for the diseases mentioned above, each has a particular factor such that if that factor were manipulated, it would control the occurrence and nonoccurrence of the disease in question. For example, manipulating dietary vitamin C provides control over whether a patient acquires scurvy or not. The same could be said for interventions on the single main causes of the other monocausal diseases mentioned above.[7] Manipulating these factors provides control over the occurrence and nonoccurrence of these disorders–they are targeted in treating, preventing, explaining, and controlling these diseases.

These monocausal diseases have another important feature. The particular factors that are identified as the single main causes of these diseases have a special type of control over them.[8] These factors have probable control over disease traits in the sense that manipulating these causes

[7]These include manipulations of the tubercle bacteria, chicken pox virus, Giardia parasite, and *huntingtin* gene variant, respectively.

[8]They actually have many special types of control over disease (Ross, forthcoming), but I focus on one type that helps clarify what is meant by multicausality.

provides a high probability of producing the occurrence and nonoccurrence of the trait.[9] In order to see this, consider a light switch on a wall and the different degrees of probable control it can exhibit over the state of the light being "on" or "off." In a first system, flipping a switch up provides a %60 chance that the light turns "on," while flipping it down provides a %60 percent chance that the light turns "off." In a second system, flipping the switch up provides nearly a %100 percent chance that the light turns "on," while flipping it down provides nearly a %100 percent chance of the light turning "off." The switch in the second system has a higher degree of probable control over the light than the first, because manipulating this switch provides a higher likelihood of changing (or controlling) the state of the light. Paradigmatic monocausal diseases approximate the second switch system. Factors that are identified as the single main causes of these diseases provide a high degree of probable control over them. This can be seen in Huntington's disease, which is caused by a mutation in the *huntingtin* gene. When a patient has this mutation her likelihood of acquiring the disease is nearly 100% and if she lacks the mutation her likelihood of *not* acquiring it is nearly 100%. Identifying single causes with a high degree of probable control is very valuable in medicine. These factors provide a reliable indication of whether a disease will manifest or not and they identify factors that can be targeted to control, explain, treat, and prevent disease.

Determining whether a *single* factor has probable control over a disease involves assessing potential background conditions that may also influence the disease outcome. Paradigmatic monocausal diseases have single causes with probable control, where this control is stable across changes in common or relevant background conditions. For example, as Kendler states "[i]f you have one copy of the pathogenic gene for Huntington's disease, it does not matter what your diet is, whether your parents were loving or harsh, or if your peer group in adolescence were boy scouts or petty criminals. If you have the mutated gene and you live long enough, you will develop the disease" (Kendler, 2005, 394). In other words, there are no additional genetic, environmental, or other factors that influence or alter the cause-effect relationship in question (Kendler, 2005, 397).

The stability of this probable control is related to the genetic concepts of penetrance and effect size.[10] Penetrance refers to the percentage of individuals in a population with a particular genotype who exhibit the corresponding phenotype, where phenotype is either present or absent. If a gene variant is 30% penetrant, then 30% of those individuals with the genotype will express the phenotype. Alternatively, the variant that causes HD is 100% penetrant–or "fully" and "completely" penetrant–because 100% of those individuals with this gene variant will express this disease phenotype (Stewart et al., 2007). This measure can be thought of as giving an indication of a gene's ability to "penetrate through to the phenotype" despite changes in other background factors (Carr, 2014). In this sense, complete or high penetrance refers to "determinative" genes for which "environmental and other factors have little effect on the phenotype" (Weiss, 2007; Carr, 2014, 283). Probable control is also related to the genetic concept of "effect size," which concerns the proportion of variation in the phenotype that is "explained by" or "attributed to" variation in the genotype (Nakagawa and Cuthill, 2007; Maier et al., 2017). Effect size is often described as capturing the "magnitude of an effect" that genotype has over phenotype and it is often used synonymously with the notion of "heritability" (Nakagawa and Cuthill, 2007, 593)(Maier et al., 2017). Genes that are considered the single main causal factor for a phenotype often have large effect sizes. In these cases,

[9]This notion of probable causal control is similar to Cheng's notion of "causal power" (Cheng, 1997).

[10]The fact that this probable control holds across a wide range of background conditions is also related to Woodward's notion of stability (Woodward, 2010) and Kender's notion of non-contingency of association (Kendler, 2005).

variation in the population-wide phenotype is explained by variation in a gene.

In the early stages of GWAS, researchers were hoping to identify gene variants with a high degree of probable causal control, a high degree of penetrance, and large effect sizes. Instead, GWAS uncovered nearly the opposite type of finding. These studies identified gene variants with a low degree of probable control, little penetrance, and small effect sizes. In other words, they identified genes that were "packing much less of a phenotypic punch than expected" (Goldstein, 2009, 1696). When researchers find single gene variants with low probable control, variable penetrance, or small effect sizes they often interpret this as an indication that other causal factors–such as other genes, environmental variables, etc.–influence and interact with these variants in producing the disease (Griffiths et al., 2008, 249). This is to say that they view these diseases as multicausal–as produced by many causal factors that work together in aggregate to produce the condition.[11] Instead of having a single gene that fully "penetrates" through to the disease trait, these genes depend on and interact with other causes in producing the trait. As Cooper states, "most carriers of the risk alleles discovered by genome-wide association studies (GWAS) may never develop the disease in question...because these variants generally only make a small contribution to the multifactorial aetiology of the condition" (Cooper et al., 2013, 1078). Researchers expect disease etiology to include factors with a high degree of probable control over disease. When a single causal factor fails to provide this type of control, they search for multiple factors that provide this type of control together. In these cases, the disease is considered multicausal as it is produced by many causes that all have a "collective impact" on the disease outcome (Ideker et al., 2011, 3). A simple example of this is phenylketonuria (PKU), which is caused by two main factors–a gene variant and a dietary factor. Acquiring this disease requires the presence of both of these factors and both are required to gain probable control over the disease state (Murphy, 1997, 113). Manipulating the variant only provides control over the disease when the dietary factor is present and manipulating the dietary factor only provides control when the gene is present. In this sense, PKU is multicausal because it takes more than one causal factor to gain probable control over the occurrence and nonoccurrence of this disease.[12]

This clarifies the rationale behind identifying a disease as monocausal versus multicausal. The number of relevant causal factors is determined on the basis of the number it takes to achieve a high degree of probable causal control over the disease trait. In this sense, the results of GWAS further support the view that most psychiatric diseases are multicausal in etiology (Price et al., 2015). As Plomin and Kovas state "it is now generally accepted that genetic influence on common disorders is caused by multiple genes of small effect size rather than a single gene of major effect size" (Plomin and Kovas, 2005, 600). Researchers do not deny that monocausal diseases exist, they just think that most of them have already been identified. In other words, diseases with single genetic causes that have "large effect sizes–the low-hanging fruit–have already been detected" (Park et al., 2010, 570). What we have left are more complicated multicausal diseases that are much more challenging to discover and understand. As Goldstein states, "[t]he modest size of genetic effects detected so far confirms the multifactorial aetiology of these conditions and suggests that complex diseases will require substantially greater research effort to detect additional genetic influences" (Goldstein, 2009, 9).

[11] Discussions of this type of causal complexity are found in the philosophical literature. This is seen in Mitchell's discussion of situations where there are "multiple causes additively or interactively contributing to the production of a major effect" (Mitchell, 2008, 24).

[12] For more on this see: Ross (Forthcoming).

How exactly does multicausality challenge scientific efforts to understand and explain these diseases? A first challenge with this type of causal complexity it that it requires identifying the many causal factors involved in producing an effect. Where providing a causal explanation of some effect involves identifying and citing its causes, this becomes more and more difficult as the number of relevant causes increases. More explanatorily relevant causal factors, means more factors to identify and appeal to. Furthermore, most psychiatric diseases do not appear to be similar to PKU in the sense of having only two main causes. Researchers hypothesize that some psychiatric diseases have hundreds of causally relevant gene variants, representing a far more extreme case of multicausality than PKU. Second, it is not enough to simply identify these factors–these explanations require providing some coherent story about how all of these factors work together to produce the disease in question. This includes specifying how various factors depend on each other in producing disease, what role they play in the pathogenic process, and what their particular effect sizes are. A third main challenge with this type of causal complexity is that scientists appear to be unsatisfied by explanations that are *too* multicausal. In cases where multicausal genetic factors balloon out to an extreme degree, scientists often suggest that these factors fail to capture the right "level" of "causal action" for the disease (Kendler, 2013, 1060). When this happens in the context of genetics, researchers can claim that such causes provide little guidance or understanding and that there is likely some alternative "level" that better captures the relevant causal etiology. This is mentioned by Goldstein who states "[i]f effect sizes were so small as to require a large chunk of the genome to explain the genetic component of a disorder, then no guidance would be provided: in pointing at everything, genetics would point at nothing" (Goldstein, 2009, 1696). This third challenge is that multicausality in the extreme is inadequate for explanation and that it suggests that the causally relevant factors are likely found at some "level" other than molecular biology. This is driven by the expectation that the right level or characterization of causal etiology should be somewhat unified and not too splintered.

If multicausallity poses these challenges to understanding and explanation, how do scientists overcome them? First, the challenge of identifying many causal factors has been approached, in part, by modifying search methods such that they are better equipped to identify causes with small effect sizes (Park et al., 2010). The second challenge–providing a coherent story about how these factors work together–is addressed by various strategies aimed at unification. Here the unification is focused on *interaction* and specifying how causes are unified on the basis of all interacting together in a single causal process that produces disease. This is sometimes accomplished by providing a "unifying" mechanism or pathway that integrates all causes with respect to the effect of interest. These unifying causal processes can clarify how the many causes interact with each other, the step-by-step or sequential order of their operation, and the magnitude of their individual effects over the outcome of interest. For example, this can be done by identifying "multiple related genes in the same functional pathway...[that]...work together to confer disease susceptibility" (Wang et al., 2010). When gene variants are unified in this way it can allow for the identification of single, unified causal processes at higher "levels." For example, multiple gene variants may all influence a higher-level cellular process, where this process captures how they all interact to produce disease. This move to a higher-level can circumvent the issue of rampant multicausality at the level of gene variants. Instead of appealing to many lower-level splintered causes, this provides the option of citing a single, unified, and coherent higher-level causal process. This strategy of unification can be understood as reworking or converting a situation of "many" causes into a situation in which "one" cause or causal process is responsible. This converts "many" causes into "one" causal process,

in which this process is typically a single mechanism or pathway. In the context of explaining a particular effect, this suggests that there is something useful about ascribing causal responsibility to a single, causal entity as opposed to pointing to some distributed set of seemingly unrelated factors.

4 Causal heterogeneity. A second type of causal complexity in this domain is causal heterogeneity, which contrasts with causal homogeneity. Starting with the later, causal homogeneity refers to a situation where distinct instances of the same effect (in this case a disease trait) are produced by the same combination of causes. In other words, these causes are "homogeneous" across different instances of the same type of effect. Many diseases that fit the monocausal model provide straightforward examples of this causal architecture. This can be seen in the case of scurvy because every instance of this disease is caused by the same factor (namely, a deficiency of dietary vitamin C). Causal homogeneity can also be met by multicausal diseases, so long as every instance of the disease is produced by the same combination of causes. An example of this is PKU, because every instance of this disease is caused by the same two factors. This shows how causal homogeneity is distinct from monocausality and multicausality. While monocausality and multicausality have to do with the number of causes for each instance of an effect, causal homogeneity has to do with whether these causes are similar or different across all of these instances.

In modern medicine, there are particular assumptions about disease causation that involve causal homogeneity. In particular, there is a common default assumption that in order for a disease trait to be "valid" and "legitimate" it should be causally homogeneous in the sense of having some shared causal etiology (Ross, 2018). This notion of shared etiology is sometimes referred to as a "disorder-specific pathophysiology" (Caspi and Moffitt, 2006, 586), a "shared causal process" (Zachar, 2014, 87), a "shared pathogenesis," or the "causal signature" for a particular disease (Murphy, 2006, 105). As these shared causes capture what unifies various instances under the same disease heading, they are referred to as "unifying cause[s]" or the "unifying theoretical underpinning" for a given disease (Egger, 2012, 1). In current medical theory, it is often expected that diseases have some unifying and singular causal story–that they have "single biological essences" at the level of etiology (Kendler, 2012, 1). The presence of this assumption about shared causal etiology is seen in various medical contexts. It figures in decisions about what are deemed "valid" disease traits and how such traits and their etiologies should be discovered. For example, in the context of psychiatry, "diagnostic validity" is defined in terms of shared causal etiology. In particular, "diagnostic validity" is "shorthand to signify definitions that capture families of closely related disorders with similar pathophysiology" (Hyman, 2010, 162). Additionally, this assumption figures in GWAS and other studies that aim to discover disease and disease etiology. This is because such studies group together patients with similar symptomology in the hope of finding some causal process that they all share or have in common. As Maeir states, "[m]ost genetic studies are based on the assumption that individuals who exhibit similar symptoms or who have been diagnosed with the same disease are representatives of the *same* underlying biology defined by a *common* genetic architecture" (Maier et al., 2017, emphasis added). These strategies assume that distinct instances of the same disease are all produced by similar or homogeneous causes.

Although causal homogeneity has figured into the set up and expectations of GWAS, many purported disease traits have failed to meet this standard. Emerging results suggest that some psychiatric diseases are causally heterogeneous–or exhibit "etiological heterogeneity"–in the sense that

distinct instances of the same disease are caused by different combinations of causal factors.[13] Psychiatric disorders that are thought to exhibit this type of causal complexity include schizophrenia, autism spectrum disorder, and bipolar disorder (Betancur, 2011; Takahashi, 2013). Causal heterogeneity is also present in other non-psychiatric (or physical medicine) diseases.[14] An example of this causal architecture is seen in Parkinson's disease, which can be produced by different causal factors in different patients with this same disease. This disease can be produced by single gene variants (C_1), single environmental factors (C_2), and combinations of genetic and environmental factors (C_3) (Nandipati and Litvan, 2016). In cases where the heterogeneous causes are genetic the disease is referred to as "genetically heterogeneous" (Barondes, 1992, 299). In this sense, "[g]enetic heterogeneity can be defined as mutations at two or more genetic loci that produce the same or similar phenotypes (either biochemical or clinical)" (McGinniss and Kaback, 2013, 7).[15] An example of this is retinitis pigmentosa, which can be caused by anywhere from 75-300 different gene mutations that can each "act alone" to produce the disease (Hyman, 2010, 163).

A key feature of causal heterogeneity is that it involves a many-to-one relationship between disease causes and the disease effect. In the context of genetically heterogeneous traits, this results in a "phenotypic convergence of independent mutations" that can involve "diverse genetic pathways to similar disease traits" or to some "common symptomology" (Hyman, 2010, 163) (Takahashi, 2013, 648). This is a kind of funneling of different causal factors or pathways onto the same final effect of interest. The causal starting points of this funnel are often described as each individually sufficient or able to "act alone" in producing the final disease outcome (Hyman, 2010, 163). In the context of genetics, this ability to act alone is captured by the fact that each heterogeneous variant is "highly penetrant" for the disease. We see this in the case of retinitis pigmentosa where "each deleterious mutation acts as a single gene 'Mendelian' disorder within a family, but in aggregate, different families are affected by a large number of distinct mutations in different genes" (Hyman, 2010, 163). In these cases, the heterogeneous genetic causes are sometimes referred to as "rare variants," because the etiology can be so varied or heterogeneous that any causal variant only occurs very "rarely," sometimes only in those individuals of a single family. From the standpoint of any particular heterogeneous gene variant, each can have a high probability of producing the disease. However, from the standpoint of the population-wide disease trait, there is no single genetic cause that is responsible for all instances of the disease. This shows up in the fact that these gene variants have small effect sizes. Variation in any individual gene variant only explains a small percentage of the variation in the population-wide trait. Some of this variation is explained by the other gene variants that are also capable of producing the disease.

How does causal heterogeneity challenge efforts to understand and explain scientific phenomena? A first challenge is that heterogeneous causes are limited in providing explanations of type-level phenomena, because no single heterogeneous cause explains all instances of its type-level effect. Heterogeneous causes are explanatorily and causally relevant to a fraction of all instances of their

[13] In other words, "[e]tiologic heterogeneity refers to a phenomenon that occurs in the general population when multiple groups of disease cases, such as breast cancer clusters, exhibit similar clinical features, but are in fact the result of differing events or exposures" (Hernandez and Blazer, 2006, 46).

[14] These include high blood pressure, hyperlipedimia, retinitis pigmentosa, Alzheimer's disease, cystic fibrosis, lipoprotein lipase and polycystic kidney disease.

[15] There is a further distinction between locus and allelic heterogeneity. Locus heterogeneity refers to mutations at different loci (or in different genes) that are capable of producing the same outcome. Allelic heterogeneity indicates that different mutations (or alleles) at the same gene produce the same outcome. My analysis focuses on locus heterogeneity.

effect as opposed to having this type of relevance to most or all of these instances. In order to see this, consider the case of Parkinson's disease, which has three different individually sufficient causes (C_1, C_2, and C_3). Appealing to any one of these causes (e.g. C_1) would fail to provide an adequate explanation of the population-wide disease trait, because no heterogeneous cause alone "makes a difference" to *all* instances of this trait. Similarly, targeting one of these factors will fail to provide causal control over most or all cases of this disease.[16] This, of course, is because some instances of the disease are caused by different causal factors entirely (e.g. C_2, and C_3).[17] Thus, one problem for heterogenous causes is that they have causal relevance and control of "narrow scope" over the type-level disease trait. Heterogeneous causes only "make a difference" to a narrow subset of all cases of the disease and they are not causally or explanatorily relevant to most or all cases of the population-wide disease trait.

Notice how this problem does not arise if a disease is causally homogeneous. For diseases that have homogeneous causal factors, these factors can be targeted to explain all (or most) instances of the disease at the population level. This is because homogeneous causes do "make a difference" to all cases of the type-level effect. Homogeneous causes have causal and explanatory relevance of "broad scope." These causes can be targeted to explain a large percentage of all instances of the population-wide trait. In addition to this explanatory advantage, this feature is also present in the type of control that homogeneous causes have over type-level effects. Homogeneous causes can be targeted to control, prevent, and cure, most or all instances of the disease in question. Again, this is because most of these instances have the same set of causes or causal etiology. Instead of aiming at a variety of heterogeneous causes, a single causal etiology can be targeted to achieve control over the population-wide disease. This helps reveal why it is valuable to identify diseases that meet this causal architecture and why there is a preference (and often assumption) that diseases have shared causal etiologies. Homogeneous causes provide a means of explaining and potentially controlling population-wide disease traits.

A second challenge posed by this type of causal complexity is that it introduces an additional question to be answered. This additional question is: why do *different* causes all produce the *same* effect? Something about this situation seem puzzling and in need of further explanation. We find situations of causal heterogeneity puzzling because they conflict with a common intuition that similar effects should have similar types of causes.[18] When this assumption is not met, we expect some further explanation for why this is the case. This puzzle is similar to cases of "universality" in science, in which some "universal" behavior is produced or exhibited by systems with vastly different microstructural or causal details (Batterman, 2002). For example, neurons with different physical details can exhibit the same firing behavior and microstructually distinct fluids can all exhibit similar features at their critical points (Ross, 2015; Batterman, 2002). We often find that these cases are puzzling and in need of further explanation. We want to know how the *same* behavior can be produced by systems with *different* microstructural details? This is similar to asking how the *same* type of disease can be produced by *different* causes. Physicians and medical researchers often expect complete disease explanations to provide some type of satisfying answer

[16] As Stegenga states, targeting these causes can "at best improve the health of a subset of people" with the disease in question (Stegenga, 2018, 67).

[17] However, notice that the control is uneven–C_1 can be used to reliably cause disease, but not to reliability prevent it. The causal framework that I rely on requires that causes have control over both contrasts of the explanatory target–namely, the presence and absence of the disease.

[18] We see this assumption in (Hume, 1738), for example.

to these questions.

Consider an objection to these purported challenges. I have suggested that heterogeneous causes fail to explain population-wide effects because they have limited causal and explanatory relevance. If this is so, why not just appeal to all of the heterogeneous causes for a population-wide disease trait? Why not appeal to a disjunctive set of causal factors that together explain all (or most) cases of the disease? One issue with this purported solution is that there can be far too many causes to make this a feasible approach. Recall that retinitis pigmentosa has anywhere from 75-300 causes and that some psychiatric disorders are thought to have many more. Expecting scientists to appeal to such a long list of factors is not a practical or realistic expectation and it does not appear to reflect actual biological practice. We do not find physicians and researchers explaining these conditions by citing hundreds of distinct causal factors. Second, this makes gaining control over the disease outcome much more difficult because of the vast number of causes that a treatment or preventive strategy would need to target. Scientists explicitly mention this in the case of retinitis pigmentosa: "[g]iven the large number of mutations that cause RP, strategies of gene therapy aimed at correcting each individual mutation may be an overwhelming task" (Chang et al., 1993, 602). They claim that finding some shared causal target "may be a much more practical approach because it would be applicable to multiple mutations" and, thus, offer treatment for multiple cases of the disease (Chang et al., 1993, 602). Third, this approach still fails to address the extra question raised by this causal architecture–namely, why do *different* causes all produce the *same* effect? Citing a disjunctive set of causes does not provide an answer to this question.

How do scientists address the challenges associated with causal heterogeneity? A first approach involves continuing to searching for some shared causal etiology that unifies the seemingly disparate heterogeneous causes. One way of doing this involves identifying a "final common pathway" that the upstream heterogeneous causes all converge on and operate through in producing the disease of interest. In this case, the convergence point of the final common pathway identifies some shared causal etiology for the disease. This shared etiology can be targeted to explain, control, and treat all (or most) cases of the population wide disease trait. For example, researchers hypothesize that the process of apoptosis (or regulated cell death) may be the final common pathway for the genetically heterogeneous disease retinitis pigmentosa (Chang et al., 1993, 595). In light of this hypothesis, they suggest that apoptosis "is a logical target for intervention for a variety of retinal degenerations" (Chang et al., 1993, 601). Targeting this final common pathway would provide a way of treating many cases of retinitis pigmentosa, no matter what their most upstream genetic causes are. This approach has another advantage. It provides an answer to the question of why different causes produce the same effect. In this case, the explanation for this is that the many different causes all funnel through the same causal process, which ultimately leads to the singular effect of interest. This final common pathway identifies causes that do "make a difference" to all (or most) cases of the disease in question and causes that can be targeted to explain, predict, and control all or most cases of the disease at the population-level. Alternatively, when a shared causal etiology can not be found, a second approach is used. This second approach involves dividing up and redefining the disease trait on the basis of the heterogeneous causes. Thus, when researchers discovered that Parkinson's disease is caused by three different individually sufficient causes, some suggested that "there is no single Parkinson disease" and that this category represents "several different diseases" (Weiner, 2008, 705)(Stayte and Vissel, 2014, 18). Both of these solutions restore causal homogeneity and the shared causal etiology standard. Furthermore, this second strategy reveals what means medical researchers and physicians are willing to go to meet the causal homogeneity and shared

causal etiology standards. They are willing to completely redefine disease traits.

5 Disease discovery and causation: A final complicating feature. These four causal architectures provide categories and distinctions that can apply to scientific contexts more generally. They specify four different ways that causal factors can relate to an effect of interest. However, there are aspects of this paper's analysis that pertain to medicine more exclusively. These aspects have to do with the fact that disease traits are often defined on the basis of their causes, while this is not always the case for other phenomena in science. This relates to an additional type of complexity involved in disease discovery and causation that deserves mention.

Recall the two step process for disease discovery, mentioned in section 2. The first step involves specifying some disease trait and its symptomology (D), while the second step involves searching for the causal factors (C) that produce this trait. In this sense, "discovering" a disease involves uncovering both its symptomology *and* causal etiology. In addition to this discovery process, recall that the gold standard for defining disease traits involves defining them on the basis of their causes. Disease categories are expected to meet particular causal requirements. Diseases are defined on the basis of factors that (i) provide causal control over the disease and that (ii) capture shared causal etiologies at the population level. If these conditions are not met, the legitimacy of the disease trait is questioned. Given this set up, consider the resulting dilemma. In order to search for the causes of a disease trait–and follow the established process of disease discovery–the trait in question first needs to be specified and defined. However, you cannot follow the gold standard way of defining the disease, because this requires knowing what its causes are and this is exactly what you are searching for. This captures a kind of catch-22 situation: you need to define diseases in order to search for their causes, but the best definitions of disease are supposed to reflect their causes. In other words, you need to define (D) to find (C), but the best definitions of (D) are supposed to reflect (C).

This situation forces psychiatrists and researchers to propose "best-guess" definitions of disease traits at the first step, before etiology is known at all. This captures how most of our current psychiatric disorders are conceptualized. The hope is that these "best-guesses" will define diseases in ways that track causes that meet various causal requirements (i, ii) for disease. However, there is absolutely no guarantee that they will be able to do this. In fact, not only is there no guarantee of this, but the researchers' ability to ultimately find these causes is highly dependent on the first guess that they make. They might choose to define a disease by symptom clusters that have heterogeneous causes and that lack any shared causal etiology. If this is the case, it will be much harder to identify the shared causal process that produces this disease, if none exists. As Hyman states, if researchers "select study populations according to a system that is a poor mirror of nature, it is very hard to advance our understanding of psychiatric disease" (Casey et al., 2013, 810). In this sense, discovering these diseases is highly is dependent on this first choice and on how diseases are initially defined. However, as captured in the dilemma above, this choice often needs to be made without knowing what the disease causes are.

Part of what this reveals is how disease classification influences causal discovery. Classification dictates where we shine the spot light in searching for causes. If diseases are initially defined in ways that do not track shared causal etiologies then this can complicate efforts to identify their causes. No matter how much you search among this group of patients, no shared causal process for their symptoms will be found, because none exists.[19] There are worries that the current classification

[19]This relates to the assumption that DSM categories group together patients with some shared biological

system in psychiatry–the diagnostic and statistical manual of mental disorders (DSM)–has defined diseases in ways that impede efforts to uncover their etiologies. In particular, there are worries that "these categories, based upon presenting signs and symptoms, may not capture fundamental underlying mechanisms of dysfunction" (Insel et al., 2010, 748). This leads researchers to refer to DSM disease categories as "diagnostic silos" and "epistemic blinders" that have not facilitated causal discovery, yet continue to be used in searching for it (Hyman, 2010) (Casey et al., 2013, 811). Researchers worry that the continued use of these invalided and "fictive" categories threatens to reify them as they continue to be used in diagnosis and experimental work (Casey et al., 2013, 811)(Hyman, 2010)(Morris and Cuthbert, 2012). Of course, we do not have proof that these categories lack shared causal etiologies–it may be that we just have not found them yet. However, the more we try to find these causes and the longer we go without making progress, the less likely this option seems.

Are there other ways to make progress in uncovering the etiologies of psychiatric disease? How should the field move forward? Some researchers caution against an approach of simply "replacing old flawed guesses with new guesses about disorder definitions" (Hyman, 2010, 171). It is not clear that our next guess will be any better or that this approach is ideal for psychiatric disease. Another way forward involves inverting the disease discovery process. Instead of starting with an effect and searching for its causes, this solution involves starting with causes and searching for their effects. This strategy has been associated with the newer research domain criteria (RDoC) framework. This framework creates a "new kind of taxonomy for mental disorders" that focuses first on phenomena (or constructs) at different levels of analysis and only then on the disorders they link up with (Insel and Lieberman, 2013). These levels of analysis include functional assessments of constructs at the level of genes, molecules, cells, neural circuits, physiology, behaviors, and self-reports (Morris and Cuthbert, 2012, 31). The hope is that by starting with more concrete physical processes helpful classifications might begin to emerge–classifications that may point to new disease divisions that are imperceptible within the current DSM framework. Instead of being constrained by DSM disease definitions, RDoC starts with potential functional impairments and tracks what downstream disease category they may lead to. As Casey et al. state "[a] main way in which the RDoC project will influence neuroscience research is that rather than taking a diagnostic group and attempting to discover its underlying neurobiological basis, the RDoC approach uses our current understanding of behaviour–brain relationships as the starting point and relates these to clinical phenomenology" (Casey et al., 2013). This allows researchers to start with potential upstream causes and search downstream for the effects, or disease categories, that they lead to.

While RDoC involves an inversion of the traditional disease discovery process it is likely that progress in unveiling the etiologies of psychiatric disease will involve more of a back-and-forth process. Researchers might start with causal factors, search for their effects and change how they isolate causes on the basis of what they find. Alternatively, they might start with a new disease category, search for its causes, and redefine the category on the basis of what they uncover. Where the goal is to link up particular causal processes with particular disease definitions, researchers will likely toggle back-and-forth between both causes and effects until they find the right match.

6 Conclusion. This paper has clarified four causal architectures and two types of causal complexity that are common in psychiatric genetics. Multicausality and causal heterogeneity capture

properties. Tabb refers to as the "assumption of diagnostic discrimination" (Tabb, 2015, 1048).

distinct types of complexity at the level of disease causation. This paper has examined how these types of causal complexity should be understood, how they challenge disease explanation, and how scientists are working to overcome these challenges. While aspects of this analysis pertain to biomedicine more specifically, these four causal architectures are likely to provide general categories and distinctions that apply to scientific contexts more broadly.

This analysis provides a different way to understand common claims that psychiatry is in a "crisis." First, it helps to clarify why explanation in psychiatry is difficult, without suggesting that psychiatric diseases are "intractable," "enigmatic," or beyond scientific understanding. In fact, this analysis reveals how scientific progress is being made in this domain. It reveals the sound methodologies that guide efforts to discover, understand, and explain psychiatric diseases, and it indicates that these methodologies are found in other medical subfields. Relatedly, it shows that these types of complexity are not unique to psychiatry, but that they are found in other areas of medicine. This is seen in disease examples such as PKU and retinitis pigmentosa, which exhibit multicausality and causal heterogeneity, respectively, despite being viewed as physical medicine or non-psychiatric diseases. Instead of being viewed as a defunct discipline in "crisis," psychiatry is better understood as a field that is at the forefront of disease discovery and that seeks to uncover and shed light on some of the more challenging diseases that confront all of medicine.[20] In many ways psychiatric is a "safe haven" for diseases of unknown etiology–it provides a place for these diseases to be taken seriously, scrutinized, and modified, so that they can be fairly judged on the basis of various foundational standards in modern medicine. The constant push for etiological understanding in psychiatry leads researchers in this area to explicitly reflect on the abstract principles that diseases are expected to meet–why such principles are important and when (if ever) they should be relaxed. These reflections reveal standards and methodologies that are not just found in psychiatry, but that are present throughout medicine more generally.

[20]Ironically, although psychiatry is sometimes criticized for only housing diseases of unknown etiology, once the etiology of some "psychiatric" conditions are uncovered, the resulting disease is often relocated to another area of medicine, such as neurology. This has occurred with various forms of dementia, which are now considered "neurologic" as opposed to "psychiatric" in nature. This can prevent psychiatry from receiving full credit for disease discovery. It seems unreasonable to criticize psychiatry for only (or mainly) dealing with diseases of unknown etiology, while at the same time recognizing that diseases are removed from this field once their etiologies are identified.

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