On the simple and the complex in psychiatry, with reference to *DSM 5* and Research Domain Criteria

Ridha Joober, MD, PhD

Douglas Mental Health University Institute and Department of Psychiatry, McGill University, Montréal, Que., Canada

> Plurality must never be posited without necessity.
> William of Occam

Aspiring to simple theories has been at the centre of the scientific quest to understand nature. In medicine, this aspiration found its best exemplars in diseases entirely attributable to specific causal factors, such as infectious diseases (microorganisms invading a body and being transmitted within populations) or Mendelian hereditary diseases (highly penetrant mutations transmitted within families). As desirable for their elegance and simplicity as these models may seem for all pathological conditions, they remain rather exceptional in medicine. Most human diseases are not causally simple, and psychiatric disorders are no exception. In contrast to many medical disciplines where biomarkers and gold-standard diagnostic tests have been well established, psychiatry nosology relies entirely on descriptive criteria, often in the form of behavioural disturbances and dysfunction, along with a few combinatory rules to define disorders. Patients' clinical presentations may differ drastically within the same diagnostic category. For example, it is possible to diagnose schizophrenia in 2 patients who do not share any symptoms. Also, using the current criteria for attention-deficit/hyperactivity disorder (ADHD), we can define more than 3000 different forms of ADHD by combining the 18 items listed in the *DSM IV*! This heterogeneity/complexity in phenotypic expression is often invoked as one of the major barriers to progress in identifying causal factors underlying psychiatric disorders and achieving the simplicity observed in Mendelian disorders or infectious diseases. Could this phenotypic complexity (plurality in Occam's dictum) be simplified to achieve causal discoveries, or is it necessary and irreducible?

In psychiatry, ultimate clinical descriptors will always rely on subjective complaints, such as sadness, anxiety, fatigue, obsessions and suicidality. Contrary to many other fields of medicine, these descriptors cannot and, I believe, will not be reduced to physical signs and symptoms that can be explained by other physical events in the same way that heart failure, for example, may be explained by a truncating mutation in a myosine gene (or other molecular failures). Nevertheless, this does not preclude the possibility that the current psychiatric syndromes, with their intrinsic subjectivity, could be reshaped in a way that their genetic, biological, neurological and psychological correlates will be easier to identify so that future classification of mental disorders will integrate some of these markers to achieve better definition of disorders and possibly better treatments.[1]

This theorizing has been rampant in psychiatric genetic research.[2] The concept of endophenotypes, or traits that are more prevalent in patients compared with the general population and that cluster in patients' nonaffected relatives, has been advanced as one of the means to study the genetics of schizophrenia and other mental disorders. These endophenotypes might be behavioural dimensions, electrophysiological abnormalities, abnormal brain structure or function, or cellular dysfunction. It is argued that complex psychiatric syndromes need to be deconstructed into simpler phenotypes to decipher their genetic underpinnings.[3,4] The popularity of this concept is evident in that a PubMed search for the term "endophenotype" (Mar. 21, 2013) yielded 1969 studies, most of which (1952) were published after the year 2000. This concept is often depicted by images where endophenotypes are midway between the risk gene and complex psychiatric disorders. These endophenotypes are also called "intermediate" phenotypes,[5] serving to bridge pathways to discovery from simple cellular effects to neural networks to more complex behavioural dimensions. It is also often stated metaphorically that endophenotypes are "closer" to the gene effect than complex disorders and that they represent simpler clues to genetic underpinnings. This simpler "geography" of behaviours and their determinants appeals to both clinicians and researchers. Indeed, the American Psychiatric Association (APA) task force on *DSM 5* proposed that a dimensional approach to psychiatric diagnoses be included in the *DSM 5* in the hope that such an approach would, among other things, improve the validity of diagnoses.[6] Parallel to these efforts,

the National Institute of Mental Health (NIMH) embraced the Research Domain Criteria (RDoC) initiative.[7] The thrust of this initiative "…is to define basic dimensions of functioning (such as fear circuitry or working memory) to be studied across multiple units of analysis, from genes to neural circuits to behaviours, cutting across disorders as traditionally defined." Its intent "…is to translate rapid progress in basic neurobiological and behavioural research to an improved integrative understanding of psychopathology and the development of new and/or optimally matched treatments for mental disorders."[8] Thus, both the APA with its dimensional approach and the NIMH with its "basic dimensions of functioning" suggest that the complexity of current syndromes is one of the stumbling blocks on the road to discovery and call for the use of dimensions or simple traits to solve, at least in part, the problems surrounding diagnostic validity and basic biological and therapeutic advances.

Remarkably, although these are major conceptual trends in our field, very little attention has been paid to the keywords and their meanings. How do we know that the proposed dimensions are simpler, closer to basic biologic mechanisms or even clinically more useful than the current categories? If we do not have a clear metric by which we can appreciate what is simpler, closer and basic, these concepts may become the "emperor's new clothes"! At least from the genetic perspective, these simpler, basic traits may be more complex than the syndromes they are supposed to deconstruct.

First, the fact that behavioural dimensions are part of the descriptors of syndromes (e.g., sadness is part of depression, hallucinations are part of schizophrenia) may entertain the idea that behavioural dimensions are included in syndromes. We logically think of parts being simpler than wholes. It is possible that this logical bias primes beliefs that sadness and hallucinations, being parts of depression and schizophrenia, respectively, are simpler than the composite diagnoses. However, these behavioural dimensions cross several disorders and are part of the normal repertoire of behaviours, which indicates that the part/whole relation between behavioural dimensions and syndromes is only an appearance.

Second, phenotypic heterogeneity/complexity is not necessarily equivalent to etiological/causal complexity. Examples abound in medicine where complex phenotypes associated with signs and symptoms in many organs and systems are traced to a single cause. For example, the Online Mendelian Inheritance in Man (OMIM) database lists more than 300 entries under "dwarfism," most of which are syndromes with specific causal mutations associated with several signs and symptoms in distinct organs. Had height, regardless of other features, been used as a dimension to decipher the causes of dwarfism, it might have been much more difficult to identify all these specific causal mutations. The same is true of mental retardation, for which more than 200 syndromes are listed in OMIM with specific mutations. Again, had we used IQ as the only dimension to identify causative genes, the task would have been much more difficult. This is because gene mutations, and probably other pathogenic factors, do not respect the constructs (e.g., height, IQ) that we deem important or relevant in medicine in general and psychiatry in particular.

Gene mutations are often pleiotropic; they affect multiple systems and lead to complex phenotypic presentations. In the 2 examples provided, and many more in medicine, it is the complexity of the phenotype along with its strong segregation in families that pointed to the genetic cause and led to a simple causal explanation: gene mutation. This same complexity helps to differentiate syndromic dwarfism from nonsyndromic short stature or mental retardation from low IQ. This differentiation is very important for causal models because nonsyndromic short stature and low IQ may be much more prevalent in the general population because numerous pathways (e.g., poor nutrition, toxins, infections, emotional neglect, polygenes) may lead to these quantitative extremes. In essence, complex syndromes help to identify specific entities that segregate in families and that are differentiated from other causes that are prevalent in the general population.

In the early '90s, Neil Risch introduced a metric that encapsulates the ideas presented in the previous paragraph.[9,10] This metric, called lambda siblings (λ_s), is the ratio of the prevalence of a disorder of interest in siblings of affected probands to its prevalence in the general population. Risch showed that this parameter is highly predictive of the genetic mappability of phenotypes; the higher the λ_s, the easier gene identification will be. High λ_s are essentially reflective of causal factors that are strongly shared within families and not shared by most of the general population, and they point to strong genetic factors and not much "contamination" by other causal factors widely distributed in the general population. All Mendelian disorders have very high λ_s (often > 1000), as they cluster strongly in siblings and they are very rare in the general population. If λ_s is low, this is often a reflection of low familial clustering and high prevalence in the general population, which in turn is often a reflection of multiple and prevalent genetic and environmental determinants underlying the phenotype in the general population. Such traits with low λ_s tend to be untractable from a genetic point of view; λ_s could be viewed as a metric of causal simplicity of a phenotype. How do endophenotypes, basic behavioural dimensions and behavioural traits stand the test of simplicity, as defined by λ_s? Although only a few studies have investigated this question, there is strong indication that they perform poorly. In 1 publication, λ_s for major endophenotypes related to schizophrenia were found to be very modest and lower than λ_s for schizophrenia as a syndrome, which is estimated to be around 10.[11] In another paper, λ_s for brain morphological changes were remarkably lower than 10 in all the brain regions.[12] Thus, using this simple metric, it turns out that what is supposed to be simpler than schizophrenia, at least from a genetic perspective, may in fact be more complex. This is because these endophenotypes are much more frequent in the general population, and their presence in a given individual may come about through many different pathways, only some of which are genetic and/or related to schizophrenia. Thus, it is possible that the syndromic definition of schizophrenia is in fact simpler, from a genetic perspective, than all the endophenotypes that have been proposed to simplify its genetic investigation! It is possible that aggregating all the signs and symptoms of schizophrenia under the same syndrome may be more

conducive to capturing the underlying pleitropy of genes involved in schizophrenia. At least we have a metric, λ_s, to attest to this, and not only images in our minds, logical as they may seem.

Another perspective in this debate about the simple and the complex is the one opposing the binary nature of syndromes to the quantitative, measurable nature of traits and endophenotypes. It is often assumed that if we can measure something, it is more amenable to scientific investigation than something that we can only categorize. Quantification is richer in information content than categorical approaches. Helena Kreamer, one of the leaders on the APA *DSM 5* task force, used this argument to illustrate the potential benefits of introducing quantitative approaches in *DSM 5* and how a dimensional approach could improve the power of genetic studies.[13] When making a binary diagnosis, we judge several items and decide, using an algorithm, whether a patient has a given disorder. This complex decision may be difficult to make reliably. The recent debate on the reliability of the diagnostic categories in *DSM 5* is a reminder of these difficulties.[14] It is true, though not without important caveats,[15] that endophenotypes or behavioural domains may be more reliably assessed using rating scales that are metrically well characterized. However, this reflects only better attention to methods and not whether the constructs being assessed are simple or complex. We can reliably evaluate the intensity of sadness using an assessment tool with several well-defined anchor points, but this reliability does not mean that sadness is a simple concept or that it is simpler than major depression. In fact all the diagnostic items used to define a psychiatric disorder can be evaluated with assessment tools, and specific cut-offs can be used to retain or reject each item to arrive at a final diagnosis. With such an approach, we can improve the reliability of categorical diagnosis to the highest level. But this increased reliability of measurement of behavioural dimensions and syndromes does not bear significance for the question of causal simplicity. Here again, if we use λ_s as a measure of simplicity, whether we use syndromes or cut-offs on quantitative rating scales to define syndromes, their simplicity will depend on how these entities cluster in families and on how prevalent they are in the general population. From this perspective, the more lenient the criteria used, the more prevalent these disorders will be in the general population. Unless these criteria result in a disproportionately greater clustering of these syndromes in families compared with the general population, λ_s will decrease, suggesting that the proposed criteria result in a genetically more complex and less tractable syndrome. It may then be expected that most of the revisions in the proposed *DSM 5*, which are more inclusive and more lenient, will result in increased prevalence of the disorders in the general population and possibly more heterogeneity and more complexity. Future validation of *DSM 5* changes of diagnostic criteria and RDoC proposed dimensions might need to calculate λ_s to gain a quantitative appreciation of the effect of these changes on genetic simplicity.

Pharmacology is a third perspective from which we can discuss the concepts of simplicity and complexity in psychiatry. Historically, the first effective psychotropic medications have been conceived as medications for diseases, as in most medical fields. Subsequent research has refined the effects of these drugs, which appear to be better conceived as drugs modulating specific behavioural dimensions rather than medications treating diseases. Neuroleptics may be better conceptualized as modulators of saliency, antidepressants as modulators of mood and benzodiazepines as modulators of anxiety. We can assume that these behavioural dimensions have some biological validity and that they are more amenable than syndromes to biological investigation. However, the response of a behavioural dimension to a drug may not say much about the causal simplicity/complexity underlying that behaviour. For example, inflammation responds to anti-inflammatories, but inflammation is a highly complex phenomenon provoked by many causes and physiological pathways. It is also clear that antipsychotics, for example, are modulators of the motor system, mood and appetite, to name a few. The same can be said for all psychotropic medications. Just as genes are pleiotropic and affect multiple systems, neuromodulator molecules interfering with neurotransmission are also pleiotropic and have a large spectrum of effects.

Other possible layers of complexity can be discussed in relation to the dimensional/trait approach proposed to simplify and streamline research in psychiatry (e.g., How do cut-offs on behavioural dimensions relate to levels of dysfunctions that are central to the definition of mental disorders? What is the stability of traits within participants over time?). The lack of clear definitions for many of the terms, including "basic," "simpler" and "closer," used in the literature is something we need to be aware of. It is important to identify the perspectives that we use (e.g., etiology, measurement, clinical description, therapeutics) and to clearly define what we mean by simplicity within each perspective. To my knowledge, only 1 metric akin to the concept of simplicity has been defined in relation to genetic causality, λ_s, and if we use this metric, most of what has been proposed as basic or simpler may in fact be more complex than the original syndromes that we are aiming to simplify.

The dimensional/endophenotype approach has been used in many empirical studies to help identify genetic and environmental risk factors for and other correlates of psychiatric disorders. Thus, we can ask whether these approaches have performed better than more traditional syndromes in research. Here again, I believe that the answer is a clear "no." Although literature comparing the 2 approaches is scarce, a few studies have investigated this question. Flint and Munafo[16] conducted a meta-analysis that sought to compare the success of molecular genetic studies using endophenotypes with those using traditional diagnoses. They concluded that the genetic effect sizes examined in relation to endophenotypes were not larger than those reported for syndromic phenotypes. Furthermore, even in animal models where quantitative measures of phenotypes relevant to psychiatric disorders are performed in model organisms using controlled laboratory experimental settings, the effect sizes of loci contributing to phenotypes closer to the biological basis of disease are not larger than those contributing to

disease itself.[16] My colleagues and I have also conducted a systematic review[17] of the effect size of popular candidate genes for ADHD in relation to several endophenotypes of relevance to this disorder. We did not identify any major gene effect beyond what is reported in genetic association studies where ADHD is taken as a binary diagnosis.[17]

Interestingly, with the advent of genome-wide association studies (GWAS), the syndromic and trait-based approaches can also be compared. Type 2 diabetes is an excellent example because it has been intensely investigated as a clinical syndrome, and many of its glycemic traits (e.g., fasting glucose, insulin) have been subjected to GWAS. Because these traits are to diabetes what endophenotypes are to psychiatric disorders, reflecting on findings from the diabetes field can shed light on our discussion. The literature very clearly indicates that glycemic quantitative traits are not simpler than type 2 diabetes. In a meta-analysis that assembled 46 186 non-diabetic and 76 558 replication individuals, 16 loci associated with fasting glucose (i.e., the defining feature of type 2 diabetes) were identified.[18] In contrast, a recent meta-analysis comparing 34 840 patients with type 2 diabetes with 114 981 controls, 62 loci (10 new and 52 previously identified) were significantly associated with diabetes.[19] Although it is difficult to compare these results without a better understanding of the statistical power and other methodological aspects, it is clear that GWAS of type 2 diabetes have better yields than those of glycemic control traits. Even more interesting is that many of the loci implicated in glycemic control are not implicated in type 2 diabetes and vice versa. The lesson here is that even with disorders that are much better defined than psychiatric disorders and with quantitative traits that are quintessential to their definition, using quantitative endophenotypes did not improve gene detection despite fasting glucose and type 2 diabetes having equivalent heritability[20,21]

In conclusion, with the advent of genomics, we are learning that the causal architecture of human complex disorders and complex traits is many orders of magnitude more complex than we may have believed. Psychiatry, with its quintessential reliance on human subjectivity, is probably even more complex. The purpose of this editorial is to discourage the indiscriminate and misleading use of words like "simpler" and "closer." Whether they express themselves along deconstructed behavioural dimensions of syndromes or along reconstructed syndromes of behavioural dimensions, clinicians need both approaches to be able to understand their patients. Scientists also will need to work on both aspects, to face the tremendous challenge of complexity and to explain the risk architecture of syndromes and their defining behaviours. Nothing is simple about behaviour. The simple/complex discourse in literature is a distraction.

Competing interests: See cma.ca/jpn/editorial_board.

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