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Multi-domain predictors of grip strength differentiate individuals with and without alcohol use disorder

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Abstract

Grip strength is considered one of the simplest and reliable indices of general health. Although motor ability and strength are commonly affected in people with alcohol use disorder (AUD), factors predictive of grip strength decline in AUD have not been investigated. Here, we employed a data-driven analysis predicting grip strength from measurements in 53 controls and 110 AUD participants, 53 of whom were comorbid with HIV infection. Controls and AUD were matched on sex, age, and body mass index. Measurements included commonly available metrics of brain structure, neuropsychological functioning, behavioural status, haematological and health status, and demographics. Based on 5-fold stratified cross-validation, a machine learning approach predicted grip strength separately for each cohort. The strongest (top 10%) predictors of grip were then tested against grip strength with correlational analysis. Leading grip strength predictors for both cohorts were cerebellar volume and mean corpuscular haemoglobin concentration. Predictors specific to controls were Backwards Digit Span, precentral gyrus volume, diastolic blood pressure, and mean platelet volume, which together significantly predicted grip strength ($R^2 = 0.255$, $p = 0.001$). Unique predictors for AUD were comorbidity for HIV infection, social functioning, insular volume, and platelet count, which together significantly predicted grip strength ($R^2 = 0.162$, $p = 0.002$). These cohort-specific predictors were doubly dissociated. Salient predictors of grip strength differed by diagnosis with only modest overlap. The constellation of cohort-specific predictive measurements of compromised grip strength provides insight into brain, behavioural, and physiological factors that may signal subtly affected yet treatable processes of physical decline and frailty.

KEYWORDS
alcohol use disorder, grip strength, machine learning, MRI

1 | INTRODUCTION

Grip strength is one of the most sensitive measures of poor health, frailty, and cardiovascular status,[1] with accelerated weakening being a precursor of hospitalization and even death.[1] Declining grip strength can result from sarcopenia, the accelerated loss of muscle strength and mass,[2] and is associated with comorbidities of aging, including musculoskeletal trauma, diabetes, and neurological and psychiatric disorders.[3] This physical decline is exacerbated by poor nutrition and other comorbidities also common in older age, including depression, anxiety, poor sleep, smoking, and sedentary lifestyle.[4] Further, grip strength is a correlate and predictor of cardiovascular reserve and disease,[5] cognitive decline,[6] frailty,[7] and regional cortical grey matter volume.[8] Research stressing the worth of assessing grip strength[4] concluded that it was perhaps the simplest and most inexpensive index of general health. This assessment was borne out of a large prospective study of healthy 45- to 68-year-old men who underwent repeat testing of motor and grip strength measures 25 years later, revealing that risk of self-care disability was more than 2 times greater in individuals with the lowest relative to the highest third of grip strength scores.[9] The power of grip strength to predict declining health related to myriad factors makes it a sensitive measure; however, a ranking of specific antecedents of weakening grip identified with objective methods has not been considered in a single, unbiased analysis.

The increasing prevalence of later-life initiation of heavy drinking and development of alcohol use disorder (AUD)[10] may complicate the understanding of factors that contribute to age-related declines in grip strength. Reports are contradictory: several studies found weaker grip in AUD than non-AUD comparison cohorts,[11,12] whereas other studies found stronger grip in people who engaged in later-life binge drinking.[13] Neural substrates have also been identified in AUD, indicating that poorer grip strength, manual dexterity, and gait and balance are each correlated with regional deformation of the corpus medullare and cerebellar vermis in AUD.[11]

The co-occurrence of human immunodeficiency virus (HIV) infection in individuals with AUD[14] highlights the importance of understanding grip strength predictors in this cohort, considering the role of declining grip strength in forecasting outcomes and well-being in people living with HIV (PLWH). In PLWH, grip strength correlates with various factors, including blood markers of nutrition and anaemia,[15] multimorbidity, diabetes, pulmonary function,[16] depressive symptoms,[17] and cognitive impairment.[6] These findings emphasize the value of identifying grip strength predictors in the AUD population with and without HIV comorbidity for research and health insights. The routine measurement of grip strength in AUD patients may be pivotal in identifying individuals at heightened risk of functional decline or even hospitalization, enabling timely implementation of targeted interventions like nutritional protein supplementation and resistance exercises.

Recognizing how a decline in grip strength relates to normal aging and conditions including AUD (which exhibits accelerated aging in multiple brain structural and functional domains), we used a data-driven approach based on multi-layer perceptrons (MLPs) to discover which commonly obtained variables in clinical research are leading predictors of poor grip strength in these cohorts. Accordingly, variables from five domains—brain structure, neuropsychological functioning, behavioural status, haematological and health status, and demographic characteristics—were available from our ongoing studies of AUD, HIV, and normal aging for analysis.[18] Based on the complex interplay of factors affecting grip strength and the unique challenges faced by individuals with AUD and HIV, we hypothesized that predictors of grip strength would differ significantly between the AUD and control cohorts. Specifically, we expected that in the AUD cohort, health-related factors (such as HIV status) and neurological markers (such as regional brain volumes) would have a greater influence on grip strength than in the control cohort. Conversely, for the control cohort, we anticipated that traditional aging-related factors (such as cognitive performance and cardiovascular health) would be more prominent predictors of grip strength than in the AUD cohort. To formally test these hypotheses, our analysis proceeded in three steps: first, our machine learning model was trained on data from participants irrespective of cohort and then fine-tuned by cohort. Second, the machine learning algorithm identified variables that best predicted grip strength for each cohort. Third, traditional correlational analysis tested the relations between the identified variables per cohort and grip strength as a check on the validity and clinical relevance of the machine learning findings.

2 | METHODS AND MATERIALS

2.1 | Participants

Between 2012 and 2019, 370 participants were enrolled in SRI International-Stanford University collaborative studies to examine the effects of aging and disease on the brain. Of them, 191 participants had the demographic and diagnostic data needed to perform the proposed study. Of those, 81 were healthy control participants and 110 participants were diagnosed with AUD of whom 53 (48.18%) were also living with HIV. We included individuals with HIV comorbidity to diversify and increase the size of the data set, which is considered best practice for machine learning-based analyses.[19] Furthermore, the healthy controls were matched using the maximum bipartite matching algorithm[20] with respect to age, sex, and body mass index to the AUD cohort reducing the number of controls to 53 and the total number of participants analysed by the study to 163 (Table 1).

This study abided by the principles of the Declaration of Helsinki. Procedures were reviewed and approved by the Institutional Review Boards of SRI International (Advarra FWA00023875; SRI FWA00007933) and Stanford University (FWA00000935). Before undergoing study procedures, the participants provided written informed consent and were screened with a breathalyser to ensure a breath alcohol level of 0.0. Participants provided demographic information (e.g. age, sex, years of formal education, and socioeconomic status (SES)[21]). Clinically trained researchers obtained a medical history and conducted the Structured Clinical interview for DSM[22] [DSM-IV-TR] and[23] [DSM-5] to establish history of DSM-IV-TR

TABLE 1 Demographic data of the control cohort and the AUD cohort.

	Controls, $N = 53$	AUD, $N = 110$
Male/female	33/20	73/37
Age, years	51.73 (13.52)	52.64 (10.73)
Socioeconomic status[a]	27.04 (11.89)	42.25 (13.87)*
Body mass index, kg/m^2	26.11 (4.02)	25.98 (4.32)
Total alcohol consumed, kg	39.86 (80.52)	1037.92 (847.09)*
Alcohol consumed in the past year, kg	1.32 (2.35)	17.63 (19.82)*

Note: () indicates standard deviation.
*Significant group difference ($p < 0.001$), otherwise non-significant.
[a]Socioeconomic status: lower values = higher socioeconomic status.

alcohol dependence or abuse or DSM-5 AUD and to exclude those with bipolar disorder or schizophrenia. Control participants did not meet DSM-IV-TR or DSM-5 criteria for any psychiatric disorder. Participants also completed a structured interview regarding their drinking history[24] from which lifetime quantity of alcohol consumed was calculated. A blood sample provided HIV serological status, complete blood count, and comprehensive metabolic data. AUD diagnosis and HIV infection were coded as binary variables.

A Karnofsky score of 70 or above ([25]; range 0–100), which measures ability to perform daily tasks, was required. Exclusions were conditions potentially affecting the central nervous system, including head trauma, stroke, epilepsy, loss of consciousness >30 min; chemotherapy for cancer, uncontrolled hypertension, uncontrolled diabetes, or ferrous metal in the body precluding MRI scanning.

2.2 | Measurements

Grip strength was tested by squeezing a hand dynamometer (Lafayette Instrument Company, Model 78010) using maximum strength while standing. The test started with the dominant hand and then continued with the other hand in the following order: for right (R) handers—R, R, L, L, R, L; the opposite order was performed for left (L) handers. Each hand was tested three times, and the score was the mean grip strength of the two hands expressed in kg.

This measure of grip strength was predicted by a machine learning approach from measurements extracted from brain MRI and non-imaging measurements from five domains, which are specified next. While all 163 participants had MRI measurements, non-imaging measurements were available for at least 50% of participants. Table S1 provides a complete list, description, and missing values percentage of the measurements.

Demographic variables included age, sex, education, and socioeconomic status (Table 1).

Haematological and health status was determined with blood chemistry obtained from blood samples yielding metabolic panel data (renal and hepatic function, electrolytes, calcium, proteins, and blood sugar), complete blood count (including haematocrit, mean corpuscular haemoglobin concentration [MCHC], mean corpuscular volume, red blood count, white blood count), and indices of nutrition (B12-folate, serum prealbumin). Physical measures included body mass index (BMI), diastolic and systolic blood pressure, and heart rate.

Behavioural indices were measures of life functioning, including the Global Assessment of Function (GAF) from the DSM-IV-TR SCID, Beck Depression Inventory, 2nd edition,[26] the eight health-related quality of life subscales of the SF-21,[27] and the Alcohol Use Disorders Identification Test (AUDIT[28]).

Neuropsychological functioning was assessed with cognitive and psychomotor speed measures from standard tests: FAS letter fluency,[29] Golden Stroop Test,[30] Rey-Osterrieth Complex Figure Test[31] (copy, immediate, and delayed recall), Trails A and B,[32] and 3 subtests of the Wechsler Memory Scale-Revised[33] (Logical Memory II, Backward Digit Span, and Backward Block Span).

MRI volumes were derived from T1-weighted Inversion-Recovery Prepared SPoiled Gradient Recalled (SPGR) images (TR = 7.068 ms, TI = 300 ms, TE = 2.208 ms, flip angle = 15°, matrix = 256 × 256, slice dimensions = 1.25 × 0.9375 × 0.9375 mm, 124 slices) acquired between 2012 and 2019 using a GE 3 T whole-body MR system (General Electric Healthcare, Waukesha, WI). MRIs were processed using the SIBIS processing pipeline.[34] Following visual inspection for image artefacts, structural T1-weighted MRI images were denoised and skull-stripped. The process of skull stripping utilized a brain mask created through majority voting, considering segmentations from FSL (v5.0.6), BET, AFNI (v16.1.15) 3dSkullStrip, and Robust Brain Extraction (ROBEX v1.2).[35] Field inhomogeneity in the MRI was corrected using ANTs (v2.1.0) N4ITK.[36] The brain mask was further refined by expanding majority voting to maps produced by previous segmentation methods and FreeSurfer MRI gcut [v5.3.0[37];] applied to the corrected MRI.

After using the resulting mask to remove the skull from the MRI, the brain was segmented into grey matter and white matter using ANTs Atropos.[38] Grey matter parcellated maps identified six lobar regions: frontal, temporal, parietal, occipital, cingulate, and insular cortices using the SRI24 atlas.[39] All regions except the insula, were subdivided into sub-regions. Subcortical areas analysed included the caudate, putamen, pallidum, and thalamus. Additional measurements comprised pons, corpus callosum, cerebellum, precentral gyrus, and vermis, which was divided into three sections approximating the[1] anterior,[2] posterior, and[3] inferior regions. To minimize the number of comparisons and because laterality hypotheses were not proposed, regional volumes from both hemispheres were combined as the analysis metric resulting in a total of 18 regions examined. Each participant was then coded by 58 (imaging and non-imaging) measurements.

2.3 | Machine learning and statistical analysis

To minimize potential confounding effects of sex, supratentorial volume was residualized from all imaging measurements with a generalized linear model (GLM). A GLM also regressed out the confounding effects of sex and socioeconomic status (SES)[40] from grip strength

and all non-imaging scores. Missing non-imaging values were imputed using the mean (continuous variables) or mode (categorical variables) based on sex and diagnosis (i.e. control or AUD). All measures, except for grip strength, were normalized between 0 and 1, based on the minimum and maximum value of each feature in the training split of each cross-validation fold and applied on the validation split of that fold.

To predict grip strength of all 163 participants, we designed a lightweight three-layer MLP (see Supplement Methods). The model was evaluated by a 5-fold cross-validation stratified by controls, AUD, and participants with AUD and HIV. Pearson correlations were then computed between predicted and actual grip strength within the control and AUD samples separately. *p* Values of the correlation were determined by both *t* statistics and permutation tests (see Supplement Methods). After training the model on all cohorts to predict grip strength, we performed "fine-tuning"[41] by training two distinct versions of the same model architecture on control and AUD separately. For the fine-tuning process, the weights from the initially trained model on all cohorts were used as initialization. This approach ensured that the cohort-specific models retained the general learning from the broader dataset while adapting to the idiosyncratic features of each cohort and enabled testing whether the predictors of grip strength diverged between the control and AUD cohorts.

For each model, the correlations among control and AUD samples were recalculated and compared via z-test. Next, the contribution of each measurement in the prediction process was quantified by computing their Shapley Additive exPlanations (SHAP) values, a commonly used metric in machine learning.[42] Based on SHAP, the measurements were ranked and the 10% (or 6) measurements with the highest SHAP values were further inspected. Lastly, we repeated the above procedures of training and fine-tuning cohort-specific models and deriving SHAP values by replacing MLP with three other models: ridge regression, support vector regression, and random forest (see Supplement Methods).

As SHAP does not provide statistical significance levels, the hierarchical relevance of each of the 6 measurements in relation to grip strength was computed via Pearson correlation (if they were continuous) or *t* test (if they were binary). For each measurement, the correlation coefficients within the control and AUD cohort were compared by a z-test. For the subset of top control-specific measurements that were weak contributors (i.e. below the top 6) to the AUD model, a robust linear regression model (RLM)[43] was separately fitted in each cohort to regress grip strength (predictor) from those measurements (independent variables) and then an *F* test examined the goodness-of-fit of the regression.[44] Likewise, *F* tests examined the power of AUD-specific measurements in explaining the variance of grip strength in each cohort separately. To ensure that insignificance of the AUD-specific measurements on the control cohort was not an artefact of sample size, we randomly sampled 53 participants 10 times from the AUD cohort and repeated the above computations.

For all experimental outcomes with associated significance statistics, *p* values ≤ 0.05 (after Bonferroni multiple comparison correction) were accepted as significant.

3 | RESULTS

3.1 | Machine learning training differentiating cohorts

When cross-validating the MLP model on all participants, the correlation between predicted and actual grip strength was $r = 0.20$ ($p = 0.141$) for controls and $r = 0.20$ ($p = 0.038$) for AUD. Following fine-tuning, the correlation of the control-specific model increased to $r = 0.34$ ($p = 0.012$) on the controls and was not significant ($r = 0.06$, $p = 0.523$) for the AUD cohort (Figure 1, top). Permutation testing resulted in similar significance levels (Supplement Results) and the z-test suggested the control-specific correlation was different from the AUD-specific correlation on a trend level ($p = 0.08$). Lastly, compared to other machine learning models (Table S2), only the MLP model resulted in significantly accurate prediction when fine-tuned on controls. We therefore focused our discussion on MLP hereafter.

The correlation of the MLP model fine-tuned on AUD was not significant ($r = 0.20$, $p = 0.148$) for controls and was significant ($r = 0.30$, $p = 0.001$) for the AUD cohort, although the z-test did not reveal significant difference between the two correlation coefficients ($p = 0.53$). Finally, for the model fine-tuned on AUD, there was no statistical difference in the model's prediction accuracy between AUD participants with and without HIV ($t = 0.47$, $p = 0.636$). To examine whether the confounder regression and imputation induced data leakage that inflated prediction accuracy, we performed regression and imputation within the training folds of each cross-validation run. Results indicate the significance outcomes of the above correlation analyses remained endured (Figure S1).

3.2 | Correlations of model-identified predictors with grip strength

The top 6 (10%) measurements according to their SHAP values (Figure 2) for the control-specific model were cerebellar white matter volume, Backward Digit Span, precentral gyrus grey matter volume, mean corpuscular haemoglobin concentration (MCHC), diastolic blood pressure, and mean platelet volume. For the AUD-specific model, two of the top 6 measurements overlapped with those of the control cohort: cerebellum white matter volume and MCHC. Four predictors unique to the AUD cohort were HIV infection status, social functioning, platelet count, and insula grey matter volume (Figure 1, Middle).

3.3 | Tests of significant predictors of grip strength

Mean platelet volume ($r = -0.442$, $p < 0.001$) significantly correlated with grip strength among the controls (Figure 1, bottom) but not in the AUD cohort ($r = -0.13$, $p = 0.174$). The z-test suggests a significant difference between the two correlation coefficients (z-score $= -1.99$, $p = 0.04$). Similarly, MCHC only correlated with grip strength of control participants ($r = 0.362$, $p = 0.008$) but not with AUD participants

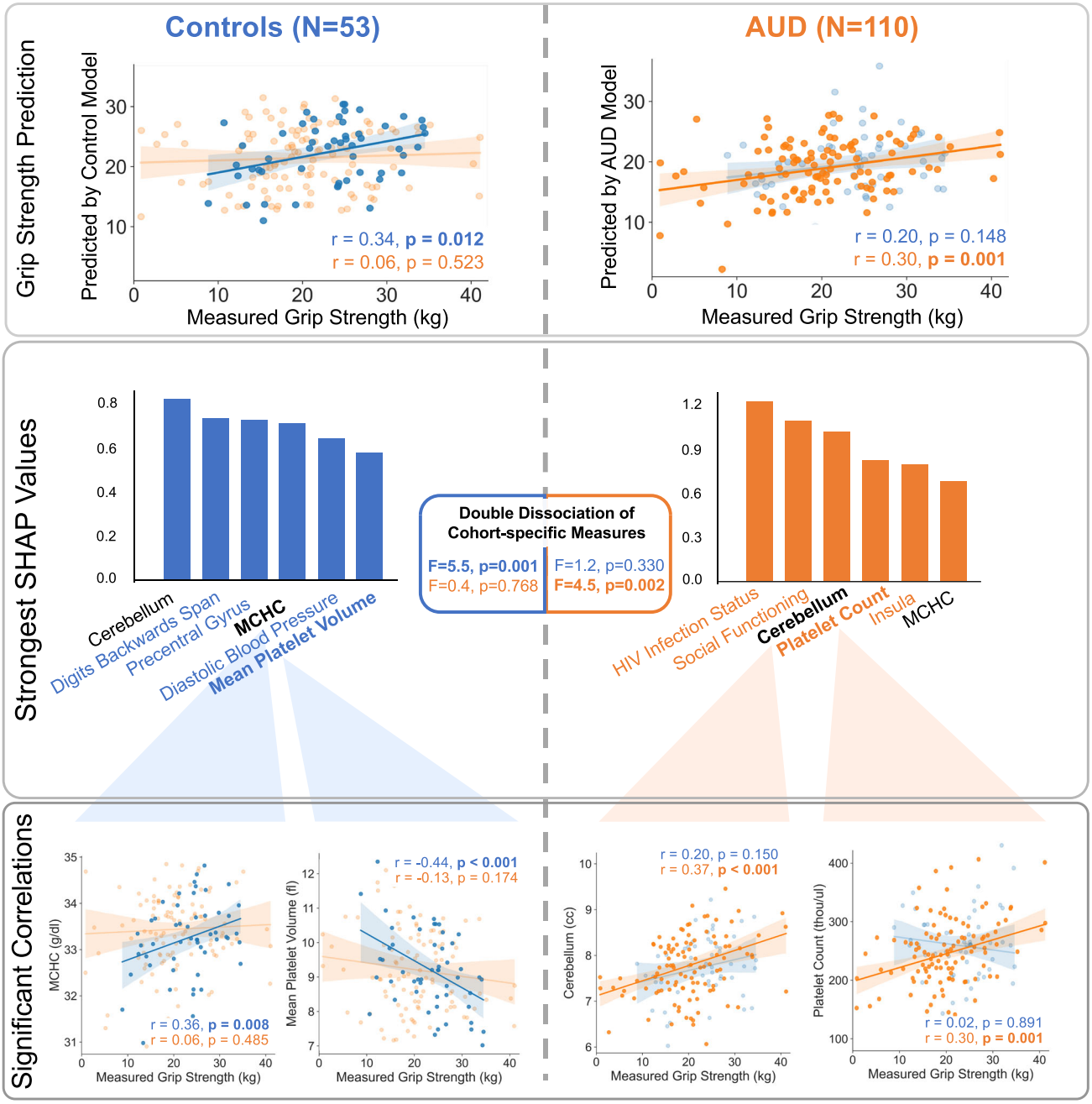

FIGURE 1 *Top*: separately for controls (blue) and AUD (orange), the machine learning model predicted grip strength using all measurements. For each cohort, the predicted grip strength values are significantly correlated with the actual grip strength values. *Middle*: salient predictors (top 10%) are ranked according to SHAP values. Mean corpuscular haemoglobin concentration is denoted as MCHC. Black font colour represents predictors that were strong for both cohorts; cohort-specific predictors are represented by the cohort-specific font colour. *F*-test applied to the cohort-specific predictors revealed a double dissociation across the cohorts. *Bottom*: salient predictors for each of the cohorts that were significantly correlated with grip strength.

($r = 0.06$, $p = 0.485$), with a trend-level difference between the two correlations (z-score = 1.84, $p = 0.06$). Moreover, the control-specific measurements predicted grip of control participants significantly better than an intercept-only RLM (*F* statistic = 5.501, $R^2 = 0.255$, $p = 0.001$). By contrast, the control-specific measurements were not able to predict grip of the AUD participants significantly (*F* statistic = 0.455, $R^2 = 0.033$, $p = 0.768$).

For the AUD cohort, cerebellar white matter volume ($r = 0.365$, $p < 0.001$) and platelet count ($r = 0.303$, $p = 0.001$) were significantly correlated with grip strength (Figure 1, bottom). They were not significantly correlated with grip strength of controls (cerebellar white matter volume ($r = 0.20$, $p = 0.150$), platelet count ($r = 0.02$, $p = 0.891$)), and the z-test suggested a trend-level difference between the two cohort-specific correlation coefficients with platelet

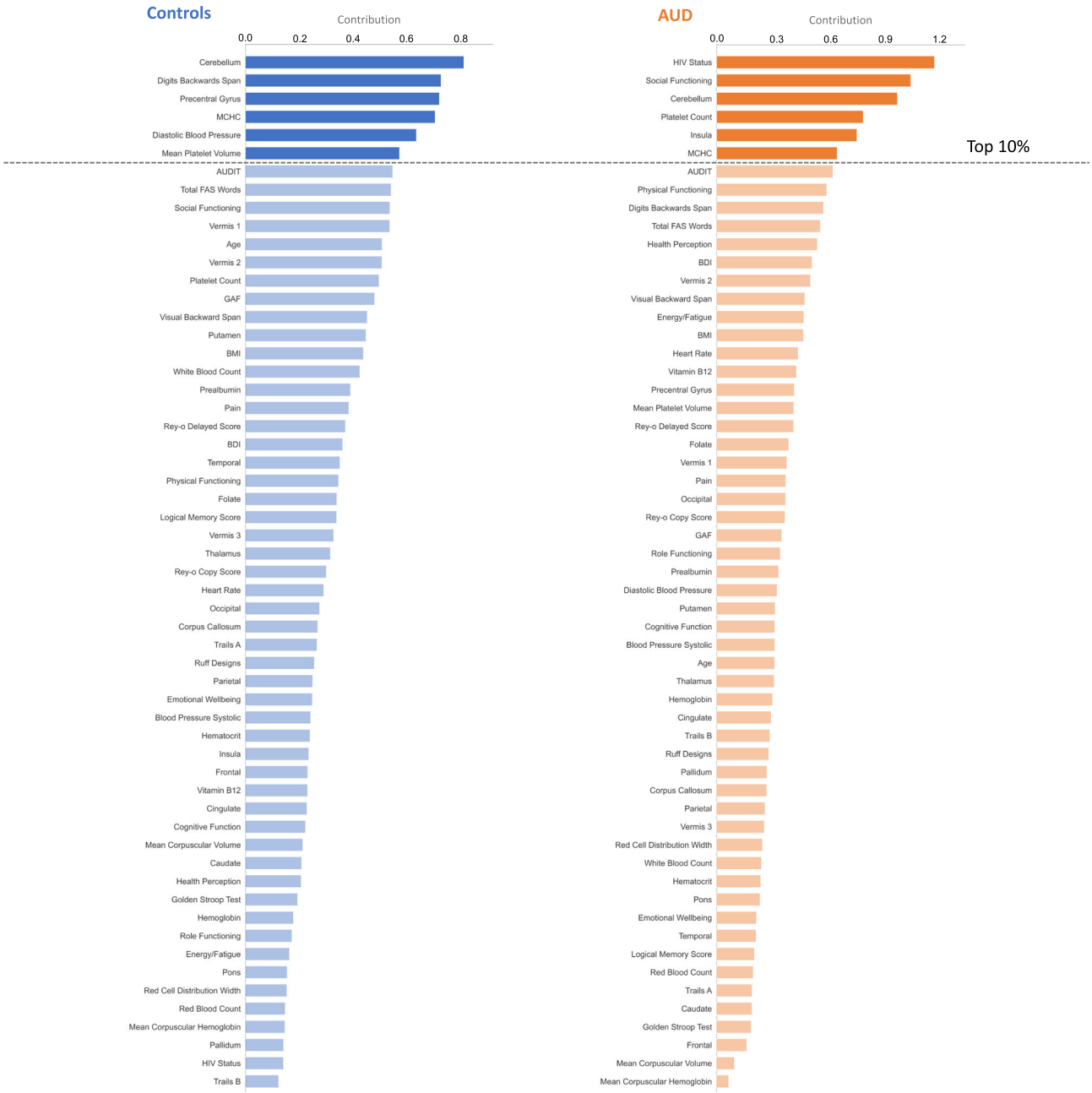

FIGURE 2 Comprehensive list of all measurements ranked by their SHAP value and their level of strength in predicting grip strength for our machine learning model. The top 10% or 6 measurements have been highlighted as the top predictors for each cohort. *Left*: SHAP values for model fine-tuned on the control cohort (blue). *Right*: SHAP values for model fine-tuned on AUD cohort (orange). Mean corpuscular haemoglobin concentration is denoted as MCHC, body mass index as BMI, global assessment of functioning as GAF, alcohol use disorders identification test as AUDIT, and Beck Depression Inventory-II as BDI.

count (z-score $= -1.69$, $p = 0.09$). Moreover, these two AUD-specific measurements were not significantly different between the AUD-only participants and AUD participants living with HIV (platelet count ($t = 0.71$, $p = 0.47$), cerebellar white matter volume ($t = -0.99$, $p = 0.32$)) (Figure 3 and Figure S2). Lastly, the AUD-specific measurements predicted grip strength of the AUD cohort significantly better than an intercept-only RLM (F statistic $= 4.515$, $R^2 = 0.162$, $p = 0.002$), even when the analysis was confined to 53 participants randomly sampled from the AUD cohort (max p value is 0.03 across 10 trials) to match the number of controls. The AUD-specific measurements were not significant (F statistic $= 1.172$, $R^2 = 0.074$, $p = 0.330$) for control grip strength. These findings remained unchanged when rerunning the RLM using the five AUD-specific features (i.e. all but MCHC) that were also identified as important by at least one of the three other machine learning models (Figure S3).

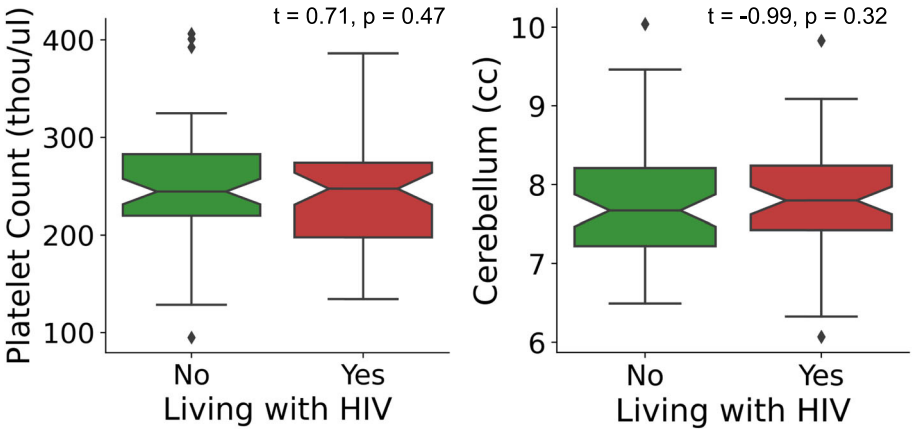

FIGURE 3 Distribution of predictors platelet count and cerebellum for AUD individuals without (green) and with (red) HIV co-morbidity. Our sample did not reveal significant difference between the AUD with and without HIV comorbidity for platelet count and cerebellum white matter (*t* test: platelet count $t = 0.71$, $p = 0.47$; cerebellum $t = -0.99$, $p = 0.32$).

4 | DISCUSSION

Based on machine learning, we identified predictors of grip strength in 110 AUD individuals and separately in the 53 controls matched in age, sex, and BMI to the AUD cohort. Our data-driven analysis uniquely identified a double dissociation, i.e. strong predictors of grip strength unique to controls, namely Backward Digit Span (a measure of spatial working memory), precentral gyrus grey matter volume, diastolic blood pressure, and mean platelet volume, were not significant predictors of the AUD grip. By contrast, predictors unique to AUD, namely HIV status, social functioning, platelet count, and insula grey matter volume, were not significant predictors of control grip. Given the broad clinical relevance of grip strength, these predictors could identify diagnostically-selective biomarkers of decline and enhance our understanding of how AUD in contrast with non-AUD individuals affects central and peripheral nervous system functions.

Critical for predicting grip strength in both cohorts was cerebellar white matter volume, which was expected given its role in motor control.[45] Critically, cerebellar volume was significantly correlated with grip strength only in the AUD cohort (Figure 1), indicating an advantage of machine learning in revealing relations that may be undetectable using simple correlational statistics. Rather than cerebellar white matter, the precentral gyrus, which is linked to voluntary motor functions, emerged as a strong predictor of grip in the control cohort. Another brain structure commonly affected in AUD is the insula,[46] and our study further revealed that it was one of the top predictors of grip strength unique to AUD patients. However, given the complex functional role of the insula, it remains unclear whether its association with motor function (such as grip strength) is mediated by other factors including perception, self-awareness, and interpersonal experience. While speculative, the involvement of the insula in grip strength could be explained through several pathways. Specifically, its role in interoception may influence effort perception during motor tasks, whereas its function in emotional regulation could impact motivation in strength-related activities.[47] The insula's connections with motor areas suggest a direct influence on motor preparation and execution. Research has shown that the anterior insula integrates interoceptive information with cognitive processes, potentially affecting motor output.[48] Studies have also demonstrated the insula's involvement in action selection and activation during hand movements.[49] These findings collectively suggest a complex interplay between insular function, motor control, and grip strength.

In addition to neuroanatomical measurements, machine learning revealed significant functional implications for grip strength in the AUD cohort. Specifically, our analysis uniquely revealed that social functioning, the degree to which one can engage with family and friends, emerged as a significant predictor of grip strength exclusively in AUD participants. This stronger correlation reflects the simultaneous effects of alcohol abuse on physical ability and functioning,[50] two factors that are less dependent in healthy individuals. Regarding cognitive performance, unique to control participants was working memory assessed with Backward Digit Span in predicting grip strength. Controls tended to have longer Backward Digit Spans than AUD ($p = 0.074$); the larger standard deviation for spans in the AUD contributed to its weaker relevance or more heterogeneous influence in the AUD than the controls. These findings extend existing evidence that the relationship between grip strength and cognitive and social functioning is different between controls and groups with neuropsychiatric disorders[51] and further underscores the role of grip strength in aligning with functional deficits and diagnostic differences in people with AUD.

Beyond brain and behavioural measures, physical health-related predictors linked to aging were relevant to both cohorts and included the MCHC. Specific to controls were diastolic blood pressure and mean platelet volume, even though these measures were not significantly different between the two cohorts. Higher mean platelet volume correlated with weaker grip strength, which comports with an increase in platelet function being linked to frailty.[52] However, age was only a marginally stronger predictor for the control than AUD cohort (11th place, Figure 2) and was basically discounted as an AUD-specific predictor (listed in the bottom half).

In addition to insular volume and social functioning, unique predictors of grip in the AUD cohort were platelet count and HIV infection status. Lower platelet count has been linked to frailty[52] and heavy drinking, especially in drinkers with HIV,[53] which might explain our finding that the correlation between platelet count and grip strength was only observed in the AUD cohort. Compared to those

without HIV comorbidity, AUD with HIV comorbidity had a lower grip strength only on a trend-level ($t = 2.61$, $p = 0.01$), even though this variable was the strongest predictor in the AUD cohort. Furthermore, our sample did not reveal significant differences between the cohorts of AUD with versus without HIV comorbidity for the two significant predictors, platelet count and cerebellum (Figure 3). Thus, the predictors specific to AUD were most likely related to the impact of AUD and not HIV infection on the overall health of an individual as AUD is known to cause muscle wasting,[54] which reduces grip strength. In contrast to the AUD cohort, predicting grip strength in controls was closely tied to cognitive and physical health.

Beyond these findings, our study has areas for future expansion. The carefully matched sample allowed for rigorous comparisons between cohorts but might confine our findings to a specific population. To find out if our findings generalize to the general population, we would need to train the model on age-matched cohorts that are larger and more diverse. Longitudinal studies could further elucidate temporal dynamics that our cross-sectional data cannot capture. Other lifestyle factors that often differ between people with AUD and healthy individuals but not collected by our study (such as diet quality and exercise history) could further explain the doubly dissociated predictors of grip differentially related to cohort. For example, AUD patients often have lower nutrient and carbohydrate intake and higher fat intake than non-drinkers.[55,56] The different food choices and risk of malnutrition could mediate the physical and neurobiological measurements in our study. Additionally, although our SHAP analysis explained the contribution of each individual feature to the prediction of grip strength, possible interactions among multiple features in relationship to grip were not examined. Despite these limitations, our rigorous statistical approach provides an objective foundation for understanding the complex relationships between AUD and grip strength, setting the stage for more comprehensive future investigations.

5 | CONCLUSION

Our data-driven analysis successfully identified predictors of waning grip strength, which is a bellwether of impending decline. Salient predictors of grip strength in the AUD cohort were related to infection comorbidity, overall health, and insula volume status. While evidence for declining grip strength in the control cohort was also forthcoming, its predictors differed from those of the AUD cohort in highlighting spatial working memory, precentral gyrus volume, and other physiological and haematological markers of health. This double dissociation between the unique predictors for each cohort underlines the heterogeneity of substrates of grip strength of this common correlate of health status. Thus, our outcomes provide a data-driven basis for continued exploration of multi-level antecedents to waning grip strength as a marker of impending frailty in health and disease.

CONFLICT OF INTEREST STATEMENT

None of the authors have conflicts of interest with the reported data or their interpretation.

PATIENT CONSENT STATEMENT

All participants provided written informed consent and received modest financial compensation for study participation.

DATA AVAILABILITY STATEMENT

The data sets generated and analysed during the current study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

This study abided by the principles of the Declaration of Helsinki. Procedures were reviewed and approved by the Institutional Review Boards (IRB) of SRI International (Advarra FWA00023875; SRI FWA00007933) and Stanford University (FWA00000935).

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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