Simulation of Mental Disorders: I. Concepts, Challenges and Animal Models

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ABSTRACT

The complexity of the human brain and the difficulties in identifying and dissecting the biological, social and contextual underpinnings of mental functions confound the study of the etiology and pathophysiology of mental disorders. Large-scale computer simulation of the human brain was recently proposed as a method to circumvent some of these difficulties. In this two-part paper, we discuss selected conceptual and pragmatic issues pertaining to the mental illness simulation in general and computer simulation in particular. We address the merits and limitations of two generic types of simulation vehicles, biological simulation in animal models (Part I) and virtual simulation in computer models (Part II), in the study of mental disorders in humans. We point to the need to tailor the vehicle and method of simulation to the goal of the simulation, and suggest future directions for maximizing the utility of mental illness simulation. We argue that at the current state of knowledge, the biological-phenomenological gap in understanding mental disorders markedly limits the ability to generate high-fidelity biological and computational models of mental illness. Simulation focusing on limited realistic objectives, such as mimicking selected distinct biological and phenomenological attributes of specific mental symptoms, may however serve as a useful tool in exploring mental disorders.

Simulation and Mental Disorders

Simulation refers to the process and product of making something appear or perform like something else (1). Accordingly, the concept of simulation can be broadly related to the concept of mental illness in various ways. For example, a defendant without mental illness can simulate a psychotic disorder in order to be exculpated from a punishment for a crime committed; a simulator of a fear-inducing stimulus, situation or activity (such as flying) may be used in order to treat patients who suffer from specific phobia disorder; or, scientists may provide beer to their laboratory rats with the aim of simulating alcohol use disorder in humans. These different semantic connections have in common the attempt to make a copy (object) look or function like the original (target). A criminal defendant (object) tries to look like a person who suffers from a psychosis (target); the flight simulator (object) is designed to emulate a real flight in an aircraft (target) and the scientist tries to mimic alcoholism in human (target) via the intoxicated rats (object). While the target or the original are real entities, the simulated object functions as an imitation of reality.

There is thus an inherent ontological gap between targets and their simulated objects. This gap can be illustrated by the “simulator sickness” phenomenon, namely, a condition where a person experiences in a simulator symptoms (e.g., headache, nausea, sweating) that he does not experience in performing the simulated task in reality. In the case of a driving simulator (2, 3), the “simulator sickness” phenomenon arises from the discrepancy between the real experience of driving (target), which is perceived by the brain via the visual, vestibular and somatosensory systems, as opposed to the simulated experience of driving (object) which in common computerized simulators relies solely on the visual system while the body remains in a relatively fixed state.

Another manifestation of the gap between targets and their simulated objects relates to the criminal system. In spite of the chance to evade punishment by raising the insanity defense plea, in many countries this plea is seldom raised and only rarely accepted (4-6). This reality probably

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emanates, at least in part, from the complexity involved in convincingly mimicking mental disorders.

In other words, in the real world the gap between targets and their simulated objects is quite significant. Thus, it is not surprising that the main practical and philosophical challenges pertaining to the concept of simulation is to clarify the nature of similarity between the simulated object, the copy, and the original target, or the reality (7-9).

However, there is also another important aspect of mental illness simulation, which gains increasing attention in the scientific and clinical community. Simulation is a major tool in experimental science (10). Can we apply it to the analysis of mental illness, namely, can we simulate mental illness using scientific approaches in order to be able to understand better the biological and contextual underpinnings of that illness? An example was recently provided by a European Flagship Project, The Human Brain Project (HBP) (https://www.humanbrainproject.eu/). The major, hotly debated goal of HBP is to simulate the human brain on a computer. The leaders of this project posit that this would permit simulation, and furthermore understanding, of mental disease. In that case, the gap between simulated objects and their real targets leads to the following type of questions: What could be the scientific vehicles for simulating mental disorders in general, and what are their merits and limitations? Is it at all possible to effectively simulate mental disorders in biological models and in silico, and if so, what are the main challenges of such simulation and how can they be addressed? What is the expected realistic contribution of simulation to our understanding of mental illness?

We will first address the unique challenges involved in simulating mental disorders in general, in light of the phenomenological approach to mental disorders of the Diagnostic and Statistical Manuel of Mental Disorders (DSM)(11). We will then proceed to discuss two major scientific vehicles, or types of models, for human mental illness simulation: the animal model (in this paper) and the computer model (in the second paper). The merits and limitations of each vehicle will be outlined.

THE CHALLENGING NATURE OF MENTAL DISORDERS

Before embarking on the discussion of types of mental illness simulation, it is pertinent to discuss the definition of mental disorders and why mental illness simulation is inherently an exceedingly challenging task.

Given that the spectrum of mental disorders is wide and that each entity may be defined in various, even opposing, ways (12), an in depth discussion pertaining to multiple approaches to the definition of types and tokens of mental illness far exceeds the scope of this article. Instead, we focus on arguably the most prevalent perspective on mental illness, especially in the realm of medical practice, which is the phenomenological approach of the Diagnostic and Statistical Manual of Mental Disorders (11). At the same time, we will argue that mental illness simulation should also refer to the biological layer of mental disorders (13, 14), currently excluded from the most recent edition of the manual, DSM-5.

Mental disorders, according to DSM-5, are defined by the presence of a combination of symptoms (and to a much lesser extent, also signs) – which are not the result of another identified medical condition or a chemical substance – conjointly occurring at a certain period of time. In addition, these symptoms must have deleterious effects on the individual's psychosocial functioning. Thus, mental symptoms, which consist mostly of behaviors, emotions and thoughts, are, according to this zeitgeist, the building blocks of mental disorders.

Mental disorders differ from each other either by the presence of different symptoms or by different combinations of the same symptoms. The fact that mental disorders are defined mainly by symptoms leads to various practical and theoretical problems whose full exploration again exceeds the scope of this article (12,15-17). We focus here only on selected key features of mental disorders in order to highlight the complexity which is involved in attempts to simulating such disorders.

a. Most mental symptoms, as defined by DSM-5, are not objective biological entities but rather subjective experiences, usually expressed by verbal self-reports (18, 19). There are no specific objective biological findings that are consistently associated with specific psychiatric symptoms. Theoretically, not only that the same symptom may emanate from different brain biological pathologies, but a pathological finding in the brain does not necessarily or consistently lead to a specific behavioral or mental symptom (20, 21). Moreover, even with regard to the relatively few cases in which a relationship between a specific mental disorder and specific brain pathology has been established, the relationship may be correlational rather than causal (22). As a result, a gap exists between the clinical phenomenon of mental dysfunction and the malfunctioning brain.

In addition, the DSM’s phenomenological categorization is a man-made epistemic taxonomy which may differ from natural types, i.e., from natural clusters of
phenomena. Namely, the phenomenological categorization of mental symptoms and disorders put together diverse, and even existentially opposing, phenomena that may each represent distinct brain-suberved entities. For example, hearing an unreal voice is being categorized as “auditory hallucination” (one of the “building blocks” of schizophrenia), regardless of the content of the voice. However, it is possible that a brain-state that “generates” a negatively-oriented voice that commands a person to jump to his death from a bridge in order to pay for his sins is functionally different from a brain-state that “generates” a positively-oriented voice that calls the person to buy a fancy car because he is about to be the next Prime Minister. To put this argument differently, from a Kantian perspective, epistemologically, we find it useful to think of these two phenomena as a single category. However, we should keep in mind that ontologically these two phenomena may be quite far from each other in terms of the biological underpinnings in the brain.

b. Following the previous point, personal life events and memories may lead to diversity pertaining to the biological manifestation of the same mental disorder among different individuals, since many facets of mental disorders are related to personal life events and memories (e.g., the source of a specific traumatic event, the content of negatively-oriented thoughts in depression, etc.). In fact, it is tempting to assume that at least from the perspective of the brain, Tolstoy’s famous dictum: “each unhappy family is unhappy in its own way,” may theoretically be true as a general principal for many psychiatric disorders, since the illness of each individual may be tightly interwoven with his or her personal memories, identity and biography (which are reflected in the brain’s biology).

c. A symptom is not a disorder. For example, anhedonia, one of the core symptoms of depression, may be considered a normal response in the context of grief (23, 24). Thus, the presence of symptoms (and possibly their neurobiological correlates) does not necessarily indicate psychopathology.

d. Many psychiatric symptoms are not pathognomonic to any specific disorder. For example, concentration difficulties may be part of depressive disorders, generalized anxiety disorder, post-traumatic stress disorders, and/or attention disorders (11).

e. Many mental disorder as currently defined in medical practice may be manifested by different combinations of symptoms. Hence two individuals may share the same diagnosis in spite of the fact that they have no shared identified symptoms. For example, schizophrenia may be diagnosed based on the combination of delusions and hallucinations or the combination of grossly disorganized speech, behavior and negative symptoms. Put differently, there is a wide phenomenological variability, in terms of symptoms, even among the clinical population of a single psychiatric disorder.

f. Mental symptoms are usually dynamic and manifested in fluctuating episodes while psychiatric diagnosis is rather stable. During “symptom-free” periods of the illness the diagnosis is still in place though it may be usually regarded as “in remission” (25). For example, a person who underwent a single manic episode (which by-definition may continue for only seven days) is being permanently diagnosed with Bipolar I Disorder. Since psychiatric symptoms may wax and wane over time, there may be a loose chronological association between an established diagnosis and the symptoms that served as the basis for establishing that diagnosis.

g. The rate of co-morbidity in psychiatry, namely, the presence of more than one psychiatric disorder in the same individual, is estimated to range from 44% to 94% (26, 27). In other words, most psychiatric patients are diagnosed as suffering from more than one mental disorder. Thus, in reality the borders between mental disorders are less distinct than the DSM seems to connote, and patients’ pathological brain entities are often not restricted to a single disorder.

THE CHALLENGE OF MENTAL DISORDERS SIMULATION

The foregoing argumentation attempted to illustrate the complex multi-dimensional characteristics of mental disorders. Hence in order to fully simulate mental disorders, not only would it be necessary to duplicate the symptoms correctly, but it should also be required to capture the dynamic and multi-dimensional nature of mental disorders, the clinical inter-individual diversity, the change of symptomatology over time, the presence of the same symptoms in different disorders, and the co-existence of different disorders in the same person at the same time. On top of these requirements, which relate to the phenomenology of the mental disorders, there is an additional set of requirements, which relates to the neurobiological, mechanistic underpinnings of this phenomenology. Thus, mental illness simulation should include two interrelated and complementary components: the biological and the phenomenological.
The biological component relates to the anatomical and physiological aspects of the brain's function and malfunction at multiple levels of organization and description, from molecules and cells to brain circuits and systems. In addition, simulation should include the phenotypic components of mental disorders expressed in behavior, emotions, and thought. Ideally, one would hope that these two components should be interrelated to each other in both bottom-up and top-down manners, so that a change in one will be accompanied by a detectable change in the other. For example, a modification in the neuronal level will result in a perceptual or a cognitive abnormality (bottom-up), and the presence of a perceptual or cognitive abnormality will be accompanied by a change in the cellular level (top-down). Thus, a major challenge for brain simulation (and mental illness simulation) is to bridge the gap between biology and phenomenology by equally mimicking all relevant aspects of brain functioning.

However, is this realistic? Given the aforementioned dynamics and heterogeneity of mental disorders (DSM-5); the high-dimensionality and assumed stochasticity of some intralevel processes in the brain (e.g., 28, 29); and the possibility that different levels of brain function may up to a point be agnostic to intralevel mechanistic processes in each other (30), we posit that a reductionist approach focusing solely on biology, or similarly on computational models built on canonical models of elementary building blocks of neuronal function (e.g., 31), will likely remain far from being able to capture the full phenomena of mental disorders. We also do not share the hope, mostly practiced implicitly, that deus ex machina will liberate the bottom-up approach to realistic mental disorder simulation from its limitations. Similarly, a phenomenological approach neglecting the biological underpinnings is expected to be of limited validity.

It is noteworthy to emphasize that, the aforesaid theoretical and practical considerations notwithstanding, the DSM phenomenological approach itself leads to a multi-layer gap between symptoms, disorders and their biological underpinnings in the brain. First, there is the “demarcation gap” that relates to the unsteady borders between symptoms and mental disorders. In addition, there is the “biological gap” between mental symptoms (or disorders) and their biological correlates in the brain. Finally, there is the “causality gap” which emanates from the fact that biological correlates may not be causal. These gaps render the task of mental illness simulation a priori difficult.

One can argue that this boundary conditions induced by the DSM reflect the overall weaknesses of the DSM phenomenological approach to mental illness diagnosis, rather than an inherent issue in mental disorders simulation. We concur that the DSM phenomenological approach is far from being perfect. Nevertheless, as long as the phenomenological approach to mental disorder is the predominant one – due to the fact that from a clinical perspective it is probably the most useful practical system available at this point – researchers who aim to simulate mental disorders cannot escape the biological-phenomenological gap challenge.

We now turn to discuss one major type of vehicles, or classes of models that are currently pursued in an attempt to approach mental illness simulation – the animal models, that attempt to simulate mental disorders in non-human species. The other type, computational models (i.e., an attempt to simulate mental disorders by mathematical models on a computer), will be discussed separately (32).

**THE ANIMAL MODEL APPROACH: NOTES ON HISTORY**

The animal model approach rests on the premise that findings potentially relevant to mental disorders could be inferred and transferred from the study of one species to another. This is often taken as a given, but could be questioned.

The epistemological leap from animals to humans is quite axiomatic in biology nowadays, yet the possibility that animals and humans are sufficiently similar to the extent that animals are capable of modeling humans is embedded in a long and convoluted history. Anthropomorphism was, and admittedly still is, common (33), culminating in the past even in the relegation to farm animals of human legal responsibility followed by prosecution in court (34, 35). However, in the context of our discussion, it is pertinent to note that highly influential cultural discourses made a clear distinction between the mental world of humans and non-humans, and considered the assumption of similarity erroneous (36). Dualistic views held explicitly by Western religions and some schools of philosophy and implicitly by many others, set clear boundaries between mind and body. According to many variants of religious beliefs, the structure of the universe is rigidly hierarchical by God(s) design, and animals are perceived as different and inferior to humans (37). Accordingly, it was argued that animals cannot serve as models for understanding humans’ maladies (38), let alone mental ones. A major controversy pertaining to the cognitive capacity of animals was directly related to the dispute about the similarity between animals and humans. Aristotle (followed by Augustine, Aquinas, Leibniz and Kant) denied thought and reasoning faculties in animals,
while other scholars, such as Galen and Locke, tended to disagree. The debate continued, for example, in the dispute between Descartes, who basically accepted the Aristotelian approach, and Hume who strongly argued against it (39).

During the sixteenth and seventeenth centuries, comparative anatomy conducted by Vesalius, Harvey and others, showed that important similarities exist between human bodies and non-human animal bodies (37). In the nineteenth century the dispute continued with the addition of new theories pertaining to evolution and physiology. The study of animals as models of humans was justified on the basis of different, at times even contradictory, views. Bernard argued that both humans and animals shared a mechanistic biology and therefore animals can foster the understanding of human biology (37). Darwin argued that animals are not mere machines but rather have cognitive capacities similar to humans (37). The Behaviorists’ work, as well as Pavlov’s, further consolidated the idea that animals and humans share mental operations that underlie their behavior (36). On top of it all, the highly productive reductionist revolution in biology demonstrated the shared molecular and cellular building blocks between even the simplest of organisms to those on the top of the evolutionary ladder, reinforcing the argument that animal models are not only valid models for neurological and some mental and cognitive functions, but also extremely useful models (40).

The above developments have gradually led to a paradigm shift pertaining to the legitimacy of studying human biology via animal models, and today animal models are being widely used in medicine (41, 42) in general, and in psychiatry in particular (43–51). Nevertheless, there is an ongoing controversy with regard to the validity and utility of this approach (52–55). One of the major contributions of animal-model simulation of human behavior and mental disorders relates to the intellectual effort that has been invested in order to address the unique methodological and theoretical challenges that are involved in animal models. Different measures, such as construct validity, face validity, content validity, and predictive validity, have been suggested in order to maximize the validity of animal-model simulation (56). These measures refer to different dimensions of similarity between the simulated copy and the original target, including the cause of the disorder, how well the model captures the various aspects of the disorder, and so on. A strong animal model shows high similarities in constructing, facing, and predicting validity as the human disease (57).

In spite of the remarkable methodological and technical developments in the study of animals as disease models, there are still scholars who doubt the validity of the approach (58–60). Consider for example the relatively basic physiological process of bone fracture healing. It may intuitively seem that this process is quite elementary and therefore much discrepancy between animal and humans with regard to bone healing should not be expected. However, there is wide variation in the biochemistry, biomechanics and anatomy of normal bone to the extent that healing processes between and within species do not necessarily reflect the properties of human bone (61–64).

Another illustration of the dissimilarity between animals and humans can be borrowed from toxicology (65). A pharmacological substance may be harmful and ineffective in animals but tolerated and useful to humans and vice versa. For example, penicillin is fatal for guinea pigs but well tolerated by humans; aspirin is teratogenic in many non-human species but not in humans (66), and thalidomide is teratogenic in humans but not in many other species (67, 68). In fact, so far it is almost impossible to a priori predict which animal would be the right model for a certain process or disease in humans and there is in most cases no way to know in advance whether a certain finding in animals can reliably be applied to humans. Because of space limitations, only a few highlights of the merits and limitations of animal-based simulation of mental illness are presented below.

**ANIMAL MODELS OF MENTAL DISORDERS**

Animal models are increasingly used in psychiatric research (for a few selected examples, see Table 1). The two major goals are elucidation of the behavioral and physiological mechanisms of psychiatric diseases, and assessment of behavioral and pharmacological treatments (57).

It is methodologically useful to dissect the actual and expected efficacy of the animal model approach in psychiatry by noting different biological levels, or levels of complexity, starting from the molecular and cellular and culminating in the systems and behavioral levels.

In general, it can be posited that a higher degree of resemblance may exist between humans and non-human species at the molecular and cellular level than at the systems level. The assumption is that basic building blocks and processes are evolutionary conserved across species; smaller resemblance is assumed as the level of analysis proceeds bottom-up (45). Yet in spite of this intuitive assumption, as has been briefly illustrated above with regard to bone healing and toxicology, the difference between basic physiological processes of animals and humans (and between
ently, the construct validity of the pathophysiological-based simulation is focused on the biological processes that are partially understood, such as Huntington's disease, an animal model may be useful and productive as long as the genetic and biochemical pathophysiological process are poorly understood. Thus, it is tempting to assume that with regard to more complex psychiatric diseases in animals is much more challenging. However, the applicability of the results with regard to humans might be limited to the biological, rather than the clinical dimension of the disease. In other words, the construct validity of the animal model of Huntington's disease is high since it basically simulates the same biological target. Therefore, it would be valid to test the biological effect of a pharmacological agent on Huntington's disease-induced monkey (70) or mice (71) as a model for Huntington's disease in humans.

Furthermore, given the fact that human high-level mental capacities are significantly different from those of animals, simulating psychiatric diseases in animals is much more complex than simulating somatic illnesses. With regard to specific neuropsychiatric disorders for which the underlying genetic and biochemical pathophysiological process are partially understood, such as Huntington's disease, an animal model may be useful and productive as long as the simulation is focused on the biological processes that are quite similar among humans and animals (69). Put differently, the construct validity of the pathophysiological-based animal model of Huntington's disease is high since it basically simulates the same biological target. Therefore, it would be valid to test the biological effect of a pharmacological agent on Huntington's disease-induced monkey (70) or mice (71) as a model for Huntington's disease in humans.

However, the applicability of the results with regard to humans might be limited to the biological, rather than the clinical dimension of the disease. In other words, the construct validity of the animal model of Huntington's disease would be lower with regard to the expected therapeutic clinical effect (i.e., in terms of alleviating the symptoms of the disease) as opposed to its effect on modifying the pathophysiological biological process (unless there is a strong association between the pathophysiological biological process and the clinical condition). Unfortunately, for most psychiatric disorders, the underlying pathophysiological biological process is poorly understood. Thus,
there is currently no credible way to validate (or falsify) an animal model to learn more about the pathophysiology of the human disorders.

The symptoms-based animal model of mental disorders, which attempts to mimic psychiatric disorders via copying symptoms that comprise the disorders, could be raised as an alternative to the biological-based animal model. The focus on symptoms as a strategy to overcome the problems that are involved in mental illness simulation seems, however, methodologically dubious. To illustrate this point, let us examine the case of schizophrenia. According to DSM-5, in order to be diagnosed with schizophrenia a person must suffer from at least two out of five of the following symptoms (including one of the first three): delusions (unrealistic thoughts), hallucinations (unrealistic perceptions), disorganized speech, grossly disorganized behavior, and negative symptoms (e.g., diminished emotional expression or avolition). These symptoms consist of damaged complex mental capacities, including cognitive misinterpretation of the external reality, inappropriate use or interpretation of language, improper social interaction, and a deviation from expected human behavior. These pathological characteristics are "mental" by definition. There is no evidence that most of them exist as distinct things outside the realm of highly developed mental capacity. Therefore, any attempt to simulate schizophrenia in animals, whose mental capacity lacks these distinct mental things in the first place, would be inadequate. Although certain psychiatric disorders may be better candidates for animal simulation than schizophrenia (especially anxiety disorders in which physiological symptoms are more prominent), the mental component is ubiquitous in all psychiatric disorders. Therefore, the methodological problems of the symptom-based animal model cannot be disentangled by restricting this methodology to only a few psychiatric disorders.

Another problem concerning the symptom-based animal model in psychiatry relates to the limited content validity of this approach. For example, "learned helplessness" (72, 73) consists of behavioral changes in animals due to inescapable and unavoidable stress. The animal fails to escape aversive stimuli in subsequent tasks where escape is possible (74, 75). These changes indeed resemble behavioral patterns that are characteristic of major depressive disorder and post-traumatic stress disorder (76, 77). Nevertheless, as clinicians can attest to, these multidimensional disorders are very different from the isolated behavioral pattern of learned helplessness. As a result, the content validity of learned helplessness with regard to major depression is low since it fails to encompass the entire phenomenon of major depression (78).

The ontological gap between animals and humans in terms of their mental capacity and, in turn, the difficulty in mimicking mental disorders in animals, have brought some scholars to the notion that there is a need for a paradigm shift from animal models to model animals (i.e., models in animals), especially for complex disorders such as schizophrenia (79, 80). Hence, whereas "animal models" attempt on the whole to copy a human disorder in animals, the "model animals" paradigm utilizes animals to clarify only a specific aspect pertaining to a mental disorder (81). Indeed, the advantage of using model animals rests on the fact that it could potentially reveal apparent causal relationship (e.g., the role of genetic mutation in causing cellular pathophysiology) rather than mere correlation (such as in human-based imaging studies). However, instead of trying to create abnormal animal behaviors that phenotypically resemble aspects of mental disorders in a realistic way (e.g., "animal models" of schizophrenia), the "model animals" approach suggests that we should try to strategically test a specific hypothesis using the most appropriate organism which is relevant to the specific question under investigation, for example, to study the mechanisms of disease by developing animals with the molecular and cellular abnormalities found in mental disorders (i.e., model organisms). According to this view, the usefulness of animal model simulation depends on how well it answers the distinct and specific question it is being used to answer rather than its capacity to duplicate the cohort of disease symptoms (82).

Another approach that has been suggested in order to address the usefulness of simulating mental disorders in animals is based on a shift from trying to simulate disorders to an attempt to simulate an individual symptom (83). As opposed to the "animal models" approach, this approach focuses on mimicking the phenomenological layer of mental disorders. Downgrading animal models from being a representation of psychiatric disorders to models that simulate a single symptom as a component of a psychiatric disorder may be a more realistically attainable goal. The accumulation of data pertaining to specific symptoms may then gradually enable us to better understand psychiatric disorders which consist of the studied symptoms. However, in the short run, the adoption of this approach would necessarily minimize the predictive validity of the findings with regard to the targeted psychiatric disorders under investigation.
SUMMARY

This is the first of a two-part article pertaining to the enterprise of mental disorders simulation. In this article we first discussed the concept of simulation in the context of mental disorders, and the complexity that is involved in simulation of mental disorders given the unique characteristics of mental illness. A major type of mental illness simulation – using animal models as simulation vehicles – has been presented, including a suggested typology of the different kinds of mental disorders simulation in non-human species. The other major type of mental disorders simulation, involving virtual, computational models, is the topic of the second part of this paper, along with a discussion pertaining to the purpose of mental illness simulation and its potential future directions.

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