Abstract

Despite the great promise that machine learning has offered in many fields of medicine, it has also raised concerns about potential biases and poor generalization across genders, age distributions, races and ethnicities, hospitals, and data acquisition equipment and protocols. In the current study, and in the context of three brain diseases, we provide experimental data which support that when properly trained, machine learning models can generalize well across diverse conditions and do not suffer from biases. Specifically, by using multi-study magnetic resonance imaging consortia for diagnosing Alzheimer’s disease, schizophrenia, and autism spectrum disorder, we find that, the accuracy of well-trained models is consistent across different subgroups pertaining to attributes such as gender, age, and racial groups, as also different clinical studies. We find that models that incorporate multi-source data from demographic, clinical, genetic factors and cognitive scores are also unbiased. These models have better predictive accuracy across subgroups than those trained only with structural measures in some cases but there are also situations when these additional features do not help.

Keywords: heterogeneity, bias, neurological disorder, MRI, distribution shift

1 Introduction

Machine learning models have shown great promise for precision diagnosis, treatment prediction, and a number of other clinical applications\textsuperscript{5-8}. This has led to increasing
interest in building systems where such models can aid human experts for accurate and efficient decision making in clinical settings. However, there are some key challenges to achieving this goal. Particularly, clinical data is highly heterogeneous. For example, neurological disorders such as Alzheimer’s disease, stem not only from diverse anatomies, overlapping clinical phenotypes, or genomic traits of different subjects, but also from operational, demographic and social aspects such as data acquisition protocols, and paucity of data for minorities. As a consequence, machine learning models often have poor reproducibility across the population.

This paper focuses on one particular aspect of this issue, namely the fact that machine learning models make biased predictions, i.e., they have different accuracy, for different genders, age and racial groups, and cohorts from different clinical studies. Recently, this issue has received wide attention. For example, a machine learning model trained on X-ray images consistently made inaccurate predictions on underrepresented genders when the imbalance in training data is beyond a threshold. Similarly, for classification of chest X-ray pathologies, minority groups such as female African-Americans and patients with low socioeconomic status are prone to be incorrectly diagnosed as healthy. Such results have raised concerns on whether machine learning models can provide unbiased predictions, and whether they can be deployed in clinical settings eventually.

This paper provides results from relatively large and diverse datasets pertaining to three neurological disorders, namely Alzheimer’s disease (AD), schizophrenia (SZ), and autism spectrum disorder (ASD), which alleviate these concerns. We build machine learning models using 3D magnetic resonance (MR) images along with demographic, clinical, and genetic factors, as also cognitive scores, from large-scale consortia—iSTAGING, PHENOM, and ABIDE; see Table 1. There exists large imbalance in this dataset, e.g., 13% and 37.4% female subjects respectively in ABIDE and PHENOM, and 70.6% European Americans, 8.8% African Americans, and 1.5% Asian Americans in iSTAGING. We show that, when trained with appropriate data pre-processing techniques and hyper-parameter tuning, machine learning models do not have biased predictions across different subgroups. This is not the case for a baseline deep neural network, which provides accurate predictions on-average across the population but suffers from bias when predictions are stratified by different attributes.

2 Results

2.1 Baseline machine learning models have accurate predictions on-average, but can be biased

The accuracy of a deep network on held-out data is $85.83\% \pm 1.76\%$ for AD, $73.29\% \pm 2.85\%$ for SZ, and $55.61\% \pm 3.61\%$ for ASD. These numbers are comparable to published results in the literature. As Fig. 1 shows, for all three neurological disorders, we find large discrepancies in the accuracy of this model on different subgroups of the population for all attributes. For example, for AD the model has a higher accuracy on females than males ($p$-value $1.59 \times 10^{-3}$); for SZ the model predicts more accurately
Figure 1: Evaluating machine learning models on subjects from different gender, age, racial groups, and clinical studies. For each of the three disorders, Alzheimer’s disease, schizophrenia, and autism spectrum disorder, we built an ensemble of machine learning models that uses data from multiple sources (structural measures, demographic, clinical variables, genetic factors, and cognitive scores). This ensemble was trained using the pre-processing and hyper-parameter optimization discussed in Sec. 4. For comparison, we also trained an ensemble that only uses structural measures as features. Data from different studies (e.g., ADNI-1, ADNI-2/3, PENN and AIBL for Alzheimer’s disease) was used to train, without using any harmonization preprocessing to remove the batch/site effects. Bar plots denote the size of the subgroup/study (%); in many cases, there is strong imbalance in the amount of data for different subgroups. Violin plots denote the test accuracy (%) on five different held-out subsets of data. Solid colors indicate that models used all features while translucent colors indicate that models were trained only on structural measures. Translucent gray denotes the accuracy of a baseline deep network (without appropriate preprocessing and hyper-parameter tuning). White dots denote the average accuracy of each subgroup/study. For the ensemble trained on multi-source data, the $p$-values shown in the figure indicate that we cannot reject the null hypothesis that the accuracy for different subgroups has the same mean (at significance level < 0.01). This is not the case for the baseline deep network; see Sec. 2.1.
for Native Americans than Asian Americans ($p$-value $1.49 \times 10^{-3}$). One may be inclined to hypothesize that this bias in accuracy comes from one subgroup having a larger sample size than the other (Table 1). This hypothesis does not hold when predictions are stratified by age. AD subjects older than 80 years, SZ subjects older than 35 years, and ASD subjects younger than 20 years, have a lower accuracy ($p$-values are $8.76 \times 10^{-3}$, $3.54 \times 10^{-3}$ and $2.80 \times 10^{-3}$ respectively) even if these subgroups are not the ones with the smallest sample size (Table 1). For all three disorders, predictions of the baseline deep network are biased ($p$-value < 0.01) except in four cases: race and clinical studies in AD, sex in SZ, and clinical studies in ASD.

2.2 Appropriately designed machine learning models are not necessarily biased

The accuracy of the ensemble learned using the methodology discussed in Sec. 4 on held-out data is $87.35\% \pm 1.18\%$ for AD, $74.76\% \pm 3.32\%$ for SZ and $60.54\% \pm 2.13\%$ for ASD; all three are slightly better than that of the baseline deep network. As Fig. 1 shows visually, the accuracy of the ensemble is more consistent. For all three neurological disorders, for all attributes, we find that we cannot reject the hypothesis that the accuracy for different subgroups does not have the same mean (at significance level < 0.01). In other words, the ensemble does not exhibit a bias, up to statistically indistinguishable levels. It is remarkable that this observation holds even in situations with extreme imbalance in the data, e.g., for ASD there are $87\%$ males as compared to $13\%$ females.

Using the same preprocessing and hyper-parameter tuning methodology as that of the ensemble, the bias of the deep network can be improved slightly. We obtained an accuracy of $86.78\% \pm 1.90\%$ on AD, $70.44\% \pm 2.78\%$ on SZ and $54.70\% \pm 4.03\%$ on ASD; these numbers, except the one for SZ, are about the same as that of the baseline deep network. The $p$-values for there being bias across subgroups now are $0.665$ (sex), $0.090$ (age), $0.690$ (race) and $0.768$ (study) for AD; $0.089$ (sex), $0.771$ (age), $0.381$ (race) and $7.86 \times 10^{-4}$ (study) for SZ; $4.77 \times 10^{-2}$ (sex), $0.356$ (age) and $0.880$ (study) for ASD. With a significance level of 0.01, this indicates that the predictions of the deep network trained with better data preprocessing achieve a similar average accuracy as that of the baseline deep network but are not biased (except across clinical studies in SZ, which is likely to be partially due to differences in clinical characteristics across patient cohorts).

2.3 Machine learning models trained on multi-source data are also unbiased and predict more accurately on average, but their subgroup-specific accuracy may not always be better than models trained on single-source data

We next trained the ensemble using demographic features, clinical variables, genetic factors and cognitive scores in addition to MR imaging features. The accuracy of this multi-source ensemble on held-out data is $91.22\% \pm 1.76\%$ for AD, $79.18\% \pm 3.29\%$ for SZ and $63.83\% \pm 3.18\%$ for ASD. All three values are better than the corresponding
ones for the ensemble trained only on structural MR imaging features ($p$-value < 6.44 \times 10^{-3} for all three). Therefore, using multi-source data improves the average accuracy of machine learning models for the three neurological disorders. This ensemble also makes unbiased predictions across different subgroups; the $p$-values are 0.106 (sex), 0.732 (age), 0.819 (race), and 0.275 (study) for AD; 0.808 (sex), 0.845 (age), 0.772 (race), and 0.012 (study) for SZ; 0.811 (sex), 0.523 (age), and 0.862 (study) for ASD.

We calculated a two-way ANOVA\textsuperscript{32} to check whether the improved average accuracy translates to improved accuracy for subgroups pertaining to each attribute. The $p$-values are 7.91 \times 10^{-4} (sex), 1.07 \times 10^{-2} (age), 8.24 \times 10^{-2} (race), and 8.10 \times 10^{-3} (study) for AD; 7.40 \times 10^{-2} (sex), 1.68 \times 10^{-2} (age), 0.566 (race), and 5.24 \times 10^{-2} (study) for SZ; 0.940 (sex), 0.150 (age), and 0.213 (study) for ASD. At a significance level of 0.01, we find that using multi-source data improves accuracy of the ensemble as compared to using features from only structural measures for subgroups pertaining to sex and clinical studies in AD, but this does not hold for other cases.

3 Discussion

**Relationship of this work to existing literature on identifying and mitigating bias.** As machine learning models are being applied to diverse problems in the clinical sciences, there is an increasing amount of discussion on bias in particular, and ethical issues in general\textsuperscript{21,23,33-35}. This literature is playing a crucial role in shaping policies for deployment of automated diagnostic models. Consequently, there is also a large amount of recent work on identifying such biases\textsuperscript{19,22,25}, and developing techniques to mitigate these biases\textsuperscript{20,36,37}. In this study, we have shown that when machine learning models are trained using well-established data preprocessing and hyper-parameter optimization techniques on data from large-scale multi-site studies for three neurological disorders, namely Alzheimer’s disease, schizophrenia, and autism spectrum disorder, the predictions of these models need not be biased. Baseline machine learning models, even performant deep neural networks, that do not use this preprocessing and hyper-parameter optimization do suffer from bias. This observation holds when predictions are stratified across four different attributes (sex, age, race and the clinical study that collected the data). Our results do not diminish the value of the existing work on bias. Instead, they provide evidence that we might be able to develop unbiased machine learning-based diagnostic models with ample, proper, and diverse training. Our results therefore provide the hope that, after appropriate checks and balances are met, we might be able to deploy machine learning models in the future, and obtain both accurate and unbiased predictions.

**Investigating existing machine learning techniques thoroughly is as important as discovering new ways to mitigate bias.** The machine learning literature has well-established ways to safeguard against poor generalization. Disregarding these procedures can lead to bias in the predictions. Our experiments indicate that a rigorous preprocessing,
training and evaluation methodology can enable ways to build machine learning models that do not suffer from biased predictions. Our work therefore provides a sound “baseline” to benchmark the performance of automated diagnostic systems. The accuracy of predictions obtained herein on three neurological disorders and across large-scale, multi-source cohorts reported in our reports is comparable to the state of the art of large-scale multi-site studies suggests that popular methods used to mitigate bias in the literature, e.g., learning invariant features, or domain-adaptation techniques, end up removing useful information from the data, e.g., correlations between gender or age with the pathology, even if they are robust to covariate shift. This tradeoff, between being invariant to the heterogeneity in the data and predictive ability, is seen in the harmonization literature more broadly and it has been argued previously that it is unavoidable.

Large-scale multi-source cohorts of data from diverse populations are desirable for building robust and accurate machine learning models, even if they are not balanced. Balanced datasets, where each subgroup has an equal number of samples, are desirable if we are to build unbiased models. But it is extremely difficult to obtain balanced data in practice. There are long-standing problems in recruiting volunteers across gender, age, and race. For example, female, minority ethnicity groups, and older subjects are less likely to participate in clinical trials as compared to white young men. Even when we are able to obtain balanced data, a machine learning model may still be biased due to unobserved confounders, e.g., severity of the disease or genetic factors. This thinking has inspired recent studies which argue for training models on extensive multi-source neuroimaging datasets. Our results corroborate these findings; large-scale cohorts of multi-source data can enable training robust and unbiased machine learning models, and equally importantly also enable thorough evaluation across different attributes.

4 Methods

We summarize our technical approach in this section and Sec. A provides more details. We use 3D magnetic resonance (MR) images along with demographic (gender, age, race, education level, marital status, employment status, handedness, smoker), clinical (diabetes, hypertension, hyperlipidemia, systolic/diastolic blood pressure and body mass index), and genetic factors (apolipoprotein E (APOE) alleles 2, 3 and 4) and cognitive scores from three large consortia—iSTAGING for AD, PHENOM for SZ, and ABIDE for ASD. We use a standard processing pipeline to compute structural features from T1-weighted MR images. All accuracies reported in this paper are calculated using 5 independent held-out test sets.

Pre-processing pipeline Some features, predominantly clinical and genetic factors, and cognitive scores, are sparsely populated; see Table 2. Continuous-valued features
are normalized to have zero mean and unit variance after median imputation; quantile normalization is used for features with highly skewed distributions. For discrete-valued features, we introduce a “unknown” category for missing values. Corresponding to each feature with missing values, we introduce an additional Boolean feature which indicates whether the value was missing. No harmonization tools\textsuperscript{15,16} are used to remove the batch/site effects.

**Hyper-parameter optimization methodology** We use a machine learning framework called AutoGluon\textsuperscript{51} which gives an easy way to train a large number of different types of models (deep networks\textsuperscript{52}, \(k\)-nearest neighbor classifiers\textsuperscript{53}, random forests\textsuperscript{54}, CatBoost\textsuperscript{55}, and LightGBM\textsuperscript{56}) and perform hyper-parameter search. Using AutoGluon we can also build ensembles of these models via bagging\textsuperscript{57}, boosting\textsuperscript{38} and stacking\textsuperscript{59}.

The baseline deep network used in Sec. 2.1 has three fully-connected layers and is also built within AutoGluon. This network is trained using data that is normalized to have zero mean and unit standard deviation after dropping missing values.

**Acknowledgments**

This work was supported by the National Institute on Aging (RF1AG054409 and U01AG068057), the National Institute of Mental Health (R01MH112070), the National Science Foundation (2145164) and cloud computing credits from Amazon Web Services.

**Bibliography**

1. Habes, M., Pomponio, R., Shou, H., Doshi, J., Mamourian, E., Erus, G., Nasrallah, I., Launer, L. J., Rashid, T., Bilgel, M., et al. The Brain Chart of Aging: Machine-learning analytics reveals links between brain aging, white matter disease, amyloid burden, and cognition in the iSTAGING consortium of 10,216 harmonized MR scans. Alzheimer’s & Dementia 17, 89–102 (2021).

2. Chand, G. B., Dwyer, D. B., Erus, G., Sotiras, A., Varol, E., Srinivasan, D., Doshi, J., Pomponio, R., Pignoni, A., Dazzan, P., et al. Two distinct neuroanatomical subtypes of schizophrenia revealed using machine learning. Brain 143, 1027–1038 (2020).

3. Jack Jr, C. R., Bernstein, M. A., Fox, N. C., Thompson, P., Alexander, G., Harvey, D., Borowski, B., Britson, P. J., L. Whitwell, J., Ward, C., et al. The Alzheimer’s disease neuroimaging initiative (ADNI): MRI methods. Journal of Magnetic Resonance Imaging 27, 685–691 (2008).

4. Yu, K.-H., Beam, A. L. & Kohane, I. S. Artificial intelligence in healthcare. Nature Biomedical Engineering 2, 719–731 (2018).

5. Myszczynska, M. A., Ojamies, P. N., Lacoste, A., Neil, D., Saffari, A., Mead, R., Hautbergue, G. M., Holbrook, J. D. & Ferriauolo, L. Applications of machine learning to diagnosis and treatment of neurodegenerative diseases. Nature Reviews Neurology 16, 440–456 (2020).
6. Abrol, A., Fu, Z., Salman, M., Silva, R., Du, Y., Plis, S. & Calhoun, V. Deep learning encodes robust discriminative neuroimaging representations to outperform standard machine learning. *Nature Communications* **12**, 1–17 (2021).

7. Zhou, S. K., Greenspan, H., Davatzikos, C., Duncan, J. S., Van Ginneken, B., Madabhushi, A., Prince, J. L., Rueckert, D. & Summers, R. M. A review of deep learning in medical imaging: Imaging traits, technology trends, case studies with progress highlights, and future promises. *Proceedings of the IEEE* (2021).

8. Singh, N. M., Harrod, J. B., Subramaniam, S., Robinson, M., Chang, K., Cetin-Karayumak, S., Dalca, A. V., Eickhoff, S., Fox, M., Franke, L., *et al.* How Machine Learning is Powering Neuroimaging to Improve Brain Health. *Neuroinformatics*, 1–22 (2022).

9. Thompson, P. M., Jahanshad, N., Ching, C. R., Salminen, L. E., Thomopoulos, S. I., Bright, J., Baune, B. T., Bertolín, S., Braelen, J., Bruin, W. B., *et al.* ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. *Translational Psychiatry* **10**, 1–28 (2020).

10. Marek, S., Tervo-Clemmens, B., Calabro, F. J., Montez, D. F., Kay, B. P., Hatoum, A. S., Donohue, M. R., Foran, W., Miller, R. L., Hendrickson, T. J., *et al.* Reproducible brain-wide association studies require thousands of individuals. *Nature*, 1–7 (2022).

11. Bethlehem, R. A., Seidlitz, J., White, S. R., Vogel, J. W., Anderson, K. M., Adamson, C., Adler, S., Alexopoulos, G. S., Anagnostou, E., Areces-Gonzalez, A., *et al.* Brain charts for the human lifespan. *Nature*, 1–11 (2022).

12. Dinsdale, N. K., Bluemke, E., Sundaresan, V., Jenkinson, M., Smith, S. & Namburete, A. I. Challenges for machine learning in clinical translation of big data imaging studies. *arXiv preprint arXiv:2107.05630* (2021).

13. Rajpurkar, P., Chen, E., Banerjee, O. & Topol, E. J. AI in health and medicine. *Nature Medicine*, 1–8 (2022).

14. Varoquaux, G. & Cheplygina, V. Machine learning for medical imaging: methodological failures and recommendations for the future. *NPJ Digital Medicine* **5**, 1–8 (2022).

15. Pomponio, R., Erus, G., Habes, M., Doshi, J., Srinivasan, D., Mamourian, E., Bashyam, V., Nasrallah, I. M., Satterthwaite, T. D., Fan, Y., *et al.* Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan. *NeuroImage* **208**, 116450 (2020).

16. Wang, R., Chaudhari, P. & Davatzikos, C. Harmonization with flow-based causal inference. *International Conference on Medical Image Computing and Computer-Assisted Intervention*, 181–190 (2021).

17. Perkonigg, M., Hofmanninger, J., Herold, C. J., Brink, J. A., Pianykhh, O., Prosch, H. & Langs, G. Dynamic memory to alleviate catastrophic forgetting in continual learning with medical imaging. *Nature Communications* **12**, 1–12 (2021).

18. Davatzikos, C. Machine learning in neuroimaging: Progress and challenges. *Neuroimage* **197**, 652 (2019).

19. Larrazabal, A. J., Nieto, N., Peterson, V., Milone, D. H. & Ferrante, E. Gender imbalance in medical imaging datasets produces biased classifiers for computer-aided diagnosis. *Proceedings of the National Academy of Sciences* **117**, 12592–12594 (2020).

20. Gao, Y. & Cui, Y. Deep transfer learning for reducing health care disparities arising from biomedical data inequality. *Nature Communications* **11**, 1–8 (2020).
21. Wilkinson, J., Arnold, K. F., Murray, E. J., van Smeden, M., Carr, K., Sippy, R., de Kamps, M., Beam, A., Konigorski, S., Lippert, C., et al. Time to reality check the promises of machine learning-powered precision medicine. *The Lancet Digital Health* **2**, e677–e680 (2020).

22. Seyyed-Kalantari, L., Zhang, H., McDermott, M., Chen, I. Y. & Ghassemi, M. Underdiagnosis bias of artificial intelligence algorithms applied to chest radiographs in under-served patient populations. *Nature Medicine* **27**, 2176–2182 (2021).

23. Finlayson, S. G., Subbaswamy, A., Singh, K., Bowers, J., Kupke, A., Zittrain, J., Kohane, I. S. & Saria, S. The clinician and dataset shift in artificial intelligence. *The New England Journal of Medicine* **385**, 283 (2021).

24. Dockès, J., Varoquaux, G. & Poline, J.-B. Preventing dataset shift from breaking machine-learning biomarkers. *GigaScience* **10**, giab055 (2021).

25. Li, J., Bzdok, D., Chen, J., Tam, A., Ooi, L. Q. R., Holmes, A. J., Ge, T., Patil, K. R., Jabbi, M., Eickhoff, S. B., et al. Cross-ethnicity/race generalization failure of behavioral prediction from resting-state functional connectivity. *Science Advances* **8**, eabj1812 (2022).

26. Satterthwaite, T. D., Wolf, D. H., Loughead, J., Ruparel, K., Valdez, J. N., Siegel, S. J., Kohler, C. G., Gur, R. E. & Gur, R. C. Association of enhanced limbic response to threat with decreased cortical facial recognition memory response in schizophrenia. *American Journal of Psychiatry* **167**, 418–426 (2010).

27. Zhang, T., Koutsouleris, N., Meisenzahl, E. & Davatzikos, C. Heterogeneity of structural brain changes in subtypes of schizophrenia revealed using magnetic resonance imaging pattern analysis. *Schizophrenia bulletin* **41**, 74–84 (2015).

28. Di Martino, A., Yan, C.-G., Li, Q., Denio, E., Castellanos, F. X., Alaerts, K., Anderson, J. S., Assaf, M., Bookheimer, S. Y., Dapretto, M., et al. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular psychiatry* **19**, 659–667 (2014).

29. Wen, J., Thibeau-Sutre, E., Díaz-Melo, M., Samper-González, J., Routier, A., Bottani, S., Dormont, D., Durrieu, S., Burgess, N., Colliot, O., et al. Convolutional neural networks for classification of Alzheimer’s disease: Overview and reproducible evaluation. *Medical image analysis* **63**, 101694 (2020).

30. Rozyczki, M., Satterthwaite, T. D., Koutsouleris, N., Erus, G., Doshi, J., Wolf, D. H., Fan, Y., Gur, R. E., Gur, R. C., Meisenzahl, E. M., et al. Multisite machine learning analysis provides a robust structural imaging signature of schizophrenia detectable across diverse patient populations and within individuals. *Schizophrenia bulletin* **44**, 1035–1044 (2018).

31. Katuwal, G. J., Cahill, N. D., Baum, S. A. & Michael, A. M. The predictive power of structural MRI in Autism diagnosis. *International Conference of the IEEE Engineering in Medicine and Biology Society*, 4270–4273 (2015).

32. Rutherford, A. *ANOVA and ANCOVA: a GLM approach* (John Wiley & Sons, 2011).

33. Wiens, J., Saria, S., Sendak, M., Ghassemi, M., Liu, V. X., Doshi-Velez, F., Jung, K., Heller, K., Kale, D., Saeed, M., et al. Do no harm: a roadmap for responsible machine learning for health care. *Nature Medicine* **25**, 1337–1340 (2019).

34. Gichoya, J. W., Banerjee, I., Bhimireddy, A. R., Burns, J. L., Celi, L. A., Chen, L.-C., Correa, R., Dullerud, N., Ghassemi, M., Huang, S.-C., et al. AI recognition of patient race in medical imaging: a modelling study. *The Lancet Digital Health* (2022).
35. Vasey, B., Nagendran, M., Campbell, B., Clifton, D. A., Collins, G. S., Denaxas, S., Denniston, A. K., Faes, L., Geerts, B., Ibrahim, M., et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. *Nature Medicine* **28**, 924–933 (2022).

36. Zhao, Q., Adeli, E. & Pohl, K. M. Training confounder-free deep learning models for medical applications. *Nature Communications* **11**, 1–9 (2020).

37. Wang, R., Chaudhari, P. & Davatzikos, C. Embracing the disharmony in medical imaging: a simple and effective framework for domain adaptation. *Medical Image Analysis* **76**, 102309 (2022).

38. Arjovsky, M., Bottou, L., Gulrajani, I. & Lopez-Paz, D. Invariant risk minimization. *arXiv preprint arXiv:1907.02893* (2019).

39. Chyzhyk, D., Varoquaux, G., Milham, M. & Thirion, B. How to remove or control confounds in predictive models, with applications to brain biomarkers. *GigaScience* **11** (2022).

40. Ganin, Y., Ustinaeva, E., Ajakan, H., Germain, P., Larochelle, H., Laviolette, F., Marchand, M. & Lempitsky, V. Domain-adversarial training of neural networks. *The journal of machine learning research* **17**, 2096–2030 (2016).

41. Tzeng, E., Hoffman, J., Saenko, K. & Darrell, T. Adversarial discriminative domain adaptation. *Proceedings of the IEEE conference on computer vision and pattern recognition*, 7167–7176 (2017).

42. Moyer, D. & Golland, P. Harmonization and the worst scanner syndrome. *arXiv preprint arXiv:2101.06255* (2021).

43. Chawla, N. V., Bowyer, K. W., Hall, L. O. & Kegelmeyer, W. P. SMOTE: synthetic minority over-sampling technique. *Journal of artificial intelligence research* **16**, 321–357 (2002).

44. Murthy, V. H., Krumholz, H. M. & Gross, C. P. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA* **291**, 2720–2726 (2004).

45. Chastain, D. B., Osae, S. P., Henao-Martinez, A. F., Franco-Paredes, C., Chastain, J. S. & Young, H. N. Racial disproportionality in Covid clinical trials. *New England Journal of Medicine* **383**, e59 (2020).

46. He, T., An, L., Chen, P., Chen, J., Feng, J., Bzdok, D., Holmes, A. J., Eickhoff, S. B. & Yeo, B. Meta-matching as a simple framework to translate phenotypic predictive models from big to small data. *Nature Neuroscience*, 1–10 (2022).

47. Schulz, M.-A., Bzdok, D., Haufe, S., Haynes, J.-D. & Ritter, K. Performance reserves in brain-imaging-based phenotype prediction. *bioRxiv* (2022).

48. Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A. & Gee, J. C. N4ITK: improved N3 bias correction. *IEEE transactions on medical imaging* **29**, 1310–1320 (2010).

49. Doshi, J., Erus, G., Ou, Y., Gaonkar, B. & Davatzikos, C. Multi-atlas skull-stripping. *Academic radiology* **20**, 1566–1576 (2013).

50. Doshi, J., Erus, G., Ou, Y., Resnick, S. M., Gur, R. C., Gur, R. E., Satterthwaite, T. D., Furth, S., Davatzikos, C., Initiative, A. N., et al. MUSE: MUlti-atlas region Segmentation utilizing Ensembles of registration algorithms and parameters, and locally optimal atlas selection. *Neuroimage* **127**, 186–195 (2016).
51. Erickson, N., Mueller, J., Shirkov, A., Zhang, H., Larroy, P., Li, M. & Smola, A. Autogluon-tabular: Robust and accurate automl for structured data. *arXiv preprint arXiv:2003.06505* (2020).
52. LeCun, Y., Bengio, Y. & Hinton, G. Deep learning. *Nature* **521**, 436–444 (2015).
53. Cover, T. & Hart, P. Nearest neighbor pattern classification. *IEEE transactions on information theory* **13**, 21–27 (1967).
54. Breiman, L. Random forests. *Machine learning* **45**, 5–32 (2001).
55. Prokhorenkova, L., Gusev, G., Vorobev, A., Dorogush, A. V. & Gulin, A. CatBoost: unbiased boosting with categorical features. *Advances in neural information processing systems* **31** (2018).
56. Ke, G., Meng, Q., Finley, T., Wang, T., Chen, W., Ma, W., Ye, Q. & Liu, T.-Y. LightGBM: A highly efficient gradient boosting decision tree. *Advances in neural information processing systems* **30** (2017).
57. Breiman, L. Bagging predictors. *Machine learning* **24**, 123–140 (1996).
58. Bartlett, P., Freund, Y., Lee, W. S. & Schapire, R. E. Boosting the margin: A new explanation for the effectiveness of voting methods. *The annals of statistics* **26**, 1651–1686 (1998).
59. Wolpert, D. H. Stacked generalization. *Neural networks* **5**, 241–259 (1992).
60. Ellis, K. A., Rowe, C. C., Villemagne, V. L., Martins, R. N., Masters, C. L., Salvador, O., Szeke, C., Ames, D. & Group, A. R. Addressing population aging and Alzheimer’s disease through the Australian Imaging Biomarkers and Lifestyle study: Collaboration with the Alzheimer’s Disease Neuroimaging Initiative. *Alzheimer’s & dementia* **6**, 291–296 (2010).
61. Doshi, J., Erus, G., Habes, M. & Davatzikos, C. DeepMRSeg: A convolutional deep neural network for anatomy and abnormality segmentation on MR images. *arXiv preprint arXiv:1907.02110* (2019).
Appendix A  Detailed methods

Data We use 3D magnetic resonance (T1-weighted) images along with demographic (gender, age, race, education level, marital status, employment status, handedness, smoker), clinical (diabetes, hypertension, hyperlipidemia, systolic/diastolic blood pressure and body mass index), and genetic factors (apolipoprotein E (APOE) alleles 2, 3 and 4), as well as cognitive scores (mini-mental state exam (MMSE), full-scale intelligence quotient (FIQ), verbal intelligence quotient (VIQ), and performance intelligence quotient (PIQ)) from three large consortia—iSTAGING\textsuperscript{1} for AD, PHENOM\textsuperscript{2,26,27} for SZ, and ABIDE\textsuperscript{28} for ASD. The subset of iSTAGING data used here consists of multiple clinical studies: AD Neuroimaging Initiative (ADNI)\textsuperscript{3}, Penn Memory Center cohort (PENN), and Australian Imaging, Biomarkers and Lifestyle (AIBL)\textsuperscript{60}. In PHENOM scans are acquired from five different sites namely Penn (United States), China, Munich, Utrecht, and Melbourne. All tasks in this study are a binary classification problem with two labels (healthy controls and patients). We only use the baseline (first time point) scans from each cohort; all follow-up sessions are excluded. This way there is no data leakage for the same participant between training and test sets. For AD, we select stable cognitive normal (CN) and AD patients based on each participant’s longitudinal diagnosis status. We only include subjects who were diagnosed as CN or AD at the baseline and stayed stable during the follow-up sessions.

Methodology for creating features from structural measures We compute features from T1-weighted MR images using a standard pipeline. Scans are bias-field corrected\textsuperscript{48}, skull-stripped with a multi-atlas algorithm\textsuperscript{49}, and then a multi-atlas label fusion segmentation method\textsuperscript{50} is used to obtain anatomical region-of-interest (ROI) masks for 119 grey matter ROIs, 20 white matter ROIs and 6 ventricle ROIs of the brain (total 145). We further segment white matter hyperintensities (WMH) using a deep learning-based algorithm\textsuperscript{61} on fluid-attenuated (FLAIR) and T1-weighted images. White matter lesion (WML) volumes are obtained by summing up the WMH mask voxels.

Evaluation methodology We report accuracy on held-out test sets as follows. We split data into 5 equal-sized folds (stratified by labels), use four for training and validation (80\%) and the fifth for testing (20\%). All hyper-parameter tuning is performed using a further 5-fold cross-validation within the 80\% data. This way, the 20\% data is a completely independent test set which is used only for reporting the final accuracy. We report mean and standard deviation of the accuracy over 5 independent test sets (one for each outer fold). This is a computationally expensive, but rigorous, evaluation methodology. The three neurological disorders consist of data from multiple clinical studies; we create the training, validation and test sets for each study independently and then concatenate them.
**Pre-processing pipeline**  Our data contains structural features such as ROI and WML volumes in addition to demographic, clinical and genetic factors, and cognitive scores. Some of these features (predominantly last three) are sparsely populated; see Table 2. For continuous-valued features, we first impute missing values with the median of each variable and normalize the feature to have zero-mean and unit-variance. We apply quantile normalization to skewed distributions. For discrete-valued features, we introduce a “unknown” category for missing values. Corresponding to each feature with missing values, we introduce an additional Boolean feature which indicates whether the value was missing. This way we preserve the evidence of absence (rather than the absence of evidence).\(^5\) We did not use any harmonization tools.\(^15,16\).

**Hyper-parameter optimization methodology**  We compare results from an optimized machine learning model, in which hyper-parameter optimization and ensemble learning were performed, with a basic network. For the former, we use a machine learning framework called AutoGluon\(^5\) which gives an easy way to train a large number of different types of models (deep networks\(^52\), \(k\)-nearest neighbor classifiers\(^53\), random forests\(^54\), CatBoost\(^55\), and LightGBM\(^56\)) and perform hyper-parameter search. For deep network models we create an input layer that concatenates the embedding of continuous-valued and categorical features; the other models can natively handle both these types of features. Using AutoGluon we can also build ensembles of these models via bagging\(^57\), boosting\(^58\) and stacking\(^59\). For each neurological disorder, for each of the 5 outer folds, we train the above different types of models using different hyper-parameters in parallel across multiple CPUs and 4 GPUs for 1 hour and build an ensemble that obtains the best classification log-likelihood on the validation data.

The baseline deep network used in Sec. 2.1 has three fully-connected layers and is also built within the same software framework. This network is trained using data that is normalized to have zero mean and unit standard deviation after dropping missing values. It does not use the pre-processing pipeline described above.

**Appendix B  Summary of the data**
Table 1: Summary of participant demographics of the iSTAGING consortium (Alzheimer’s disease), the PHENOM consortium (Schizophrenia), and the ABIDE datasets (Autism spectrum disorder) used in this study.

| Alzheimer’s Disease | ADNI-1 (22.81%) | ADNI-2/3 (30.58%) | PENN (33.40%) | ABL (13.22%) | Total |
|---------------------|------------------|------------------|--------------|-------------|-------|
| **Subjects**        |                  |                  |              |             |       |
| Control             | 173              | 261              | 228          | 119         | 781   |
| Patient             | 191              | 227              | 305          | 92          | 815   |
| **Sex (%)**         |                  |                  |              |             |       |
| Female              | 10.90            | 15.66            | 21.37        | 8.08        | 56.02 |
| Male                | 11.90            | 14.91            | 12.03        | 5.14        | 43.98 |
| **Age (%, years)**  |                  |                  |              |             |       |
| 0–65                | 1.50             | 3.51             | 6.33         | 1.82        | 13.16 |
| 65–70               | 1.94             | 8.15             | 7.02         | 2.57        | 19.67 |
| 70–75               | 7.27             | 6.95             | 6.83         | 3.76        | 24.81 |
| 75–80               | 6.52             | 6.89             | 6.58         | 2.57        | 22.56 |
| > 80                | 5.58             | 5.08             | 6.64         | 2.51        | 19.80 |
| **Race (%)**        |                  |                  |              |             |       |
| White               | 21.18            | 16.98            | 25.13        | 7.33        | 70.61 |
| Black               | 1.19             | 0.88             | 6.70         | -           | 8.77  |
| Asian               | 0.31             | 0.56             | 0.63         | -           | 1.50  |

| Schizophrenia       | Penn (22.28%)    | China (13.94%)   | Munich (29.64%) | Utrecht (20.12%) | Melbourne (14.03%) | Total |
|---------------------|------------------|-----------------|-----------------|------------------|---------------------|-------|
| **Subjects**        |                  |                 |                 |                  |                     |       |
| Control             | 131              | 76              | 157             | 115              | 84                  | 563   |
| Patient             | 96               | 66              | 145             | 90               | 59                  | 456   |
| **Sex (%)**         |                  |                 |                 |                  |                     |       |
| Female              | 11.87            | 6.77            | 7.75            | 6.97             | 4.02                | 37.39 |
| Male                | 10.40            | 7.16            | 21.88           | 13.15            | 10.01               | 62.61 |
| **Age (%, years)**  |                  |                 |                 |                  |                     |       |
| 0–25                | 5.79             | 4.91            | 9.42            | 10.11            | 5.89                | 36.11 |
| 25–30               | 6.28             | 2.36            | 7.26            | 4.12             | 2.16                | 22.18 |
| 30–35               | 3.53             | 2.16            | 5.99            | 2.85             | 1.37                | 15.90 |
| > 35                | 6.67             | 4.51            | 6.97            | 3.04             | 4.61                | 25.81 |
| **Race (%)**        |                  |                 |                 |                  |                     |       |
| Native              | 10.50            | -               | -               | -                | -                   | 10.50 |
| Asian               | 7.36             | -               | -               | -                | -                   | 7.36  |

| Autism Spectrum Disorder | ABIDE-1 (62.78%) | ABIDE-2 (37.22%) | Total |
|--------------------------|------------------|------------------|-------|
| **Subjects**             |                  |                  |       |
| Control                  | 224              | 138              | 362   |
| Patient                  | 196              | 111              | 307   |
| **Sex (%)**              |                  |                  |       |
| Female                   | 6.73             | 6.28             | 13.00 |
| Male                     | 56.05            | 30.94            | 87.0  |
| **Age (%, years)**       |                  |                  |       |
| 0–20                     | 21.97            | 11.66            | 33.63 |
| 20–25                    | 17.49            | 11.06            | 28.55 |
| > 25                     | 23.32            | 14.50            | 37.82 |
Table 2: Summary of variables in the data from the iSTAGING consortium (Alzheimer’s disease), the PHENOM consortium (Schizophrenia), and the ABIDE datasets (Autism spectrum disorder) used in this study.

| Variables                  | iSTAGING | PHENOM | ABIDE |
|----------------------------|----------|--------|-------|
| **MR imaging**             |          |        |       |
| Region-of-interest volumes | ✓        | ✓      | ✓     |
| White matter lesion volume | ✓        |        |       |
| **Demographics**           |          |        |       |
| Gender                     | ✓        | ✓      | ✓     |
| Age                        | ✓        | ✓      | ✓     |
| Race                       | ✓        | ✓      |       |
| Education level            | ✓        |        |       |
| Marital status             | ✓        |        |       |
| Employment status          | ✓        |        |       |
| Handedness                 | ✓        | ✓      | ✓     |
| Smoking status             | ✓        |        |       |
| **Clinical**               |          |        |       |
| Diabetes                   | ✓        |        |       |
| Hypertension               | ✓        |        |       |
| Hyperlipidemia             | ✓        |        |       |
| Blood pressure (systolic/diastolic) | ✓ |     |
| Body mass index            | ✓        |        |       |
| **Genetic factor**         |          |        |       |
| Apolipoprotein E alleles 2, 3 and 4 | ✓        |       |
| **Cognitive scores**       |          |        |       |
| Mini-mental state exam     | ✓        |        |       |
| Full-scale intelligence quotient | ✓ |     |
| Verbal intelligence quotient | ✓      |       |
| Performance intelligence quotient | ✓ |     |