VIEWPOINT

How normative modeling can reframe autism’s heterogeneity

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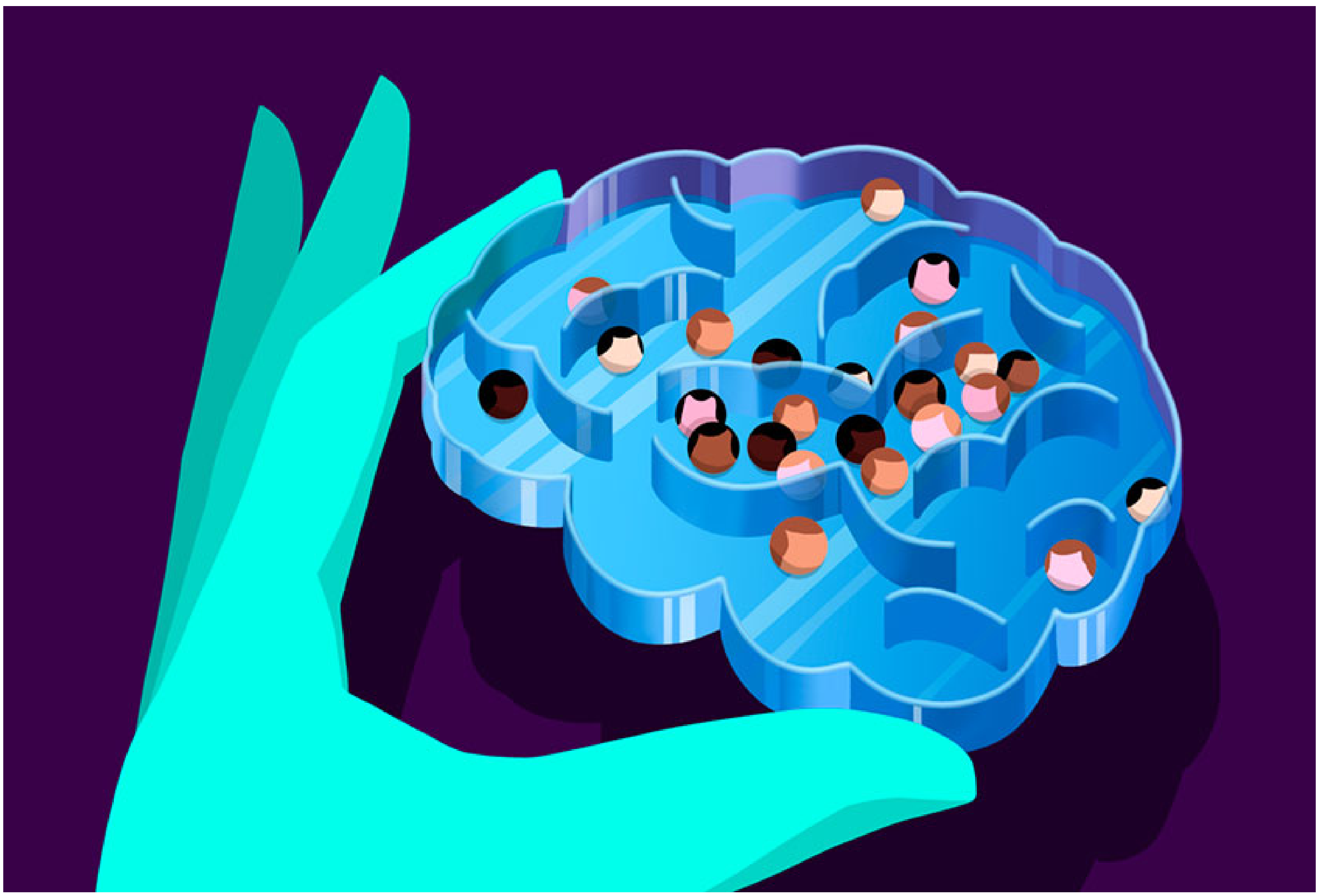

It is not uncommon to see news articles or even peer-reviewed scientific studies use phrases such as: “Autism is characterized by … ” or “Science reveals people with autism are more … ”.

An oft-hidden assumption in these types of articles is that autism comprises a homogenous, well-defined group of people, and most of the studies report group differences between individuals with and without an autism diagnosis.

This is called a ‘case-control’ approach. As most people with autism know — and the scientific field is beginning to acknowledge — this assumption is erroneous: Autism is not homogenous.

People with autism may share a broad diagnostic label and face similar challenges in their everyday lives, but every person on the spectrum is unique. Clinicians recognize this to be true because they treat individuals, not groups.

However, the condition’s heterogeneity poses a challenge for research that aims to find group differences. How do we capture and quantify this individual variability in a scientific and meaningful way?

‘Normative modeling’ — with the term normative referring to a population norm — is an emerging statistical framework that aims to capture variability and allows for individualized assessments. The framework is perhaps easiest to conceptualize as being analogous to the growth charts used in a pediatrician’s office.

We should emphasize here that deviation from the population ‘norm’ does not mean an individual is ‘deviant’ or ‘abnormal’ in any sense. Instead, each individual contributes to the broader heterogeneity of the population’s trajectory.

Smart predictions:

In the context of brain development, normative modeling can map the trajectory along which different properties and aspects of the brain change as a person gets older. For example, we can look at how the thickness of specific layers and regions in the brain change over the course of development.

Given enough population data, we can construct a brain growth chart for these various properties and estimate where on this trajectory each person falls at a given time during her development. This framework also allows us to make inferences about a person’s likely future development in much the same way a pediatrician may make predictions about a child’s height or weight.

A key factor that makes normative modeling an intuitive and useful framework for studying autism is that it would enable us to map distinct patterns and trajectories of individuals without the need for that individual to be part of a coherent group sharing the same pattern.

Two studies from our labs in the past couple of years have eloquently demonstrated how researchers can use this framework to parse the heterogeneity of potential alterations in cortical thickness in autistic people[1,2]. Crucially, both studies showed that there are few consistent group differences between individuals with and without an autism diagnosis.

These studies also highlight that previously reported case-control differences are likely to be driven by a subset of individuals who show the most atypical pattern and thus are not likely to be representative of all individuals on the spectrum.

The framework instead showed that, despite a lack of group-wide differences, autistic people have highly individualized patterns of cortical thickness compared with the normative trajectory. One of the studies also showed that these unique individual patterns are associated with the severity of autism traits.

Another study published last year confirmed this finding[3]. That study also indicated an association between the severity of autism traits and the degree of deviation from the normative trajectory on a number of brain developmental features.

Because normative modeling assesses the developmental trajectory, we might also be able to make cautious predictive inferences about how a given individual's position may change within the normative range as she gets older.

In this way, normative modeling provides a framework that can provide predictions and help scientists understand conditions at the level of a single individual. It does not require a level of consistency within a cohort to make these assessments. It also conceptualizes conditions as extremes of a normal range rather than as something outside the normal range altogether.

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