

Data-Driven Exploration of Brain Structure Using Statistical Machine Learning: Validity of Derived Diagnostic Patterns in Alcohol Use Disorder and Human Immunodeficiency Virus Infection

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With advances in neuroimage acquisition and processing approaches, we have created an immense sandbox within which to explore vast amounts of imaging-derived phenotypes [i.e., neuroimaging metrics such as structural volumes (1)], both within modalities and across modalities. The potential for exciting new discoveries is nearly unlimited, although this may strain the field's traditional model-driven hypothesis testing, which requires corrections for multiple comparisons, limiting the number of comparisons and confounds that one may incorporate into a single study (1,2). The complementary use of statistical machine learning and classification methods provides a powerful data-driven opportunity to explore these same data by reducing the number of metrics into derived patterns or features. This data reduction addresses multiple comparisons from a different perspective and lends itself well to integrating large-scale datasets across neuroimaging modalities, cognition, and genetics. Furthermore, it has great potential in the study of complex disorders and commonly comorbid conditions that often present constraints on statistical power because of complex hypothetical models and the traditional need to consider (or control for) many independent factors. Clinical applications include prediction of diagnostic conditions using patterns or features derived using statistical learning and linking such patterns to cognition and behavior (2).

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Adeli *et al.* (3) advance a sparse classification method and apply the statistical machine learning technique to the study of alcohol use disorder (AUD) (as defined by DSM criteria), human immunodeficiency virus (HIV) infection, and the common comorbid conditions of AUD plus HIV (AUD+HIV). Alcohol abuse and disorders remain common globally, and people living with HIV are classified as current heavy drinkers at a rate double the national average in the United States, with a lifetime AUD prevalence more than twice that of the general population (3–5). Previous work has shown that HIV disease severity is influenced by alcohol use (4–6) and describes both independent and overlapping brain areas affected by these conditions, with an emphasis on common frontostriatal and white matter effects (4,6). Both AUD and HIV infection target the frontal cortex, basal ganglia, and white matter regions as well as the hippocampus in some studies, as assessed using structural magnetic resonance imaging (MRI). Structural MRI metrics include volume and, for the neocortical ribbon, thickness, surface area, and curvature

for a considerable number of (typically atlas-derived) regions [e.g., using FreeSurfer as in Adeli *et al.* (3)], providing users with vast datasets for brain structure alone. This setting is suitable for exploration with statistical machine learning methods that may determine patterns across these metrics that best define diagnostic conditions. In this study, a statistical machine learning method reduced these structural metrics to patterns defining each condition (AUD, HIV, and AUD+HIV) relative to control subjects ($n = 549$; 25–75 years of age). These derived patterns were then applied to each individual's MRI, and a single diagnostic score was calculated and associated with cognitive performance.

Adeli *et al.* (3) reported that the singular diagnostic groups of AUD and HIV included fewer metrics in their defining patterns than the AUD+HIV group (13, 15, and 25 metrics, respectively), and predictive classification accuracy was greater with the inclusion of more metrics in the pattern (from ~70% for AUD and HIV to 78.1% for AUD+HIV). Interestingly, several metrics were selected in defining all three groups relative to control subjects, including volumes of white matter hyperintensities, precentral gyrus, thalamus, and hippocampus as well as the surface area of the posterior cingulate. It should be noted that an association with the frontal cortex was reflected in all group patterns as well, although different measurement types stood out; the meaning of capturing different measurement types, such as volume, surface area, or cortical thickness, may be difficult to interpret given the interdependence of cortical volume and its components of surface area and cortical thickness. The frontostriatal system, inclusive of white matter, has been shown to be impacted by both AUD and HIV infection in previous studies, with hippocampal effects more variably reported (6). Of note, all diagnostic scores from each group also predicted worse learning and memory performance, in line with previous work in AUD and HIV infection (7). Whether these commonalities in comparison to control subjects are specific to AUD and HIV or if this is a more general pattern that is common to broader classes of neurodegeneration is not known, given the susceptibility of white matter and the hippocampus to several disease states. The application of this approach to other disorders and the comparison between diagnostic groups may provide greater insight into the disease specificity of these common effects.

Beyond the shared metrics noted above (white matter hyperintensities, precentral gyrus, thalamus, hippocampus, and posterior cingulate), HIV infection and AUD patterns

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included additional affected regions. The pattern for HIV infection included broader parietal, temporal, and frontal areas, with unexpectedly little representation of the basal ganglia, and less commonly reported areas that may reflect differences in underlying treatment or immune histories (6,8). Cognitive performance associations with the diagnostic scores were strong for speed of information processing, a commonly reported deficit in HIV infection (4), and this association also was found within the AUD+HIV group, further supporting recent findings (7). In comparison, the AUD pattern included superior frontal and caudate volumes, with the AUD+HIV pattern incorporating additional frontal area metrics as well as basal ganglia and broader temporal areas across measurement types, findings that are in line with previous reports (4,5,7). The AUD diagnostic score was strongly linked to executive function performance as expected (4), although the AUD+HIV group did not show this association. Adeli *et al.* (3) noted that the AUD group had greater alcohol consumption and more recent use relative to the AUD+HIV group, which may drive this difference in the strength of these effects. These findings encourage the validity of this statistical machine learning method in searching out appropriate neuroimaging and cognitive effects.

The work of Adeli *et al.* (3) is of interest both for the development and application of a novel classification method and for validating findings related to AUD, HIV infection, and the common comorbid nature of these conditions. The diagnostic accuracy of the study's improved novel classification method [described in the Supplement in Adeli *et al.* (3)] was superior to that of two other strong approaches: 1) joint feature-sample selection and 2) sparse feature selection followed by a support vector machine classifier, encouraging broader testing of this novel method. The derived structural neuroimaging phenotypes for AUD, HIV, and AUD+HIV can now be applied to other HIV and AUD cohorts to assess reproducibility and generalizability, and the method itself can be applied to explore other disorders and assess the broader applicability of its approach. Finally, recent work in the fields of HIV and AUD further suggests that the reported diagnostic accuracy (in the range of 70%–78%) may be improved by incorporating broader data fields, beyond structural MRI, into statistical machine learning approaches. The reported importance of white matter disease to diagnostic classification relative to control subjects in this study alongside white matter effects recently reported in AUD and HIV suggest that classification may be improved by the inclusion of additional imaging-derived phenotypes from modalities such as diffusion tensor imaging (6,9). Furthermore, individual characteristics such as age have the strong potential to interact with or influence the presentation of AUD and HIV (4,7,10) and could be considered more directly as factors in the larger dataset to exploit all the available information.

Statistical machine learning and classification methods provide powerful data-driven exploration of vast datasets by reducing the number of available metrics across different neuroimaging modalities and other variables into derived patterns or features, and ultimately single diagnostic scores. As demonstrated by Adeli *et al.* (3), this approach complements

the more traditional model-based hypothesis testing and has the potential to lead to new discoveries. Data-driven data reduction allows for broader exploration of brain integrity, cognitive performance, and genetics to provide imaging feature and pattern phenotypes of disease and risk states that may improve diagnosis and risk prediction as well as increase the reproducibility of classification studies. It will be exciting to see future studies assess the application of these derived patterns to other AUD and HIV cohorts, examine the influence of including additional variables to increase diagnostic accuracy, and study other disorders to determine the generalizability of the improved statistical machine learning method.

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Article Information

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