MedicalXpress

Exploring the mechanisms underpinning individual differences in autism spectrum disorder using machine learning

April 20 2023, by Ingrid Fadelli

Autism spectrum disorder (ASD) is a developmental disorder associated with difficulties in interacting with others, repetitive behaviors, restricted interests and other symptoms that can impact academic or professional performance. People diagnosed with ASD can present varying symptoms that differ in both their behavioral manifestations and intensity.

As a result, some autistic individuals often require far more support than others to complete their studies, learn new skills and lead a fulfilling life. Neuroscientists have been investigating the high variability of ASD for several decades, with the hope that this will aid the development of more effective therapeutic strategies tailored around the unique experiences of different patients.

Researchers at Weill Cornell Medicine have recently used machine learning to investigate the molecular and neural mechanisms that could underlie these differences among individuals diagnosed with ASD. Their paper, published in *Nature Neuroscience*, identifies different subgroups of ASD associated with distinct functional connections in the brain and symptomatology, which could be related to the expression of different ASD-related genes.

"This work was a follow-up study initiated and led by the first author Dr. Amanda Buch while she was a graduate student in the lab led by Dr.

Conor Liston," Dr. Logan Grosenick, co-senior author of the paper, told Medical Xpress. "It was directly inspired by previous work from the Liston lab) where we introduced new machine learning (ML) methods to discover different subtypes of and biomarkers for depression."

The study's lead author, Dr. Buch, explained, "A key motivation of our study is that a significant barrier to developing therapies for ASD is that the diagnostic criteria are broad. This means the ASD diagnosis describes a large and phenotypically diverse group of people with different underlying biological mechanisms. To personalize therapies for individuals with ASD, it will be important to understand and take into consideration this biological diversity. It is hard to identify the optimal therapy when everyone is treated as being the same, when they are each unique."

The primary goal of the recent work by Dr. Buch, Dr. Grosenick, Dr. Liston and their colleagues was to examine differences in the behavior and brain connectivity among patients with ASD and outline biologically different subtypes of the disorder. They were unsure about whether these subtypes actually existed, thus they used machine learning tools to analyze clinical data and search for possible recurring patterns and replicated their findings in an independent group of autistic individuals.

"If such subtypes existed, we next wanted to see if their differences in brain connectivity might be related to differences in gene expression across the brain, and what protein networks could be involved," Dr. Grosenick said.

To conduct their study, the researchers relied on two publicly available datasets containing information about the behavior of different individuals diagnosed with ASD, as well as functional magnetic resonance imaging (fMRI) scans and other brain-related data. They also used gene expression data gathered by the Allen Human Brain Atlas and

other past research efforts.

"Using machine learning, we discovered robustly reproducible brain-behavior dimensions underlying ASD, and that ASD individuals clustered into four subgroups in this space," Dr. Grosenick explained. "Interestingly, the brain connectivity that was different from non-ASD controls was quite different in each subgroup, and this connectivity was explained by different gene expression patterns and protein–protein interaction networks across individuals. Critically, these subgroups replicated robustly in data from another study, as well as in an independent text-mining analysis of the biomedical literature."

Overall, the findings collected by this team of researchers suggest that there are different robust subtypes of ASD, each associated with distinct molecular signaling pathways and neural connectivity patterns. The team identified four subgroups of ASD so far, but further studies could unveil additional ones.

In the future, this recent work could improve the present understanding of ASD, while potentially also guiding the development of therapies targeting the different clinical subgroups it uncovered. Meanwhile, Dr. Buch, Dr. Grosenick, Dr. Liston and their colleagues plan to continue their research in this area, in the hope to better understand the characteristic patterns they uncovered.

"Technically, the machine learning approach provides a template for future studies linking genes, brain connectivity, and behavior in psychiatry," Dr. Grosenick added. "We now plan on extending this work to even larger and richer ASD datasets that are emerging (as well as to other heterogenous psychiatric diagnoses), and we are actively working on improved ML methods for personalized psychiatry and subtyping of this kind."

Dr. Buch concurred and noted, "We hope our approach will one day lead to new, personalized approaches for the diagnosis of and targeted therapies for individuals with ASD as well as new approaches for other neuropsychiatric diagnoses."

More information: Amanda M. Buch et al, Molecular and network-level mechanisms explaining individual differences in autism spectrum disorder, *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01259-x