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Computational whole-body-exposome models for global precision brain health

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The worldwide rise of neurological and psychiatric conditions poses major challenges. However, current global research remains fragmented, dominated by limited cohorts and poorly integrated datasets that disconnect whole-body health, exposome, and brain health. Theories rarely unify brain measures with extracerebral factors or capture heterogeneity in individual trajectories. We introduce multimodal diversity, a non-linear, non-simplistic causal and ecological construct integrating data representation, whole-body and exposomic factors, and computational modeling to address this situated, embedded, and embodied complexity. This heuristic metamodel integrates global, multilevel data into personalized predictions fostering population inclusion, multimodal integration, diagnostic precision, and equitable, context-sensitive advances in brain health.

The global prevalence of neurological, neurodevelopmental, neurodegenerative, and psychiatric disorders has risen significantly[1–3]. Epidemiological, social, and economic estimates suggest that these diseases pose significant burdens and financial costs, impacting human health and societal welfare[1,4]. Together, they heighten the risk of comorbidity, chronic systemic diseases and mortality[3]. Brain disorders remain among the top ten leading causes of disability worldwide[5,6]. Neurological conditions were the most prevalent of the leading causes of disability in 2021, accounting for 443 million disability-adjusted life years (DALYs)[1,5,6]. The number of people living with dementia is projected to rise from 57.4 million in 2019 to 152.8 million by 2050, with the highest increase anticipated in low- and middle-income countries[7]. DALYs due to Alzheimer's disease (AD) and Alzheimer's disease and related dementias (ADRD) worldwide increased from 9.66 million to 25.28 million between 1990 and 2019[1]. Psychiatric conditions accounted for 125.3 million DALYs[4] in 2019. Between 1990 and 2019, DALYs rates for psychiatric conditions in adults increased from 803.8 to 833.2 per 100,000[8]. These stark estimates have spurred international calls to advance brain health through enhanced research, public health initiatives, policy development, targeted interventions, and improved treatments. The scientific fields require more diverse, complex, multilevel, accurate, global, robust, and multimodal approaches[7,9–13].

Multimodal diversity in brain health[12] (Box 1, Fig. 1) refers here to a multilevel construct that combines three dimensions (Table 1): (i) *data representation*, encompassing heterogeneous sources ranging from omics to neuroimaging, behavioral, and clinical indicators; (ii) *multilevel integration of brain and extracerebral influences*, including whole-body health metrics (e.g., cardiometabolic status, immune function, gut microbiome, interoception) and environmental factors (physical and social determinants or exposome); and (iii) *computational architectures*, capable of handling the intrinsic multimodal complexity, heterogeneity, and probabilistic trajectories inherent to such diverse

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BOX 1
Multimodal Diversity

Multimodal diversity refers to different layers of precision brain health, encompassing data representation, multiple modality integration, and computational approaches. In socio-political terms, diversity often highlights inclusion across demographic groups (e.g., race, ethnicity, sex), but here the term extends to heterogeneity in data and methods across multiple domains[12].

Data representation: Refers to the inclusion of data from global populations (especially those historically underrepresented) in brain health research. It entails collecting and analyzing information from diverse regions and cultures, rather than focusing only on high-income majority cohorts. This approach is crucial not just for ethical representation but for scientific validity: including underrepresented groups reveals unique genetic, environmental, and social factors influencing brain health that may be missed in homogeneous samples. Embracing data diversity helps move beyond one-size-fits-all models and enhances global understanding of brain disorders, enabling more effective and equitable interventions.

Multimodal data integration: It involves combining multiple dimensions of health-related data to capture the full context of brain health. This includes traditional brain health metrics (e.g., brain imaging and cognitive assessments) alongside whole-body health indicators (e.g., cardiovascular and metabolic markers, omics, interoception) and exposome factors (cumulative physical and social exposures across the lifespan). Merging brain data with systemic health and environmental context allows researchers to capture complex interactions between neural processes, bodily conditions, and external influences.

Computational metamodels: Addressing multimodal diversity requires advanced computational structures. These are metamodels designed to synthesize and integrate heterogeneous data. Such a framework should incorporate heterogeneity-robust methods to accommodate diverse data distributions, ensuring models remain generalizable across populations. It emphasizes extracerebral modeling and integration, meaning algorithms jointly model brain metrics alongside extracerebral factors (e.g., environmental exposures, whole-body health measures). Additionally, individual trajectories are accounted for by longitudinal and dynamic modeling, capturing how a person's brain health changes over time under various influences. Together, these strategies form an metamodel encoding multimodal diversity.

data. Unlike traditional approaches that consider single modalities or levels of analysis, multimodal diversity emphasizes synergistic modeling that integrates biological, systemic, and environmental measures to generate more accurate, and individualized predictions[12–16]. This definition transcends traditional notions of diversity (often confined to gender, ethnicity, race, or minority status) by focusing on complex model interactions that exhibit significant variation across individuals and populations due to stochastic and probabilistic dynamics (i.e., the random but structured processes driving heterogeneous outcomes across the lifespan[16]).

Theoretically and methodologically, this concept emphasizes synergistic computational modeling and integration of multimodal data[10,12–16] in neurology and psychiatry[11,17–24]. There are urgent calls to address methodological barriers, global collaboration, and improved computational models[10,15,17,25–31]. However, challenges related to underrepresentation, the reliance on single-level approaches in global settings (e.g., those limited to a single data type such as genetic variants, or neuroimaging), and the need for theoretical frameworks that integrate biological, behavioral, and environmental layers must be addressed jointly[12].

This perspective begins by highlighting how the limited funding, insufficient samples representation, inadequate global data sharing, and the absence of unified theoretical frameworks undermines advancements in brain health. While our framework is focused mainly on brain health, we use AD/ADRD as an illustrative case, while also highlighting applications to psychiatric and neurodevelopmental disorders. We propose a heuristic framework that emphasizes integrating global and multimodal data and theoretical models to tackle the core challenges for computational modeling. We discuss the core ethical, social, and technical barriers of this initiative. Finally, we outline a future agenda and recommendations to enhance computational models, deep phenotyping, neuroecological links, transdisciplinary collaboration, and inclusive brain health research.

Why multimodal diversity is essential for precision brain health

Our perspective focuses on some of the main challenges of precision in brain health driven by funding constraints, methodological hurdles, and broader scientific infrastructures. A core barrier is the limited funding and consequent lack of substantial multimodal data in global settings. Current research approaches often fail to represent diverse populations and incorporate various data types[32,33], leading to simplified predictions[34,35] and restricted applicability[11,36]. By constraining the focus to single data types[29,37] and excluding environmental-biology interactions, approaches can neglect important factors that impact brain health[38–41].

First, limited representation of diverse populations[17,18,22,23] leads to a lack of generalizability[24], decreasing the effectiveness of diagnosis and treatments[12,24,25]. Genome-wide association studies (GWAS) and polygenic risk studies are predominantly based on European descent populations, biasing the identification of risk factors[36,42–46] and hindering tailored prediction models and treatments[29,37]. Ancestry diversity affects the understanding of disease prevalence, genetic and biological mechanisms, and brain phenotypes[47]. Reduced population diversity limits specificity[48–51], neglecting complex biological mechanisms[52] and diminishing clinical insights[50], risk identification[53,54], cognitive evaluations[53,55], and neuroimaging characterization[56]. These gaps have a negative impact on accurate diagnosis, biomarker development, and successful clinical trials[36,49,57,58].

Multiple factors contribute to increased data variability in underrepresented populations from Latin America, Africa, Middle East and Asia. These populations often exhibit more significant genetic admixture[51,59] than in the U.S. or European populations. Greater multimodal heterogeneity is also evident, particularly in whole-body and environmental data[12,60]. Populations in the Global South frequently experience higher burdens of cardiometabolic conditions[61] and show stronger biological embedding of structural inequalities. Most predictive models are trained on large U.S. and European datasets. These problems are observed across Global South populations and minorities within countries such as the US[62,63]. When applied to underrepresented populations with different data distributions, these models often exhibit poor generalizability and higher misclassification rates[34,56,62].

Second, most research in brain health concentrates on isolated genetic and brain data[13,49,64], neglecting the influence of whole-body health and multi-omics[60,65]. Approaches usually focus on single-level

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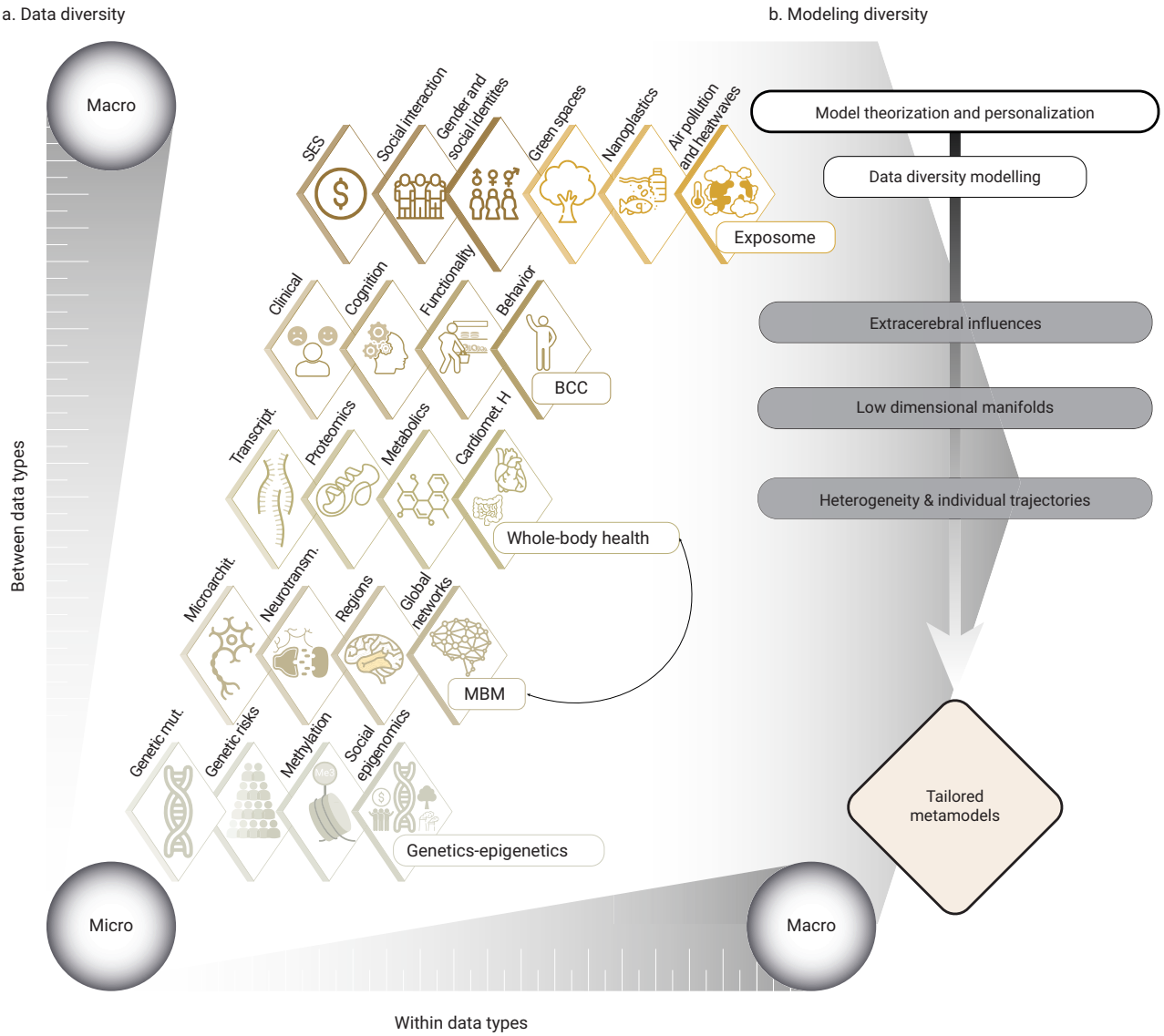

Fig. 1 | Multimodal diversity framework. The figure illustrates the dimensions of multimodal diversity, showcasing data diversity (**a**) and its integration into personalized models through advanced modeling approaches (**b**). **a** depicts data diversity with the hierarchical data layers contributing to brain health determinants, spanning micro- to macro-levels between and within data types. The first level focuses on genetic and epigenetic factors, including genetic risks, mutations, DNA methylation, and social epigenomics. The second level represents multimodal brain models (MBM), encompassing brain microarchitecture, neurotransmission, structures, functions, and global networks. The third level integrates whole-body biology, combining multi-omics data such as transcriptomics, proteomics, metabolomics, and microbiomics with systemic health indicators like cardiometabolic health. The fourth level incorporates behavioral, cognitive, and clinical data (BCC). The fifth level includes exposome factors, such as social determinants (e.g., socioeconomic status, social interactions, and social identities) and physical exposures (e.g., green spaces, nanoplastics, air pollution, and heatwaves). **b** outlines the diversity in modeling approaches required to effectively integrate multimodal data diversity into brain health research. It emphasizes data diversity, the generation of low-dimensional brain representations, the incorporation of extracerebral influences such as whole-body health and exposome data, and the need to account for heterogeneity and individual trajectories. This framework highlights the potential of multimodal diversity to advance precision medicine by addressing complex brain health determinants and personalizing interventions. *SES* socioeconomic status.

explanations, such as genetics[36,42–46] while overlooking biology-environment interactions[14,15,64] or vice versa. Although some models (see below) emphasize how the body serves as a dynamic interface linking the environment and the brain, most existing research remains predominantly theoretical. The exposome[13] refers to the totality of exposures an individual experiences throughout their lifetime encompassing physical (e.g., pollutants, heat waves) and social influences (socioeconomic status, political stress, loneliness, poverty, and cultural factors). The exposome has only recently begun to be applied to brain health[9,13,58] with few examples combining it with genetics, whole-body health, and brain function[10,66,67]. These brain-body-environment interactions require new conceptual models[9,68] for data integration[69,70]. How to systematically model extracerebral factors is poorly understood, limiting predictive accuracy[69]. Models that rely on averages frequently miss critical individual differences, leading to inaccurate predictions, especially in diverse populations[34]. A metamodel may enables a comprehensive understanding of brain health by integrating biology-environment interactions, and population heterogeneity[15,71], informing global health policies and advancing precision medicine[72,73].

Third, computational modeling often fails to integrate global data and account for heterogeneity, thereby hampering the development of tailored diagnostic tools and treatments[34,35]. The under-representation of non-White and diverse populations in global

Table 1 | Challenges and potential solutions for multimodal diversity in precision brain health

Domain	Challenges and limitations	Potential solutions
1. Data representation	- Underrepresentation of global and minority populations in datasets. - Bias toward US/European ancestry in genetics, imaging, and clinical cohorts. - Reduced generalizability of predictive models due to narrow population samples.	- Expand and integrate datasets to include diverse ancestries, socioeconomic backgrounds, and environmental contexts. - Promote equity-driven data collection strategies, particularly in the Global South. - Implement deep phenotyping across different populations to capture heterogeneity and unique risk/protective factors.
2. Multimodal integration of extracerebral measures	- Brain health research overly focused on brain-specific measures, neglecting systemic, exposome, and whole-body interactions. - Limited frameworks for modeling biology- environment interactions. - Sparse integration of omics, cardiovascular, metabolic, and environmental data in brain health models.	- Systematic integration of multimodal data, combining brain, body, and exposome metrics. - Leverage organ clocks, multi-omics, and exposome profiling to capture systemic and environmental impacts on brain health. - Adopt ecological and One Health perspectives to link social, environmental, and biological domains in brain health.
3. Computational and theoretical structures supporting diversity	- Existing models mainly based on low-dimensional, single-domain data. - Poor adaptability to heterogeneity and individual variability. - Lack of temporal integration between brain dynamics, extracerebral influences, and environmental exposures in predictive modeling.	- Develop multimodal metamodels combining: (i) spatiotemporal dimensionality reduction to generate low-dimensional latent representations of brain-body-exposome dynamics; (ii) biophysical whole-brain generative models to integrate multimodal biological measures; (iii) embodied models linking extracerebral (organ, exposome) states to brain dynamics; and (iv) Digital twins and probabilistic frameworks to model heterogeneous individual trajectories across the lifespan.

datasets compromises the generalizability, fairness, and clinical utility of artificial intelligence (AI) and machine learning models[56,74,75]. Models trained on demographically skewed data risk misclassification, poor prediction, and reinforcement of systemic inequities. Equitable modeling requires transparent reporting (clear documentation of data sources, methods, and limitations), interdisciplinary validation (cross-field review and replication of findings), and stakeholder engagement (involving community and policy representatives)[76]. Key needs include assessing data heterogeneity, incorporating multimodal inputs (i.e., systemic biology and exposomic layers[9,28,77]) and applying individualized probabilistic modeling to capture complex risk trajectories[73]. These strategies are essential for advancing truly equitable, globally relevant brain health research. A structured metamodel -a computational framework designed to handle data heterogeneity, integrate multimodal sources, and model individual trajectories and extracerebral influences-, is crucial for advancing brain health research[29].

Multimodal diversity frameworks in data and models

We present the building blocks of a heuristic framework incorporating synergistic computational architectures[10–16,53,77–83] and personalized models[72,73,84]. We first summarize emerging evidence on multimodal diversity. Then, we explore how integrating computational approaches can provide promising pathways for improved theorization and prediction.

Emerging evidence in brain health and disease

Evolving evidence and calls from the World Health Organization (WHO), the Alzheimer's Association, and the National Institute on Aging highlight the importance of incorporating population diversity, loneliness, social determinants of health, and complex biological, neuropathological, and exposomic measures in brain health research[36]. Research requires addressing infrastructural, methodological, and funding barriers that hinder the development of diverse, biologically and contextually informed datasets. Despite advances from initiatives like UK Biobank[85] and FINNGEN[86], these datasets face challenges regarding population heterogeneity, rich ancestries, and global representation[39,87,88]. Bridging these gaps demands global collaboration to build inclusive, multilevel, lifespan-oriented cohorts. Key priorities include lifespan enrollment[89–92] and the development of biorepositories to reduce disparities in genomic and biomarker data[74,93–96].

Funding agencies supporting large-scale initiatives have started to promote increased data diversity and multimodal integration and comparisons across global datasets are now more feasible. Examples include the NIH *All of Us* program (with 77% of participants having underrepresented backgrounds), UK Biobank; the Innovative Medicines Initiative (IMI) – European Union; the Precision Medicine Initiative (PMI, NIH, USA); the NIH - Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative (USA); the NIH - Research Domain Criteria (RDoC) Initiative (USA), the NIH ECHO program, as well as programs in the Global South[10,26–29,31,62,97–103]. Initiatives such as H3Africa[104], FINGER[105], BrainLat[96,106] and ReDLat[107] demonstrate that ethically governed, context-sensitive infrastructures are feasible in the Global South, though broader implementation is needed. These programs evidence feasible, collaborative pathways supporting large-scale inclusion across populations. Sustained progress will require coordinated international efforts, culturally grounded design, regional leadership, and structural reforms (federated data sharing, open-access platforms, and long-term ethical governance) to ensure equity and generate actionable insights for global brain health.

Genetic diversity and scientific discovery

The number of well-powered, large-scale genetic studies using GWAS and polygenic risk scores worldwide, particularly in the Global South, for psychiatric (i.e., schizophrenia[108], bipolar[109] or depression[110]), and neurological conditions (i.e., Parkinson's disease[111] and stroke[112]) is small but growing. Over 40 new genetic risk variants not previously reported in European populations have been identified. These findings can potentially generate discriminative models across different ancestries. Distinct linkage disequilibrium and haplotype patterns in Global South populations sharpen fine-mapping and causal inference. Polygenic risk scores (PRS) trained mainly on European datasets underscore the need for ancestry-aware discovery and validation[113]. Local-ancestry–aware methods such as Tractor enable robust GWAS in

admixed populations, producing ancestry-specific effect estimates and recent schizophrenia GWAS across African, Latino, and East Asian cohorts confirm their value[114]. Large, multi-ancestry cohorts such as NeuroGAP-Psychosis in Africa and the Latin American Genomics Consortium are examples of this effort[115,116]. Asian GWAS have also identified new pleiotropic loci for depression and schizophrenia (e.g., 1q25.2)[117], while large East Asian–European meta-analyses revealed 53 novel schizophrenia loci through trans-ancestry fine-mapping[118]. Rare CNV variants for major psychiatric disorders[119] and specific genetic footprints associated with stroke[120] have also been reported in Chinese populations.

AD/ADRD

Specific mutations not previously reported in Europe and the US, include the *PSEN1* E280A mutation (*the Paisa mutation*), found in Medellin, Colombia, and responsible for the largest early-onset AD population in the world. The high prevalence of the PSEN1 E280A mutation in the Colombian population stems from a founder event, with ancestral origins predominantly traced to Spanish lineage[121–123]. APOE effects on AD/ADRD vary by haplotype and local ancestry in the Global South. Protective variants such as APOE ε3 Christchurch[124] and RELN[125], identified in LAC, renew genetics-informed trial prospects[51]. In African-ancestry cohorts, meta-analyses identified MPDZ and 11 additional AD-risk loci[126] and showed attenuated APOE ε4 risk compared with Europeans[43]. APOE ε2 is generally more protective in Europeans than in other ancestries, while the ε2/ε3 genotype confers ~8-fold higher AD risk in African Americans yet reduced risk in Europeans[127]. These findings stress the need for diverse cohorts to expand discovery and enable ancestry-informed therapies.

Whole-body health

Whole-body health offers a systemic framework to elucidate how physiological networks across the cardiometabolic, inflammatory, and immune domains mediate the brain's adaptation to environmental demands[11–13,60,64,128–133]. This approach allows to embed exposomic perturbations within multi-organ and multi-omics architectures to provide a mechanistic bridge linking external exposures to neurobiological trajectories of resilience and disease[13,16]. Multi-omics has emerged as a promising path in psychiatry[65] and neurology[41,65,134,135]. Combining omics with clinical, neuropathological, and neuroimaging data improves greater prediction accuracy[41,65,136,137]. Inflammation processes have become relevant in psychiatry, neurology[138], and neurodegeneration[129,134,136,139]. Pro-inflammatory cytokines, including mediators such as Interleukin-1β (IL-1β), IL-6, and the nucleotide-binding and oligomerization domain like receptor (NLR) family, are critical for synaptic dysfunction and allostatic load in brain disorders[140]. Corticosteroids and sex hormones (testosterone and estradiol) play crucial roles in modulating neurodevelopment, brain structure, and function[141]; and their dysfunction is associated with multiple conditions[141].

Proteome-wide analyses of brain tissue and peripheral fluids have identified proteins and pathways linked to conditions such as schizophrenia and other mental disorders[142]. Integrating proteomic QTLs, transcriptomic QTLs, and GWAS signals enables prioritization of candidate genes beyond what genomics alone can achieve[142]. Proteome-wide association studies, Mendelian randomization, and imaging phenotypes have linked proteins such as EGFR and TMEM106B to both brain structure and risk for schizophrenia or neurodevelopmental disorders[143]. Transcriptomics–MRI integration further shows how gene expression aligns with structural and functional changes in mental illness[144], while multimodal fusion uncovers hidden pathophysiological links[145]. Spatial multi-omics and mass spectrometry-based neuroproteomics has provided detailed maps of protein-level changes (post-translational modifications and protein–protein interactions) which are central to the pathogenesis of diseases[146,147].

AD/ADRD

The AT(N) (A=amyloid-beta, T=tau, and N=neurodegeneration) framework reflects AD brain changes but most likely is insufficient for accurate diagnosis in global settings[47,148–150]. Combining this framework with multi-omics and neuroimaging can enhance predictions[145,151], clinical characterization[152] and the discovery of treatment targets[152]. RNA sequencing and proteomic screening evidence upregulation of transcription- and chromatin-related genes, including histone acetyltransferases for *H3K27ac* and *H3K9ac*[153]. One study[154] identified 137 proteins with distinct trajectories in causative models of AD, including many that changed before traditional AD biomarkers. GWAS have identified AD-susceptible genes involved in amyloid plaque and neurofibrillary tangle formation, cholesterol metabolism, endocytosis, and the innate immune system[155]. AD/ADRD loci impact immune mechanisms in AD[155]. Among other multi-omics markers[136,137], metabolomics has revealed brain insulin dysfunction. Transcriptomics reveal a significant impact of ancestry, particularly affecting immune pathways[156]. Postmortem brain multi-omics data and in vivo samples are very limited. Biophysical and semi-empirical modeling can help to incorporate these scarce data via prios[36,157,158]. Other more accessible modalities (i.e., plasma proteomics, cell transcriptomics) offer promising non-invasive proxies for brain health[41,159,160] and multi-modal integration[41,159,161]. Brain-blood correspondence in animal models[69,162] can also validate peripheral multi-omics biomarkers.

Epigenomics also evidence the impact of diversity[163–165]. Ancestral epigenetic profiles demonstrate differential DNA methylation signatures in imprinted gene regulatory zones within the inflammasome (e.g., *NLRP1* and *MEST/MESTIT1*) across individuals with AD[166]. Early developmental alterations in DNA methylation may contribute to ancestry risk[166]. Differences in DNA methylation age acceleration (e.g., epigenetic clocks) have been linked to immune system aging and inflammation, influenced by environmental and lifestyle factors[167]. Organ clocks (the biological age measures and mechanisms within specific organs that regulate their function) utilize transcriptome, epigenome, and proteome to integrate the physiological rhythms and aging processes of heart, liver, kidneys, gut, and brain[168]. The combination of genomics, particularly polygenic risk scores, with organ clocks represents a powerful strategy for predicting mortality indices, disease pathology, resiliency, and healthy aging[16,169]. Whole-body health, including cardiometabolic factors are critical predictors of brain health and disorders[60,61]. Gut microbiome health is sensitive to exposome influences and is a crucial predictor of brain health[66]. Cardiovascular, metabolic, and gut microbiome are key predictors of behavior and clinical outcomes[60,170].

Despite these advances, several fields of omics remain immature and underdeveloped. Whole-body modeling frameworks that integrate longitudinal multi-omics at the individual level are still in their infancy, particularly in underrepresented populations. The gut-brain axis, although promising, lacks standardized protocols and causal models in human studies. Postmortem brain multi-omics data, essential for validation, are scarce and geographically skewed, limiting global generalizability. Conversely, promising advances are emerging from the integration of epigenetic clocks, peripheral omics (e.g., plasma proteomics), and organ-specific biological age measures.

Biology–environment interactions

Understanding biology-environment interactions[58,171] requires multimodal frameworks[70] capturing the biological embedding of macrosocial factors (e.g., country-level inequality) on biology and brain health. The One-Health approach emphasizes the interconnectedness of human, animal, and environmental health and is critical for precision brain health[13]. Water and air pollution, plastics and nanoplastics, climate change, and heat waves are essential to the physical exposome[9,13]. Social inequality, loneliness, political polarization, and

injustice are social exposomes[9,48] highlighting the need to examine macro- and individual-level determinants[9,13,48,54,172,173].

Environmental exposures strongly influence brain biology and increase the risk of psychiatric and neurological disorders. Long-term air pollution, particularly PM2.5 and NO_x[174] have also been linked to structural and functional brain alterations, as well as to depression and other mental disorders, through mechanisms involving inflammation, oxidative stress, and genetic susceptibility[175,176]. Socioeconomic factors such as lower family income, parental education, and neighborhood disadvantage predict reduced cortical surface area and a greater risk of neurodevelopmental conditions[48,177–180]. Furthermore, early adversities have been consistently associated with structural and functional brain changes and with the development of psychiatric disorders[181,182].

External exposomes dysregulate internal biological processes[13]. Life adversity, unhealthy lifestyles, and loneliness are associated with impaired hypothalamic-pituitary-adrenal (HPA) axis activity, reducing glucocorticoid sensitivity, triggering insulin resistance, and causing endothelial dysfunction[183]. These adversities are linked to inflammation, elevated peripheral inflammatory cytokines[184–187], and impacts on the microbiome, ultimately increasing the risk of non-communicable diseases, neuropsychiatric and neurological conditions[184,186,187]. The prediction of clinical outcomes increases when biological variables are integrated with exposomes[10,29,79,80]. Different factors, including socioeconomic status, environmental factors, perceived discrimination, and country-level inequality levels[10,67,79,80,173,188] influence neuroendocrine, brain-gut microbiome[66], and neurocognitive markers[10]. Social determinants of health[48] predict healthy aging better than sex and age in diverse populations[53,188,189].

Social epigenomics[163,190,191] combines exposomes and epigenetics. Social determinants of health, discrimination, exclusion, and socioeconomic adversities influence DNA methylation[191]. Epigenome-wide association studies (EWAS) of socioeconomic status and social mobility have implicated genes involved in inflammation, immune function, stress response, metabolic processes, and neural development. Biological age is influenced by ancestry, lifestyles, and social factors[190,192,193]. Hispanic populations have lower intrinsic epigenetic age acceleration, indicating slower cellular aging (i.e., the Hispanic paradox, with slower aging processes despite having increased risk factors)[167,194]. Effects of social disparities on epigenetics can also be mitigated by lifestyle changes in some ethnic groups. Methylomics and transcriptomics analyses from the human postmortem brain and studies on genetic variation reveal a significant impact of genetic ancestry, particularly affecting genes involved in immune response pathways[156].

AD/ADRD

Different exposomes impact the brain structure-functioning[48,171], health[53,189], and disease[10]. Ancestry and social exposome influence biomarkers for AD/ADRD[195]. Hispanic populations have increased adverse physical and social exposomes and higher AD biomarkers AT(N) such as $A\beta_{40}$ and reduced neurofilament plasma levels compared to non-Hispanic White populations in the US[196]. Cardiometabolic diseases, unequally distributed worldwide and influenced by the internal and social exposomes, modulate AT(N) biomarkers[195]. Socioeconomic factors affect the relationship between brain markers and ancestry[195]. Cerebrospinal fluid $A\beta_{42}/_{40}$ levels are negatively correlated with total tau and p-tau181 in Caucasians, but the correlation is weaker in non-Hispanic Black individuals[51]. CSF $A\beta_{42}/_{40}$, total tau, and p-tau181 demonstrate weaker correlations with cognitive measures in Black than White participants[197]. Effects of ancestry and social disparity in AD/ADRD have also been reported in organ[194,198], circadian[198], and brain clocks[10].

The dependence on proxies is an important limitation, as these are indirect indicators used when direct measures are unavailable. Unlike endophenotypes (biologically grounded intermediate traits) or surrogate outcomes (validated substitutes for clinical endpoints), proxies provide pragmatic but non-causal markers. Although much of the evidence is not causal, progress in the field is already evident[1–5]. A hierarchy of exposome factors[5–7] can situate biological mechanisms alongside broader social, economic, and environmental factors. A new generation of methods is actively tackling this challenge[8], including the NIH Gateway Exposome Coordinating Center, and the predictive exposome databases[9] are bringing multiple innovations. High-resolution exposure assessment[10], and evaluations of exposure-wide association studies (ExWAS) can improve specificity and granularity[1,10–13]. Compared to traditional self-report instruments, which are prone to recall and response bias, these emerging biomarker-based tools offer greater accuracy, temporal resolution, and translational value.

Modeling and theorization

Different computational and theoretical architectures are required to assess the flexibility and complexity needed to incorporate multimodal diversity (Box 2). Specific examples include dynamic causal modeling[199], Bayesian architectures[200], active inference models[201], and biophysical modeling[78]. These methods have proven effective in integrating multimodal data while being generative, recursive, and continuously updated as new information becomes available[15]. Data-driven generative approaches enable the development of single-subject and personalized translational models[65,71,84]. This framework does not support the idea of extensive, universal, or one-size-fits-all models of brain health. Instead, it advocates for tailored models in which the relevance of predictors and outcomes varies according to population-specific data, contextual variables, and multimodal variation. The metamodel framework requires tailored procedures that can be instantiated using different techniques (Tables 2 and 3). We propose four main avenues to develop future computational architectures.

Low-dimensional integration of multilevel brain measures

Multimodal diversity can be mapped to low-level biological mechanisms using methods from artificial intelligence[202] and dynamic systems modeling[15]. On the one hand, non-linear deep learning dimensionality reduction techniques enable the generation of highly informative low-dimensional latent representations of brain spatiotemporal dynamics. Non-linear low-dimensionality reduction approaches can more accurately characterize different conditions than the traditional statistical approaches relying on assumptions of linearity and stationarity[82,83,203]. Machine learning can be complemented by theory-driven dynamical system measures, such as metastability (the brain's ability to transition between globally integrated and segregated states[204]), irreversibility (linked to brain complexity, entropy and flexible brain transitions[205]), and criticality (a metric of proximity to a dynamic regime in-between order and chaos), which have proven effective in capturing and conveying the structural and functional complexity of the brain across levels in brain disorders[205].

Generative biophysical whole-brain models help to investigate mechanisms underlying data-driven characterizations[15]. These models integrate multiple heterogeneous data sources, encompassing brain structure and function, connectomics, neurochemistry, synaptic processes, or cytoarchitecture[206]. Moreover, those models can track brain circuitry integrity and function at multiple spatial and temporal scales combining fMRI, electroencephalography (EEG), magnetoencephalography (MEG), or PET, enhancing model predictive power and multilevel consistency[206].

Embodied and generative models for extracerebral influences

Combining different organ clocks with computational architectures helps to characterize brain health and disorders[168,169,198]. Accelerated aging in particular organs, such as the heart, is linked to increased risks

BOX 2

Main computational concepts

We provide some of the most relevant concepts incorporated in computational metamodeling.

Low-dimensional data representations: Machine learning techniques identify lower-dimensional spaces (manifolds) in high-dimensional data structures[289]. Mapping data into these manifolds yields low-dimensional latent representations preserving essential features, patterns, or relationships. Manifolds can be identifiable linear spaces using principal component analysis, but more complex methods like t-distributed stochastic neighbor embedding detect non-linear manifold structures in high-dimensional spaces. Latent representations typically reduce dimensionality but also preserve essential properties[15]. They maintain the metric structure of the original data, support generative capacity (mapping latent points back to realistic data), and allow continuous trajectories aligned with intrinsic or extrinsic variables (e.g., age, exposomic profiles). These features provide a basis for validating that the representation retains relevant biological and exposome signals.

Generative statistical models: These models learn the mapping from low-dimensional latent representations to the original space, allowing the production of information with meaningful statistical properties. Applied to brain data, models like deep generative autoencoders and generative adversarial networks can synthesize new observations without additional experiments.

Whole-brain modeling: Whole-brain activity data can be generated using a bottom-up approach based on simulating local dynamics of brain regions coupled by the structural connectome. These dynamics represent biophysical properties of neural populations, enabling inference of multi-scale biological mechanisms[290] underlying observed data. Alternatively, phenomenological models aim to reproduce dynamic behaviors (e.g., oscillatory versus non-oscillatory patterns)[207].

Perturbational approach in modeling: Generative models can undergo systematic perturbations that are challenging to implement experimentally. Mapping how neural systems react to these perturbations provides insights into their functionality and stability[82]. Simulated perturbations can also rehearse personalized treatments by incorporating data on different neurotransmitter systems to assess pharmacological interventions.

Individualized trajectory modeling: Probabilistic methods can model and predict the evolution of individual trajectories over time. Bayesian inference iteratively combines new observations with prior knowledge, allowing adaptive learning about hidden states or parameters. Markovian modeling predicts the system's future based on its current state, as seen in Markov chains and hidden Markov models.

Dynamic causal modeling (DCM): This approach assesses causal interactions in response to experimental manipulations from brain activity recordings. The method fits differential equations with varying levels of biological detail to time series at regions of interest to determine the strength and directionality of interactions. Bayesian model comparison assesses models according to the evidence provided by the generative dynamical system.

Active inference: This framework explains how agents—biological or artificial—interact with their environment by minimizing "free energy," a measure of prediction error[201]. This approach unifies perception, action, and learning within a single probabilistic model. Active inference models incorporate allostatic interoception, where the brain anticipates and regulates bodily states and related cognitive processes[128] to respond to environmental demands in health and disease[129–131].

of brain disorders[168]. For AD, such risk is independent of the blood-based biomarkers[168]. The global effects of such *extracerebral influences* can be modeled as descriptors of the global state of the system (order parameters), capturing and summarizing the nature of dynamic interactions within the brain[15]. Order parameters can include whole-body signals, such as autonomic responses, or exposome factors, thus addressing biology-environmental interactions[15,].

From a data-driven approach, the effect of extracerebral influences on the brain can be determined using low-dimensional latent representations of spatiotemporal neural dynamics[207]. A concrete example are variational autoencoders, generative models combining deep learning with probabilistic inference, to track low-dimensional latent representations of multilevel brain states in health and disease[82,203]. This approach could be extended to incorporate integrated representations of the brain, bodily states, and exposome, providing a set of variables simultaneously encoding multiple dimensions[15]. These representations can be studied in response to changes in extracerebral factors, including dietary inputs, physical activity, stress exposure, and other exposomes[9,82].

Incorporating heterogeneity and individual trajectories

Individual and personalized analyses are critical for global healht[208]. This requires single-subject data and estimates of how individual's biology interacts with heterogeneous environmental factors. In biophysical generative models, country-level heterogeneities can be studied as modulators of parameters linked to neural activity, metabolism, structural atrophy, and pathological proteins[82,206,208]. Examples are found in the BigBrain project[209], integrating tissue models and neuroanatomical individual data across scales and providing microstructural maps enriched with cellular and molecular levels merged with fMRI connectivity models, as well as simulations of diverse brain disorders. Other initiatives provide personalized transcriptomic[210], proteomic[211], and neurochemical maps[212] to enrich biophysical generative models.

Perturbational approaches can be used for personalized medicine[15], where the effect of changing variables (perturbations) on the observed phenotype can be systematically mapped[213]. This approach can also be used as a data augmentation technique to enhance deep learning frameworks, generating synthetic data that incorporates the characteristics of underrepresented groups, improving sensitivity and generalizability[214]. Another way to increase personalization is by Bayesian models, which provide a probabilistic framework that continuously updates predictions as individual data becomes available. This adaptability is essential for personalized brain health assessments that have facing scarce and heterogeneous data, enabling the integration of individual-specific data into models originally built from large population datasets.

Personalized models and individual trajectories can be complementary. Personalized models integrate prior information (genetic, clinical, or environmental data) to tailor predictions to individuals. These models can employ supervised learning and probabilistic frameworks that adapt group-level findings to individual profiles[215]. In contrast, models of individual trajectories focus on within-person changes over time, capturing temporal dynamics like disease

Table 2 | Guidance on data modalities

Data Modality	Typical measurement methods	Example datasets	Prototypical computational approaches
Genetics	Genome-wide association studies (GWAS) via SNP genotyping arrays; whole-genome or exome sequencing (next-generation sequencing)	UK Biobank; 1000 Genomes Project	Polygenic risk score modeling (aggregating risk variants); gene network and pathway analysis for variant interpretation; Bayesian integrative models combining genetic profiles with other modalities (for personalized prediction)
Epigenetics	DNA methylation profiling (Illumina methylation arrays) with epigenome-wide association studies (EWAS); chromatin accessibility assays (ATAC-seq); histone modification mapping (ChIP-seq)	NIH Roadmap Epigenomics Project; PsychENCODE Consortium (brain epigenomics)	Epigenetic clocks to estimate biological aging (methylation-based age); EWAS linking environmental factors (e.g., stress, SES) to gene regulation changes; integrative multi-omics models combining epigenomic, genomic, and neuroimaging data for disease prediction.
Omics	High-throughput proteomics (mass spectrometry, multiplex immunoassays); metabolomics profiling (LC–MS, NMR spectroscopy); transcriptomics (RNA sequencing, gene expression microarrays)	ADNI (multimodal biomarkers in Alzheimer's); GTEx (tissue transcriptomes); AMP-AD (multi-omic Alzheimer's cohorts)	Dimensionality reduction and factor analysis (e.g., PCA, structural Bayesian factor analysis) to integrate high-dimensional omics; network and pathway analysis to identify affected biological pathways; generative models (e.g., variational autoencoders) and machine learning for multi-omic data fusion
Whole-Body Health	Systemic health (vitals, BMI, blood pressure, metabolic panels); wearable sensor tracking of physiology (heart rate, sleep, physical activity); gut microbiome sequencing (16S rRNA profiles)	Framingham Heart Study; UK Biobank	Multi-factor risk scores combining health biomarkers to predict brain outcomes; multi-system network models linking organ health metrics to brain aging; generative extracerebral models incorporating whole-body signals into brain simulations (treating body indices as inputs to brain models); multi-organ aging clocks (integrating genomic and proteomic markers of heart, liver, etc.) to predict neurological disease risk
Brain Health	Multimodal imaging (f/MRI; vascular imaging) and PET for brain structure/function and molecular imaging; EEG/MEG electrophysiology for neural activity dynamics; standardized cognitive test batteries (memory, executive function, cognitive screening exams)	ABCD Study (pediatric imaging & cognitive data); EuroLad EEG consortium; ReDLat Consortium	Connectome and network analysis (graph-theoretical metrics of brain connectivity); biophysical whole-brain network models (simulate neural dynamics across regions, integrating multimodal neural data); dynamic causal modeling (Bayesian causal inference of directed brain connectivity); hidden Markov models for brain state transitions or cognitive decline trajectories; deep learning for multimodal brain data integration (e.g., combining f/MRI, M/EEG, and clinical features)
Exposome	Surveys and questionnaires capturing lifetime exposures (e.g., education, diet, stress, socioeconomic status); environmental monitoring and geospatial data (air pollution levels, climate metrics, neighborhood characteristics); socioeconomic and psychosocial indices (income, social networks, inequality)	CHIMGEN (Chinese imaging genetics cohort with cross-ethnic and cross-geographic data); ReDLat (Latin American dementia cohort with socio-environmental diversity); HELIX project (early-life exposome in birth cohorts): UK Biobank (linked lifestyle and environmental data)	Exposome-wide association studies (scanning multiple exposures for links to health outcomes, analogous to GWAS); geospatial and multilevel models mapping environmental factors to brain aging or pathology; causal inference frameworks (e.g., Bayesian networks, structural equation modeling) to disentangle correlated exposures; multimodal integration of exposome with biology (combining SES, lifestyle, and environmental data with genetics and neuroimaging for personalized risk prediction)

progression or treatment response. Techniques such as Bayesian updating, hidden Markov models, and state-space modeling are commonly used to estimate these temporal trajectories[216,217]. Combining both strategies enables more accurate, dynamic, and context-sensitive assessments, advancing individualized approaches throughout the lifespan.

Health and disease are inherently variable and not suited to one-size-fits-all approaches[218]. Normative modeling generates population-based reference trajectories, quantifies individual deviations, enabling detection of atypical patterns in healthy and clinical populations[219–222]. Normative modeling uses continuous trait modeling (e.g., brain age deviation), thresholding to define clinical significance, and hybrid models[222]. Hierarchical Bayesian methods and data integration have enhanced their biological relevance[222,223]. Lifespan-informed designs demonstrate how these models improve representativeness and mechanistic insight[220,221]. Medical digital twins[132] represent a natural evolution of these models, allowing real-time simulation of individualized biological systems. The combination of multimodal data spanning organ-level dynamics, omics, and exposomic inputs can help AI-driven digital twins to provide personalized aging clocks of health and disease.

A metamodeling heuristic framework

Current theoretical explanations do not systematically address the challenges posed by integrating brain measures with extracerebral information into individual trajectories[15,34]. New computational strategies can help to incorporate multimodal diversity in psychiatry[224] and neurology[185,225]. The combination of multimodal data, brain-extracerebral integration, and personalized approaches provides bona fide examples, handling population heterogeneity, multilevel metrics, and neuroecological links[10] with emerging applications[77,78,81,82,208,214].

Table 3 | Key methodological instantiations for the metamodel

A. Data heterogeneity

Technique (example)	Required data	Complexity	Interpretability	Computational cost	Multimodal integration	Robustness
Large-Scale deep learning (accelerated brain age in large cohorts)[10]	Large annotated and balanced datasets required	High complexity	Limited and indirect	High computational demands for model training	Integration possible, but not directly built in the model	High, when trained with sufficient data and/or data augmentation
Normative modeling (population reference distributions)[98]	Requires large samples with good reference data coverage across diversity axes	Variable, depends on the specific model	Supports subject-level interpretation	Computationally expensive for high-dimensional data	Variable, depends on the specific model	Inherently models uncertainty and robust to heterogeneities
Federated learning (distributed training to keep privacy)[282]	Distributed data requirements	Variable, depends on the specific model	Variable, depends on the specific model	Convergence issues with non-independent and identically distributed data, limited by the least resourced sites	Variable, depends on the specific model	Enhances representation of diverse populations, mitigates site-specific biases, evolves as new data is available

B. Multimodal integration (brain + extracerebral metrics)

Technique (example)	Required data	Complexity	Interpretability	Computational cost	Multimodal integration	Robustness
Whole-brain biophysical modeling (perturbations and extracerebral modulation)[283]	Low, allows single-subject modeling	Variable, but limited by high computational cost	Both mechanistic and causal interpretability	High computational demands for model training	Can integrate systemic and environmental modulators via priors or order parameters	Sensitive to assumptions about coupling between neural regions
Dynamic causal modeling (DCM, neuropharmacological dynamics)[284]	Low, allows single-subject modeling	Variable, but limited by high computational cost	Causal interpretability of directed brain connectivity, rigorous Bayesian model comparison, physiologically meaningful parameters	High computational demands for parameter optimization	Supports multimodal extensions	Requires strong a priori model specification, sensitive to model specification details
Active inference (Generative brain-body models)[285]	Low, allows single-subject modeling	Variable, but limited by high computational cost	Limited empirical application, abstract constructs require biological mapping.	High computational demands for parameter optimization	Unifies perception, action, and regulation	Explicit uncertainty modeling but difficult model specification
Deep multimodal learning (joint representation models)[286]	Requires large multimodal datasets	High complexity, can approximate arbitrary non-linear decision functions	Limited and indirect	High computational demands for model training	Captures non-linear cross-modal interactions	Prone to modality dominance, limited native uncertainty estimation

C. Individual level trajectories

Technique (example)	Required data	Complexity	Interpretability	Computational cost	Multimodal integration	Robustness
Bayesian sequential Inference (state-space models)[287]	High for high-dimensional or poorly sampled systems	High model complexity	Interpretability in terms of personalized trajectories	High computational demands for high-dimensional systems	Integration possible, but not directly built in the model	Adaptive updating with new observations, explicit uncertainty quantification, handles irregular sampling and noise
Markov chain models (e.g., Markov & hidden Markov models for spatiotemporal brain dynamics)[288]	Large amounts of data needed for rare transitions	Low complexity, memoryless assumption can oversimplify dynamics, discretization may lose information	Simple interpretability, analytically tractable, clear clinical stage modeling	Low computational demands	Integration possible, but not directly built in the model	Sensitive to model initialization

Description of the dimensions used in the table:

Required data: Reflects both the amount and organization of data required to train the models. Ranges from individual datasets of relatively low complexity to large structured and annotated databases spanning thousands of individual participants.

Complexity: The capacity of the model to detect complex and non-linear patterns in the data. While complex models are capable of more powerful generalizations, they are computationally demanding, and parameter optimization is data intensive. A downside of complex models is their tendency to overfit if trained with insufficient data, or when lacking adequate regularization.

Interpretability: The extent of understanding gained by analyzing the models. Interpretable models yield valuable insights concerning the underlying mechanisms driving model predictions and can also inform neurobiological and causal relationships in the data.

Computational cost: Reflects the combined amount of processing power and data storage demand required by each technique.

Multimodal integration: The capacity of the model to process inputs combining dissimilar data sources, for instance, different neuroimaging modalities. While some models can trivially integrate data sources when combined in the inputs, others offer more parsimonious and streamlined integration capabilities.

Robustness: Refers to the capacity of the model to yield meaningful predictions facing noisy, uncertain and/or heterogeneous data, including missing and/or potentially misleading samples. Robust models are also stable against methodological choices, such as the specification of hyper-parameters and prior assumptions, and can be easily adapted to handle new data as it becomes available.

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Future models must effectively integrate diverse data sources while accounting for individual differences and the specific needs of diverse populations. While current methods show promise, they require significant enhancements to better capture non-linear interactions and individual variability[15]. Achieving this will require integrating advanced tools, such as synthetic data generation and probabilistic modeling. Additionally, balancing simplification and precision is crucial in future developments to avoid oversimplifying complex interactions while ensuring practical and actionable outcomes.

There is an overreliance on causal models and explanations of brain health, especially in neuroscience research[226]. Causality, although bolstered by powerful technologies, is fundamentally limited[15]. Studying isolated neural components or perturbing circuits offers causal claims about necessity and sufficiency but fails to reveal the embedded principles that govern behavior, largely due to ecological constraints, brain degeneracy, multiple realizability, and the lack of a direct mapping between structure and function. Pure causal models often fall into the mereological fallacy (attributing organismal or environmental functions to parts like neurons or isolated factors), overlooking brain health as ecological phenomenon. They lack the capacity to explain why and how health and disease emerge beyond mechanical causation. Brain health must move beyond pure causal manipulation towards a pluralistic approach that prioritizes precise neurosyndemics as a foundational step[15]. Understanding this embedded and situated nature through complexity science can help uncover emergent properties triggered by exotype-endotype interactions[9]. Synergistic explanatory frameworks[13,172,227–229] better capture the complexity of brain health through integration across levels, enhancing both explanatory power and translational relevance. Bona fide examples of such integrative models include brain and organ aging clocks[168,169,230], allostatic load[131,231–235], and the biological embedding of adversity[236–238].

Dimensional approaches for psychiatry and neurology

Although our perspective is mainly focused on brain health, multimodal diversity in research supports a neurological and psychiatric dimensionality. The core heuristics apply equally to psychiatric disorders. Neuropsychiatric genomics continues to be underrepresented in populations with high genetic admixture, distinct environmental exposures, and healthcare disparities, limiting equity in precision psychiatry[239,240]. GWAS including African and Latino participants have identified novel variants for depression, schizophrenia, anxiety, and bipolar disorder—missed in European-only studies[116,240]. Studies from the Middle East have uncovered multiple novel gene–phenotype associations in psychiatric disorders. In autism spectrum disorder (ASD), numerous novel candidates include *GLT8D1, HTATSF1, OR6C65, ITIH6*, and *DDX26B* in Saudi families[241], *DPP4*, *TRHR*, and *MLF1* in Lebanese families[242], and *TRPC4* and *SCFD2* in Qatari cohorts[243]. Copy number studies in Lebanon further implicated *PTDSS1* and *AREG* as novel ASD susceptibility loci[244]. In schizophrenia, Israeli trio and founder-population studies revealed a burden of rare damaging de novo mutations[245], while Iranian families carrying *AGO1* truncating variants showed a spectrum from autism to schizophrenia[246]. For bipolar disorder, Turkish multiplex families yielded novel variants in *TMTC1* and *STARD9*[247]. These findings underscore how Middle Eastern cohorts are expanding the catalog of rare and novel genetic contributors to psychiatric disease.

Environmental, cultural, and social determinants shape psychiatric conditions[14,15,64,177,178]. Global exposomic variation, combined with individual and societal-level risks, has been linked to general psychopathology[248–250]. In schizophrenia and bipolar disorder, factors such as urbanization, gross domestic product per capita, employment, and air pollution influence clinical expression[251], underscoring the need for context-sensitive diagnosis and treatment[250]. Computational psychiatry has improved classification and prediction by integrating neuroimaging, genetics, behavior, and environmental data[252–254]. Investigating dimensional biological and exposome pathways in psychiatry and neurology[14,64,255] is critical to advance the field. There is a high prevalence of neurodegenerative conditions among patients with anxiety, depression, schizophrenia, bipolar disorder, personality disorders, and stress-related conditions[256], with overlapping genetic causes[257], shared omics mechanisms[256], and social risks[5]. Addressing these shared multifactorial interactions[255] requires adopting transdiagnostic, dimensional, and integrative approaches.

Emerging models guided by the BePRECISE consortium[20], emphasize integrating diverse datasets and transparent methodologies to ensure inclusivity, reproducibility, and actionable outcomes for psychiatry and neurology. These approaches align with the principles proposed here, incorporating genetic, biological, and exposome data to refine predictive models and improve clinical interventions.. In psychiatry, deep phenotyping following BePRECISE guidelines combines neuroimaging, genetic markers, and environmental exposures to enable the identification of depression subtypes associated with specific treatment responses[47]. These dimensional frameworks can help advance the fields of psychiatry and neurology and lay the groundwork for inclusive tackling of the real-world complexity of health and disease.

BOX 3

The prototypical case of Alzheimer's disease and related disorders

The Alzheimer's Association has recently defined AD as a biological entity: people who have biomarker evidence of amyloid-β and tau proteins in the brain or peripheral fluids according to these criteria have AD, regardless of their clinical or cognitive condition. This definition reflects a long-standing goal in neurology to find a static, single, universal, and straightforward biomarker and treatment approach for ADRD, captured in the idea that amyloid protein aggregation is the primary cause of AD. However, the overfocus on amyloid may have occurred at the expense of other critical pathophysiological pathways[291] and clinical manifestations[148]. Therapies aimed at reducing amyloid- β accumulation have shown a modest impact. A complex interaction of immune system disturbances, inflammatory reactions, cellular stress, microbiome alterations, and mechanisms related to allostatic load is observed in ADRD[154,185,291,292]. Heterogeneities in exposome[48], biomarker profiles, genetic variants, proteinopathies, and clinical-cognitive-behavioral profiles[15] suggest that a one-size-fits-all strategy may not be effective[148]. Proteomics studies indicate that proteins' trajectories changed before traditional amyloid-β and tau biomarkers[154]. Novel research using a more synergetic framework with genomics, proteomics, and neuroimaging shows promise for disease prediction and diagnosis[139,225]. Non-linear interactions between pathophysiological processes and behavioral changes that address dynamic frameworks can help advance ADRD research[78,81,82,135,151,208]. Allostatic and probabilistic models incorporating multimodal risk elements and interactions are increasingly considered[129,185,292]. These models still require further development[13,15] and inclusion of underrepresented and more diverse populations[10,139]. Future studies that incorporate varied and multimodal data and biology- environment interactions[13,15] are needed.

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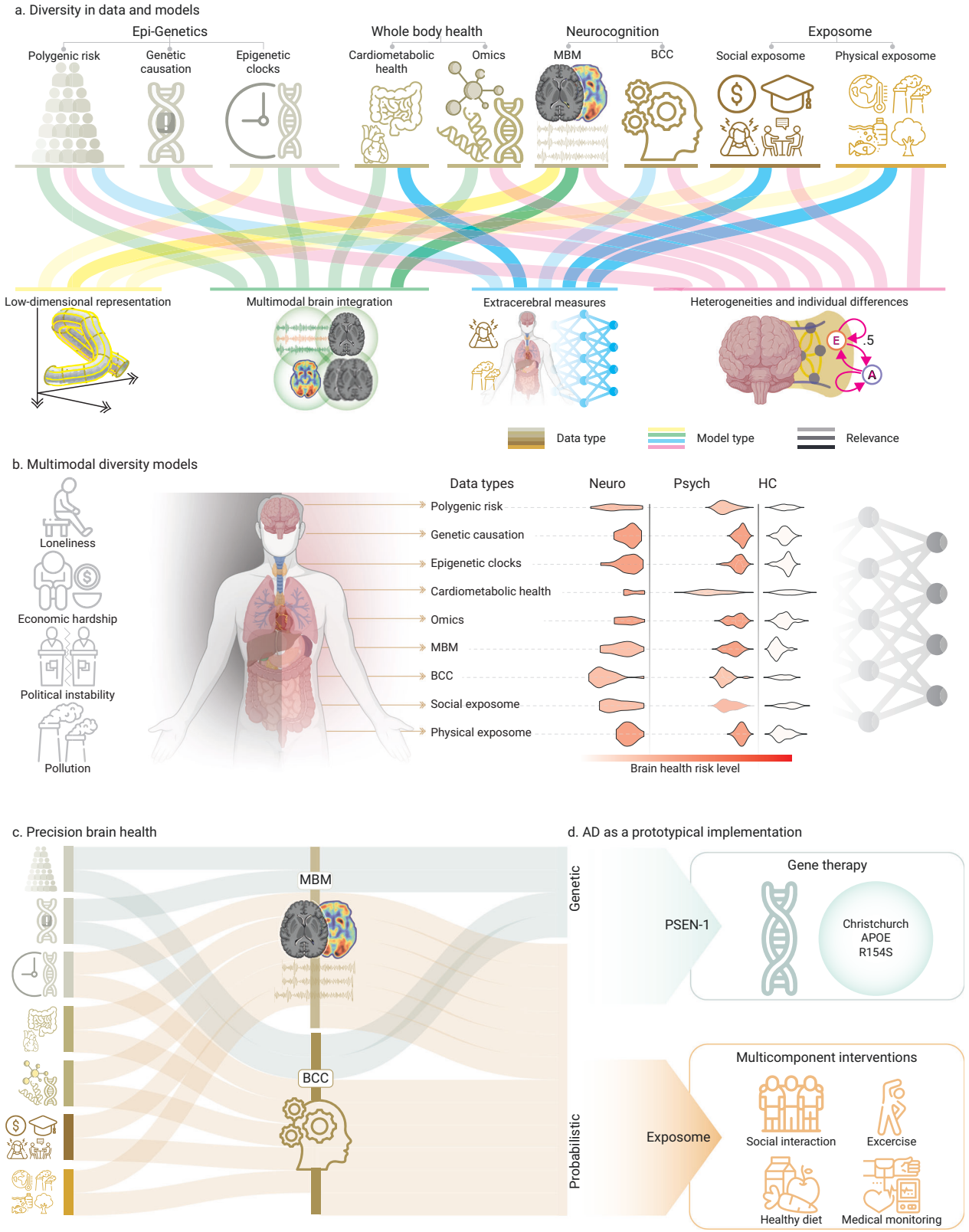

Conclusions: a future agenda

Recent promising advances in specific fields (Box 3) call for a more comprehensive science of precision brain health. Developing a neurosyndemic framework, incorporating diverse, multimodal models, and accounting for individual variability are essential to achieving a meaningful impact in real-world applications. We outline future strategies to provide more holistic, ecologically valid models that better reflect the complexities of human brain health (Table 1).

Critical steps are required to develop the advanced metamodeling frameworks (Fig. 2). These must simultaneously combine different strategies (spatiotemporal modeling via dimensionality reduction, whole-brain biophysical modeling, deep learning, and probabilistic

Fig. 2 | Future frameworks for precision brain health. A framework for multimodal diversity that fosters precision medicine approaches needs to address the complexity of brain health and disorders while guiding personalized strategies. The **a** illustrates the concept of diversity in data and models for brain health, integrating inputs from epi/genetics (polygenic risk, genetic causation, epigenetic clocks), whole-body health (cardiometabolic measures, omics), neurocognition (MBM: multimodal brain measures; and BCC: behavior, cognitive and clinical levels), and the exposome (social and physical factors). These heterogeneous data streams converge into different combinations of computational approaches (lower part of the panel) addressing low-dimensional latent representations, multimodal brain integration, extracerebral measures, and individual heterogeneity, ultimately enabling tailored model types that enhance precise brain health. **b** shows multimodal diversity models integrating social factors (e.g., loneliness, economic hardship, political influences, and pollution) with data from genetic risks to exposome exposures. A nested modeling approach (hierarchical method in which a simpler model is embedded within a more complex one, allowing refinement across levels of complexity) supports the differentiation of risk profiles in individuals with brain disorders (neurological and psychiatric) and healthy controls (HC). **c** exemplifies the utility of this framework in brain health, highlighting how integrating multiple biological levels enhances the predictive power of biomarkers, clinical profiles, and neurocognitive data for brain health and disorders. **d** illustrates derived precision health applications in Alzheimer's Disease (AD). This approach accounts for cases with differential genetic and probabilistic (environmental) burdens. Examples of future tailored interventions include gene therapy for individuals with high genetic burdens (e.g., inspired by the Christchurch protective gene for the *PSEN1* mutation) and multicomponent interventions (e.g., enhanced social interactions, physical activity, healthy diets, and medical monitoring) tailored for those with probabilistic burdens. Created in BioRender. Migeot, J. (https://BioRender.com/l00oejq) (brain, body, and organs illustrations).

structures) to effectively incorporate data representation and integration, extracerebral influences, inherent heterogeneity, and personalized modeling. Model perturbation strategies can be relevant to gain mechanistic insights[15]. Future metamodel frameworks should focus on human behavior and neural activity within real-world environments with more naturalistic and ecologically valid research paradigms[11,258]. Wearables, natural speech analysis, virtual reality, augmented reality, real-time neuroimaging and neurofeedback, citizen science, and ecological simulations may help better assess diversity[11,258].

Deep phenotyping is essential for precision medicine, especially when it enables detailed clinical phenotypes (e.g., symptoms, disease progression) and endophenotypes across the whole body. Future efforts could lead to new disorder subtypes based on fine-grained clinical and biological correlates[259]. These advancements would support the creation of more global and extensive databases, tracking population representations and clinical subtypes. Developing human digital twins for brain health[132] could integrate deep phenotyping data with temporal monitoring and prediction. These in silico replicas would enable scenario testing for future prevention and treatment, linking multi-organ and multi-omics to public health and clinical applications.

Research incorporating biological and environmental interactions requires further granularity. Regional public health strategies can benefit from integrating individual risk profiles and personalized interventions combining macro (i.e., aggregate-level exposome) and micro (i.e., individual-level brain health) factors[16]. Deep phenotyping in longitudinal cohorts can help to identify individual protective or risk factors that may influence broader geographical regions. In contrast, personalized medicine technologies in health and disease can help to improve healthcare accessibility, especially for marginalized communities. Implementing convergences between regional and individual models requires complexity modeling and big data[32], while prioritizing data privacy and equity. Integrating population admixtures and multimodal data is essential for predicting clinical diagnoses characterizing healthy variation, clarifying frequent and infrequent phenotypes, and measuring individual trajectories. Such models help distinguish normative variability from clinically relevant deviations, a persistent challenge in neurology and psychiatry. For example, accounting for ancestry, lifestyle, social risks, and environmental exposures improves the identification of subclinical brain aging or stress-related vulnerabilities and resilience before disease onset[16,192,193,218]. Prediction models should support a broader goal: understanding how individuals respond to environmental risks and interventions across the life course[16], rather than simply classifying disease states.

Future research should also bring more science of neurodevelopmental factors. Studying these factors can help minimize the risk of overemphasizing or misattributing the influence of factors from adulthood or older age in brain disorders[260]. Early-life adversities such as adversity, malnutrition, infections, and lack of cognitive stimulation are linked to disruptions in critical neurodevelopmental stages[261] and contribute to the onset of psychiatric[262] and neurological conditions[263,264]. This approach can explain mechanistically how such adversities affect biological pathways leading to brain disorders[260]. Despite the importance of early exposures in brain disorders[89–91,256], yet most large-scale datasets lack of further assessment of neurodevelopmental measures to trace these trajectories. Expanding lifespan cohorts that capture neurodevelopmental milestones is crucial to understanding how early-life pathways contribute to midlife psychiatric and neurological disorders and their progression to late-life diseases[220,221]. Developmentally informed computational approaches, drawing on dynamic causal modeling, biophysical modeling, and normative modeling[265] may enable more precise, equitable predictions by identifying deviations across lifespan that impact brain health outcomes.

Transdisciplinary collaboration is required to achieve multimodal diversity in clinical sciences, neuroscience, biology, epidemiology, computational modeling, and public health. Cutting-edge technologies (e.g., AI and biophysical modeling), knowledge sharing[266], and open science practices and, are essential for future development. The brain capital[267] and syndemics[172,268,269] agendas can drive transdisciplinary innovation regarding critical challenges (climate change, pollution/plastics, conflict and stress, economic innovation) for brain and mental wealth[13,267].

Towards addressing ethical, social, and technical barriers

Structural inequities shape data access, governance, and commercialization, reinforcing disparities in data ownership and use. Academia sets priorities, industry monetizes data, and policymakers regulate access—roles that can perpetuate or challenge injustice. Expanding datasets without safeguards risks eroding participant rights and centralizing control. Diversity must be valued not only for scientific validity but as a core ethical principle. To prevent harm, frameworks like WHO, STANDING Together, and FAIR[36,39,103,218,270–275] can promote participatory governance, transparency, and fair benefit-sharing. AI bias on health data often arises from underrepresentation and uneven data quality[100], compromising fairness, generalizability, and impact[276,277]. Restricted diversity can entrench health disparities[100], but the solution must go beyond correcting algorithmic bias to embed ethical oversight, structural awareness, and stakeholder inclusion into equitable brain health modeling. Models must capture real-world heterogeneity, integrate multilevel data, and be co-developed with communities. Transparent governance[276,278], global data-sharing frameworks[103], and accountability are required prevent AI from reinforcing disparities. Other ethical risks linked to AI and big data, corporate misuse, circular predictions, confirmation bias, and automated decisions in low-interpretability models should not be underestimated[276]. Data protection, especially in the context of

generative models capable of re-identifying individuals and challenging anonymization efforts need to be addressed[32,113,279].

Citizen science[280], community-based system dynamics, digital technologies, and participatory research approaches[267,280] can help to democratize this framework. These strategies promote culturally competent recruitment and radical collaboration with community stakeholders, informing the equitable mapping of complex systems influencing health outcomes, including social determinants, healthcare access, and cultural factors[281]. Promoting equitable data sharing across jurisdictions, fostering public-private partnerships, building capacity in low-resource settings for active participation in discoveries, and reducing institutional and national barriers are crucial for advancing brain health interventions globally[281]. Such methods identify critical leverage points to improve data representation and accuracy, leading to practical, sustainable data capture tools and meaningful interventions for diverse populations[267,280]. We believe this framework will help to establish frank global brain health research agenda that benefits all populations, ensuring equity in knowledge and care across regions.

The proposed framework leverages advances in global multilevel data, theoretical and computational modeling, and transdisciplinary collaboration to build more comprehensive precision models of brain health. This approach may enhance our future understanding of complex brain health dynamics and intrinsically commit to equity, warranting scientific advancements benefit all people across the world.

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AI conceived the proposal. AI and HSG wrote the first draft and supervised and coordinated the work. J.M. prepared the figures under the supervision of AI and HSG. S.B., S.F., C.C.O., H.A.E., B.L., C.Y., P.S.S., V.H., K.F., and E.T. coordinated specific manuscript sections. A.I., C.D.A., J.M., S.B., S.F., C.C.O., H.A.E., C.U.M., H.Z., S.A., C.S., I.H.R., S.Fz., T.F., J.L.M.O., S.S., F.C., P.V.S., J.X., C.Y., L.G., B.L., P.S.S., K.Y., V.H., K.F., E.T., and H.S.G. reviewed, edited, provided critical comments, and approved the manuscript before submission.

Competing interests

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