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Using machine learning to explain the heterogeneity of schizophrenia. Realizing the promise and avoiding the hype

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ABSTRACT

Despite extensive research and prodigious advances in neuroscience, our comprehension of the nature of schizophrenia remains rudimentary. Our failure to make progress is attributed to the extreme heterogeneity of this condition, enormous complexity of the human brain, limitations of extant research paradigms, and inadequacy of traditional statistical methods to integrate or interpret increasingly large amounts of multidimensional information relevant to unravelling brain function. Fortunately, the rapidly developing science of machine learning appears to provide tools capable of addressing each of these impediments. Enthusiasm about the potential of machine learning methods to break the current impasse is reflected in the steep increase in the number of scientific publication about the application of machine learning to the study of schizophrenia. Machine learning approaches are, however, poorly understood by schizophrenia researchers and clinicians alike. In this paper, we provide a simple description of the nature and techniques of machine learning and their application to the study of schizophrenia. We then summarize its potential and constraints with illustrations from six studies of machine learning in schizophrenia and address some common misconceptions about machine learning. We suggest some guidelines for researchers, readers, science editors and reviewers of the burgeoning machine learning literature in schizophrenia. In order to realize its enormous promise, we suggest the need for the disciplined application of machine learning methods to the study of schizophrenia with a clear recognition of its capability and challenges accompanied by a concurrent effort to improve machine learning literacy among neuroscientists and mental health professionals.

1. Introduction

There are few developments that have had as much impact on scientific discovery or generated as much excitement over the past decade as machine learning (ML). Enabled by the exponential expansion of their power and capacity, computers are now not only able to store and process sizable amounts of data but also to "intuitively" decipher the structure of these data and discern patterns and connections between them. As the sheer volume and complexity of data ("Big Data") overwhelm the capacity of the human mind and traditional analytic methods, ML provides the tools and capability to make sense of these data and generate "data-driven" predictions and inferences "free from human assumptions and theoretical biases" (Appenzeller, 2017; Camacho et al., 2018; Lai et al., 2019). Among researchers, neuroscientists are particularly enthusiastic about the potential of ML to finally help unravel the functioning of the human brain (Cornblath et al., 2019; Glaser et al., 2019; Huys et al., 2016; Redish and Gordon, 2016; Vu et al., 2018). Focused efforts to better understand brain function have intensified across the world (BRAIN (Jorgenson et al., 2015), Human Brain Project (Amunts et al., 2016), Brainnetome (Fan et al., 2016), Brain/MINDS (Okano et al., 2015) among others) and are generating prodigious amounts of multidimensional data. ML is a sine qua non to our ability to analyze and interpret these complex data and integrate information across different high-throughput technologies (multiomics- connectomics, genomics, metabolomics, proteomics, transcriptomics, epigenetics, etc., Grabowski and Rappsilber, 2019; Lin and Lane, 2017).

Translation of even rudimentary advances in neuroscience to an improved understanding of psychiatric disorders is additionally complicated by the fact that mental function and dysfunction involves recursive, dynamic interactions between an individual's brain and his or her physical and social environment. The potent capabilities of ML to process and integrate vast amounts of interacting, multidimensional, multi-level information has led to the rapid development of the discipline of computational psychiatry (Anticevic et al., 2015; Bassett et al., 2018; Bzdok and Meyer-Lindenberg, 2018; Ferrante et al., 2019; Fornito and Zalesky, 2018; Huys et al., 2016; Kas et al., 2019; Valton et al., 2017; Zitnik et al., 2019).

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Whereas the non-viability of the current construct of schizophrenia is evident (Tew, 2017; Goluksuz and van Os, 2018), there is no alternative at the present time that can better explain the range of phenomena observed among individuals diagnosed with this condition (Nasrallah et al., 2011). Enthusiasm about the potential of machine learning methods to break the current impasse is evident in the steep increase in the number of scientific publication about the application of machine learning to the study of schizophrenia (Shatte et al., 2019); in this Journal itself, the number of ML-related articles per year has increased from one until a few years ago to twenty in 2017, twenty-five in 2018, and a projected 45 in the current year.

Machine learning approaches are, however, poorly understood by schizophrenia researchers and clinicians alike. Exactly what is the "magic" of ML? What can it do and what can it not? How do we make sense of its output? How do we separate the "hype" from reality with regards to its potential? In this paper, we provide a simple description of the nature of machine learning and highlight its potential and limitations in the study of schizophrenia with illustrations from the six articles on ML in schizophrenia published in this issue of the Journal (Honnorat et al., 2019; Mothi et al., 2019; Palaniyappan et al., 2019; Winterburn et al., 2019; Xiao et al., 2019; Zarogianni et al., 2019). We then present some guidelines for researchers, readers, science editors and reviewers of the burgeoning machine learning literature and suggest a framework to most effectively harness the potential of machine learning in elucidating the nature of what we call schizophrenia.

2. What is machine learning and what it is not

Machine Learning is becoming a catch-all term for a set of tools, approaches and resources that are increasingly applied in myriad fields of study. We provide a cursory simplified overview of the essence of ML and summarize its array of tools and potential applications with particular relevance to the study of schizophrenia. In an effort to further elucidate the nature of ML, we then briefly clarify some common misconceptions about ML and outline a simple approach on how to approach the burgeoning ML literature. It should be emphasized that this is only a brief primer; several recent comprehensive reviews of ML and its application to neuroscience and psychiatry are available (Bzdok and Yeo, 2017; Camacho et al., 2018; Cao et al., 2018; Dwyer et al., 2018; Iniesta et al., 2016; Rutledge et al., 2019; Wainberg et al., 2018; Zitnik et al., 2019).

2.1. The essence of machine learning

2.1.1. Brief description

With its origins in the three disciplines of artificial intelligence, computational statistics, and pattern recognition, ML is defined as an ensemble of computational techniques of data analytics based on learning from data for the purpose of data-driven prediction, description, or explanation (Camacho et al., 2018; Dwyer et al., 2018; Rutledge et al., 2019). We find the best way to understand the crux of ML is to break the term down into its two components: machine and learning. The machine part refers primarily to the computational resources being employed. Because of their incredible power and capacity, these computers (the "machines") currently allow us to "run" many thousands of models in a matter of seconds, giving us unprecedented power to test out many ideas ("informed guesses") about the structure of a given data set. These "machines" also come with increased storage and memory capacity, allowing us to load significantly larger amounts of data than ever before ("big data"). The learning part refers to the idea that the computers can "learn" from these many guesses, adjusting a model little by little as they compare one guess after the other. In general, the computer's algorithms will iterate in this manner in an effort to generate the best guess or model about relationships or structure in the data set by exploiting the dataset's variance. Model parameters are thus found through a series of back and forth steps, where model parameters are estimated, the model performance is evaluated, errors are identified and corrected, and then the process is repeated until model error is minimized.

2.1.2. Steps of machine learning

Application of ML characteristically involves three stages: data preparation, learning, and evaluation (Fig. 1). Once a dataset from which learning is to occur has been defined, the raw data needs to be processed to get it into the "right form" for subsequent learning. This step typically involves data cleaning (e.g., treatment of missing data), data transformation (e.g., scaling), and data reduction (e.g., feature selection), although feature selection can also occur as part of the next stage of learning. At this time, the original dataset may be divided into two or three subsets: training, (validation), and test.

Once the data has been properly prepared, the "machine" begins the learning process which typically includes three steps- choice of estimator class from the ML toolbox, parameter learning through an iterative process of model tuning, and estimator parameter regularization. Theoretically, an infinite number of learning algorithms are available to be applied to learn from a given dataset from which the investigator must choose a particular family of estimators. This estimator's parameters are "learned" by repeated analysis of the training dataset with application of the algorithm to the data and minimizing the difference between the model-predicted and actual outputs. In addition to parameters, many ML models also have 'hyperparameters' which relate to model structure, and these may need to be optimized. The step of estimator regularization involves simplification or "smoothing the fit" in the phase of cross-validation (either in the validation data subset or other cross-validation method). The third and final phase of learning is that of estimator evaluation where the derived algorithm or parameter is applied to the test data subset and its performance is assessed.

2.1.3. Types of machine learning

Based on how they learn, ML algorithms can broadly be divided into supervised, unsupervised, and reinforcement learning categories. There is also a hybrid between supervised and unsupervised ML called semi-supervised ML. Supervised and semi-supervised ML have a specified output (akin to dependent variable or "y") and a dataset with some or all output labelled (value of "y' is known for part or all of the sample in the dataset). Unsupervised ML find patterns or structure within the data by themselves as there is either no specific defined output variable or the training dataset contains no values for "y". Reinforcement ML uses input data to generate outputs with learning mediated by rewards or penalties as consequences of the action or output- this is often used in robot control and thus far has had limited application in biomedical research.

2.1.4. Some key assumptions and biases

ML algorithms make assumptions about the 'best' function or series of functions that fits the data in the dataset. Since multiple functions can potentially fit with a given dataset, the ML algorithm needs to make assumptions about the distribution of the function being modelled in order to choose among them. In addition to their implicit assumptions, ML methods vary in flexibility. In comparison to more restrictive methods, flexible methods are more complex and generally provide a closer fit to the data; on the other hand, they are less easily interpretable. Furthermore, the more closely the flexible model fits to the training data subset ("less bias"), the greater the likelihood of it not fitting the test data subset ("more variance"); this tension between overfitting versus underfitting in the training dataset is what is known as the bias-variance trade-off in machine learning (James et al., 2013). A model that minimizes both bias and variance is obviously desirable, but the 'best' model for a given dataset would be determined principally by the structure of the dataset and the specific purpose for which the algorithm or model is being developed. Since different ML algorithms have different underlying assumptions and strengths/limitations (in terms of

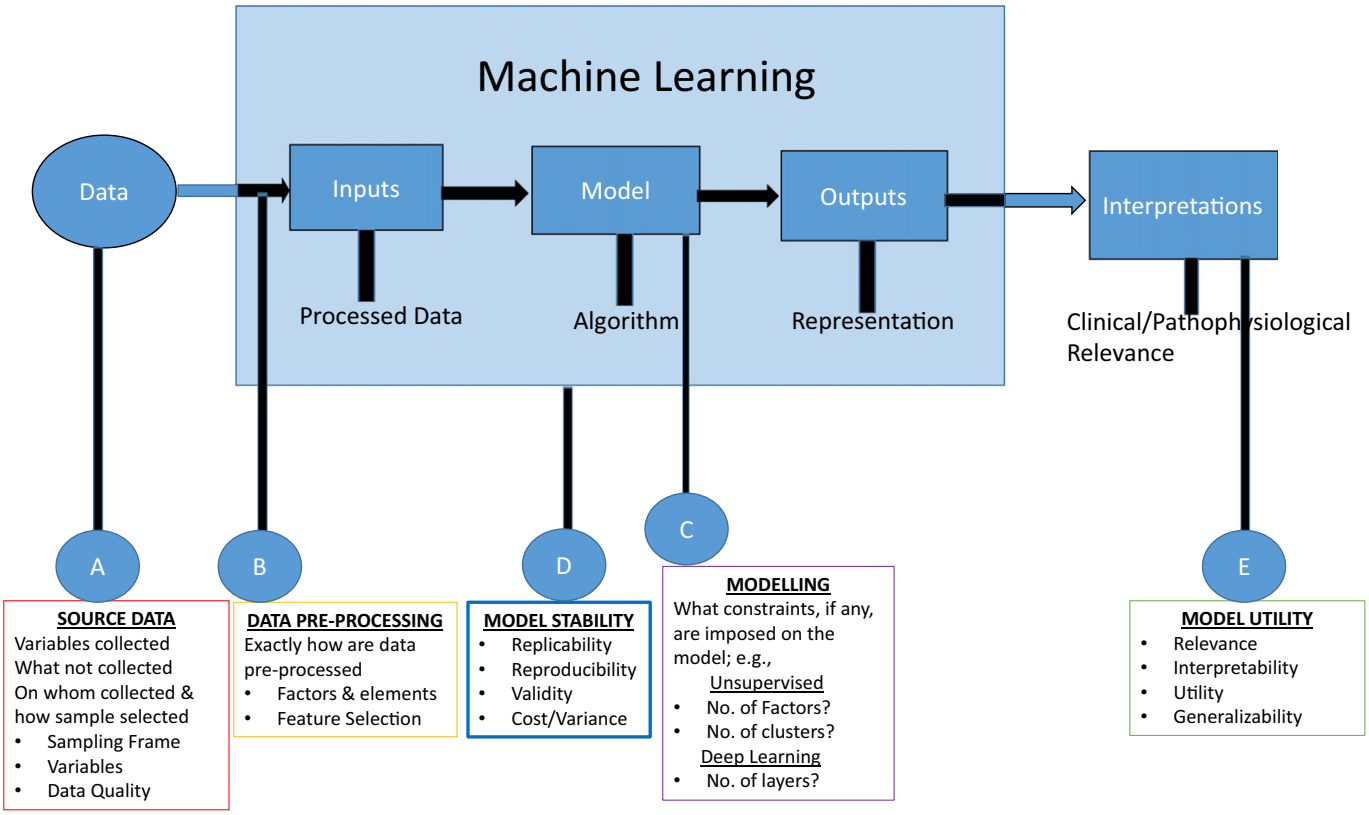

Fig. 1. Steps of machine learning and factors affecting its output.

flexibility, interpretability, accuracy, generalizability, etc.), it is important to recognize that there is no best ML method for all applications and that selection of the most appropriate method is critical in the useful application of ML.

2.2. Misconceptions about machine learning

2.2.1. Data quality and sampling frame are inconsequential in ML

Since ML is data-driven, the quantity and quality of data significantly impact its performance. Sample size, data accuracy and completeness are critical elements as is the representativeness of the sample whose data drive ML. There is a growing tendency to utilize ML algorithms in settings where there are a large number of variables and the sample size is small because ML will find some structure among the variables in the dataset, but this is likely to be unstable and poorly generalizable (Rutledge et al., 2019). Because ML will offer some simple pattern, it is important not to over-read data and 'see' phenomena that are not really there (Carlson et al., 2019). Data errors and sample biases often tend to be amplified in ML (Bzdok and Yeo, 2017; Cox et al., 2018; Kolossa and Kopp, 2018). **Rigorous validation in an independent sample is essential**. Furthermore, because of the "black box" nature of ML, errors caused by ML-algorithms can be difficult to detect. ML-generated models should not be applied to populations substantially different from those on whom they were generated.

2.2.2. Machine learning is nothing but computer application of usual statistical methods

Because statistics and ML share many objectives and applications and a number of traditional statistical techniques are utilized in machine learning (Ceri, 2018), some believe that ML is merely statistics on powerful computers. In fact, one of the best introductory texts on ML (James et al., 2013) is entitled "An Introduction to Statistical Learning". Despite their many similarities, however, there are some key differences. ML involves an iterative process of learning by progressive testing of models and step-step reduction of error to minimize the gap between model predictions and actual data. Furthermore, ML assumes a significant relationship between a set of independent variables and dependent variable and seeks to find the path that most strongly links the two. In contrast, statistics first requires establishment of a significant relationship between variables before generating the equation or function linking them.

2.2.3. ML is completely data-driven without any human decision-making

Although machine learning is by definition data-driven, human decisions at several stages of the process affect ML (Tandon and Tandon, 2018). From data collection to pre-processing to estimator class selection, a series of consequential decisions that can potentially bias ML are made by humans.

2.2.4. Models generated by ML are of no value if they are not fully interpretable

Although it is useful to understand the basis for the relationships in datasets uncovered by ML methods, generated algorithms can be useful for purposes of prediction or inference even in the presence of an incomplete understanding (Bzdok and Ioannidis, 2019). It is important, however, for the algorithm to be rigorously validated in independent samples and its superior utility/accuracy over other methods demonstrated prior to its deployment.

2.2.5. Cross-validation of ML is analogous to independent replication of findings

This reflects a misunderstanding of ML terminology. Cross-validation in ML refers to applying the specific model generated on the training subset to the test subset of the original sample dataset. Challenges due to limitations in data collection and biases inherent in the dataset are not addressed by any method of cross-validation. In fact, performance has been found to degrade when validation has been explicitly attempted on an independent sample (Dacrema et al.,

2019; Rutledge et al., 2019). In the ML literature in schizophrenia, there are only a handful of efforts at such truly independent validation.

2.2.6. Since ML is data-driven, formulation of an a-priori research question is not necessary

The specific purpose of applying tools of ML to a particular dataset should be specified before undertaking the effort (Bzdok and Ioannidis, 2019). That will facilitate selection of the appropriate ML estimator as also the comparative evaluation of the ML-generated algorithm to other methods that seek to address the same problem or serve the same purpose. Such formal evaluation has often found ML not to be superior and often inferior to more conventional approaches in addressing the specific purpose for which it was purportedly developed (Dacrema et al., 2019; Evangelia et al., 2019).

3. Evaluating an ML study

With this understanding of the essence of ML and awareness of its strengths and limitations, the following set of questions will assist the reader in examining the replicability, validity, robustness, relevance, utility, and applicability of an algorithm or model generated by any ML study:

1. What is the precise question that the study addresses or exactly what is the problem that the model or algorithm seeks to solve?
   Since application of ML methods to a dataset will generate models and reveal patterns of association among the variables, it is important that the resultant algorithm or equation provide a solution to a pre-specified problem rather than simply detecting associations. In most ML studies in psychiatry to date, a specific question is not precisely defined, complicating assessment of the utility or relevance of the model generated. Applying an ML method to a dataset and obtaining results that are interesting and seem relevant to answering a broad biological question may appear useful. The meaning or relevance of such findings in the absence of a specified question, however, is unclear. Furthermore, the absence of an explicit purpose for the algorithm makes comparison to alternative methods impossible. The appropriateness of the dataset or chosen ML method also becomes difficult to evaluate.
2. How well have the results been validated?
   Were the results cross-validated and was the appropriate cross validation method employed? This step is necessary but insufficient to make a claim about generalizability. For that, one needs full confirmation or replication in independent sets of data. Consequently, the next question to ask is: has the model been evaluated in independent samples; specifically, have the authors of the ML study themselves sought to test their model on an independent sample?
3. Exactly what data went into the "black box" in which the model or algorithm was developed?
   No matter how complex or sophisticated the ML method, a poor-quality dataset or one poorly matched to the question being addressed will not be useful. Measurement and selection biases apply to ML as to any other form of data analysis; in fact, they may be amplified. In the words of Bergstrom and West (2017), "even if you don't know how an algorithm or some statistical test works, you can still spot BS by looking carefully at what goes in and what comes out".
4. What is the exact purpose of the model that was generated? Is it to describe, explain, or predict?
   Outputs from ML yield models that serve the purpose of describing the dataset (as in most unsupervised ML) or perform the function of explanation or prediction. General validation principles apply to all types of models (Bassett et al., 2018). Understandability and biological plausibility are emphasized in explanatory models whereas independent replication in new datasets is prioritized in predictive models. Different ML methods are better suited to predictive versus explanatory modelling that, in turn, have distinctive scientific and practical application (Schmueli, 2010).
5. Are the results reproducible?
   There has been a mounting problem of false positive findings in science (Ioannidis, 2005), especially in cognitive neuroscience (Szucs and Ioannidis, 2017). Compounding this problem in ML studies is the fact that results are difficult to replicate given the lack of transparency about data and source code. The result of any ML application is an algorithm; to replicate the algorithm, one needs to know the exact equation or source code - this is rarely provided.
6. Are the results transferable? Are they actionable? If not, what are the next steps towards making this happen?
   Most ML investigations in schizophrenia are proof-of-concept studies, i.e., they report that an ML method applied to a schizophrenia dataset generates a model that is potentially interesting and can have some biological meaning. Frequently, there is no discussion of exactly where, when, how, or to whom the algorithm should be applied. Furthermore, there needs to be an explicit consideration of specific, necessary next steps in the development of this model in order to make it more useful or broadly applicable. Of note, several factors can contribute to a training-application gap in ML (Wainberg et al., 2018).

4. The promise and the challenge of ML in the dissection of Schizophrenia

Machine learning is an essential and incredibly powerful tool in our efforts to extricate ourselves from the quagmire with regards to our current understanding of the nature of schizophrenia. ML also has significant constraints that warrant its thoughtful utilization and careful application. The possibilities and challenges are both demonstrated in the studies described in the six research papers on ML in this issue (Honnorat et al., 2019; Mothi et al., 2019; Palaniyappan et al., 2019; Winterburn et al., 2019; Xiao et al., 2019; Zarogianni et al., 2019). Their examination through the lens of the evaluation strategy noted above reveals:

(i) each of these ML studies sought to address an important question relevant to schizophrenia, albeit with different degrees of specificity;

(ii) reasonable cross-validation was utilized in every study, although replication in an independent sample was only attempted in one (Winterburn et al., 2019). Of note, authors of two studies (Mothi et al., 2019; Zarogianni et al., 2019) have datasets enabling testing of their model in an independent sample (B-SNIP2 and Zarogianni et al., 2017, respectively);

(iii) whereas sample characteristics, selection process, and data elements are described in each of the studies, implications of the sampling frame and data collection methods for interpretation and generalizability of their generated ML-model are not discussed. All six studies utilized brain imaging data (five used sMRI whereas one [Palaniyappan et al., 2019] employed fMRI) but challenges in deciphering human brain imaging findings (Ioannidis, 2011; Weinberger and Radulescu, 2016) and their impact on model interpretation are not considered. Furthermore, as Vieira et al. (2019) caution, when proper methodological precautions are adopted to avoid overoptimistic results, "the current evidence for the diagnostic value of ML and structural neuroimaging should be reconsidered towards a more cautious interpretation";

(iv) while four of these studies explicitly sought to generate predictive models (Palaniyappan et al., 2019; Winterburn et al., 2019; Xiao et al., 2019; Zarogianni et al., 2019), the other two had an explanatory/descriptive purpose;

(v) none of the studies provided access to raw data or source code, rendering impossible efforts at independent replication of the models that they generated; and

(vi) none of the ML models generated in these six studies are directly actionable or transferable. Furthermore, explicit next steps in the development of the model to make them more meaningful or broadly applicable are not spelled out.

An important omission in each of these reports is the lack of discussion of other ML studies addressing the same problem. For example, Mothi et al. (2019) applied unsupervised ML to define three "psychosis biotypes", utilizing clinical and neuroimaging data derived from people with schizophrenia, schizo-affective disorder, and psychotic bipolar disorder. There have been several other ML studies that have utilized similar data to evaluate individuals with schizophrenia and psychotic bipolar disorder, including one in this special issue (Palaniyappan et al., 2019). That study and several others actually find accurate discrimination between these two disorders (e.g., Jauhar et al., 2018), in contrast to the suggestion made by Mothi and co-workers. Moreover, the extent to which the solution generated by an ML study shares the same limitations as the problem it seeks to address merits discussion- in an elegant neuroimaging study to map the heterogeneous phenotypes of schizophrenia and bipolar disorder (Wolfers et al., 2018), the authors noted "even though biological stratification of mental disorders may be useful, our results suggest that potential emerging biological strata are like smaller than previously anticipated; inter-individual differences are vast and will not easily boil down to reliable and robust biological subtypes." Additionally, there are many other ML studies that seek to identify biological clusters or "biotypes" utilizing neuroimaging data in persons with psychosis, including one in this issue (Honnorat et al., 2019); how these models compare is not explored. Furthermore, there are numerous non-ML studies addressing identical questions in similar populations and their findings are at best only partially considered. Any data that are incompatible with the authors' interpretation of their findings need to be deliberated. The other five ML studies in this issue share these limitations.

To be sure, these challenges are not unique to the six ML studies in this issue of the Journal. They pervade a significant majority of machine learning studies in schizophrenia and are, in fact, evident in other studies that do not utilize machine learning. It is important to recognize, however, that while ML techniques are powerful tools, they cannot compensate for sampling or methodological limitations impacting the quality of input data. The value of an ML model is constrained by the quality of the experimental design that it is derived from. There are a range of human choices made in ML studies (Tandon and Tandon, 2018) and their implications for interpretation of the model generated merit consideration.

5. Conclusion

Techniques of machine learning are very powerful tools. In schizophrenia research, as exemplified in this special issue, researchers have begun to seize on the opportunities presented by ML to advance our understanding of this disorder. There are many pitfalls, however, in the application of ML to meaningfully advance our comprehension or conceptualization of schizophrenia. All segments of the scientific community have a role in ensuring appropriate and efficient utilization of ML to allow it to live up to its promise in elucidating the nature of schizophrenia. Funding and regulatory entities must ensure rigorous data management and sharing, transparency, and "good science" (Gleeson et al., 2017; Luo et al., 2016; Nichols et al., 2017; Wilkinson et al., 2016; Wilson et al., 2014) Researchers in the field need to be more self-critical in their construction and presentation of their models and make available their data and source code to enable independent replication. The precise application and comparative value of the model and next steps in its development need to be clearly articulated (recommendations for ML researchers are summarized in Tandon and Tandon, 2019). Journal editors and reviewers have an important responsibility in critical evaluation of ML articles (guidelines with a checklist are also available in Tandon and Tandon, 2019). Readers need to improve their understanding of computational psychiatry and ML. The field at large needs to view ML literacy as being essential to schizophrenia research on par with required knowledge of basic statistics (Goldman and Fee, 2017).

While our field's exuberance about the promise of machine learning is justified (Janssen et al., 2018; Teufel and Fletcher, 2016), much caution and significant discipline are warranted. We are certain to be inundated by increasing reports of ML findings in schizophrenia over the next several years. Whether these studies generate models that lie on deserted islands or become part of an archipelago of a more meaningful understanding of schizophrenia will be determined by our collective efforts (Tandon, 1999).

Declaration of competing interest

Drs. Neeraj Tandon and Rajiv Tandon report no conflicts of interest with regard to the development and finalization of this manuscript.

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