

















REVIEW ARTICLE

Artificial intelligence for neurodegenerative experimental models

Sarah J. Marzi^{1,2}  | Brian M. Schilder^{1,2}  | Alexi Nott^{1,2}  | Carlo Sala Frigerio³  |
 Sandrine Willaime-Morawek⁴  | Magda Bucholc⁵  | Diane P. Hanger⁶  |
 Charlotte James⁷  | Patrick A. Lewis^{8,9}  | Ilianna Lourida⁷  | Wendy Noble¹⁰  |
 Francisco Rodriguez-Algarra¹¹  | Jalil-Ahmad Sharif^{1,2}  | Maria Tsalenchuk^{1,2} |
 Laura M. Winchester¹²  | Ümran Yaman³  | Zhi Yao¹³ | The Deep Dementia
 Phenotyping (DEMON) Network | Janice M. Ranson⁷  | David J. Llewellyn^{7,14}

¹UK Dementia Research Institute, Imperial College London, London, UK

²Department of Brain Sciences, Imperial College London, London, UK

³UK Dementia Research Institute at UCL, London, UK

⁴Faculty of Medicine, University of Southampton, Southampton, UK

⁵School of Computing, Engineering & Intelligent Systems, Ulster University, Derry, UK

⁶Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

⁷University of Exeter Medical School, Exeter, UK

⁸Royal Veterinary College, London, UK

⁹Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK

¹⁰Faculty of Health and Life Sciences, University of Exeter, Exeter, UK

¹¹The Blizard Institute, School of Medicine and Dentistry, Queen Mary University of London, London, UK

¹²Department of Psychiatry, University of Oxford, Oxford, UK

¹³LifeArc, London, UK

¹⁴Alan Turing Institute, London, UK

Correspondence

Sarah J. Marzi, UK Dementia Research Institute, Imperial College London, 515 Burlington Danes Building, DuCane Road, London, W12 0NN, UK.
Email: s.marzi@imperial.ac.uk

Janice M. Ranson and David J. Llewellyn are considered as joint senior authors.

Funding information

Alzheimer's Research UK; Medical Research Council, Grant/Award Number:

Abstract

INTRODUCTION: Experimental models are essential tools in neurodegenerative disease research. However, the translation of insights and drugs discovered in model systems has proven immensely challenging, marred by high failure rates in human clinical trials.

METHODS: Here we review the application of artificial intelligence (AI) and machine learning (ML) in experimental medicine for dementia research.

RESULTS: Considering the specific challenges of reproducibility and translation between other species or model systems and human biology in preclinical dementia

Alexi Nott, Carlo Sala Frigerio and Sandrine Willaime-Morawek contributed equally to this study.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. Alzheimer's & Dementia published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

MR/X005674/1; National Institute on Aging/National Institutes of Health, Grant/Award Number: RF1AG055654; Edmond and Lily Safra Early Career Fellowship Program; UK Dementia Research Institute; Alzheimer's Association; Alan Turing Institute/Engineering and Physical Sciences Research Council, Grant/Award Number: EP/N510129/1; Economic and Social Research Council, Grant/Award Number: ES/W010240/1; EU (SEUPB) INTERREG, Grant/Award Number: ERDF/SEUPB; Michael J. Fox Foundation; Parkinson's UK; National Institute for Health Research (NIHR) Applied Research Collaboration South West Peninsula; National Health and Medical Research Council (NHMRC)

research, we highlight best practices and resources that can be leveraged to quantify and evaluate translatability. We then evaluate how AI and ML approaches could be applied to enhance both cross-model reproducibility and translation to human biology, while sustaining biological interpretability.

DISCUSSION: AI and ML approaches in experimental medicine remain in their infancy. However, they have great potential to strengthen preclinical research and translation if based upon adequate, robust, and reproducible experimental data.

KEYWORDS

animal models, artificial intelligence, comparative biology, dementia, experimental models, FAIR, in silico, in vitro, in vivo, iPSC, machine learning, neurodegeneration, preclinical, reproducibility, translation

Highlights

- There are increasing applications of AI in experimental medicine.
- We identified issues in reproducibility, cross-species translation, and data curation in the field.
- Our review highlights data resources and AI approaches as solutions.
- Multi-omics analysis with AI offers exciting future possibilities in drug discovery.

1 | INTRODUCTION

The past decades have seen a steep rise in the availability of quantitative biological data within the context of experimental medicine.¹ Preclinical experimental models for dementia research are no exception with large amounts of genomic, cellular, and functional phenotyping data generated and released in relation to neurodegenerative diseases.² As a testing ground for biological hypotheses and novel drugs, these models are of crucial importance to the field. A multitude of studies are published each year, with in vitro work spanning cell culture,^{3–5} induced pluripotent stem cell (iPSC)-derived cultures,^{6–8} organotypic slice cultures,^{9,10,11} and organoids,^{12–15} while most preclinical research using in vivo model systems focuses on rodents, including transgenic animals,¹⁶ knock-ins,^{17,18} exposure models^{19,20} and more recently, multi-species models, such as human-mouse chimeras.²¹ Other model species such as non-human primates offer some advantages over murine models due to their phylogenetic similarity with humans, longer lifespans, and natural presentation of histological, neuroanatomical, or cognitive features of disease pathology.²² Yet, despite this plethora of models, what stands out is the failure rate of clinical trials for neurodegenerative disease treatments, particularly in Alzheimer's disease (AD).²³ This raises questions not only about the biological hypotheses underpinning drug discovery, but also the appropriateness of existing animal models and whether methods used to translate insights from the model to human biology are up to the task.²⁴ Improvements to clinical translation will require high quality experimental work in robust and valid model systems, in which both experimental screening and validation,²⁵ as well as improved prediction of

clinical effectiveness harnessing artificial intelligence (AI) approaches and machine learning (ML) will be important. In this position paper we discuss AI approaches used in experimental medicine, specifically focusing on approaches used to translate between model systems and human disease biology. Any advanced data analytical approaches, including ML, require robust and reproducible data as input, but equally can contribute to improving reproducibility in experimental research. This review discusses the key challenges of reproducibility, cross-species translation, data curation, and interpretability of AI and ML approaches. We provide recommendations and future directions for driving forward progress in this relatively new field of application. This review is one of a series of eight articles in a Special Issue on "Artificial Intelligence for Alzheimer's Disease and Related Dementias" published in *Alzheimer's & Dementia*. Together, this series provides a comprehensive overview of current applications of AI to dementia, and future opportunities for innovation to accelerate research. Each review focuses on a different area of dementia research, including experimental models (this article), drug discovery and trials optimization,²⁶ genetics and omics,²⁷ biomarkers,²⁸ neuroimaging,²⁹ prevention,³⁰ applied models and digital health,³¹ and methods optimization.³²

2 | REPRODUCIBILITY

2.1 | Defining reproducibility

Reproducibility is the extent to which the results of a study can be recreated by applying the same analysis code and data used in the

original study³³ and can be stratified as computational, empirical (data), and statistical.³⁴ Complementing this, replicability is often discussed in concert with reproducibility and refers to the degree to which a future study employing the same method produces the same scientific conclusions with independent analysis of new data. Both are essential to generate findings that are robust and generalizable and will be discussed collectively as reproducibility. Any advanced data analytical approaches, including ML, will only yield accurate and meaningful results if the underlying data are high quality and reproducible. Conversely, ML approaches can be used to improve computational aspects of reproducibility. Robust datasets should provide qualitatively similar outputs across analytical approaches and should be generalizable across studies.³⁵ Publishing reproducible experiments will be critical for meta-analysis of datasets across laboratories, will accelerate advancements, and maximize research investments. To address this, the Turing Way project (the-turing-way.netlify.app) has provided open access guidance on project design, communication, collaboration, and ethics of reproducibility in data science. In addition, the FAIR Guiding Principles for scientific data management and stewardship have provided actionable recommendations to improve the Findability, Accessibility, Interoperability, and Reuse of digital assets.³⁶ Reproducibility issues can also be inherent to the data type, for example, issues associated with technical noise and bias in single cell genomics data. Tools such as single-cell variational inference (scVI) use deep neural networks and stochastic optimization to account for batch and sensitivity effects when approximating gene expression distributions across cell types.³⁷ Deep learning strategies can also map single-cell datasets onto existing references: single-cell architectural surgery (scArches)³⁸ allows integration across experimental models (including mapping of disease-affected tissue onto control references).

2.2 | Reproducibility issues in stem cell technologies

Acquiring high-quality ex vivo neural tissue samples directly from human patients is usually either ethically infeasible or logistically intractable. However, in recent years stem cell technologies such as human iPSCs have allowed brain cell types to be derived from patient biopsies, opening a new era for modeling neurodegenerative diseases. iPSC models have allowed researchers to study disease mechanisms and genotype-phenotype associations in cell type-specific, physiologically relevant human models. iPSCs are as genetically diverse as the donors they are derived from, enabling researchers to study sporadic disease and polygenic risk factors, while simultaneously presenting major challenges in reproducibility. The Human Induced Pluripotent Stem Cells Initiative (HipSci) reported that 5% to 46% of phenotype variation is due to individual genetic background.³⁹ Another source of heterogeneity in iPSC models are somatic mutations that arise from environmental factors, such as UV exposure, and through the reprogramming process.⁴⁰ Non-genetic contributions to heterogeneity include the differentiation protocols, as well as cell culture and storage conditions. A study across five laboratories using standard-

RESEARCH IN CONTEXT

- 1. Systematic review:** Experimental models in dementia research are important tools for fundamental medical research and drug discovery. Here we reviewed challenges in preclinical experimental neurodegenerative disease modeling and translation to clinic, highlighting machine learning (ML) and artificial intelligence (AI) approaches used to overcome these issues.
- 2. Interpretation:** We identified four key challenges: a lack of reproducibility, poor data curation, species divergence, and insufficient interpretability. We offer recommendations and examples of how to address these challenges, using careful experimental design and targeted ML/AI approaches.
- 3. Future directions:** While only recently adopted in preclinical dementia research, AI and ML models have great potential to improve prediction, diagnostics, and biological understanding of neurodegenerative diseases. With high quality, well-curated data and the specific adaptation of approaches including transfer learning, structural equation modeling (SEM), simulations and neural networks, both reproducibility and cross-species translation could be improved, while continued efforts should address the interpretability of these models.

ized protocols on identical iPSC lines found that laboratory-based sources of variation can overpower genotypic effects.⁴¹ The development of multiple iPSC-derived cell type co-culture systems and 3D organoids has allowed modeling of neurodegeneration at the tissue and organ level. However, heterogeneity remains a major challenge again due to genetic variability of iPSC lines, in addition to the complex protocols required for multi-cellular models that introduce further layers of non-genetic variabilities. Encouragingly, studies have reproducibly generated human brain organoids exhibiting consistent cell type diversity and developmental trajectories.⁴² However, consistency remains to be demonstrated for disease-relevant readouts. Challenges to reproducibility may also arise if the origin of the iPSC is patient-derived and allogeneic or genetically modified from a control group. Finally, iPSCs fail to capture gene regulatory signatures caused by environmental factors during a person's lifetime.⁴³

2.3 | Challenges to reproducibility in mouse models

Mice represent the most commonly used animal model in neurodegenerative disease research, complementing human and in vitro studies with a relatively quick reproduction time, inbred strains that minimize genetic heterogeneity, and easy commercial availability across multiple

strains. For mouse studies the genetic background of the line can have a major influence on reproducibility.⁴⁴ For example, mice expressing human amyloid precursor protein (hAPP) when backcrossed to different strains exhibit differences in viability,⁴⁵ disease course,⁴⁶ and neuronal excitability.⁴⁷ Specific genetic loci have since been identified that modify net amyloid- β ($A\beta$) accumulation in these lines.^{48,49} The Jackson laboratory recently crossed the 5xFAD mouse model of AD onto diverse genetic backgrounds to explore the contribution of genetic variation in AD. This approach more closely mirrored variation within human disease and identified marked effects of background-line specific genetic variation on the molecular and behavioral phenotypes of the AD model mice.^{50,51} Such efforts are beyond the scope of most laboratories and may be prohibitively costly. However, we recommend whole-genome sequencing (WGS) of new genetic mouse lines by the host lab. To improve reproducibility, and to allow the identification and further investigation of key background genetic modifiers of the disease phenotype, ideally sequencing should be repeated after extensive backcrossing by academic laboratories, and if mice are bred to congenic lines by commercial suppliers.

3 | TRANSLATING BETWEEN SPECIES

3.1 | Quantifying translatability of model species

Translating biological insights from model systems, particularly non-human species to human disease biology, is one of the primary challenges in preclinical dementia research. Notably, reproducibility is a prerequisite for animal use in drug-discovery pipelines: Poor reproducibility and design of experiments undermine the practical relevance of any model system, impairing clinical trial design and translation.⁵² Beyond this, limitations of the models themselves further complicate and restrict what can be learned about human disease. Induced and genetically engineered models for Parkinson's disease (PD), AD, frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) recreate initial biochemical events, such as misfolded protein aggregates, RNA toxicity or repeat expansion mutations,^{53–59} but often fail to reproduce the whole breadth of downstream cellular and phenotypic responses. For AD, effects of drug treatment are poorly predicted by current models, as highlighted by the divergent outcomes presented by different models when treated with the same drug; their efficacy varies by type of intervention and species, with best results achieved for cholinergic/glutamatergic drugs.⁶⁰ For example, use of transgenic mice¹⁶ and macaques⁶¹ enabled prediction of cognitive and behavioral improvements from administration of donepezil.⁶² In the context of aging, dogs have been considered as suitable models for preclinical studies of AD, to investigate effects of dietary factors, behavior, and therapies targeting $A\beta$ aggregation.^{63–65} To quantify the extent to which AD models can reflect human AD pathologies, integrated omics platforms for studying the molecular signatures of neurodegenerative diseases in preclinical models and *post mortem* human brains have proven useful,⁶⁶ and led to increased under-

standing of disease-specific cellular responses to disease. AD models have provided valuable insights into disease mechanisms, yet their translation rate to late-stage clinical trials has been extremely low, likely due to the complexity of human pathogenesis.^{67–70} Drugs targeting N-methyl-D-aspartate (NMDA) and cholinergic receptors provide only symptomatic treatments for patients,⁷¹ and phase II/III clinical failures of anti- $A\beta$ antibodies^{72,73} have led to a reevaluation of the $A\beta$ cascade hypothesis.⁷⁴ However, promising recent results in stage III clinical trials of lecanemab⁷⁵ and donanemab⁷⁶ have put monoclonal $A\beta$ antibodies back at center stage. At the same time concerns remain regarding the efficacy and costs of anti-amyloid immunotherapy as well as adverse side effects, most commonly in the form of amyloid-related imaging abnormalities (ARIA).^{77–79}

3.2 | Challenges to cross-species translation

Translating a drug or treatment from the bench to the bedside is a considerable challenge. Lack of reproducibility within the same model, or across other models, is a major impediment to translatability. As discussed above, the adoption of rigorous standards should be a priority to make drug discovery more efficient and avoid wasted time and resources.⁸⁰ Similarly, negative results and replication failures are often not reported even though they would help raise red flags early on and would prevent other researchers from treading down futile paths.⁸¹ Perhaps the greatest stumbling block in developing an effective drug for dementia remains our imperfect knowledge of dementia biology. This is compounded by models that do not faithfully reproduce all aspects of a pathology, prompting over-interpretation and over-extrapolation of experimental results. The appropriate choice of an experimental model for the question at hand should involve not only consideration of whether aspects of biology under investigation are being captured (eg, is the neuronal circuitry conserved? To what extent is the gene of interest conserved, expressed and part of the same network?), but also involves practical and ethical considerations. Model choice will also be affected by the type of research question: A basic science biological experiment, for example, discovery of the mechanism of action of a gene or protein, may require a different setup than a pharmacological analysis—such as the quantification of a drug's bioavailability in the brain. A frequently neglected aspect is the role of sex-related differences in dementia biology and incidence. Given that women are more likely to be affected by AD, while prevalence of PD is substantially higher in men, sex-related biological differences are clearly relevant and need to be investigated rigorously.^{82,83} However, many rodent experiments are conducted in animals of one sex only (often males) for practical reasons, leading to conceivably biased findings and often overlooking the sex-specific efficacy of drugs.⁸⁴ It is therefore important to assess sex-balanced cohorts, both at pre-clinical and clinical drug development stages. The correct use and development of better preclinical models should prevent several pitfalls of clinical phases in drug development, such as proper evaluation of pharmacokinetics and pharmacodynamics.⁷⁰

Further exacerbating these challenges is the lack of a controlled ontology when describing or annotating results of a model experiment, relating these terms across species. This can include, for example, the mouse phenotypes that correspond to specific symptoms of AD or PD in humans. The Human Phenotype Ontology (HPO)^{85,86} and its counterparts in non-human species aim to catalogue the full breadth of clinical, behavioral, morphological, functional, physiological, and cellular phenotypes observed in each species. All terms in these ontologies are logically organized in a controlled hierarchical structure, which helps reduce ambiguity when comparing results within and across species. The Unified Phenotype Ontology (uPheno)^{87,88} further extended this by providing mappings between homologous terms across species, including human, mouse, frog, zebrafish, fly, worm, and fission yeast. Adopting these standardized ontologies will help minimize misinterpretations, enable downstream meta-analyses, and provide extensive labelled training datasets for more complex ML models. uPheno and other ontologies can be accessed and searched through public resources such as Bioportal.^{89,90}

3.3 | Strategies and positive examples of translation

In thinking about how insights from models of neurodegeneration can be translated more effectively and considering improvements over the years, it stands out that we still lack a model which recapitulates any given neurodegenerative disease in its entirety. To effectively translate between models of disease, experimental design must account for disease-relevant factors such as developmental age, biomarker choice, and appropriateness of model species. There is a critical need for identifying dementia biomarkers present in both preclinical models and patients. An informative and quantifiable biomarker would enable earlier diagnosis, assessment of disease progression, and evaluation of treatment efficacy. Advances have been made in peripheral biomarkers. For example, serum tau protein levels correlate with cognitive impairment in AD and with progression of pathology in a transgenic mouse model of AD,⁹¹ although they lack the accuracy and consistency of imaging-based primary biomarkers. Positron emission tomography (PET) imaging studies using ¹⁸F-fluorodeoxyglucose (FDG) have illustrated consistent patterns in AD patients and various mouse models of AD,^{92,93} although there are concerns that rodent models are too small for imaging studies to be translatable. Another class of systems which may prove vital in advancing preclinical models for dementia research are humanized animal models, wherein human genes are introduced into a mouse genome, or human cells are grafted into mouse tissue. A humanized mouse model of ALS expressing human fused in sarcoma (FUS) protein has already proved to better recapitulate the disease in mice, namely, exhibiting midlife-onset progression of motor-neuron degeneration not seen in previous models. The use of the FUS Delta14 mouse has already yielded novel insights into ALS development, demonstrating that neurodegeneration occurs even in the absence of FUS protein accumulation.⁹⁴

3.4 | How evolution impedes (and promotes) translation

Augmenting many of the above challenges is the fact that animal models are highly evolutionarily divergent from humans. Humans last shared a common ancestor with macaques ~30 million years ago (MYA), with rodents ~90 MYA, with zebrafish ~430 MYA, and with fruit flies ~800 MYA.⁹⁵ The degree of homology (conserved features) varies across anatomical regions, cell types, pathways, and genes.^{96,97} For example, while it is well-established that the nervous system is homologous across vertebrates and invertebrates, even rodents and macaques do not possess all brain regions, cell types, and connections present in humans.⁹⁸ Furthermore, brain structures central to dementia pathology, such as the hippocampus,^{99,100} striatum,¹⁰¹ and prefrontal cortex,^{102,103} have undergone extensive anatomical and molecular reorganization, strongly indicating equally drastic changes in function.⁹⁸ At the level of genes, mice share only a subset of identifiable 1:1 orthologs with humans (around 75%),^{103,104} a problem that is further exacerbated in more distant species (Figure 1). This means that biomarkers and cell type markers discovered in one species may not be readily applicable to another. It also implies that the introduction of transgenically humanized animal models may only partly alleviate this issue, as the broader genetic background in which the humanized genes are acting is still drastically different. The degree of evolutionary conservation varies across molecular pathways¹⁰⁵ and cell types (eg, neurons,¹⁰⁶ astrocytes,¹⁰⁷ microglia,^{108,109} oligodendrocytes¹¹⁰). Therefore, systematic and quantitative investigation is first needed to assess a feature's degree of conservation, and thus validity, when using a given species to model human biology,¹¹¹ including in the development of novel dementia therapeutics.

At the same time, interspecies variation can be a powerful source of information to fuel ML models, because each species reflects billions of years of natural experiments. State-of-the-art protein folding models such as AlphaFold2¹¹² and ESMFold¹¹³ use multi-species protein sequences to help accurately predict 3D protein structure. Another application of ML models is to predict the effect of genetic variants by learning the mapping between DNA sequence and functional genomic annotations. Specifically, PrimateAI¹¹⁴ and its successor PrimateAI-3D¹¹⁵ predict whether genetic variants observed in humans are likely to be deleterious or benign based on whether the variant is common in non-human primate populations. The underlying premise being that if a variant is tolerated in species closely related to humans, it is more likely to be benign in humans as well. In this way data from non-human species can be a valuable source of information for human clinical research. Other genetic variant to function prediction models including Enformer,¹¹⁶ Basenji,¹¹⁷ and a semi-supervised deep learning approach proposed by Mourad¹¹⁸ implementing a convolutional neural network within a graph neural network (CNN-GNN) all observed significantly boosted performance when training on data from multiple species, as opposed to a single species. The developers of Nvwa,¹¹⁹ a deep learning model designed to learn DNA sequence motifs controlling cell type-specific gene expression, also observed a boost in

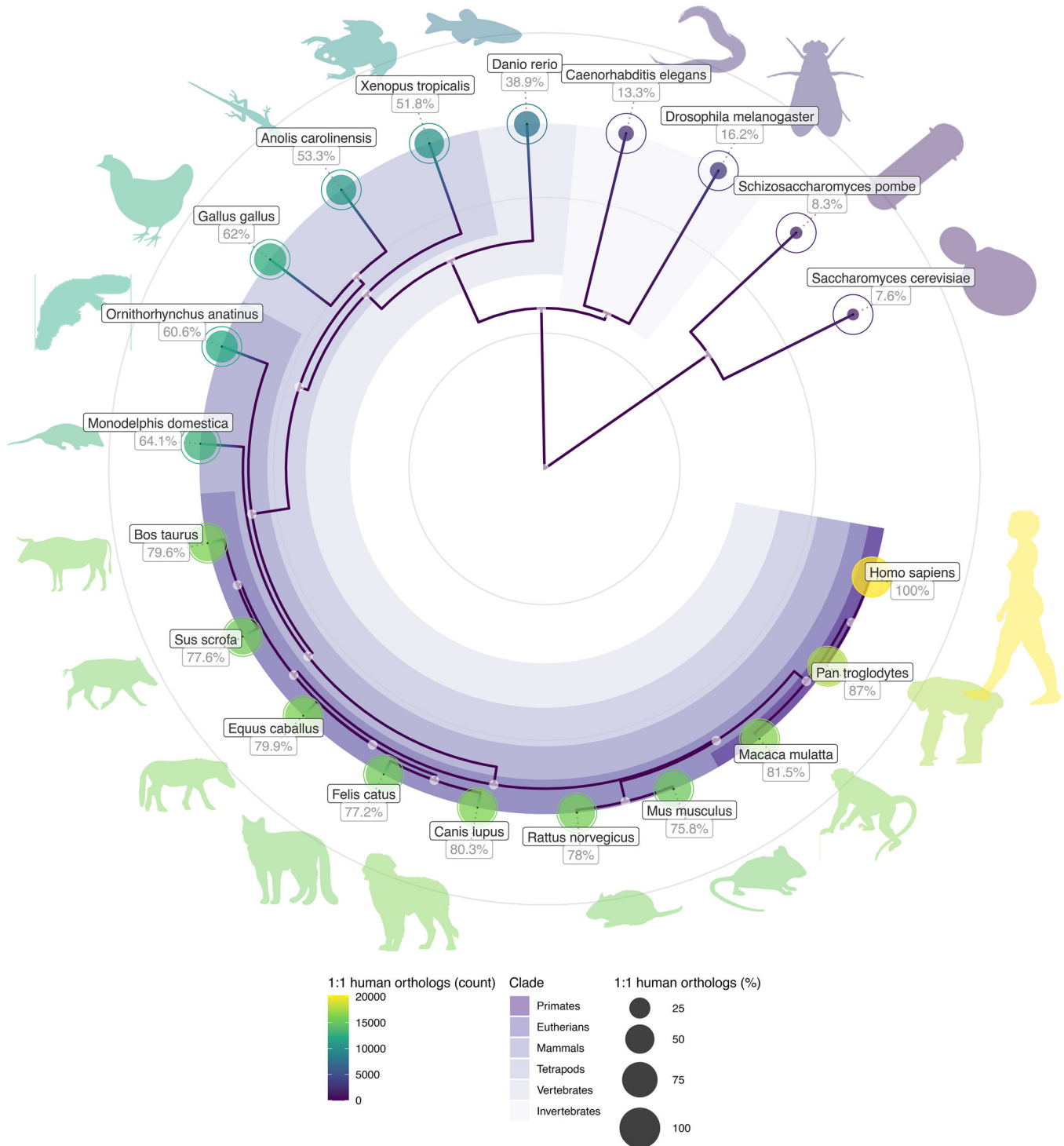


FIGURE 1 Genes shared between humans and non-human species. Phylogenetic tree annotated with the percentage of human genes that have 1:1 orthologs in each species (shown numerically and as the filled proportion of each circle). The absolute number of 1:1 orthologs shared with humans are plotted as the color of each circle. Constructed using the *orthogene* R package.⁹² Key: *Anolis carolinensis*, green anole; *Bos taurus*, cattle; *Caenorhabditis elegans*, roundworm; *Canis lupus familiaris*, dog; *Danio rerio*, zebrafish; *Drosophila melanogaster*, fruit fly; *Equus caballus*, horse; *Felis catus*, cat; *Gallus gallus*, chicken; *Homo sapiens*, human; *Macaca mulatta*, rhesus macaque; *Monodelphis domestica*, gray short-tailed opossum; *Mus musculus*, house mouse; *Ornithorhynchus anatinus*, platypus; *Pan troglodytes*, chimpanzee; *Rattus norvegicus*, brown rat; *Saccharomyces cerevisiae*, baker's yeast; *Schizosaccharomyces pombe*, fission yeast; *Sus scrofa*, pig; *Xenopus tropicalis*, western clawed frog.

performance when the model was trained on multiple closely related species at once. Others like the melanoma enhancer prediction model DeepMEL¹²⁰ successfully trained on cancer cell lines in one species (human) to predict in another species (dog), which can be considered a form of transfer learning.

4 | RESOURCES

4.1 | Existing major initiatives

In order to facilitate systematic and quantitative analyses of cross-model and -species translatability, we describe a variety of resources that can be applied to experimental modeling of dementia (Table 1). Available databases include atlases of gene expression and genetic variation in humans and some animal models, as well as phylogenetic resources. However, the rapid increase in knowledge relating to somatic genomic and gene regulatory variation requires an additional level of detail and curation to identify disease-specific determinants. Limited proteomic information is available for proteins identified as being involved in the pathogenesis of dementia, although this is supported in part by detailed compilations of types of protein post-translational modifications, many of which are dependent on manual curation. Since protein conformation is directly related to protein function, there is a critically important role for structural biology databases to predict secondary and tertiary structures of disease-associated proteins and their interactors. Recent breakthroughs by models such as AlphaFold2¹¹² and ESMFold (Evolutionary Scale modeling)¹¹³ have enabled the prediction of near-perfect 3D protein structure prediction at scale across many species. Precomputed predictions for millions of proteins have already been deposited in public databases, such as the AlphaFold Protein Structure Database^{112,121} and the ESM Metagenomic Atlas,^{113,122} rapidly accelerating a wide variety of biomedical research fields.¹²³ Combining verified structures of biologically relevant proteins with information available in pharmacological and pathway databases is essential for the identification of new potentially druggable targets. Harmonizing these databases will promote more sophisticated design of small molecules and other therapies targeting specific proteins or pathways and thereby expedite drug development. Validating biomarkers for dementia, whether identified by imaging or biochemical means, brings with it the challenge of determining which are the most accurate and informative predictors of disease progression and/or response to therapeutic intervention. It will thus become increasingly important to establish detailed and accurate databases that can be linked to each other as well as to electronic health records of individuals to advance the prospect of personalized medicine for dementia.

4.2 | Resource gaps and how to fill them

Validating new models and biomarkers is an essential part of the diagnostic and therapeutic discovery process. However, benchmarks

for validation are not always readily identified. When human data are available, were they collected at the same time points, both in terms of age and disease progression? Are they reproducible across labs, and across populations? When using animal and in vitro models, how do you match developmental and aging stages with human progression?¹⁴⁷ Are benchmarks reproducible across models, genetic backgrounds, and different laboratories? How can data from in vitro experiments best be linked with model organisms and to human disease? To answer some of these questions, closer integration of the available data on disease pathogenesis needs to be pursued, with meta-data on timelines, genetic background and other relevant variables pertaining to models and experiments that are not always systematically and accurately reported. Better patient stratification and quality control of genetic and functional metadata recording would increase the selection accuracy of optimum benchmarks. It would also enhance information determining the choice of a specific model for a given hypothesis to be tested. For example, whether the model accurately recapitulates the neural circuit or the signaling pathway in question will considerably affect the choice of model. Integration of the various existing datasets, coupled with a user-friendly database query mechanism, would be ideal to facilitate the design of high-quality experimental studies relevant to human disease.

5 | USING ML TO SOLVE REPRODUCIBILITY AND TRANSLATION CHALLENGES

5.1 | Structural equation modeling

Despite widespread adoption and necessity of experimental models in preclinical research, they present significant limitations both in terms of reproducibility of results within models, and translation from models to human patients.^{148,149} Various computational approaches, including ML, have been implemented to address each of these issues. Here we highlight several approaches that have been used to enhance reproducibility and translation, including those that have yet to be adopted in dementia research. A more comprehensive overview of ML/AI methodology can be found in the methods optimization paper from the same series.³² Mathematical and statistical modeling of experimental models based on prior domain knowledge (eg, structural equation modeling [SEM]) is an approach that can be used to support hypothesis generation and testing, provide insight into biological mechanisms, and predict the effects of interventions.¹⁵⁰ In contrast to conventional deterministic approaches in SEM, in which fixed, predefined parameters determine predicted outcomes, probabilistic simulation-based modeling allows researchers to operationalize and test the effects of uncertainty at multiple levels within the model system. This includes inputs (eg, drug uptake or sequestering), model structure (eg, variation in body size or genetic background), and experimental measurements (eg, behavioral outcomes, molecular assay readouts).¹⁵¹⁻¹⁵³ Simulation has been used within preclinical mouse models of metabolic disease to predict disease onset and progression and to more accurately estimate the impact of pharmacological interventions,^{154,155} though these

TABLE 1 Major initiatives to share datasets applicable to experimental modeling of dementia.

Resource	Description	Link	Reference
AD Knowledge Portal	Data, analyses, and tools from the National Institute on Aging's Alzheimer's Disease Translational Research Program	https://adknowledgeportal.synapse.org	124
AlphaFold	Protein structure database	https://alphafold.ebi.ac.uk/	112
AlzGene	Human AD variants	http://www.alzgene.org	125
Alzforum	AD related biomarkers, genes, mutations, risks, rodent models, therapeutics, tools	https://www.alzforum.org/databases	
Clinico-Genomic Database (CGDB)	Detailed, curated, electronic health records linked with comprehensive genomic profiling data of over 300 cancer related genes for over 60,000 oncology patients	https://www.roche.com/about/priorities/personalised_healthcare/combining_data-to-advance_personalised_healthcare.html	
Dementias Platform UK	Online environment to work with some of the richest cohort data optimized for dementia research.	https://www.dementiasplatform.uk/	126
ESMFold	Protein structure prediction using a large language model	https://esmatlas.com/	113
FlyBase	<i>D. melanogaster</i> resources	http://flybase.org	127
Gene Ontology	Gene function compendium	http://geneontology.org	128
Genotype-Tissue Expression (GTEx)	Human genotype-tissue expression	https://gtexportal.org/home/	129
GnomAD	Human genetic variation	https://gnomad.broadinstitute.org	130
Human Integrated Protein-Protein Interaction Reference (HIPPIE)	Human protein-protein interaction networks	http://cbdm-01.zdv.uni-mainz.de/~mschaefer/hippie/	131
Model AD Explorer	Gene expression and pathology data from AD mouse models developed by the MODEL-AD consortium	https://sagebio.shinyapps.io/MODEL_AD_Explorer/	
Mouse Genomes Project	Catalog of all forms of genetic variation between the common laboratory mouse strains and construction and annotation of reference genomes for the key strains	https://www.sanger.ac.uk/data/mouse-genomes-project/	132
MRC-Wellcome Trust Human Developmental Biology Resource	Tissue bank of human embryonic and fetal tissues since 1999	https://www.hdbi.org/	133
Neuro C-BIG Repository (Canada)	Collection of biospecimens, longitudinal clinical and neuropsychiatric information, imaging and genetic data from patients with neurological disease as well as healthy controls	https://cbigr-open.loris.ca/	134
orthogene	R package for easy and comprehensive mapping of orthologous genes across hundreds of species	https://github.com/neurogenomics/orthogene	104
Open Targets	Drug target identification and prioritization	https://www.opentargets.org	135
PhosphoNET	Repository of known and predicted information on human phosphorylation sites, their evolutionary conservation, the identities of protein kinases that may target these sites and related phosphosites	http://www.phosphonet.ca/	136
PhosphoSitePlus	Information and tools for the study of protein post-translational modifications including phosphorylation, acetylation, and more	https://www.phosphosite.org/	137
Protein Lysine Modifications Database (PLMD)	Lysine modifications	http://plmd.biocuckoo.org/	138

(Continues)

TABLE 1 (Continued)

Resource	Description	Link	Reference
quantification of Post-Translational Modifications (qPTM) database	Database of 6 types of PTMs in 4 different organisms including human, mouse, rat and yeast	http://qptm.omicsbio.info/	139,140
Reactome	Pathway database	https://reactome.org	141
RSCB Protein Data Bank	3D structure data for large biological molecules (proteins, DNA, and RNA)	https://www.rcsb.org	142
scArches	Python package to computationally integrate scRNA-seq datasets into existing ML models	https://github.com/theislab/scarches	38
UK Biobank	Biomedical database containing in-depth genetic and health information from half a million UK participants	https://www.ukbiobank.ac.uk/	143
UK Brain Banks Network	Various tissue resources, supplies tissue samples to academic and industry researchers	https://brainbanknetwork.ac.uk/	
UKCRC Tissue Directory and Coordination Centre (TDCC)	UK's only register of sample collections that covers multiple diseases	https://biobankinguk.org/	
UK Stem Cell Bank	Facilitates the use and sharing of quality-controlled stem cell lines	https://www.nibsc.org/ukstemcellbank	144
UniPep	Library of putative glycopeptides	http://www.unipep.org/	145
WormBase	Genetics, genomics and biology of <i>C. elegans</i> and related nematodes	https://wormbase.org/	146

approaches have not yet been extended to experimental models of dementia.

5.2 | (Semi-)supervised ML approaches

Relative to both deterministic SEM and probabilistic simulations, ML approaches deviate even further from reliance on predefined model assumptions and manual parameter assignment.¹⁵⁶ Instead, ML generates an in silico model of the experimental system learned primarily, if not entirely, from data. Regarding the issue of reproducibility, supervised and semi-supervised ML has been applied to learn more robust generalizations when mapping experimental inputs to outputs. Read-across structure activity relationships (RASAR) was trained on hundreds of thousands of animal toxicology experiments to learn the relationship between binarized chemical fingerprints and safety outcome metrics, achieving an average prediction accuracy greater than that of any single animal experiment.¹⁵⁷ Other ML approaches have been used to address the issues of translatability by predicting experiment outcomes in humans from matched in vivo or in vitro model data. Efforts such as the systems biology verification (sbv) project's IMPROVER Species Translation Challenge aimed to advance methods for cross-species translation but were met with limited success in part due to insufficient training data.¹⁵⁸ Later attempts trained various ML architectures on matched pairs of mouse models and human disease samples to predict disease-associated gene signatures in the latter.¹⁵⁹⁻¹⁶¹ However, this paired interspecies case-control approach is limited by the time it takes to manually curate such datasets. It also

presupposes the a priori validity of the animal model when learning model-to-human mappings.

High-quality data with large sample sizes are not always available in human cohorts. Another variant of supervised ML uses transfer learning, which is often a general ML architecture for pretraining a model on a larger dataset that is less specific to your task (eg, histological images from a large cohort of animal models) to learn basic features common to all data of that modality (eg, anatomical borders, cell contours, subcellular features), and then fine-tuning the model with a smaller but more task-specific dataset (eg, disease-associated pathologies in *post mortem* histological samples). Substantial progress has recently been made in applying AI-based strategies towards rapid and accurate quantification of hallmark AD and PD pathologies at both the micro- (eg, microscopy) and macro- (eg, magnetic resonance imaging) scales.¹⁶²⁻¹⁶⁴ Transfer learning is also more regularly being applied to omics data. For example, Stumpf et al. (2020) employed this strategy to first train a cell type classifier using single-cell transcriptomic profiles from mouse bone marrow, and then accurately predict human bone marrow cell types.¹⁶⁵

5.3 | Unsupervised ML approaches

Unlike supervised learning, unsupervised ML aims to learn an in silico model of the data using only the data itself (without the need for labels). Within the domain of single-cell omics (eg, genomics, transcriptomics, epigenomics, proteomics, and multi-omics) there has been an explosion of such methods.^{166,167} Specific unsupervised ML frameworks

like autoencoders and generative adversarial networks (GANs) have been used extensively for dimensionality reduction, data denoising (eg, dropout correction), artifact removal (eg, batch, species), feature selection (eg, differential gene expression), data labelling (eg, cell type, disease state), data integration (eg, across datasets and/or omics modalities), clustering, data visualization, and other downstream analyses.¹⁶⁶⁻¹⁶⁹

Unsupervised ML methods can also be applied to the problem of reproducibility. Despite the large number of cells, the number of donors in a given single-cell dataset is usually quite low (often just a few individuals per study). This small effective sample size of “large” datasets can introduce inflated false positive rates (eg, differentially expressed genes between cases and controls) when trying to reproduce the results in other datasets derived from different individuals using traditional statistics.¹⁷⁰⁻¹⁷² Here too, ML can be of great utility. Resources like the scArches database³⁸ store models previously trained on one or more datasets (eg, an unsupervised dimensionality reduction model trained on a large single-cell dataset of cell lines from controls). Other users can then download these pretrained models and apply them to their own smaller datasets (eg, embedding single-cell data from a cohort from AD and control group cell lines into the same low-dimensional space as the large dataset). In this example of unsupervised transfer learning, models can learn patterns across many datasets, increasing the effective sample size and the likelihood that the results will generalize to new unseen datasets. It also obviates the need for direct access to all of the pretraining datasets, which can be non-trivial to acquire and reprocess. Similar transfer learning approaches have been used to successfully predict the effect of novel drug-induced perturbations in cancer cell lines from previously learned latent embeddings.^{173,174} Recently, several models trained on a large corpus of scRNA-seq data (eg, single-cell Generative Pre-Trained Transformer [scGPT],¹⁷⁵ single-cell bidirectional encoder representations from transformers [scBERT],¹⁷⁶ Geneformer¹⁷⁷), have been put forward as generalist base models to be fine-tuned by users with smaller, more targeted datasets. The goal of such resources is to make transfer learning both more robust and easily accessible to the research community.³⁸

Finally, unsupervised learning methods can be flexibly combined with supervised ML, simulations, SEM and/or traditional statistical approaches to form innovative solutions to problems inadequately addressed by any one method. GNNs are particularly adept at utilizing supervised and/or supervised ML architectures and can efficiently handle hierarchical or semi-structured data.¹⁷⁸ Specifically, they have been used to predict pathway-specific disease mechanisms,¹⁷⁹ protein function across multiple species,¹⁸⁰ disease-associated disruptions in brain connectivity,¹⁸¹ AD status,^{182,183} rare disease gene targets,¹⁸⁴ and drug response,^{185,186} as well as to integrate multi-modal data.^{187,188} In this way, ML can be used to aid in the design, reproduction, interpretation, and translation of studies in experimental models even prior to investment of extra time and resources in new experiments or clinical trials.

5.4 | Interpretability and trust in ML approaches

Despite their many advantages, a major hurdle for the widespread adoption of cutting-edge ML approaches is the lack of trust in black-box predictions,¹⁸⁹ particularly in healthcare environments where there are concerns of patient safety and privacy.^{190,191} This lack of trust is not entirely unfounded, as ML algorithms exploit patterns in data, even if they are not relevant to the problem of interest.¹⁹² To minimize this risk, there is increasing focus on making models more easily interpretable,¹⁹³ less biased,¹⁹⁴ and less susceptible to adversarial attacks.¹⁹⁵ Interpretability is a particularly difficult challenge as improvement in this domain is often (though certainly not always) accompanied by decreased predictive performance.¹⁹⁶ Nevertheless, advances continue to be made by way of text-based explanations, visualizations, explanations by example or simplification, and feature relevance.^{194,197} These techniques have increasingly been applied to biomedical sciences and healthcare,^{178,198,199} such as for drug discovery^{200,201} and prediction of drug-drug interactions.²⁰² Advances have particularly been reported in the domain of medical imaging analysis,²⁰³ employing techniques such as visual attention,²⁰⁴ saliency maps,²⁰⁵ and SHapley Additive exPlanations (SHAP)²⁰⁶ for dementia diagnosis based on neuroimaging data. Overall, the adoption of explainable and interpretable AI for dementia-related applications, however, remains scarce to date, leaving ample opportunities for progress.

5.5 | Future applications

Recent advances in AI, driven by composite deep learning models with near human-like intelligence, have the potential to change the landscape of neurodegenerative research in the future. The success of these approaches often relies on large-scale, high-dimensional, uniform datasets, which are required for training complex algorithms. For experimental researchers, generating such datasets is both costly and time consuming. To keep up with the pace at which AI is advancing, rather than wait for large uniform datasets to be created, researchers should focus on developing novel, composite methods for large heterogeneous datasets, integrated from different sources, such as those recently developed in the single-cell genomics field.^{175-177,37,38} Focusing on developing methods that do not rely on high-dimensional uniform data will ensure experimental research into neurodegenerative disease advances alongside AI.

Large-scale population cohorts are likely to facilitate the development of massive uniform datasets that lend themselves to application of AI approaches. UK Biobank has collected genetic information and deep phenotyping data on half a million individuals in the UK.²⁰⁷ In the context of neurodegeneration, there is an important argument to facilitate brain donation from UK Biobank participants in the future, so that phenotypic data can be linked to neuropathological measures and genetic variation. Complementing this, WGS data collected to screen for genetic disorders as a part of the Newborn Genomes

Programme may be instrumental in accelerating the diagnostic process of infants born with rare genetic conditions.²⁰⁸ Automated AI analysis pipelines could streamline the process of detecting rare genetic variants or phenotypic associations. For example, pathogenic variants could be filtered and ranked using deep phenotype integration based on natural language processing of the medical literature. In the context of dementia, the detection of variants known to increase risk of AD could be used as a proxy for testing family members. In the long run, ML could be used for evaluating genotype–phenotype correlations,²⁰⁹ biomarker identification,²¹⁰ to predict individual disease risk and gene function.²¹¹ This improved knowledge of disease biology could then be experimentally validated in model systems to develop better diagnostics and therapeutics.

Generative large language models (LLMs) are generalist AI models trained on a massive corpus of text to achieve convincing natural language capabilities with an extensive breadth of knowledge. Open-access implementations of LLMs, including OpenAI's chatGPT, Google's Bard, Bing, or Meta's LLaMA, have recently gained much public interest. Iterations of these models are rapidly evolving, even as they continue to be applied to a wide variety of real-world problems, including biology²¹² and medicine.^{213,214} Several examples that have been specifically trained to synthesize, mine, or infer biomedical knowledge are Flan-PaLM/Med-PaLM (instruction fine-tuned/ medical Pathways Language Models),²¹⁵ BiomedGPT (Biomedical Generative Pre-trained Transformer),²¹⁶ PubMedGPT/BioMedLM,²¹⁷ GeneGPT,²¹⁸ BioGPT,²¹⁹ PubMedBERT,²²⁰ BioLinkBERT,²²¹ Galactica,²²² and BioMegatron.²²³ These approaches have even been adapted for non-language based biological data (eg, scRNA-seq).^{175,176} While static versions of LLMs trained on a snapshot of data from a particular time point are prone to hallucinations (ie, providing real-sounding but objectively false answers), this can be partly ameliorated through the addition of internet-search capabilities. Open-source projects like AutoGPT²²⁴ seek to extend this even further by forcing the model to query itself in order to identify what information it is currently lacking to answer the user's question, enabling a semi-automated loop of knowledge gathering and knowledge synthesis. While there are plenty of remaining challenges to address, LLMs are uniquely positioned to offer human-understandable justifications for their reasoning by querying them with natural language, just as one would with another human. For example, one may ask an LLM to predict whether a particular drug will have a side effect of motor impairment in mice, whether this side effect will also occur in humans, and to provide well-cited justifications for its reasoning. In combination with proper validation, human oversight, and ethical implementation, LLMs are likely to open entirely new avenues of biomedical research and healthcare at scale.

5.6 | Key recommendations

To improve the quality and scope of the application of AI to experimental models of neurodegenerative diseases and overcome major existing challenges (Figure 2), we make four key recommendations:

Enhancing reproducibility across model systems and experiments: To enhance applications of AI and ML approaches in model systems, reproducibility should become a priority, driven by large enough, well-controlled experiments, that allow the statistical study and resolution of biases and artifacts. Conversely, ML approaches including simulations can improve model reproducibility in experimental research, as can pretrained unsupervised clustering methods in the context of single-cell genomics.

Improving upon small and disjointed datasets: AI and ML methods often require large and high-dimensional training datasets to yield robust and appropriately fitted models. We recommend increasing experimental sample sizes and enhancing integration of existing data resources with biological and clinical data to facilitate this. Numerous data resources are already openly available spanning genomics, proteomics, phylogeny, and clinical databases. These should be expanded and leveraged for ML analyses in experimental dementia research. Ultimately, we should aim to generate massive, uniform datasets, while continuing to develop methods to deal with heterogeneity in the meantime.

Accounting for species divergence through evolution: Inherent differences in biology between species, some driven by millions of years of evolution, complicate translation of biological insights from animal models to human disease. We recommend using information on evolutionary distances in combination with transfer learning or autoencoder approaches to improve cross-species translation.

Enhancing interpretability and transparency of AI/ML approaches: As with applications of AI and ML more generally, there is a risk for opacity and distrust in the methods, especially where clinical data are concerned. A focus on addressing these issues by adapting existing approaches and continued research advances in this domain are needed to increase trust and model interpretability.

6 | CONCLUSIONS

Animal models are an important tool for assessing mechanisms of neurodegenerative disease in complex in vivo settings and prioritizing therapeutic approaches. However, promising drugs in animal models have repeatedly shown high failure rates in human clinical trials. Here we reviewed challenges to translation from model to human, including issues surrounding reproducibility, with the aim of making recommendations to enhance reproducible research and translatability via the adoption of AI approaches. Successful applications of AI and ML in the domain of experimental dementia research are limited; however, other biomedical research fields have witnessed promising advances. Such methodological developments and applications can be adapted to research questions in neurodegeneration, building on existing and novel high-dimensional datasets, including single-cell and spatial omics, proteomics, metabolomics, and biomarker profiles. With the projected growth of quantitative data on preclinical models for dementia research, we are optimistic that increased translational

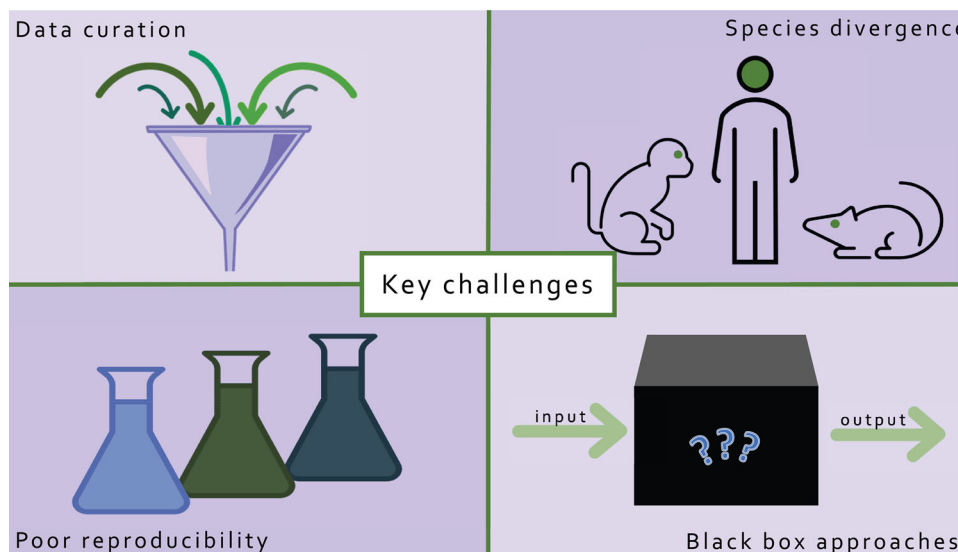


FIGURE 2 Key challenges which need to be overcome to enhance the application of machine learning (ML) and artificial intelligence (AI) approaches for experimental models in dementia research.

efficiency and improved model reproducibility can be enhanced by appropriate and careful application of AI and ML approaches in the field.

AUTHOR CONTRIBUTIONS

Sarah J. Marzi contributed to the conception of the work, coordinated the writing team, and contributed to drafting and revising the manuscript for intellectual content. Brian M. Schilder, Alexi Nott, Carlo Sala Frigerio, and Sandrine Willaime-Morawek contributed to coordinating the writing team, and to drafting and revising the manuscript for intellectual content. Wendy Noble, Jalil-Ahmad Sharif, Zhi Yao, Maria Tsalenchuk, Ümran Yaman, Diane P. Hanger, Patrick A. Lewis, Magda Bucholc, Charlotte James, Francisco Rodriguez-Algarra, and Laura M. Winchester contributed to drafting and revising the manuscript for intellectual content. Janice M. Ranson and David J. Llewellyn contributed to the conception of the work, conceived and organized the symposium from which this paper and others in the series originated, revised the manuscript for intellectual content, and harmonized the manuscript with other papers in the series. Ilianna Lourida revised the manuscript for intellectual content and harmonized the manuscript with other papers in the series. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

This manuscript was facilitated by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), through the AI for Precision Dementia Medicine Professional Interest Area (PIA). The views and opinions expressed by authors in this publication represent those of the authors and do not necessarily reflect those of the PIA membership, ISTAART, or the Alzheimer's Association. With thanks to the Deep Dementia Phenotyping (DEMON) Network State of the Science symposium participants (in alphabetical order): Peter Bagshaw, Robin Borchert,

Magda Bucholc, James Duce, Charlotte James, David Llewellyn, Donald Lyall, Sarah Marzi, Danielle Newby, Neil Oxtoby, Janice Ranson, Tim Rittman, Nathan Skene, Eugene Tang, Michele Veldsman, Laura Winchester, Zhi Yao. This paper was the product of a DEMON Network State of the Science symposium entitled "Harnessing Data Science and AI in Dementia Research" funded by Alzheimer's Research UK. JMR and DJL are supported by Alzheimer's Research UK and the Alan Turing Institute/Engineering and Physical Sciences Research Council (EP/N510129/1). DJL also receives funding from the Medical Research Council (MR/X005674/1), National Institute for Health Research (NIHR) Applied Research Collaboration South West Peninsula, National Health and Medical Research Council (NHMRC), and National Institute on Aging/National Institutes of Health (RF1AG055654). SJM and AN are funded by the Edmond and Lily Safra Early Career Fellowship Program and the UK Dementia Research Institute, which receives its funding from UK DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society, and Alzheimer's Research UK. MB is supported by Alzheimer's Research UK, Economic and Social Research Council (ES/W010240/1), EU (SEUPB) INTERREG (ERDF/SEUPB), and HSC R&D (COM/5750/23). PAL acknowledges generous support from the Michael J. Fox Foundation and Parkinson's UK. CJ and LMW are supported by Alzheimer's Research UK.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the [supporting information](#).

ORCID

Sarah J. Marzi <https://orcid.org/0000-0002-3924-2053>

Brian M. Schilder <https://orcid.org/0000-0001-5949-2191>

Alexi Nott <https://orcid.org/0000-0002-2029-7193>

Carlo Sala Frigerio <https://orcid.org/0000-0003-4038-6449>

Sandrine Willaime-Morawek  <https://orcid.org/0000-0002-1121-6419>

Magda Bucholc  <https://orcid.org/0000-0002-8417-1602>

Diane P. Hanger  <https://orcid.org/0000-0002-3044-9816>

Charlotte James  <https://orcid.org/0000-0003-4850-5318>

Patrick A. Lewis  <https://orcid.org/0000-0003-4537-0489>

Ilianna Lourida  <https://orcid.org/0000-0003-4439-2192>

Wendy Noble  <https://orcid.org/0000-0002-7898-4295>

Francisco Rodriguez-Algarra  <https://orcid.org/0000-0002-4134-2141>

Jalil-Ahmad Sharif  <https://orcid.org/0000-0001-7642-9143>

Laura M. Winchester  <https://orcid.org/0000-0003-3826-7694>

Ümran Yaman  <https://orcid.org/0000-0003-4469-8407>

Janice M. Ranson  <https://orcid.org/0000-0001-9491-3940>

REFERENCES

- Grapov D, Fahrman J, Wanichthanarak K, Khoomrung S. Rise of deep learning for genomic, proteomic, and metabolomic data integration in precision medicine. *OMICS*. 2018;22:630-636. [10.1089/omi.2018.0097](https://doi.org/10.1089/omi.2018.0097)
- Mullane K, Williams M. Preclinical Models of Alzheimer's Disease: relevance and Translational Validity. *Curr Protoc Pharmacol*. 2019;84:e57. [10.1002/cpph.57](https://doi.org/10.1002/cpph.57)
- Choi SH, Kim YH, Hebisch M, et al. A three-dimensional human neural cell culture model of Alzheimer's disease. *Nature*. 2014;515:274-278. [10.1038/nature13800](https://doi.org/10.1038/nature13800)
- Stansley B, Post J, Hensley K. A comparative review of cell culture systems for the study of microglial biology in Alzheimer's disease. *J Neuroinflammation*. 2012;9:115. [10.1186/1742-2094-9-115](https://doi.org/10.1186/1742-2094-9-115)
- Kwak SS, Washicosky KJ, Brand E, et al. Amyloid-β42/40 ratio drives tau pathology in 3D human neural cell culture models of Alzheimer's disease. *Nat Commun*. 2020;11:1377. [10.1038/s41467-020-15120-3](https://doi.org/10.1038/s41467-020-15120-3)
- Penney J, Jalvenius WT, Tsai L-H. Modeling Alzheimer's disease with iPSC-derived brain cells. *Mol Psychiatry*. 2020;25:148-167. [10.1038/s41380-019-0468-3](https://doi.org/10.1038/s41380-019-0468-3)
- Fujimori K, Ishikawa M, Otomo A, et al. Modeling sporadic ALS in iPSC-derived motor neurons identifies a potential therapeutic agent. *Nat Med*. 2018;24:1579-1589. [10.1038/s41591-018-0140-5](https://doi.org/10.1038/s41591-018-0140-5)
- Schweitzer JS, Song B, Herrington TM, et al. Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease. *N Engl J Med*. 2020;382:1926-1932. [10.1056/NEJMoa1915872](https://doi.org/10.1056/NEJMoa1915872)
- Croft CL, Futch HS, Moore BD, Golde TE. Organotypic brain slice cultures to model neurodegenerative proteinopathies. *Mol Neurodegener*. 2019;14:45. [10.1186/s13024-019-0346-0](https://doi.org/10.1186/s13024-019-0346-0)
- Avossa D, Grandolfo M, Mazzarol F, Zatta M, Ballerini L. Early signs of motoneuron vulnerability in a disease model system: characterization of transverse slice cultures of spinal cord isolated from embryonic ALS mice. *Neuroscience*. 2006;138:1179-1194. [10.1016/j.neuroscience.2005.12.009](https://doi.org/10.1016/j.neuroscience.2005.12.009)
- Humpel C. Organotypic brain slice cultures: a review. *Neuroscience*. 2015;305:86-98. [10.1016/j.neuroscience.2015.07.086](https://doi.org/10.1016/j.neuroscience.2015.07.086)
- Papaspyropoulos A, Tsolaki M, Foroglou N, Pantazaki AA. Modeling and targeting Alzheimer's disease with organoids. *Front Pharmacol*. 2020;11:396. [10.3389/fphar.2020.00396](https://doi.org/10.3389/fphar.2020.00396)
- Zhao J, Fu Y, Yamazaki Y, et al. APOE4 exacerbates synapse loss and neurodegeneration in Alzheimer's disease patient iPSC-derived cerebral organoids. *Nat Commun*. 2020;11:5540. [10.1038/s41467-020-19264-0](https://doi.org/10.1038/s41467-020-19264-0)
- Smits LM, Reinhardt L, Reinhardt P, et al. Modeling Parkinson's disease in midbrain-like organoids. *NPJ Parkinsons Dis*. 2019;5:5. [10.1038/s41531-019-0078-4](https://doi.org/10.1038/s41531-019-0078-4)
- Monzel AS, Smits LM, Hemmer K, et al. Derivation of Human Midbrain-Specific Organoids from Neuroepithelial Stem Cells. *Stem Cell Rep*. 2017;8:1144-1154. [10.1016/j.stemcr.2017.03.010](https://doi.org/10.1016/j.stemcr.2017.03.010)
- Kounnas MZ, Danks AM, Cheng S, et al. Modulation of gamma-secretase reduces beta-amyloid deposition in a transgenic mouse model of Alzheimer's disease. *Neuron*. 2010;67:769-780. [10.1016/j.neuron.2010.08.018](https://doi.org/10.1016/j.neuron.2010.08.018)
- Webster SJ, Bachstetter AD, Van Eldik LJ. Comprehensive behavioral characterization of an APP/PS-1 double knock-in mouse model of Alzheimer's disease. *Alzheimers Res Ther*. 2013;5:28. [10.1186/alzrt182](https://doi.org/10.1186/alzrt182)
- Saito T, Matsuba Y, Mihira N, et al. Single App knock-in mouse models of Alzheimer's disease. *Nat Neurosci*. 2014;17:661-663. [10.1038/nn.3697](https://doi.org/10.1038/nn.3697)
- Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci*. 2000;3:1301-1306. [10.1038/81834](https://doi.org/10.1038/81834)
- Cannon JR, Greenamyre JT. The role of environmental exposures in neurodegeneration and neurodegenerative diseases. *Toxicol Sci*. 2011;124:225-250. [10.1093/toxsci/kfr239](https://doi.org/10.1093/toxsci/kfr239)
- Mancuso R, Van Den Daele J, Fattorelli N, et al. Stem-cell-derived human microglia transplanted in mouse brain to study human disease. *Nat Neurosci*. 2019;22:2111-2116. [10.1038/s41593-019-0525-x](https://doi.org/10.1038/s41593-019-0525-x)
- Mckean NE, Handley RR, Snell RG. A review of the current mammalian models of Alzheimer's disease and challenges that need to be overcome. *Int J Mol Sci*. 2021;22:13168. [10.3390/ijms222313168](https://doi.org/10.3390/ijms222313168)
- Anderson RM, Hadjichrysanthou C, Evans S, Wong MM. Why do so many clinical trials of therapies for Alzheimer's disease fail? *Lancet*. 2017;390:2327-2329. [10.1016/S0140-6736\(17\)32399-1](https://doi.org/10.1016/S0140-6736(17)32399-1)
- McGonigle P, Ruggeri B. Animal models of human disease: challenges in enabling translation. *Biochem Pharmacol*. 2014;87:162-171. [10.1016/j.bcp.2013.08.006](https://doi.org/10.1016/j.bcp.2013.08.006)
- Sukoff Rizzo SJ, Masters A, Onos KD, et al. Improving preclinical to clinical translation in Alzheimer's disease research. *Alzheimers Dement*. 2020;6:e12038. [10.1002/trc2.12038](https://doi.org/10.1002/trc2.12038)
- Doherty T, Yao Z, Khleifat AA, et al. Artificial intelligence for dementia drug discovery and trials optimization. *Alzheimers Dement*. Portico. 2023. [10.1002/alz.13428](https://doi.org/10.1002/alz.13428)
- Bettencourt C, Skene N, Bandres-Ciga S, et al. Artificial intelligence for dementia genetics and omics. *Alzheimers Dement*. Portico. 2023. [10.1002/alz.13427](https://doi.org/10.1002/alz.13427)
- Winchester LM, Harshfield EL, Shi L, et al. Artificial intelligence for biomarker discovery in Alzheimer's disease and dementia. *Alzheimers Dement*. Portico. 2023. [10.1002/alz.13390](https://doi.org/10.1002/alz.13390)
- Borchert RJ, Azevedo T, Badhwar A, et al. Artificial intelligence for diagnostic and prognostic neuroimaging in dementia: A systematic review. *Alzheimers Dement*. Portico. 2023. [10.1002/alz.13412](https://doi.org/10.1002/alz.13412)
- Newby D, Orgeta V, Marshall CR, et al. Artificial intelligence for dementia prevention. *Alzheimers Dement*. Accepted.
- Lyll DM, Kormilitzin A, Lancaster C, et al. Artificial intelligence for dementia—Applied models and digital health. *Alzheimers Dement*. Portico. 2023. [10.1002/alz.13391](https://doi.org/10.1002/alz.13391)
- Bucholc M, James C, Khleifat AA, et al. Artificial intelligence for dementia research methods optimization. *Alzheimers Dement*. Portico. 2023. [10.1002/alz.13441](https://doi.org/10.1002/alz.13441)
- Claerhout JF, Karrenbach M. Electronic documents give reproducible research a new meaning. SEG Technical Program Expanded Abstracts 1992, Society of Exploration Geophysicists. 1992. [10.1190/1.1822162](https://doi.org/10.1190/1.1822162)

34. Stodden V, Leisch F, Peng RD. *Implementing Reproducible Research*. CRC Press; 2014.
35. Plesser HE. Reproducibility vs. replicability: a brief history of a confused terminology. *Front Neuroinform*. 2017;11:76. [10.3389/fninf.2017.00076](https://doi.org/10.3389/fninf.2017.00076)
36. Wilkinson MD, Dumontier M, Aalbersberg IJJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data*. 2016;3:160018. [10.1038/sdata.2016.18](https://doi.org/10.1038/sdata.2016.18)
37. Lopez R, Regier J, Cole MB, Jordan MI, Yosef N. Deep generative modeling for single-cell transcriptomics. *Nat Methods*. 2018;15:1053-1058. [10.1038/s41592-018-0229-2](https://doi.org/10.1038/s41592-018-0229-2)
38. Lotfollahi M, Naghypourfar M, Luecken MD, et al. Mapping single-cell data to reference atlases by transfer learning. *Nat Biotechnol*. 2022;40:121-130. [10.1038/s41587-021-01001-7](https://doi.org/10.1038/s41587-021-01001-7)
39. Kilpinen H, Goncalves A, Leha A, et al. Corrigendum: common genetic variation drives molecular heterogeneity in human iPSCs. *Nature*. 2017;546:686. [10.1038/nature23012](https://doi.org/10.1038/nature23012)
40. D'Antonio M, Benaglio P, Jakubosky D, et al. Insights into the mutational burden of human induced pluripotent stem cells from an integrative multi-omics approach. *Cell Rep*. 2018;24:883-894. [10.1016/j.celrep.2018.06.091](https://doi.org/10.1016/j.celrep.2018.06.091)
41. Volpato V, Smith J, Sandor C, et al. Reproducibility of molecular phenotypes after long-term differentiation to human iPSC-Derived neurons: a multi-site omics study. *Stem Cell Rep*. 2018;11:897-911. [10.1016/j.stemcr.2018.08.013](https://doi.org/10.1016/j.stemcr.2018.08.013)
42. Velasco S, Kedaigle AJ, Simmons SK, et al. Individual brain organoids reproducibly form cell diversity of the human cerebral cortex. *Nature*. 2019;570:523-527. [10.1038/s41586-019-1289-x](https://doi.org/10.1038/s41586-019-1289-x)
43. Doss MX, Sachinidis A. Current Challenges of iPSC-Based disease modeling and therapeutic implications. *Cells*. 2019;8:40. [10.3390/cells8050403](https://doi.org/10.3390/cells8050403)
44. Jankowsky JL, Zheng H. Practical considerations for choosing a mouse model of Alzheimer's disease. *Mol Neurodegener*. 2017;12:89. [10.1186/s13024-017-0231-7](https://doi.org/10.1186/s13024-017-0231-7)
45. Carlson GA, Borchelt DR, Dake A, et al. Genetic modification of the phenotypes produced by amyloid precursor protein overexpression in transgenic mice. *Hum Mol Genet*. 1997;6:1951-1959. [10.1093/hmg/6.11.1951](https://doi.org/10.1093/hmg/6.11.1951)
46. Lehman EJH, Kulnane LS, Gao Y, et al. Genetic background regulates β -amyloid precursor protein processing and β -amyloid deposition in the mouse. *Hum Mol Genet*. 2003;12:2949-2956. [10.1093/hmg/ddg322](https://doi.org/10.1093/hmg/ddg322)
47. Jackson HM, Onos KD, Pepper KW, et al. DBA/2J genetic background exacerbates spontaneous lethal seizures but lessens amyloid deposition in a mouse model of Alzheimer's disease. *PLoS One*. 2015;10:e0125897. [10.1371/journal.pone.0125897](https://doi.org/10.1371/journal.pone.0125897)
48. Ryman D, Gao Y, Lamb BT. Genetic loci modulating amyloid-beta levels in a mouse model of Alzheimer's disease. *Neurobiol Aging*. 2008;29:1190-1198. [10.1016/j.neurobiolaging.2007.02.017](https://doi.org/10.1016/j.neurobiolaging.2007.02.017)
49. Morihara T, Hayashi N, Yokokoji M, et al. Transcriptome analysis of distinct mouse strains reveals kinesin light chain-1 splicing as an amyloid- β accumulation modifier. *Proc Natl Acad Sci USA*. 2014;111:2638-2643. [10.1073/pnas.1307345111](https://doi.org/10.1073/pnas.1307345111)
50. Neuner SM, Heuer SE, Huentelman MJ, O'Connell KMS, Kaczorowski CC. Harnessing genetic complexity to enhance translatability of Alzheimer's disease mouse models: a path toward precision medicine. *Neuron*. 2019;101:399-411.e5. [10.1016/j.neuron.2018.11.040](https://doi.org/10.1016/j.neuron.2018.11.040)
51. O'Connell KMS, Ouellette AR, Neuner SM, Dunn AR, Kaczorowski CC. Genetic background modifies CNS-mediated sensorimotor decline in the AD-BXD mouse model of genetic diversity in Alzheimer's disease. *Genes Brain Behav*. 2019;18:e12603. [10.1111/gbb.12603](https://doi.org/10.1111/gbb.12603)
52. Ransohoff RM. All (animal) models (of neurodegeneration) are wrong. Are they also useful? *J Exp Med*. 2018;215:2955-2958. [10.1084/jem.20182042](https://doi.org/10.1084/jem.20182042)
53. Chesselet M-F, Richter F. Modelling of Parkinson's disease in mice. *Lancet Neurol*. 2011;10:1108-1118. [10.1016/S1474-4422\(11\)70227-7](https://doi.org/10.1016/S1474-4422(11)70227-7)
54. Puzzo D, Gulisano W, Palmeri A, Arancio O. Rodent models for Alzheimer's disease drug discovery. *Expert Opin Drug Discov*. 2015;10:703-711. [10.1517/17460441.2015.1041913](https://doi.org/10.1517/17460441.2015.1041913)
55. Ashe KH, Zahs KR. Probing the biology of Alzheimer's disease in mice. *Neuron*. 2010;66:631-645. [10.1016/j.neuron.2010.04.031](https://doi.org/10.1016/j.neuron.2010.04.031)
56. LaFerla FM, Green KN. Animal models of Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2:a006320. [10.1101/cshperspect.a006320](https://doi.org/10.1101/cshperspect.a006320)
57. Price DL, Tanzi RE, Borchelt DR, Sisodia SS. Alzheimer's disease: genetic studies and transgenic models. *Annu Rev Genet*. 1998;32:461-493. [10.1146/annurev.genet.32.1.461](https://doi.org/10.1146/annurev.genet.32.1.461)
58. Roberson ED. Mouse models of frontotemporal dementia. *Ann Neurol*. 2012;72:837-849. [10.1002/ana.23722](https://doi.org/10.1002/ana.23722)
59. Ittner LM, Halliday GM, Kril JJ, Götz J, Hodges JR, Kiernan MC. FTD and ALS—translating mouse studies into clinical trials. *Nat Rev Neurol*. 2015;11:360-366. [10.1038/nrneuro.2015.65](https://doi.org/10.1038/nrneuro.2015.65)
60. Veening-Griffioen DH, Ferreira GS, van Meer PJK, et al. Are some animal models more equal than others? A case study on the translational value of animal models of efficacy for Alzheimer's disease. *Eur J Pharmacol*. 2019;859:172524. [10.1016/j.ejphar.2019.172524](https://doi.org/10.1016/j.ejphar.2019.172524)
61. Vardigan JD, Cannon CE, Puri V, et al. Improved cognition without adverse effects: novel M1 muscarinic potentiator compares favorably to donepezil and xanomeline in rhesus monkey. *Psychopharmacology (Berl)*. 2015;232:1859-1866. [10.1007/s00213-014-3813-x](https://doi.org/10.1007/s00213-014-3813-x)
62. Shin CY, Kim H-S, Cha K-H, et al. The effects of Donepezil, an acetylcholinesterase inhibitor, on impaired learning and memory in rodents. *Biomol Ther*. 2018;26:274-281. [10.4062/biomolther.2017.189](https://doi.org/10.4062/biomolther.2017.189)
63. Cotman CW, Head E. The canine (dog) model of human aging and disease: dietary, environmental and immunotherapy approaches. *J Alzheimers Dis*. 2008;15:685-707. [10.3233/jad-2008-15413](https://doi.org/10.3233/jad-2008-15413)
64. Neus Bosch M, Pugliese M, Gimeno-Bayon J, Jose Rodriguez M, Mahy N. Dogs with cognitive dysfunction syndrome: a natural model of Alzheimer's disease. *Curr Alzheimer Res*. 2012;9:298-314. [10.2174/156720512800107546](https://doi.org/10.2174/156720512800107546)
65. Van Dam D, De Deyn PP. Animal models in the drug discovery pipeline for Alzheimer's disease. *Br J Pharmacol*. 2011;164:1285-1300. [10.1111/j.1476-5381.2011.01299.x](https://doi.org/10.1111/j.1476-5381.2011.01299.x)
66. Hampel H, Nisticò R, Seyfried NT, et al. Omics sciences for systems biology in Alzheimer's disease: state-of-the-art of the evidence. *Ageing Res Rev*. 2021;69:101346. [10.1016/j.arr.2021.101346](https://doi.org/10.1016/j.arr.2021.101346)
67. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. *Nat Biotechnol*. 2014;32:40-51. [10.1038/nbt.2786](https://doi.org/10.1038/nbt.2786)
68. Munos B. Lessons from 60 years of pharmaceutical innovation. *Nat Rev Drug Discov*. 2009;8:959-968. [10.1038/nrd2961](https://doi.org/10.1038/nrd2961)
69. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov*. 2012;11:191-200. [10.1038/nrd3681](https://doi.org/10.1038/nrd3681)
70. Cummings J. Lessons learned from Alzheimer disease: clinical trials with negative outcomes. *Clin Transl Sci*. 2018;11:147-152. [10.1111/cts.12491](https://doi.org/10.1111/cts.12491)
71. Tan C-C, Yu J-T, Wang H-F, et al. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2014;41:615-631. [10.3233/JAD-132690](https://doi.org/10.3233/JAD-132690)

72. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370:311-321. [10.1056/NEJMoa1312889](https://doi.org/10.1056/NEJMoa1312889)
73. Doody RS, Raman R, Farlow M, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med*. 2013;369:341-350. [10.1056/NEJMoa1210951](https://doi.org/10.1056/NEJMoa1210951)
74. Uddin MS, Kabir MT, Rahman MS, et al. Revisiting the amyloid cascade hypothesis: from Anti-A β therapeutics to auspicious new ways for Alzheimer's disease. *Int J Mol Sci*. 2020;21:5858. [10.3390/ijms21165858](https://doi.org/10.3390/ijms21165858)
75. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388:9-21. [10.1056/NEJMoa2212948](https://doi.org/10.1056/NEJMoa2212948)
76. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical Trial. *JAMA*. 2023;330:512-527. [10.1001/jama.2023.13239](https://doi.org/10.1001/jama.2023.13239)
77. Tampi RR, Forester BP, Agronin M. Aducanumab: evidence from clinical trial data and controversies. *Drugs Context*. 2021;10. [10.7573/dic.2021-7-3](https://doi.org/10.7573/dic.2021-7-3)
78. Howard R, Liu KY. Questions EMERGE as Biogen claims aducanumab turnaround. *Nat Rev Neurol*. 2020;16:63-64. [10.1038/s41582-019-0295-9](https://doi.org/10.1038/s41582-019-0295-9)
79. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-Related imaging abnormalities in 2 Phase 3 Studies evaluating Aducanumab in patients with early Alzheimer disease. *JAMA Neurol*. 2022;79:13-21. [10.1001/jamaneurol.2021.4161](https://doi.org/10.1001/jamaneurol.2021.4161)
80. Freedman LP, Inglese J. The increasing urgency for standards in basic biologic research. *Cancer Res*. 2014;74:4024-4029. [10.1158/0008-5472.CAN-14-0925](https://doi.org/10.1158/0008-5472.CAN-14-0925)
81. Mlinarić A, Horvat M, Šupak Smolčić V. Dealing with the positive publication bias: why you should really publish your negative results. *Biochem Med*. 2017;27:030201. [10.11613/BM.2017.030201](https://doi.org/10.11613/BM.2017.030201)
82. Mazure CM, Swendsen J. Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol*. 2016;15:451-452. [10.1016/S1474-4422\(16\)00067-3](https://doi.org/10.1016/S1474-4422(16)00067-3)
83. Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. *Front Neuroendocrinol*. 2014;35:370-384. [10.1016/j.yfrne.2014.02.002](https://doi.org/10.1016/j.yfrne.2014.02.002)
84. Beery AK, Zucker I. Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev*. 2011;35:565-572. [10.1016/j.neubiorev.2010.07.002](https://doi.org/10.1016/j.neubiorev.2010.07.002)
85. Robinson PN, Köhler S, Bauer S, Seelow D, Horn D, Mundlos S. The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease. *Am J Hum Genet*. 2008;83:610-615. [10.1016/j.ajhg.2008.09.017](https://doi.org/10.1016/j.ajhg.2008.09.017)
86. Köhler S, Gargano M, Matentzoglou N, et al. The Human Phenotype Ontology in 2021. *Nucleic Acids Res*. 2021;49:D1207-D1217. [10.1093/nar/gkaa1043](https://doi.org/10.1093/nar/gkaa1043)
87. Matentzoglou N, Osumi-Sutherland D, Balhoff JP, et al. uPheno 2: Framework for standardised representation of phenotypes across species 2019. [10.7490/f1000research.1116540.1](https://doi.org/10.7490/f1000research.1116540.1)
88. Köhler S, Doelken SC, Ruef BJ, et al. Construction and accessibility of a cross-species phenotype ontology along with gene annotations for biomedical research. *F1000Res*. 2013;2:30. [10.12688/f1000research.2-30.v2](https://doi.org/10.12688/f1000research.2-30.v2)
89. NCBO BioPortal n.d. Accessed July 14, 2023. <https://bioportal.bioontology.org/>
90. Whetzel PL, Noy NF, Shah NH, et al. BioPortal: enhanced functionality via new Web services from the National Center for Biomedical Ontology to access and use ontologies in software applications. *Nucleic Acids Res*. 2011;39:W541-W545. [10.1093/nar/gkr469](https://doi.org/10.1093/nar/gkr469)
91. Nam E, Lee Y-B, Moon C, Chang K-A. Serum tau proteins as potential biomarkers for the assessment of Alzheimer's disease progression. *Int J Mol Sci*. 2020;21. [10.3390/ijms21145007](https://doi.org/10.3390/ijms21145007)
92. Ou Y-N, Xu W, Li J-Q, et al. FDG-PET as an independent biomarker for Alzheimer's biological diagnosis: a longitudinal study. *Alzheimers Res Ther*. 2019;11:57. [10.1186/s13195-019-0512-1](https://doi.org/10.1186/s13195-019-0512-1)
93. Platt B, Drever B, Koss D, et al. Abnormal cognition, sleep, EEG and brain metabolism in a novel knock-in Alzheimer mouse, PLB1. *PLoS One*. 2011;6:e27068. [10.1371/journal.pone.0027068](https://doi.org/10.1371/journal.pone.0027068)
94. Devoy A, Kalmar B, Stewart M, Park H, Burke B, Noy SJ. Humanized mutant FUS drives progressive motor neuron degeneration without aggregation in "FUSDelta14" knockin mice. *Brain*. 2017;140(11):2797-2805.
95. Kumar S, Stecher G, Suleski M, Hedges SB. TimeTree: a resource for timelines, timetrees, and divergence times. *Mol Biol Evol*. 2017;34:1812-1819. [10.1093/molbev/msx116](https://doi.org/10.1093/molbev/msx116)
96. Martin T, Fraser HB. Comparative expression profiling reveals widespread coordinated evolution of gene expression across eukaryotes. *Nat Commun*. 2018;9:4963. [10.1038/s41467-018-07436-y](https://doi.org/10.1038/s41467-018-07436-y)
97. Chen J, Swofford R, Johnson J, et al. A quantitative framework for characterizing the evolutionary history of mammalian gene expression. *Genome Res*. 2019;29:53-63. [10.1101/gr.237636.118](https://doi.org/10.1101/gr.237636.118)
98. Striedter GF. Précis of principles of brain evolution. *Behav Brain Sci*. 2006;29:1-12. [10.1017/S0140525X06009010](https://doi.org/10.1017/S0140525X06009010). discussion 12-36.
99. Patzke N, Spocter MA, Karlsson KÅE, et al. In contrast to many other mammals, cetaceans have relatively small hippocampi that appear to lack adult neurogenesis. *Brain Struct Funct*. 2015;220:361-383. [10.1007/s00429-013-0660-1](https://doi.org/10.1007/s00429-013-0660-1)
100. Schilder BM, Petry HM, Hof PR. Evolutionary shifts dramatically reorganized the human hippocampal complex. *J Comp Neurol*. 2020;528:3143-3170. [10.1002/cne.24822](https://doi.org/10.1002/cne.24822)
101. Barger N, Hanson KL, Teffer K, Schenker-Ahmed NM, Semendeferi K. Evidence for evolutionary specialization in human limbic structures. *Front Hum Neurosci*. 2014;8:277. [10.3389/fnhum.2014.00277](https://doi.org/10.3389/fnhum.2014.00277)
102. Smaers JB, Gómez-Robles A, Parks AN, Sherwood CC. Exceptional evolutionary expansion of prefrontal cortex in great apes and humans. *Curr Biol*. 2017;27:1549. [10.1016/j.cub.2017.05.015](https://doi.org/10.1016/j.cub.2017.05.015)
103. NCBI Resource Coordinators. Database resources of the National Center for biotechnology information. *Nucleic Acids Res*. 2017;45:D12-D17. [10.1093/nar/gkw1071](https://doi.org/10.1093/nar/gkw1071)
104. Schilder BM. Orthogene: Interspecies gene mapping. 2021. [10.18129/B9.bioc.orthogene](https://doi.org/10.18129/B9.bioc.orthogene)
105. Enard W. The molecular basis of human brain evolution. *Curr Biol*. 2016;26:R1109-R1117. [10.1016/j.cub.2016.09.030](https://doi.org/10.1016/j.cub.2016.09.030)
106. Dennis MY, Nuttle X, Sudmant PH, et al. Evolution of human-specific neural SRGAP2 genes by incomplete segmental duplication. *Cell*. 2012;149:912-922. [10.1016/j.cell.2012.03.033](https://doi.org/10.1016/j.cell.2012.03.033)
107. Li J, Pan L, Pembroke WG, et al. Conservation and divergence of vulnerability and responses to stressors between human and mouse astrocytes. *Nat Commun*. 2021;12:3958. [10.1038/s41467-021-24232-3](https://doi.org/10.1038/s41467-021-24232-3)
108. Geirsdottir L, David E, Keren-Shaul H, et al. Cross-Species single-cell analysis reveals divergence of the primate microglia program. *Cell*. 2020;181:746. [10.1016/j.cell.2020.04.002](https://doi.org/10.1016/j.cell.2020.04.002)
109. Sharma K, Bisht K, Eyo UB. A comparative biology of microglia across species. *Front Cell Dev Biol*. 2021;9:652748. [10.3389/fcell.2021.652748](https://doi.org/10.3389/fcell.2021.652748)
110. Berto S, Mendizabal I, Usui N, et al. Accelerated evolution of oligodendrocytes in the human brain. *Proc Natl Acad Sci USA*. 2019;116:24334-24342. [10.1073/pnas.1907982116](https://doi.org/10.1073/pnas.1907982116)
111. Nguyen A, Bionaz M. Analysis of model organism viability through an interspecies pathway comparison pipeline using the dynamic impact approach. *bioRxiv* 2019:2019.12.18.448985. [10.1101/2019.12.18.448985](https://doi.org/10.1101/2019.12.18.448985)
112. Jumper J, Evans R, Pritzel A, et al. Highly accurate protein structure prediction with AlphaFold. *Nature*. 2021;596:583-589. [10.1038/s41586-021-03819-2](https://doi.org/10.1038/s41586-021-03819-2)

113. Lin Z, Akin H, Rao R, et al. Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science*. 2023;379:1123-1130. [10.1126/science.ade2574](https://doi.org/10.1126/science.ade2574)
114. Sundaram L, Gao H, Padigepati SR, et al. Predicting the clinical impact of human mutation with deep neural networks. *Nat Genet*. 2018;50:1161-1170. [10.1038/s41588-018-0167-z](https://doi.org/10.1038/s41588-018-0167-z)
115. Gao H, Hamp T, Ede J, et al. The landscape of tolerated genetic variation in humans and primates. *Science*. 2023;380:eabn8153. [10.1126/science.abn8197](https://doi.org/10.1126/science.abn8197)
116. Avsec Ž, Agarwal V, Visentin D, et al. Effective gene expression prediction from sequence by integrating long-range interactions. *Nat Methods*. 2021;18:1196-1203. [10.1038/s41592-021-01252-x](https://doi.org/10.1038/s41592-021-01252-x)
117. Kelley DR. Cross-species regulatory sequence activity prediction. *PLoS Comput Biol*. 2020;16:e1008050. [10.1371/journal.pcbi.1008050](https://doi.org/10.1371/journal.pcbi.1008050)
118. Mourad R. Semi-supervised learning improves regulatory sequence prediction with unlabeled sequences. *BMC Bioinform*. 2023;24(1). [10.1186/s12859-023-05303-2](https://doi.org/10.1186/s12859-023-05303-2)
119. Li J, Wang J, Zhang P, et al. Deep learning of cross-species single-cell landscapes identifies conserved regulatory programs underlying cell types. *Nat Genet*. 2022;54:1711-1720. [10.1038/s41588-022-01197-7](https://doi.org/10.1038/s41588-022-01197-7)
120. Minnoye L, Taskiran II, Mauduit D, et al. Cross-species analysis of enhancer logic using deep learning. *Genome Res*. 2020;30:1815-1834. [10.1101/gr.260844.120](https://doi.org/10.1101/gr.260844.120)
121. Database APS. AlphaFold Protein Structure Database n.d. Accessed July 14, 2023. <https://alphafold.ebi.ac.uk/>
122. ESM Metagenomic Atlas n.d. Accessed July 14, 2023. <https://esmatlas.com/>
123. Akdel M, Pires DEV, Pardo EP, et al. A structural biology community assessment of AlphaFold2 applications. *Nat Struct Mol Biol*. 2022;29:1056-1067. [10.1038/s41594-022-00849-w](https://doi.org/10.1038/s41594-022-00849-w)
124. Greenwood AK, Montgomery KS, Kauer N, et al. The AD Knowledge Portal: a repository for multi-omic data on Alzheimer's disease and aging. *Curr Protoc Hum Genet*. 2020;108:e105. [10.1002/cphg.105](https://doi.org/10.1002/cphg.105)
125. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet*. 2007;39:17-23. [10.1038/ng1934](https://doi.org/10.1038/ng1934)
126. Bauermeister S, Orton C, Thompson S, et al. The Dementias Platform UK (DPUK) Data Portal. *Eur J Epidemiol*. 2020;35:601-611. [10.1007/s10654-020-00633-4](https://doi.org/10.1007/s10654-020-00633-4)
127. Larkin A, Marygold SJ, Antonazzo G, et al. FlyBase: updates to the *Drosophila melanogaster* knowledge base. *Nucleic Acids Res*. 2021;49:D899-D907. [10.1093/nar/gkaa1026](https://doi.org/10.1093/nar/gkaa1026)
128. The Gene Ontology resource: enriching a GOld mine. *Nucleic Acids Res*. 2021;49:D325-D334.
129. Lonsdale J, Thomas J, Salvatore M, et al. The Genotype-Tissue Expression (GTEx) project. *Nat Genet*. 2013;45:580-585. [10.1038/ng.2653](https://doi.org/10.1038/ng.2653)
130. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*. 2020;581:434-443. [10.1038/s41586-020-2308-7](https://doi.org/10.1038/s41586-020-2308-7)
131. Alanis-Lobato G, Andrade-Navarro MA, Schaefer MH. HIPPIE v2.0: enhancing meaningfulness and reliability of protein-interaction networks. *Nucleic Acids Res*. 2016;45:D408-D414. [10.1093/nar/gkw985](https://doi.org/10.1093/nar/gkw985)
132. Keane TM, Goodstadt L, Danecek P. Mouse genomic variation and its effect on phenotypes and gene regulation. *Nature*. 2011;477:289-294. [10.1038/nature10413](https://doi.org/10.1038/nature10413)
133. Lindsay S, Copp AJ. MRC-wellcome trust human developmental biology resource: enabling studies of human developmental gene expression. *Trends Genet*. 2005;21:586-590. [10.1016/j.tig.2005.08.011](https://doi.org/10.1016/j.tig.2005.08.011)
134. Das S, Abou-Haidar R, Rabalais H, et al. The C-BIG repository: an institution-level open science platform. *Neuroinformatics*. 2022;20:139-153. [10.1007/s12021-021-09516-9](https://doi.org/10.1007/s12021-021-09516-9)
135. Ochoa D, Hercules A, Carmona M, et al. Open Targets Platform: supporting systematic drug-target identification and prioritisation. *Nucleic Acids Res*. 2021;49:D1302-D1310. [10.1093/nar/gkaa1027](https://doi.org/10.1093/nar/gkaa1027)
136. Safaei J, Mañuch J, Gupta A, Stacho L, Pelech S. Prediction of 492 human protein kinase substrate specificities. *Proteome Sci*. 2011;9(Suppl 1):S6. [10.1186/1477-5956-9-S1-S6](https://doi.org/10.1186/1477-5956-9-S1-S6)
137. Hornbeck PV, Zhang B, Murray B, Kornhauser JM, Latham V, Skrzypek E. PhosphoSitePlus, 2014: mutations, PTMs and recalibrations. *Nucleic Acids Res*. 2015;43:D512-D520. [10.1093/nar/gku1267](https://doi.org/10.1093/nar/gku1267)
138. Liu Z, Wang Y, Gao T, et al. CPLM: a database of protein lysine modifications. *Nucleic Acids Res*. 2014;42:D531-D536. [10.1093/nar/gkt1093](https://doi.org/10.1093/nar/gkt1093)
139. Yu K, Zhang Q, Liu Z, et al. qPhos: a database of protein phosphorylation dynamics in humans. *Nucleic Acids Res*. 2019;47:D451-D458. [10.1093/nar/gky1052](https://doi.org/10.1093/nar/gky1052)
140. Yu K, Wang Y, Zheng Y, et al. qPTM: an updated database for PTM dynamics in human, mouse, rat and yeast. *Nucleic Acids Res*. 2023;51:D479-D487. [10.1093/nar/gkac820](https://doi.org/10.1093/nar/gkac820)
141. Jassal B, Matthews L, Viteri G, et al. The reactome pathway knowledgebase. *Nucleic Acids Res*. 2020;48:D498-D503. [10.1093/nar/gkz1031](https://doi.org/10.1093/nar/gkz1031)
142. Burley SK, Bhikadiya C, Bi C, et al. RCSB Protein Data Bank: powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences. *Nucleic Acids Res*. 2021;49:D437-D451. [10.1093/nar/gkaa1038](https://doi.org/10.1093/nar/gkaa1038)
143. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779. [10.1371/journal.pmed.1001779](https://doi.org/10.1371/journal.pmed.1001779)
144. O'Shea O, Abranches E. UK stem cell bank. *Stem Cell Res*. 2020;49:102019. [10.1016/j.scr.2020.102019](https://doi.org/10.1016/j.scr.2020.102019)
145. Zhang H, Loriaux P, Eng J, et al. UniPep—a database for human N-linked glycosites: a resource for biomarker discovery. *Genome Biol*. 2006;7:R73. [10.1186/gb-2006-7-8-R73](https://doi.org/10.1186/gb-2006-7-8-R73)
146. Harris TW, Arnaboldi V, Cain S, et al. WormBase: a modern model organism information resource. *Nucleic Acids Res*. 2020;48:D762-D767. [10.1093/nar/gkz920](https://doi.org/10.1093/nar/gkz920)
147. Agoston DV. How to translate time? the temporal aspect of human and rodent biology. *Front Neurol*. 2017;8:92. [10.3389/fneur.2017.00092](https://doi.org/10.3389/fneur.2017.00092)
148. Perel P, Roberts I, Sena E, et al. Comparison of treatment effects between animal experiments and clinical trials: systematic review. *BMJ*. 2007;334:197. [10.1136/bmj.39048.407928.BE](https://doi.org/10.1136/bmj.39048.407928.BE)
149. van der Worp HB, Howells DW, Sena ES, et al. Can animal models of disease reliably inform human studies? *PLoS Med*. 2010;7:e1000245. [10.1371/journal.pmed.1000245](https://doi.org/10.1371/journal.pmed.1000245)
150. Baker RE, Peña J-M, Jayamohan J, Jerusalem A. Mechanistic models versus machine learning, a fight worth fighting for the biological community? *Biol Lett*. 2018;14: 20170660. [10.1098/rsbl.2017.0660](https://doi.org/10.1098/rsbl.2017.0660)
151. Mirams GR, Pathmanathan P, Gray RA, Challenor P, Clayton RH. Uncertainty and variability in computational and mathematical models of cardiac physiology. *J Physiol*. 2016;594:6833-6847. [10.1113/JP271671](https://doi.org/10.1113/JP271671)
152. Vanlier J, Tiemann CA, Hilbers PAJ, van Riel NAW. An integrated strategy for prediction uncertainty analysis. *Bioinformatics*. 2012;28:1130-1135. [10.1093/bioinformatics/bts088](https://doi.org/10.1093/bioinformatics/bts088)
153. Vanlier J, Tiemann CA, Hilbers PAJ, van Riel NAW. Parameter uncertainty in biochemical models described by ordinary differential equations. *Math Biosci*. 2013;246:305-314. [10.1016/j.mbs.2013.03.006](https://doi.org/10.1016/j.mbs.2013.03.006)
154. Rozendaal YJW, Wang Y, Paalvast Y, et al. In vivo and in silico dynamics of the development of Metabolic Syndrome. *PLoS Comput Biol*. 2018;14:e1006145. [10.1371/journal.pcbi.1006145](https://doi.org/10.1371/journal.pcbi.1006145)

155. Tiemann CA, Vanlier J, Oosterveer MH, Groen AK, Hilbers PAJ, van Riel NAW. Parameter trajectory analysis to identify treatment effects of pharmacological interventions. *PLoS Comput Biol*. 2013;9:e1003166. [10.1371/journal.pcbi.1003166](https://doi.org/10.1371/journal.pcbi.1003166)
156. Breiman L. Statistical modeling: the two cultures (with comments and a rejoinder by the author). *SSO Schweiz Monatsschr Zahnheilkd*. 2001;16:199-231. [10.1214/ss/1009213726](https://doi.org/10.1214/ss/1009213726)
157. Luechtefeld T, Marsh D, Rowlands C, Hartung T. Machine Learning of Toxicological Big Data Enables Read-Across Structure Activity Relationships (RASAR) outperforming animal test reproducibility. *Toxicol Sci*. 2018;165:198-212. [10.1093/toxsci/kfy152](https://doi.org/10.1093/toxsci/kfy152)
158. Rhrrisorakrai K, Belcastro V, Bilal E, et al. Understanding the limits of animal models as predictors of human biology: lessons learned from the sbv IMPROVER species translation challenge. *Bioinformatics*. 2015;31:471-483. [10.1093/bioinformatics/btu611](https://doi.org/10.1093/bioinformatics/btu611)
159. Anvar SY, Tucker A, Vinciotti V, et al. Interspecies translation of disease networks increases robustness and predictive accuracy. *PLoS Comput Biol*. 2011;7:e1002258. [10.1371/journal.pcbi.1002258](https://doi.org/10.1371/journal.pcbi.1002258)
160. Brubaker DK, Proctor EA, Haigis KM, Lauffenburger DA. Computational translation of genomic responses from experimental model systems to humans. *PLoS Comput Biol*. 2019;15:e1006286. [10.1371/journal.pcbi.1006286](https://doi.org/10.1371/journal.pcbi.1006286)
161. Normand R, Du W, Briller M, et al. Found in translation: a machine learning model for mouse-to-human inference. *Nat Methods*. 2018;15:1067-1073. [10.1038/s41592-018-0214-9](https://doi.org/10.1038/s41592-018-0214-9)
162. Perosa V, Scherlek AA, Kozberg MG, et al. Deep learning assisted quantitative assessment of histopathological markers of Alzheimer's disease and cerebral amyloid angiopathy. *Acta Neuropathol Commun*. 2021;9:141. [10.1186/s40478-021-01235-1](https://doi.org/10.1186/s40478-021-01235-1)
163. Signaevsky M, Prastawa M, Farrell K, et al. Artificial intelligence in neuropathology: deep learning-based assessment of Tauopathy. *Lab Invest*. 2019;99:1019-1029. [10.1038/s41374-019-0202-4](https://doi.org/10.1038/s41374-019-0202-4)
164. Xie C, Zhuang X-X, Niu Z, et al. Amelioration of Alzheimer's disease pathology by mitophagy inducers identified via machine learning and a cross-species workflow. *Nat Biomed Eng*. 2022;6:76-93. [10.1038/s41551-021-00819-5](https://doi.org/10.1038/s41551-021-00819-5)
165. Stumpf PS, Du X, Imanishi H, et al. Transfer learning efficiently maps bone marrow cell types from mouse to human using single-cell RNA sequencing. *Commun Biol*. 2020;3:736. [10.1038/s42003-020-01463-6](https://doi.org/10.1038/s42003-020-01463-6)
166. Eraslan G, Avsec Ž, Gagneur J, Theis FJ. Deep learning: new computational modelling techniques for genomics. *Nat Rev Genet*. 2019;20:389-403. [10.1038/s41576-019-0122-6](https://doi.org/10.1038/s41576-019-0122-6)
167. Argelaguet R, Cuomo ASE, Stegle O, Marioni JC. Computational principles and challenges in single-cell data integration. *Nat Biotechnol*. 2021;39:1202-1215. [10.1038/s41587-021-00895-7](https://doi.org/10.1038/s41587-021-00895-7)
168. Cao Z-J, Wei L, Lu S, Yang D-C, Gao G. Searching large-scale scRNA-seq databases via unbiased cell embedding with Cell BLAST. *Nat Commun*. 2020;11:3458. [10.1038/s41467-020-17281-7](https://doi.org/10.1038/s41467-020-17281-7)
169. Xiang R, Wang W, Yang L, Wang S, Xu C, Chen X. A comparison for dimensionality reduction methods of single-cell RNA-seq data. *Front Genet*. 2021;12:646936. [10.3389/fgene.2021.646936](https://doi.org/10.3389/fgene.2021.646936)
170. Lazić SE. The problem of pseudoreplication in neuroscientific studies: is it affecting your analysis? *BMC Neurosci*. 2010;11:5. [10.1186/1471-2202-11-5](https://doi.org/10.1186/1471-2202-11-5)
171. Squair JW, Gautier M, Kathe C, et al. Confronting false discoveries in single-cell differential expression. *Nat Commun*. 2021;12:5692. [10.1038/s41467-021-25960-2](https://doi.org/10.1038/s41467-021-25960-2)
172. Murphy AE, Skene NG. A balanced measure shows superior performance of pseudobulk methods in single-cell RNA-sequencing analysis. *Nat Commun*. 2022;13:7851. [10.1038/s41467-022-35519-4](https://doi.org/10.1038/s41467-022-35519-4)
173. Lotfollahi M, Wolf FA, Theis FJ. scGen predicts single-cell perturbation responses. *Nat Methods*. 2019;16:715-721. [10.1038/s41592-019-0494-8](https://doi.org/10.1038/s41592-019-0494-8)
174. Lotfollahi M, Susmelj AK, De Donno C, et al. Learning interpretable cellular responses to complex perturbations in high-throughput screens. *bioRxiv* 2021:2021.04.14.439903. [10.1101/2021.04.14.439903](https://doi.org/10.1101/2021.04.14.439903)
175. Cui H, Wang C, Maan H, Pang K, Luo F, Wang B, scGPT: Towards Building a Foundation Model for Single-Cell Multi-omics Using Generative AI. *bioRxiv* 2023:2023.04.30.538439. [10.1101/2023.04.30.538439](https://doi.org/10.1101/2023.04.30.538439)
176. Yang F, Wang W, Wang F, et al. scBERT as a large-scale pretrained deep language model for cell type annotation of single-cell RNA-seq data. *Nature Machine Intelligence*. 2022;4:852-866. [10.1038/s42256-022-00534-z](https://doi.org/10.1038/s42256-022-00534-z)
177. Theodoris CV, Xiao L, Chopra A, et al. Transfer learning enables predictions in network biology. *Nature*. 2023;618:616-624. [10.1038/s41586-023-06139-9](https://doi.org/10.1038/s41586-023-06139-9)
178. Zhang X-M, Liang L, Liu L, Tang M-J. Graph neural networks and their current applications in bioinformatics. *Front Genet*. 2021;12:690049. [10.3389/fgene.2021.690049](https://doi.org/10.3389/fgene.2021.690049)
179. Burkhart JG, Wu G, Song X, et al. Biology-inspired graph neural network encodes reactome and reveals biochemical reactions of disease. *Patterns Prejudice*. 2023;4:100758. [10.1016/j.patter.2023.100758](https://doi.org/10.1016/j.patter.2023.100758)
180. You R, Yao S, Mamitsuka H, Zhu S. DeepGraphGO: graph neural network for large-scale, multispecies protein function prediction. *Bioinformatics*. 2021;37:i262-i271. [10.1093/bioinformatics/btab270](https://doi.org/10.1093/bioinformatics/btab270)
181. Ktena SI, Parisot S, Ferrante E, et al. Metric learning with spectral graph convolutions on brain connectivity networks. *Neuroimage*. 2018;169:431-442. [10.1016/j.neuroimage.2017.12.052](https://doi.org/10.1016/j.neuroimage.2017.12.052)
182. Song T-A, Chowdhury SR, Yang F, et al. Graph convolutional neural networks for Alzheimer's disease classification. In: 2019 IEEE 16th International Symposium on Biomedical Imaging (ISBI 2019). IEEE; 2019:414-417. [10.1109/ISBI.2019.8759531](https://doi.org/10.1109/ISBI.2019.8759531)
183. Klepl D, He F, Wu M, Blackburn DJ, Sarrigiannis P. EEG-based graph neural network classification of alzheimer's disease: an empirical evaluation of functional connectivity methods. *IEEE Trans Neural Syst Rehabil Eng*. 2022;30:2651-2660. [10.1109/TNSRE.2022.3204913](https://doi.org/10.1109/TNSRE.2022.3204913)
184. Rao A, Vg S, Joseph T, Kotte S, Sivadasan N, Srinivasan R. Phenotype-driven gene prioritization for rare diseases using graph convolution on heterogeneous networks. *BMC Med Genomics*. 2018;11:57. [10.1186/s12920-018-0372-8](https://doi.org/10.1186/s12920-018-0372-8)
185. Liu Q, Hu Z, Jiang R, Zhou M. DeepCDR: a hybrid graph convolutional network for predicting cancer drug response. *Bioinformatics*. 2020;36:i911-i918. [10.1093/bioinformatics/btaa822](https://doi.org/10.1093/bioinformatics/btaa822)
186. Singha M, Pu L, Shawky A-E-M, et al. GraphGR: A graph neural network to predict the effect of pharmacotherapy on the cancer cell growth. *bioRxiv* 2020:2020.05.20.107458. [10.1101/2020.05.20.107458](https://doi.org/10.1101/2020.05.20.107458)
187. Kazi A, Shekarforoush S, Arvind Krishna S, et al. *Graph Convolution Based Attention Model for Personalized Disease Prediction*. *Medical Image Computing and Computer Assisted Intervention - MICCAI 2019*. Springer International Publishing; 2019:122-130. [10.1007/978-3-030-32251-9_14](https://doi.org/10.1007/978-3-030-32251-9_14)
188. Wang T, Shao W, Huang Z, et al. MOGONET integrates multi-omics data using graph convolutional networks allowing patient classification and biomarker identification. *Nat Commun*. 2021;12:3445. [10.1038/s41467-021-23774-w](https://doi.org/10.1038/s41467-021-23774-w)
189. Goodman B, Flaxman S. European union regulations on algorithmic decision-making and a "right to explanation. *AIMag*. 2017;38:50-57. [10.1609/aimag.v38i3.2741](https://doi.org/10.1609/aimag.v38i3.2741)
190. Chen JH, Asch SM. Machine learning and prediction in medicine—beyond the peak of inflated expectations. *N Engl J Med*. 2017;376:2507-2509. [10.1056/NEJMp1702071](https://doi.org/10.1056/NEJMp1702071)
191. Wang F, Kaushal R, Khullar D. Should health care demand interpretable artificial intelligence or accept "black box" medicine? *Ann Intern Med*. 2020;172:59-60. [10.7326/M19-2548](https://doi.org/10.7326/M19-2548)

192. Heaven D. Why deep-learning AIs are so easy to fool. *Nature*. 2019;574:163-166. [10.1038/d41586-019-03013-5](https://doi.org/10.1038/d41586-019-03013-5)
193. Lapuschkin S, Wäldchen S, Binder A, Montavon G, Samek W, Müller K-R. Unmasking Clever Hans predictors and assessing what machines really learn. *Nat Commun*. 2019;10:1096. [10.1038/s41467-019-08987-4](https://doi.org/10.1038/s41467-019-08987-4)
194. Barredo Arrieta A, Díaz-Rodríguez N, Del Ser J, et al. Explainable Artificial Intelligence (XAI): concepts, taxonomies, opportunities and challenges toward responsible AI. *Inf Fusion*. 2020;58:82-115. [10.1016/j.inffus.2019.12.012](https://doi.org/10.1016/j.inffus.2019.12.012)
195. Finlayson SG, Bowers JD, Ito J, Zittrain JL, Beam AL, Kohane IS. Adversarial attacks on medical machine learning. *Science*. 2019;363:1287-1289. [10.1126/science.aaw4399](https://doi.org/10.1126/science.aaw4399)
196. Martens D, Vanthienen J, Verbeke W, Baesens B. Performance of classification models from a user perspective. *Decis Support Syst*. 2011;51:782-793. [10.1016/j.dss.2011.01.013](https://doi.org/10.1016/j.dss.2011.01.013)
197. Guidotti R, Monreale A, Ruggieri S, Turini F, Giannotti F, Pedreschi D. A survey of methods for explaining black box models. *ACM Comput Surv*. 2018;51:1-42. [10.1145/3236009](https://doi.org/10.1145/3236009)
198. Wiens J, Saria S, Sendak M, et al. Do no harm: a roadmap for responsible machine learning for health care. *Nat Med*. 2019;25:1337-1340. [10.1038/s41591-019-0548-6](https://doi.org/10.1038/s41591-019-0548-6)
199. Tjoa E, Guan C. A survey on explainable artificial intelligence (XAI): toward medical XAI. *IEEE Trans Neural Netw Learn Syst*. 2021;32:4793-4813. [10.1109/TNNLS.2020.3027314](https://doi.org/10.1109/TNNLS.2020.3027314)
200. Jiménez-Luna J, Grisoni F, Schneider G. Drug discovery with explainable artificial intelligence. *Nature Machine Intelligence*. 2020;2:573-584. [10.1038/s42256-020-00236-4](https://doi.org/10.1038/s42256-020-00236-4)
201. Kirboğa KK, Abbasi S, Küçüksille EU. Explainability and white box in drug discovery. *Chem Biol Drug Des*. 2023;102:217-233. [10.1111/cbdd.14262](https://doi.org/10.1111/cbdd.14262)
202. Vo TH, Nguyen NTK, Kha QH, Le NQK. On the road to explainable AI in drug-drug interactions prediction: a systematic review. *Comput Struct Biotechnol J*. 2022;20:2112-2123. [10.1016/j.csbj.2022.04.021](https://doi.org/10.1016/j.csbj.2022.04.021)
203. van der Velden BHM, Kuijf HJ, Gilhuijs KGA, Viergever MA. Explainable artificial intelligence (XAI) in deep learning-based medical image analysis. *Med Image Anal*. 2022;79:102470. [10.1016/j.media.2022.102470](https://doi.org/10.1016/j.media.2022.102470)
204. Cole J, Wood D, Booth T. Visual attention as a model for interpretable neuroimage classification in dementia. *Alzheimers Dement*. 2020;16:e037351. [10.1002/alz.037351](https://doi.org/10.1002/alz.037351)
205. Essemli A, St-Onge E, Descoteaux M, Jodoin P-M. Understanding Alzheimer disease's structural connectivity through explainable AI. In: Arbel T, Ben Ayed I, de Bruijne M, Descoteaux M, Lombaert H, Pal C, eds. *Proceedings of the Third Conference on Medical Imaging with Deep Learning*. PMLR; 217-229. PMLR; 06-08 Jul 2020.
206. El-Sappagh S, Alonso JM, Islam SMR, Sultan AM, Kwak KS. A multilayer multimodal detection and prediction model based on explainable artificial intelligence for Alzheimer's disease. *Sci Rep*. 2021;11:2660. [10.1038/s41598-021-82098-3](https://doi.org/10.1038/s41598-021-82098-3)
207. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562:203-209. [10.1038/s41586-018-0579-z](https://doi.org/10.1038/s41586-018-0579-z)
208. England G. Newborn genomes programme. Genomics England. 2022. Accessed July 14, 2023. <https://www.genomicsengland.co.uk/initiatives/newborns>
209. Ritchie MD, Holzinger ER, Li R, Pendergrass SA, Kim D. Methods of integrating data to uncover genotype-phenotype interactions. *Nat Rev Genet*. 2015;16:85-97. [10.1038/nrg3868](https://doi.org/10.1038/nrg3868)
210. Kulasingam V, Pavlou MP, Diamandis EP. Integrating high-throughput technologies in the quest for effective biomarkers for ovarian cancer. *Nat Rev Cancer*. 2010;10:371-378. [10.1038/nrc2831](https://doi.org/10.1038/nrc2831)
211. Nariai N, Kolaczyk ED, Kasif S. Probabilistic protein function prediction from heterogeneous genome-wide data. *PLoS One*. 2007;2:e337. [10.1371/journal.pone.0000337](https://doi.org/10.1371/journal.pone.0000337)
212. Zhang S, Fan R, Liu Y, Chen S, Liu Q, Zeng W. Applications of transformer-based language models in bioinformatics: a survey. *Bioinform Adv*. 2023;3:vbad001. [10.1093/bioadv/vbad001](https://doi.org/10.1093/bioadv/vbad001)
213. Haupt CE, Marks M. AI-Generated Medical Advice-GPT and Beyond. *JAMA*. 2023;329:1349-1350. [10.1001/jama.2023.5321](https://doi.org/10.1001/jama.2023.5321)
214. Cheng K, Guo Q, He Y, Lu Y, Gu S, Wu H. Exploring the Potential of GPT-4 in biomedical engineering: the dawn of a new era. *Ann Biomed Eng*. 2023;51:1645-1653. [10.1007/s10439-023-03221-1](https://doi.org/10.1007/s10439-023-03221-1)
215. Singhal K, Azizi S, Tu T, et al. Large language models encode clinical knowledge. *Nature*. 2023;620:172-180. [10.1038/s41586-023-06291-2](https://doi.org/10.1038/s41586-023-06291-2)
216. Zhang K, Yu J, Yan Z, et al. BiomedGPT: A Unified and Generalist Biomedical Generative Pre-trained Transformer for Vision, Language, and Multimodal Tasks. arXiv [csCL]. 2023.
217. BioMedLM. BioMedLM n.d. Accessed July 29, 2023. <https://github.com/stanford-crfm/BioMedLM>
218. Jin Q, Yang Y, Chen Q, Lu Z. GeneGPT: Augmenting Large Language Models with Domain Tools for Improved Access to Biomedical Information. ArXiv 2023.
219. Luo R, Sun L, Xia Y, et al. BioGPT: generative pre-trained transformer for biomedical text generation and mining. *Brief Bioinform*. 2022;23:bbac409. [10.1093/bib/bbac409](https://doi.org/10.1093/bib/bbac409)
220. Gu Y, Tinn R, Cheng H, et al. Domain-specific language model pre-training for biomedical natural language processing. arXiv [csCL]. 2020.
221. Yasunaga M, Leskovec J, Ling P. LinkBERT: Pretraining Language Models with Document Links. arXiv [csCL]. 2022.
222. Taylor R, Kardas M, Cucurull G, et al. Galactica: A Large Language Model for Science. arXiv [csCL]. 2022.
223. Shin H-C, Zhang Y, Bakhturina E, et al. BioMegatron: Larger Biomedical Domain Language Model. arXiv [csCL]. 2020.
224. Auto-GPT: An experimental open-source attempt to make GPT-4 fully autonomous. Github; n.d.

SUPPORTING INFORMATION

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

How to cite this article: Marzi SJ, Schilder BM, Nott A, et al. Artificial intelligence for neurodegenerative experimental models. *Alzheimer's Dement*. 2023;19:5970-5987. <https://doi.org/10.1002/alz.13479>