What Is the Role of Theories in the Study of Schizophrenia?

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This issue of Schizophrenia Bulletin includes several articles offering updates on some of the major theoretical perspectives on the etiology and pathophysiology of schizophrenia.2–4 In developing this section, the guest editors had in mind that theories are important at this stage in the evolution of this branch of science. That is, a body of knowledge has been developed, consisting of a basic set of empirical observations about schizophrenia that a theory of the disorder should account for.5 This formulation is implicitly a statement of the relative maturity of the field. A sufficient number of observations or “facts” about schizophrenia have come to light to permit the development and testing of theories that can account for particular sets of these observations. Given this, it seems pertinent to ask how should these theories then be used in guiding research on schizophrenia? How do we select between them to the extent that they compete with each other in explaining certain aspects of the disorder? How could we maximize the effectiveness of theories of schizophrenia in advancing our understanding of this disorder? In developing some possible answers to these questions, it may be instructive first to review briefly some basic philosophy of science principles concerning the changing role of theories in the evolution of field and to evaluate the relationship of theories to the types of phenomena that are deemed relevant for study.

The Evolving Role of Theory in Science

The role or definition of theory varies across different domains of inquiry. In this discussion, I will use concepts and definitions that pertain to the natural sciences, within which the field of schizophrenia research resides. In the early phase of a developing branch of natural science, the focus is on elucidating a set of basic observations, rather than on building or testing theories, because the latter approaches naturally constrain the range of observations deemed important, and it is generally premature to constrain the scope of observation until a sufficient number of important “facts” are brought to light. As such a knowledge base accrues, a natural progression of the field is the development of theories, using inductive principles, to explain particular sets of the accrued observations. One notices patterns of observations and builds models of the phenomena that account for these patterns or co-occurrences. In this phase, theories come “after the

As an epilogue to the themed papers on “Theories of Schizophrenia” in this issue of Schizophrenia Bulletin, this article reviews some basic philosophy of science principles in regard to the role of theories in the evolving state of a natural science discipline. While in early phases inductive and abductive logic are the primary vehicles for organizing observations and developing models, when a critical set of “facts” have been elucidated which can be explained by competing theoretical perspectives, hypothetico-deductive logic provides a more robust and efficient approach to scientific progress. The key principle is to determine where two or more theories predict different observations and then to devise studies that collect critical observations—correlations or experimental outcomes that are predicted differentially by the competing theories. To a large extent, current theories of schizophrenia (eg, focusing on aberrant dopaminergic signaling, neural dysconnectivity, and disrupted neural development) are not (and are not intended by their authors to be) mutually exclusive of each other. Rather, they provide explanations that differ in relative emphases, eg, on distal vs proximal causes and on broad vs narrow behavioral end points. It is therefore possible for all of them to be “right” at least in a general sense. This non-exclusivity is problematic when considered in light of the strong inferences principles characteristic of a mature natural science discipline. The contrast points are likely to be found in constructions that integrate influences across different levels of analysis, as in additive vs interactive models, direct effects vs mediation models, and developmental vs deteriorative models.

Key words: schizophrenia/theory/philosophy of science

The human intellect cannot grasp the full range of causes that lie behind any phenomenon. But the need to discover causes is deeply ingrained in the spirit of man.—Leo Tolstoy1

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fact” of the empirical observations but represent models that could explain such observations and be used to predict future observations. This approach is limited, however, because multiple models may account for the same pattern of observations and may make the same predictions concerning future observations. Given that the competing theories were derived from the data rather than used to generate observations that could provide critical points of contrast between them, there is not an obvious way of determining which is correct. As a result, abductive logic tends to be used to make inferences about which theory provides the best explanation. In this approach, a given theory may come to be seen as the most likely to be correct if it accounts for more observations than its competitors. Abduction clearly has a major role in a maturing branch of science and also suffers from a significant weakness in that it does not allow one to exclude competing theories.

In the mature phases of a field, theories are tested using hypothetico-deductive principles. That is, theories guide the design of experiments by specifying conditions or observations that constitute critical tests of a theory. These critical tests (hypotheses or little theories) have the form of a deductive proof focusing on falsification: theory X predicts A and not B; if B is observed, then theory X is not correct. Given that at its heart, a theory is a model of causation, experiments provide the foundation for conducting critical tests of causal hypotheses because the predicted causal factor is made to be present in one condition and not another, holding all other things constant. This experimental-deductive approach allows for the efficient refinement of theories by specifying what observations are most important and by a rather straightforward accounting of whether particular theories do or do not account for those critical observations. It should be noted that a theory may specify some form of prediction that is lawfully borne out by data but nevertheless fail to explain fully the underlying causal mechanism. This would likely be considered a “partial” account of the phenomenon.

The Role of Theory in Experimental Vs Correlational Science

A major source of difficulty in translating this hypothetico-deductive approach into the study of psychiatric disorders such as schizophrenia is that, outside of treatment studies and animal models, true experimental manipulation of hypothetically causal factors is clearly not ethically possible. Thus, for the most part, studies in this field assess for correlations between different naturally occurring variables. Given that correlation does not equate with causation, and considering that theories are fundamentally models of causation, how could theory be relevant to the design of studies that cannot experimentally manipulate the putative causal factors?

Theory still plays a role in correlational studies either explicitly or implicitly, depending on whether a theory guides the selection of variables for study or the interpretation of the patterns of association among those variables or both. Consider what is shown in a correlational study: A covaries with B. Theory X may specify that A causes B. The problem is not so much that theory X is not relevant to the kind of observation (because theory X in fact predicts that A will covary with B) but rather that this kind of observation cannot by itself tell us whether theory X is correct or whether it provides a better account of the A-B relationship than other potential theories (e.g., A and B are correlated because both are caused by C).

In fact, it is possible to apply the strong inference principles of experimental-deductive science to correlational science by focusing on the contrasting predictions of alternative theories. This approach may be applied to theories that represent “complete models” of schizophrenia or to theories that compete in their explanation of a particular feature or observation. One first develops a list of all the things that must be true if theory X is correct. If theory Y is its major competitor, one does the same for theory Y. The next step is to determine where the two theories predict different observations. Observations that are predicted by both theories are of much less interest because those observations cannot be used to determine which theory provides the better account. Studies are then designed to collect critical observations (correlations that are predicted differentially by theories X and Y). If a correlational study attempts to disconfirm an alternative theory at the same time as it affirms a prediction of a preferred theory, it will be employing the principles of deductive logic required for strong inference concerning causal hypotheses. Although the evidence that derives from correlational studies is not as conclusive on the issue of causality as that from a true experiment, a plausible theory whose causal predictions are supported by purely correlational data will nevertheless come to be seen as likely to be true. That is, if the theory is plausible, if its predictions are observed correlationally, and if the predictions of rival theories can be shown to be false, the particular theory will become the accepted account even in the absence of experimental proof of causation. This approach is clearly on stronger inferential footing than abduction given its focus on elucidating observations that can be used to exclude competing alternatives.

It is important to keep in mind that failure to reject the null hypothesis is a weak basis for scientific inference. This is based partly on the issue of statistical power—inferring that the failure to observe a prediction of a theory negates that theory rests on there having been an adequately powered statistical test of that prediction. We are on stronger inferential footing by excluding theories by means of positive statistical observations with which they are incompatible.
**Typology of Causes**

All would agree that schizophrenia is a complexly determined phenomenon, whereby multiple causal influences that are separated in time and place and distinct in terms of mechanism of effect integrate in the determination of a heterogeneous and nonstatic behavioral end point. The multiplicity and multilevel nature of the putative causes of schizophrenia present challenges to theory building and hypothesis testing because the theories must specify in what manner each factor is considered causal and how factors that have different mechanisms of effect in influencing behavior come together.

One manner in which the causes of schizophrenia vary is in terms of **spatiotemporal proximity** to the illness phenotype. Whereas distal causes typically refer to types of influences (eg, genes or toxic exposures occurring during brain development in utero) that represent fundamental initiating processes relevant to disease etiology, proximal causes typically refer to the mechanisms through which distal causes achieve their effect on the behavioral end point (eg, dysconnectivity), as in disease pathophysiology. As is recognized by the theoretical accounts offered in this special issue, both distal and proximal causal influences are of interest, given that understanding both will be critical for developing a complete model of schizophrenia, and both may present targets for therapeutic or preventive intervention.

Another dimension along which causal influences vary is in terms of their degree or frequency of causal relation to the behavioral end point. Necessary causes are those that are always present in the histories of patients with schizophrenia, while sufficient causes are those that, though not necessarily present in every case, when present, guarantee occurrence of the disorder. It remains unclear whether any of the putative causal factors in schizophrenia are necessary, sufficient, or both, either to the syndrome overall or particular clinically defined subgroups. All or the vast majority of etiological factors are likely to be contributing causes that are neither necessary nor sufficient in isolation but that aggregate together in determining disease risk, as is specified in the neurodevelopmental theory of schizophrenia. However, a number of distal factors may be causally related to a behavioral end point via a final common pathophysiological mechanism, which is considered a **proximal sufficient cause**, as in the dopamine and dysconnectivity theories of schizophrenia.

It must be kept in mind that we are rarely in a position to measure putative causal influences directly. Rather, we measure indicator variables or markers of factors or processes that are suspected to be causal. In a multilevel framework, we could be investigating multiple indicators of the same fundamental causal process, but from different perspectives, or we may be investigating multiple different causal processes that interact in complex ways. We will generally be in a position to know whether a particular indicator or marker variable is strictly speaking causal and if so its manner of causal relation to the behavioral end point only after extensive investigation in which other interpretations of its role (eg, epiphenomenon, secondary factor) have been ruled out. An indicator variable that is in itself not causal may nevertheless be quite valuable in etiologic research; eg, such a variable may be more directly or reliably assessed than the causal factor or process it marks.

**Integration of Causes Across Levels of Analysis**

As noted above, theories of schizophrenia must specify the manner in which multiple causal influences exert their effects on the behavioral end point of interest via different mechanisms. There are at least 4 ways in which this causal integration may be achieved: summation, transduction, interaction, and cascade. These concepts are of course already familiar in etiologic research on schizophrenia; the descriptions given below emphasize their meanings and utility in regard to building models integrating causal influences across levels of analysis.

**Summation**

Two or more causal influences may affect the behavioral end point independently via different proximal mechanisms. In this circumstance, their causal effects in relation to that end point are additive (ie, their joint occurrence does not have a larger causal impact than the sum of their independent influences). This mode of integration may be relatively common in schizophrenia, in which diagnosis is defined in terms of different possible groupings of multiple symptoms and signs, the causes of which may differ. To the extent that the different symptoms or dimensions of an illness phenotype are determined independently, by different causal factors, the influences of these factors are integrated additively with respect to determination of the overall phenotype. This form of causal integration may apply, eg, in explaining positive and negative symptoms of schizophrenia. Note that additivity of risk factors or causes does not mean that each factor contributes equally—in fact different risk factors will likely vary in their effect size on the outcome in question.

**Transduction**

Some (typically distal) causal influences are transduced into proximal mechanisms of behavioral effect. Genetic influences are examples of this form. A behavioral end point that is under partial genetic control is not encoded directly by the genes that contribute to the trait variance. Rather, such genes encode or regulate specific proteins that operate via particular biochemical pathways in the central nervous system (CNS). The genetic contribution to the behavioral end point in question is thus transduced...
via its effects on the CNS. It is important to emphasize that evidence of such transduction does not necessarily mean that a complete etiologic model has been achieved. In this example, the particular CNS changes encoded by the "disease genes" are at least proximal sufficient causes of the genetic component of the trait variance but may not be strictly necessary for at least some cases of the disease phenotype. Likewise, though the relevant disease genes may be sufficient for producing the CNS changes that lead to the behavioral end point, there may be many other nongenetic causes of such changes among the population of affected cases. It is also important to note that schizophrenia is not under complete genetic determination, so a model specifying exclusively the genetic component of a disease phenotype is in this context necessarily incomplete.

**Interaction**

The causal influences of 2 or more factors on the behavioral end point may depend on their mutual occurrence. This form of causal integration would seem necessarily to apply to many environmental risk factors that are relatively common in the population, such that not all individuals exposed to that event or condition develop the illness. Some form of prior vulnerability or predisposition would seem to be required to explain this selectivity of effect. In some cases, the requisite vulnerability may have been acquired via prior environmental risk exposures. In other cases, the predisposing factors with which environmental risk exposures interact may be inherited, such that different genotypes respond differently to particular environments. In this case, the "character" encoded for by the gene products is not the disease phenotype per se but a trait or traits that confer vulnerability to particular types of environmental events or conditions.

**Cascade**

Influences at different levels of analysis may occur as sets of cascading influences, where a particular causal influence is transduced or otherwise integrated into another causal influence, which in turn is transduced or otherwise integrated into a third influence, and so on. In this case, an influence occurring early in the cascade may or may not itself continue to be an active, operative cause of the behavioral end point. Certain of such influences may become "fixed" trait-like features that are necessary for disease vulnerability but do not participate directly in symptom formation. Integration of causal influences via cascades is intrinsic to the concept of development and plays a relatively prominent role in the neurodevelopmental theory of schizophrenia. Cascades are also common in neuroscience models because the effect of a particular initiating event (eg, cell depolarization) sets off a chain reaction involving electrical, chemical, and structural changes before it is expressed in behavior.

**The Role of Theory in the Study of Schizophrenia**

The theoretical perspectives offered by the authors of the articles in this special section of the Schizophrenia Bulletin focus on the roles of aberrant dopaminergic signaling, N-methyl-D-aspartate receptor-mediated dysconnectivity, and neurodevelopment in the etiology and/or pathophysiology of the disorder. All are explicitly multilevel models; each clearly has merit in explaining a range of observations that are considered more or less established facts about the disorder, and within each there are clearly identified causal hypotheses. In many ways, the presence of these theories at this stage of knowledge is a reassuring indicator of a maturing branch of science because enough generally established "facts" have been elucidated to support model building of this sort.

At the same time, it is also clear that these theories are not (and are not intended by their authors to be) mutually exclusive of each other. Rather, they provide explanations that differ in relative emphasis, eg, on distal vs proximal causes and on broad vs narrow behavioral end points. It is therefore possible for all of them to be "right" in at least a general sense. Hypothesizing a causal role of aberrant dopaminergic signaling in schizophrenia does not rule out a causal role of glutamatergic signaling (ie, because the 2 systems interact or are differentially relevant to certain cases or features of the disorder), and both systems can be influenced by disruptions of cellular connectivity that in turn may derive from the influences of multiple risk factors during the course of brain development. Thus, although constructed separately and with some theory-specific features, the 3 theoretical accounts offered in this special issue can nevertheless be pieced together into a whole, as in the different modules of the International Space Station.

Although not the fault of the authors of these theoretical articles, who were not asked to build competing models, this nonexclusivity is problematic and likely to hinder the pace of progress because we cannot make use of the efficiency of deductive logic by focusing our data collection efforts on differential predictions of models. If the extant models do not make differential causal hypotheses, they are not truly competitors as explanatory theories of schizophrenia. The task is then to recognize those aspects of proposed theoretical models that are compatible with each other as reflecting the same fundamental causal hypotheses, but at different levels of analysis, putting empirical evaluation of those aspects aside, and to focus attention on causal hypotheses that are potentially differential between competing theoretical views.

In principle, the contrast points will be found in theoretical constructions that implicitly or explicitly refer to integration of causes across levels of analysis. A causally
additive formulation differs in its predictions about the structure of relationships among observed variables than a causally interactive formulation (i.e., as in whether a multiplicative term adds to or subsumes the variance accounted for by multiple independent terms in a multiple regression analysis). A causally transductive vs directly causal process can be tested using the principles of mediation analysis, whereby a variable A either influences another variable B directly or through A’s effects on a third variable C. These points of theoretical contrast find ready application in the statistical models (ANOVA, regression, structural equation modeling) commonly used in correlational science.

Conclusions

The history of schizophrenia research is replete with examples of theories that were held so closely by their adherents as to become ideology for a period but were later discredited. Twice, thrice, etc, burned, we seem to evolved to a phase in which our theories are largely mutually compatible with each other. This state of affairs may help to maintain a certain social decorum that is to be appreciated, but from a philosophy of science perspective, this nonexclusivity is problematic and will likely hinder our progress unless we can identify those components of the various theories that represent competing models of underlying causal phenomena. Paradoxically, in many ways, the concept of schizophrenia itself is a theory or, perhaps better, an “open concept.” Nevertheless, the recognition of this uncertainty of definition and boundary of the core phenomena is itself a step forward, in as much as it leads to the design of studies that can test competing predictions of the different definitions (e.g., category vs continuum).

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