Functional Connectome-Based Predictive Modeling in Autism

Supplemental Information

Predictive modelling and machine learning in psychiatry

Machine learning (ML) is a growing field, commonly referenced in biological psychiatry, where there is an increasing focus on generalizability (1). ML is defined by the use of algorithms to learn patterns in training data, which can be leveraged for automated decision-making on unseen data (2). There are several important decision points in choosing which algorithm suits your needs. Some of these decisions may include whether to use a supervised or unsupervised algorithm, using a regression or classification framework, and how complex a model to use.

These decisions can be influenced by whether you wish to use the algorithm for explanation or prediction. Unsupervised methods (in which patterns are learned from unlabeled data—performing a clustering analysis to determine the number of subtypes in a dataset, for instance) can help to uncover previously unknown relationships in your dataset. However, if one then uses the relationship to automate a decision or predict an outcome, the approach falls within predictive modelling. Broadly speaking, one can be thought of having a predictive approach if you are building a model that can estimate a variable of interest from unseen data, whereas explanatory analyses often focus on deriving causal links, focusing more on interpretation than model performance (3). Many neuroimaging ML applications involve both predictive and explanatory aspects and they can be complementary (4).

This paper has focused on predictive approaches in autism, which rely on supervised algorithms. Supervised approaches (in which data labels are known) can be used to leverage existing data for prediction of categorical variables using a classification approach (autism diagnosis in case-control studies) or prediction of continuous variables using regression (autism-related phenotypes in dimensional studies). One of the benefits of supervised is using priors pre-generated from previous studies. These priors can help ensure that models are less likely to overfit your dataset, due to added (favorable) bias and reduced variance (i.e., bias-variance tradeoff) (5). The downside is that these priors might not fit the dataset well, and you may miss some unique and useful information in the dataset leading to an underfit model which does not perform well enough.

Returning to unsupervised approaches, these methods tend to be more well-suited to explanatory analyses. However, they can still be used as part of a predictive framework. Two prominent types of unsupervised algorithms are clustering and association. Clustering is analogous to classification in that it tends to produce a categorical output (subtyping of autism), while association is analogous to regression (new dimensions of brain variation), as it produces a dimensional output, along which the relationship is continually varying. Unsupervised models can benefit from a lack of bias, as they work with less stringent priors than supervised methods, and can uncover previously unknown relationships in the dataset. However, the lack of bias can also lead to increased variance in the estimated model parameters across different datasets, resulting in overfit models which capture more noise than signal. For a more in-depth discussion of issues associated with supervised and unsupervised learning in fMRI, see Khosla et al. (6).

Another important factor in model selection is model complexity. Simpler models may miss complex relationships in the data but can yield much more interpretable parameters. This may be important in the context of gaining biological insight. On the other hand, if the underlying biological relationships are of less concern, and one wishes to derive a model with the best possible performance (i.e. for accurate diagnosis of autism status), one could opt for a more complex algorithm. Complex algorithms tend to perform better on unseen data due to their capacity to capture complex patterns, but can hinder interpretability, (see Figure 1 of Bzdok et al. (7). The complexity of the model can also impact generalizability, as complex models are more likely to overfit a dataset due to the increased number of parameters that can be optimized. The balance of complexity and interpretability is a key consideration in selecting an algorithm for predictive modelling in functional neuroimaging.

The ethics of predictive modelling in autism

The use and implementation of predictive models to diagnose autism requires careful ethical consideration (8). Recent research has revealed that brain-based changes in autism precede the development of behavioral symptoms (9), which has ushered in the creation of predictive models to forecast diagnosis before the emergence of symptoms. Moreover, it may become possible to identify the likelihood of autism *in utero*. These studies open the possibility for pre-symptomatic intervention, which could potentially alter developmental trajectories sufficiently to prevent the development of autism (9). However, in these scenarios, several ethical matters should be considered.

Autism is an extremely heterogeneous condition with a complex phenotype. Individuals with autism can range from having profound difficulties and disabilities to being highly successful and independent. Autism can manifest with significant intellectual difficulties with no or minimal functional language capabilities or with extremely high intelligence and highly articulate language capacities. However, our current predictive models are not able to identify which infants will develop which phenotype later in life. Further, neurodevelopment in the perinatal period has tremendous plasticity, and it is likely that autism emerges as a sequala of numerous genetic and environmental effects acting in concert (10). Therefore, there is risk for inaccuracy and imprecision in models that could have devastating effects on families.

Additionally, infants who are identified with a high likelihood of developing autism through MRI or other tools incorporated into predictive models will not yet have developed the core features of autism. Thus, existing interventions that focus on addressing autism-associated difficulties would not yet be suitable for this population and new interventions would need to be developed (9). This raises the question: is earlier diagnosis beneficial if it is not possible to provide support services? Current guidelines for newborn screening for other disorders, such as phenylketonuria and hypothyroidism, suggest that a diagnosis should only be made if there is a known and accepted treatment (11). When applying these principles to predictive models for early identification of autism, a key difference arises. While pre-symptomatic interventions do not currently exist for autism and it will initially be unlikely to begin intervention as soon as a diagnosis is made, during this initial period the infants' development can be carefully tracked and existing early intervention services can be provided to optimize developmental outcomes, until new interventions can be developed.

In addition, for many individuals with a diagnosis, autism is a core tenet of their identity and being "atypical" does not equate to impairment. The neurodiversity movement maintains

that autism should be conceptualized as a difference rather than a disability (12). Some have contended that efforts to predict and prevent development of autism are attempts to eliminate neurodiversity (13, 14). Further, rather than focusing on early childhood diagnostic tools, many adults with autism would prefer research funding to be directed towards programs and services for individuals living with autism (15). However, the goal of pre-symptomatic intervention is not to eliminate neurodiversity, but rather to provide opportunities to achieve developmental milestones that are critical for subsequent adaptive functioning and independence (9).

Some issues for consideration with dense scanning and prediction in autism

An approach that has proven useful in neurotypical young adults is dense scanning (16-18), in which the same individuals are scanned many times. Such studies have led to exciting insights, including the fact that participants exhibit remarkable stability of individual-specific networks (16) and such individualized networks exhibit brain state-dependent organization (19). Using a dense scanning paradigm and prediction-based approaches could similarly inform our understanding of autism neurobiology and symptom expression. For example, do models generalize to predict fluctuations in individual patients over time, as has been shown in attention (20)? The large amounts of data from dense-scanning studies have been used to obtain exquisitely detailed areal parcellations within individual participants (e.g., (16)). Would similar participant-specific parcellations help increase the utility of dimensional predictions in autism? Could these large amounts of scanning data be combined with other data types to better subtype individuals with autism and construct more specific clinical models?

A major hurdle that has to be overcome if dense scanning studies are to be conducted is ensuring the data are of high quality, as participants with autism can be difficult to scan (21). Another barrier is determining whom to scan—given the heterogeneity of autism, what type of symptom profile will allow the research community to draw generalizable conclusions? Should we aim for a broad array of individuals (22), or should we instead focus on a single symptom dimension? Based on the work of Byrge and Kennedy (23), more data per participant reduced classification accuracy of autism status to around chance levels. Thus, large numbers of participants are possibly needed in dense scanning studies to achieve discriminative utility. What does this mean for predictive modelling studies--how many participants do we need to densely scan to help us build useful models, and is this feasible?

Furthermore, what sort of scanning data should we collect—simply resting-state scans or a variety of task-based scans covering as many aspects of the Research Domain Criteria (RDoC) matrix as possible? How do we motivate participation? Would an individual with autism be open to weekly scans over the course of a year, if they stand to gain little beyond financial compensation?

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