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Pursuit of precision medicine: Systems biology approaches in Alzheimer's disease mouse models

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Abstract

Alzheimer's disease (AD) is a complex disease that is mediated by numerous factors and manifests in various forms. A systems biology approach to studying AD involves analyses of various body systems, biological scales, environmental elements, and clinical outcomes to understand the genotype to phenotype relationship that potentially drives AD development. Currently, there are many research investigations probing how modifiable and nonmodifiable factors impact AD symptom presentation. This review specifically focuses on how imaging modalities can be integrated into systems biology approaches using model mouse populations to link brain level functional and structural changes to disease onset and progression. Combining imaging and omics data promotes the classification of AD into subtypes and paves the way for precision medicine solutions to prevent and treat AD.

Keywords

Alzheimer's disease; Imaging; Systems biology; Resilience; Precision medicine

1. Introduction

Alzheimer's Disease (AD) is a multifaceted neurodegenerative disease that currently has no cure or clinically effective treatments. AD is the most common form of dementia, the 7th leading cause of death globally, and the 6th leading cause in the USA, with more than 6.2 million Americans living with this disease (The Top 10 Causes of Death, 2020). This frequency is estimated to further increase in the US by 2050; however, these estimations may not accurately reflect disease prevalence as many cases likely go undetected due to diagnostic challenges that arise from the highly variable presentation of the disease (Taylor et al., 2017). The lack of consensus about disease manifestation and its typical progression emphasizes the need for improved predictive diagnostic factors. Additionally, the field would benefit from collectively taking a more holistic approach to studying this disease as

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Declaration of Competing Interest

None.

a series of interacting biological systems and factors rather than examining each involved system in isolation.

The aim of this review is to describe studies that have aided in the understanding and classification of AD using systems biology approaches that exploit imaging methods. We summarize the various factors that influence AD progression, the variable presentation of AD among individuals, and how the field of AD research is evolving to take more systems-level approaches. We focus on studies that successfully link the components of systems biology to clinical outcomes, specifically using imaging data as an intermediate to analyze disease state.

1.1. Types of AD

AD is a debilitating disease that causes progressive decline in cognitive and motor function that significantly reduces one's quality of life. A definitive diagnosis can only be determined by the postmortem detection of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles (NFT). While these two hallmarks of AD correlate with disease progression, their presence is not completely predictive of AD development as their prevalence varies based on type of AD. Plaque and tangle pathology only account for about 41% of variation in cognitive decline between individuals with AD (2020 Alzheimer's Disease Facts and Figures, 2020; Boyle et al., 2013).

Traditionally, AD cases are initially classified by genetic inheritance pattern and the age at onset (AAO) of disease symptoms. Thereafter, AD progression is characterized on a continuum based on the extent of cognitive decline and pathological load(s) (Braak et al., 2006; Braak and Braak, 1991; Markesbery, 1997). The two broad categories of AD are early onset AD (EOAD) and sporadic late onset AD (LOAD). EOAD can be subdivided to reflect cases that result from mendelian or nonmendelian inheritance of casual mutations. Mendelian, or familial, AD (FAD), is characterized by the inheritance of highly penetrant, autosomal dominant causal mutations in the genes *APP*, *PSEN1*, and *PSEN2* (Mendez, 2017; Tanzi, 2012). These mutations only account for a small percentage of FAD cases, and variation in age of onset and severity of symptoms exists among individuals, suggesting that additional genetic and environmental factors modify disease pathogenesis and clinical manifestation (Ryman et al., 2014). Nonmendelian, or non-familial, EOAD is classified by the aggressive onset of cognitive symptoms before the age of 65; however, individuals with this form of AD develop symptoms sporadically and have inconsistent inheritance patterns (Joshi et al., 2012; Reitz et al., 2020).

LOAD is the most common form of AD, occurring in individuals 65 years and older, with highly variable presentation of symptoms, which also vary in severity. Age is the greatest risk factor for LOAD, but research suggests that there are also additional causal genetic and environmental factors. According to twin and family studies, LOAD is approximately 58% to 79% heritable and gene variants in *APOE* and *TREM2* are established LOAD risk factors (Belloy et al., 2019; Corder et al., 1993; Gatz et al., 2006; Pedersen et al., 2004; Räihä et al., 1996; Roses, 1996; Strittmatter et al., 1993a; Strittmatter et al., 1993b). To date, more than 30 genetic risk variants and susceptibility loci have been identified by genome-wide association studies (GWAS) or phenome-wide association studies (PheWAS), including

CLU, *BIN1*, *ABCA7*, and *SORL1* (Andrews et al., 2020; Backman et al., 2021; Bellenguez et al., 2020; Kunkle et al., 2019; Lambert et al., 2013; Pimenova et al., 2018; Wang et al., 2016b; Wightman et al., 2021; Zhao et al., 2019). Individually, each AD-associated locus or gene variant has a relatively small effect on the likelihood of developing AD. AD risk increases with each genetic variant inherited, which overall has an additive effect on AD severity; this is referred to as polygenic risk. The compilation of genes identified using GWAS allows for the assignment of polygenetic risk scores which can aid in predicting risk or disease progression; however, additional factors such as sex and environment also need to be taken into consideration to gain a comprehensive understanding of the disease and how it manifests in individuals (Dunn et al., 2019).

Recent studies have begun to reprioritize GWAS hits by integrating multiscale data collected from relevant brain regions of interest (e.g. hippocampus) to generate network-based functional prediction methods and gene-related imaging biomarkers (e.g. brain atrophy) (Elliott et al., 2018; Knutson et al., 2020; Meng et al., 2020; Shen et al., 2010; Wachinger et al., 2018; Xu et al., 2017). Additionally, GWAS methods and imaging data have been aggregated to identify loci associated with image-derived phenotypes (Cruchaga et al., 2013; Elsheikh et al., 2020; Furney et al., 2011; Grasby et al., 2020; Hofer et al., 2020; Li et al., 2017; Matoba and Stein, 2021; Meda et al., 2012; Nativio et al., 2020; Ramanan et al., 2015; Smith et al., 2021). Ultimately, this method of combining omics and imaging data to link changes in gene expression, the biological pathways associated with those genes, and functional and structural changes in the brain, may allow researchers to further assess both EOAD and LOAD and potentially narrow down these disease classifications in subtypes.

1.2. Sex differences

Females have a higher prevalence of AD and experience more severe cognitive and noncognitive symptoms than men (2019 Alzheimer's Disease Facts and Figures, 2019). Previously, this unequal distribution of cases was attributed to the longer average lifespan of females, but in recent years more specific evidence linking sex and AD progression has been identified (Mielke et al., 2014). Among those with FAD, global amyloid load and greater tau deposition in the frontal, inferior parietal, and temporal lobes was higher in females (Groh et al., 2020; Oveisgharan et al., 2018). Interestingly, sex differences in AD development varies based on pathology load. Both males and females with low pathology load have similar risks of developing AD, whereas in individuals with moderate to high levels of pathology, disease risk is greater in females (Barnes et al., 2005). Females diagnosed with AD also experience a faster progression of hippocampal atrophy compared to males (Ardekani et al., 2016). With increased numbers of study participants to enhance statistical power, as well as computational resources and large collaborative research teams, sex-stratified GWAS have led to identification of sex-specific genetic factors that drive pathology and AD progression (Deming et al., 2018; Nazarian et al., 2019; Prokopenko et al., 2020). Expression quantitative trait loci (eQTL) mapping was performed on putative sex-specific GWAS loci to identify candidate genes that were associated with a range of AD markers for each sex. Using this method, a single nucleotide polymorphism (SNP) of the candidate locus *MAPT* was positively associated with NFT specifically in males (Dumitrescu et al., 2019). Until recently, sex was typically controlled or adjusted for as a demographic factor in

most human studies, but as experiments continue to highlight the importance of sex-specific differences in AD risk and development, it is apparent that sex needs to be more thoroughly studied in a controlled manner, while taking environmental exposures into consideration, via longitudinal investigations.

1.3. Environmental control

The relationship between AD and environmental factors has increasingly become a research topic of interest as correlations and comorbidities between AD and modifiable behaviors have been uncovered. Strikingly, recent meta-analyses have found that up to 40% of dementia and AD cases may be attributed to controllable environmental factors throughout a person's life (Barnes and Yaffe, 2011; Livingston et al., 2020; Livingston et al., 2017). Links between the interrelated health factors or AD "exposomes" including diet, exercise, chronic stress, other environmental exposures, and AD development have been acknowledged (Biessels et al., 2006; Cui et al., 2018; De la Rosa et al., 2020; Finch and Kulminski, 2019; McGrattan et al., 2019; Wild, 2012; Yang and Song, 2013). Environmental considerations also include investigating epigenetics and gene by environment (GxE) interactions by implementing GWAS to better understand genetic regulators of environmental effects and provide novel insights and targets for precision medicine solutions (Dhana et al., 2020; Eid et al., 2019; Hohman and Kaczorowski, 2020). The list of modifiable environmental factors that potentially impact AD progression continues to increase as research techniques and technology evolve to better survey large populations. Each of these factors and many others play a synergistic role and likely interact with genes to modify expression resulting in a certain phenotype. These factors and their effects are conditional in their role in AD development and progression (Chouliaras et al., 2010). For instance, aspects of weight control have been subjected to evaluation as certain diets and exercise regimes have proven to be beneficial to long term health and reduced disease incidence in later life. Reduced weight is often seen as a biomarker for AD that can occur even a decade before the onset of cognitive symptoms (Barrett-Connor et al., 1996; Buchman et al., 2005; Gillette-Guyonnet et al., 2000; Johnson et al., 2006; Wolf-Klein et al., 1992). When relating body mass index (BMI) and polygenetic risk scores calculated using all SNPs from a recent AD GWAS in humans, lower BMI and higher polygenic risk score significantly predicted conversion to AD (Moody et al., 2021). Conversely, early and mid-life increased weight and obesity, including that linked to high-fat/high sugar Western diet consumption is associated with increased risk of AD and dementia (Naderali et al., 2009; Profenno et al., 2010; Tabassum et al., 2020). Overall, studying environmental effects on AD in human populations is extremely challenging due to lack of experimental control and wide amount of environmental variation humans are exposed to. This is further exacerbated because most studies rely on participant self-reporting and these results are often inaccurate and inconsistent (Cherbuin and Anstey, 2012; Otaegui-Arrazola et al., 2014; Rueda et al., 2015; Singh et al., 2014; Yusufov et al., 2017). When these inconsistencies are paired with the overwhelming amount of genetic diversity among humans, attempts to elucidate GxE interactions that influence AD are experimentally difficult.

1.4. Opportunity to complete longitudinal studies

While sex and environmental factors contribute to the development and progression of AD, age is the greatest non-modifiable risk factor and the primary driver of developing AD. Disease risk dramatically increases after 60 years of age, but AD is not a normal aspect of aging, and not all individuals that exhibit hallmark AD pathology or symptoms develop AD (Hebert et al., 2013; Sonnen et al., 2011; Toepper, 2017). The definition of AD stages has evolved and become more dynamic as researchers have determined that disease development varies between individuals. Initially, the stages of AD were defined at the autopsy of individuals that showed clinical signs of AD, like severe memory impairment, in life. Postmortem analysis of AD stages were ultimately based on the regional distribution, type, and density of brain pathology (Braak and Braak, 1991). Recently, preclinical and presymptomatic stages of AD were identified based on pathology in the post-mortem analysis of brains of cognitively unimpaired people. This suggests that disease onset can be defined differently depending on the evaluation of brain pathology versus clinical symptoms (Dubois et al., 2016; Hubbard et al., 1990; Sandberg et al., 2001; Villemagne et al., 2011). The discovery that AD-related changes in the brain and pathology accumulation can begin potentially decades before the onset of clinical symptoms revealed potential confounds in previous AD cross-sectional studies that only analyzed individuals with MCI and AD versus “cognitively healthy control” subjects, as their control groups could have included pre-symptomatic individuals with AD pathology (Aisen et al., 2017; Bennett et al., 2006; Driscoll and Troncoso, 2011; O’Brien et al., 2009; Price et al., 2009). In addition to identifying asymptomatic and prodromal phases of AD, recognition of hallmark AD pathology in cognitively intact individuals has also led to the classification of resilience and susceptibility to AD-related decline (Aiello Bowles et al., 2019; Driscoll and Troncoso, 2011; Dumitrescu et al., 2020; Hampel et al., 2019a; Hohman et al., 2016; Negash et al., 2013; Neuner et al., 2017b; Stern et al., 2020; Walker and Herskowitz, 2020). Longitudinal efforts to identify biomarkers and endophenotypes that allow for refined stage assessment are more crucial than ever as preclinical stages at which hallmark symptoms are not detectable may be an opportune period to engage in disease slowing or prevention measures. Additionally, understanding what factors shield resilient individuals versus those that cause others to be severely susceptible to AD development may provide key insight for treatment advancement (Seto et al., 2021). Longitudinal studies allow for the evaluation of AD as a continuum, but most of these studies only follow up with patients for an average of 1–2.5 years with limited repeated measures (Lawrence et al., 2017). Furthermore, only a few longitudinal human studies and designated aging cohorts such as the Religious Order Study, Mount Sinai Brain Bank study, or Rush Memory and Aging Project have the capacity to comprehensively assess disease progression (Bennett et al., 2018; De Jager et al., 2018; Wang et al., 2018). Current human biomarkers measured longitudinally lack the sensitivity to identify early disease stages and disease subtypes (Cummings, 2019). Ultimately, there is a need for model systems to better investigate the early stages of AD, AD causation, and to take a higher resolution look at changes in brain structure that occur with age and disease progression, especially during the stage when AD is clinically silent, and no overt symptoms are detected.

1.5. The call for mouse models of AD

Mouse models of AD offer the opportunity to study the disease longitudinally and in a more controlled manner to gain a better understanding how it manifests and progresses in humans. Mouse models are particularly advantageous because they can provide replicable genomes in controlled environments across relatively short lifespans, which can be implemented to address gaps in human research. Although many models are pathology-centric, there are currently over 205 existing AD mouse models that vary in their presentation of plaques, tangles, neuronal loss, gliosis, and synaptic dysfunction (Research Models: Alzheimer's Disease, 2021). These models mostly consist of transgenic, knock-in (KI), or out (KO) modifications of single genes or a combination of genes associated with human AD, including *APP, PSEN1/2, APOE, Trem2, BACE1, BACE2, MAPT* and other GWAS-identified genes on various background strains (Drummond and Wisniewski, 2017). These models display AD-related phenotypes that can be accurately assessed and associated with disease progression (Götz et al., 2018; Granic et al., 2010; Keene et al., 2016; Romberg et al., 2013).

Recapitulating human AD (particularly LOAD) in mouse models has proven difficult; therefore, choosing the appropriate AD model mouse population is crucial since many models selectively display different aspects of the disease and mouse findings have not translated well to humans (Cao et al., 2018; Cummings et al., 2014; Franco and Cedazo-Minguez, 2014; Jankowsky and Zheng, 2017; King, 2018). A reason for this lack of translatability is that most traditional mouse models of AD are made using genetically identical mice and lack the genetic diversity present in humans (Moore et al., 2020; Onos et al., 2016). While traditional mouse models, which were needed, timely, and useful for their era, were a great starting point for using model systems to study AD, it is now apparent that they are not the most translationally relevant models available and that genetic diversity is crucial for both the development of models and AD mouse research moving forward.

1.6. Translatable mouse models

To combat the limitations of traditional mouse models, mouse models with diverse genetic backgrounds have recently been generated and utilized to study AD in a more translational manner (Neff, 2019; Neuner et al., 2019a; Neuner et al., 2017a; Neuner et al., 2020; O'Connell et al., 2019; Onos et al., 2019; Yang et al., 2021). For example, genetic diversity can be added to standard AD mouse models with the incorporation of BXD recombinant inbred strains. The BXD panel is the product of independent advanced intercrosses between C57BL/6 J (B6) and DBA/2 J (D2) progenitor strains (Peirce et al., 2004). Application of the BXD panel is conducive to systems biology approaches, as the panel has a genetically defined diverse background that can be easily manipulated in a reproducible manner. The BXD family segregates at over five million common genetic variants and more than 140 strains are currently available (Wang et al., 2016b). These additional BXD strains offer greater mapping power and the ability to refine mapping precision (Ashbrook et al., 2021). The BXD population has been highly characterized in a variety of studies, creating a wealth of phenotyping and omics data (Studies Involving BXD RI Panel, 2021). The BXD population was demonstrated to be a valuable resource for creating the first mouse model that better recapitulates the complex heterogeneity of genetic, molecular and cognitive

features of human cognitive aging and AD (Neuner et al., 2016; Neuner et al., 2019a; Neuner et al., 2017a). The AD-BXD population was generated by crossing the commonly used B6–5XFAD AD mouse model with strains from the BXD panel. The AD-BXD panel offers all of the advantages of the BXD population in an AD mouse model, and, importantly, this model mouse panel exhibits a range in age at onset and variation in AD symptom severity that is comparable to LOAD in human populations (Neuner et al., 2019b; Neuner et al., 2017a; Ryman et al., 2014). This panel also exhibits a high degree of genetic and transcriptomic overlap with human LOAD (Heuer et al., 2020; Lambert et al., 2013; Neuner et al., 2019a; Neuner et al., 2017a; Wan et al., 2020). Ultimately, genetically diverse panels like the AD-BXD that recapitulate multiple facets of AD offer the scientific community a more applicable model system to study the genetic mechanisms that modify the onset and progression of AD across a population.

1.7. Use of systems biology to better understand the complexity of AD

Following the advent of the amyloid beta cascade hypothesis as a proposed cause of AD, numerous clinical trials targeted the reduction and prevention of amyloid plaques in an attempt to lessen the symptoms and progression of AD (Hardy and Selkoe, 2002; Hardy and Higgins, 1992; Lemere and Masliah, 2010; Reitz, 2012; Schneider et al., 2014). None of these trials successfully alleviated pathology progression, neurodegeneration, or major long-term symptoms, therefore forcing the research community to acknowledge the immense complexity of AD (2020 Alzheimer's Disease Facts and Figures, 2020; Cao et al., 2018; Chen et al., 2017; Langley, 2014). Since this realization, AD researchers more commonly utilize systems biology approaches to better understand interactions between various systems in the human body and how they impact, and are impacted by, AD (Alberghina and Colangelo, 2006; Castrillo et al., 2018; Lista et al., 2016; Rosario et al., 2020). The fact that we observe similar disease phenotypes despite differences in genetic modulators (ex: between FAD and LOAD) suggests that the different causes of disease are not unrelated but are rather likely due to dysregulation of similar biological networks. Systems biology is a field of study built on the organization of sub fields responsible for complex behaviors and outcomes, including identifying the links between genes and behavior according to the net interactions of varying components (Liu, 2005). Modern systems biology involves interdisciplinary, data-driven approaches with a greater focus on untangling complex interactions between genetic, epigenetic, physiological, and environmental factors at multiple system levels within an organism. Recent advancements in biotechnology have made this approach more feasible and enable genome-wide and multi-omics studies to be conducted with multiple disease-mediated factors (Heuer et al., 2020; Lam et al., 2020). Systems biology puts a greater emphasis on connection, integration and modularity of genes and pathways rather than single causal gene predictions. This approach is crucial for the study of complex diseases like AD because their cures require multifaceted treatments tested in diverse and translatable models. Development of such a treatment requires the implementation and integration of transcriptomics, proteomics, metabolomics, genomics, epigenomics, lipidomics, and/or micro-biomics to gain a wholistic understanding of complex systems across representative populations (Fig. 1) (Ahn et al., 2006; Ehrenberg et al., 2003; Hiesinger and Hassan, 2005; Kirschner, 2005; Kitano, 2002b; Liu, 2005; Weston and Hood, 2004). Ultimately, the harmonization of multiple data types

across various body systems will provide a better method of surveying the many components involved in the development and progression of AD.

Expanding beyond correlational analyses, systems biology has also benefitted from the advent of causal inference methods in establishing links between genotype and phenotypes, and all systems in between (Haas et al., 2016; Shen et al., 2020). Adopting this approach to studying AD, national and international human and mouse focused consortia were launched to integrate data types to gain a better understanding of the brain and the changes that occur in response to onset of AD. Initiatives by The Alzheimer's Association, Human Brain Project, and Foundation for the National Institutes of Health Biomarkers Consortium have all taken steps to implement systems biology approaches to studying AD. The National Institute on Aging's AD Translational Research also established programs including Accelerating Medicines Partnership- AD (AMP-AD), Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease (M2OVE-AD), Translational Center for Model Development and Evaluation for Late Onset Alzheimer's Disease (MODEL-AD), Cognitive Resilience to Alzheimer's Disease (Resilience-AD), and Neuropsychiatric Symptoms in Alzheimer's Disease (Psych-AD), which are dedicated to uncovering the multifaceted roots of AD. Furthermore, there are initiatives dedicated to including specific methods such as the Alzheimer's Disease.

2. AD diagnosis: from the lab to the clinic

2.1. Imaging modalities to assess AD

With advancements in technology, imaging modalities have recently become a highly effective method for identifying and monitoring age-and AD-related structural and functional changes in the brain. Modern forms of microscopy implemented in mouse models allows for better spatial and temporal resolution images than ever before. Cross sectional whole 2D and 3D brain mapping at different disease stages and ages can now be used to identify regional vulnerability to pathology or changes in specific cell types, especially in deeper brain regions difficult to access *in vivo* (Chen et al., 2018a; Gail Canter et al., 2019; Lichtenegger et al., 2018; Munoz-Castaneda et al., 2021; Whitesell et al., 2019). These techniques can also be applied in transgenic mice or those injected with specific tracers, such as those used to label active neurons during a memory task, to establish connections between regional activation and behavior (Roy et al., 2019; Vetere et al., 2017). While the application of imaging modalities can be readily applied in mouse models, currently these methods have been most thoroughly investigated in humans.

Improvements in *in vivo* imaging resolution and accessibility now allow for human AD diagnoses prior to pathology and atrophy detection at death. The most commonly utilized methods include the minimally-invasive magnetic resonance imaging (MRI) and positron emission tomography (PET), which give researchers and medical teams a better look at the active brain to then make a diagnosis and assess disease state (Marcus et al., 2014; Márquez and Yassa, 2019; Scheltens, 2009; Smith, 2002). Various imaging approaches (outlined in Table 1) allow for the detection of neural connectivity deficits, the presence and progression of pathology, tissue atrophy, and even metabolic measures. These measures can then aid in the discovery of brain regions vulnerable to specific measures collected during each

imaging processes (Johnson et al., 2012; Pini et al., 2016; Reiman and Jagust, 2012; Teipel et al., 2015; Young et al., 2020). Since many features of AD can be detected non-invasively, imaging can be readily used to increases the accuracy of clinical assessments and monitored longitudinally (Jack et al., 2013; Jack Jr. et al., 2010; Jagust et al., 2006; Karow et al., 2010; Oishi et al., 2011; Ota et al., 2015; Zhang et al., 2011). Identification of predictive AD biomarkers and patterns in structural and functional changes can be used as endophenotypes to relate to other aspects of systems biology to address the biological mechanisms driving AD progression. This integration of imaging and omics data collected with systems biology approaches, or neuroimaging-omics, is an emerging field dedicated to characterizing genetic, biological, and phenotypic clusters which can then be used to develop methods for detecting, treating, or possibly preventing disease development with early intervention (Hampel et al., 2021; Mroczek et al., 2021; Richiardi et al., 2015). Many neuroimaging-omics studies employ machine learning frameworks to multi-modal data to predict potential AD risk in MCI and pre-symptomatic patients (Basaia et al., 2019; Khanna et al., 2018; Scelsi et al., 2018). Neuroimaging-omics has the potential to untangle genetic mutations, gene expression patterns, and protein-protein interactions and determine how they are linked to large-scale structural and functional network deficits and disease manifestation.

2.2. Technology's contribution to enhancing the imaging field and AD experiments

Disease characterization and identification of AD biomarkers with imaging analyses have significantly progressed due with advances in modern technology. Methods to accommodate the large datasets required to power systems biology experiments are being streamlined to reduce the significant subjectivity and time commitment previously required to obtain and interpret results from imaging studies. Using automated pipelines that incorporate standard brain atlases, like the Allen Brain Atlas Common Coordinate Frame, comprehensive connectivity maps are being developed to better understand mammalian brain circuitry (Denk et al., 2012; Wang et al., 2020). The Mouse Brain Architecture Project, Allen Mouse Brain Connectivity Atlas project, and Mouse Connectome Project each have taken on the challenge of systematically mapping the spatial profiles and the connectivity of neuronal populations throughout the brain (Bohland et al., 2009; Furth et al., 2018; Helmstaedter and Mitra, 2012; Mitra, 2014; Oh et al., 2014; Osten and Margrie, 2013). Through these investigations and others, a myriad of image analysis pipelines been created to investigate links between regional brain activity, gene expression, and behavior (Feng et al., 2015; Freeman et al., 2014; Ji et al., 2014; Ng et al., 2009; Renier et al., 2016). Computational biologists are also creating these workflows to increase reproducibility, make machine learning and automated imaging processing methods more accessible to biologists, and allow high-throughput processing across the brain. Semi-automatic registration methods with all parameters shared with the scientific community encourage non-experts to analyze high resolution MRI, DTI, histology, and two-photon tomography results (Anderson et al., 2019; Budin et al., 2013; Esteban et al., 2019; Furth et al., 2018; Liu et al., 2020; Niedworok et al., 2016; Pagani et al., 2016; Pallast et al., 2019; von Chamier et al., 2021; Winnubst et al., 2019; Yates et al., 2019). The recent combination of neuroimaging, computer-aided diagnosis techniques, and machine learning methods (e.g. linear discriminant, logistic regression, random forest, and neural networks analyses) have allowed researchers and clinicians alike to establish data-driven AD classification standards (Basheera and Sai

Ram, 2019; Dimitriadis et al., 2018; Leandrou et al., 2018; Liu et al., 2019; Wen et al., 2020). Integrating multi-omics data is also increasingly more feasible and approachable for biologists with the development and improvement of omics technologies aimed at aiding the combination and analysis of multiple data types (outlined in Table 2). The availability and application of current tools have also been thoroughly reviewed (Adil et al., 2021; Graw et al., 2021; Huang et al., 2017; Krassowski et al., 2020; Ma et al., 2020; Misra et al., 2018; Nicora et al., 2020; Subramanian et al., 2020; Worheide et al., 2021). One noted drawback of many of the mentioned tools in these reviews is that they do not necessarily have the capacity to incorporate imaging or behavioral phenotyping data in addition to the varying omics data.

Moreover, systematic machine-learning assisted approaches to imaging are no longer exclusively restricted to post-processing analyses but also to assist in experimental parameter design to enhance microscopy techniques and output. This field of “smart microscopy” integrates feedback from the microscope to adjust computer assisted imaging algorithms to optimize sample coverage, extend the field of view, or improve spatial resolution and signal strength (Durand et al., 2018; He and Huisken, 2020; Mahecic et al., 2020; Royer et al., 2016). Researchers are now equipped with the ability to map regional behavior-induced brain activity, which can prove to be highly valuable in determining which regions, cell types, and circuits are most heavily affected by AD and in response to certain tasks assessing clinical symptoms.

3. Incorporating imaging outcomes in mouse systems biology studies to predict cognitive outcomes and AD progression

Imaging approaches have proven to be an invaluable resource to the field of AD research in terms of assessing changes in neuroanatomy and neural connections; however, attempts to link imaging measures and multi-omics data to phenotypic disruptions associated with AD in model systems remain scarce. Furthermore, many of these studies are not sufficiently powered with the number of mice needed for the application of systems biology approaches. Although current approaches for assessing the brain using imaging methods do not allow for the discovery of the mechanisms and interacting relationships driving these changes, efforts to link imaging measures to cognitive outcomes are underway. Imaging modalities used to visually assess disease progression provides researchers with an intermediate to model the relationship between structure and function in model mice.

Depending on the study of interest, imaging data is independently compared to or directly correlated with cognitive functioning within cohorts of model mice to assess functional or connectivity properties in relation to level of AD-related decline. MRI studies using a variety of model mouse lines have described changes in regional neuronal activity, differences in volume, and structural integrity to identify vulnerable brain regions. For example, manganese enhanced MRI (MEMRI) can be used to map complex brain circuits involved in spatial memory. Decrease in MEMRI signal after Morris water maze (MWM) testing corroborates the reduced neuronal activity in memory circuits typically seen in old AD mice (Badea et al., 2019). Similarly, identification of regional atrophy in relation to

behavioral outcomes can also be explored. Among several types of AD model populations, atrophy at the whole brain level, as well as memory associated areas like the hippocampus, entorhinal cortex, amygdala, and temporal association cortex has been observed in mice with reduced spatial memory (Liang et al., 2017; Tang et al., 2016). Depending on the mouse line used, these changes in brain structure and connectivity can be observed as early as 2 months of age, preceding the onset of amyloid deposition and severe cognitive decline (Badea et al., 2010; Falangola et al., 2007). Studies that validate changes in MRI volume with histology provide further evidence that MRI outcomes that identify regional atrophy correspond to reductions in neuron counts and poor spatial memory performance (Badea et al., 2019). However, currently there is a lack of consensus regarding regional atrophy or enlargement in mice and how this difference relates to reduced cognitive performance on memory tasks and certain ages (Badhwar et al., 2013; Maheswaran et al., 2009).

Brain metabolism has also been related to cognitive performance using fluorodeoxyglucose (FDG) PET. Correlation analyses have showed that hippocampal standardized uptake values were significantly correlated with MWM parameters at the symptomatic-AD stage (Li et al., 2016). Aged Tg4-42 transgenic animals with compromised spatial memory also display neuron loss, regional volume decreases, and hypometabolism – as measured by reduced tracer uptake, in the hippocampus, forebrain, hypothalamus, amygdala and midbrain (Bouter et al., 2018). Likewise, neuroinflammatory response supported by histology shows significant effects of age and genotype on translocator protein (TPSO) tracer uptake in the hippocampus and cortex exist in $APP_{swe} \times PS1_{\Delta e9}$ transgenic mice, but their working memory performance greatly varied with age (Chaney et al., 2018). Serial PET measures of TSPO and amyloid with terminal spatial memory assessment in PS2APP model mice, followed by immunohistochemical analyses of microglia, amyloid, and synaptic density revealed that high microglial activation at the onset of amyloidosis (8 m of age) predicts better cognitive performance in PS2APP mice at follow-up 5 months later (13 m of age), when amyloid pathology is extensive. Highest TSPO PET signal was found in areas associated with spatial learning and negatively correlated with Iba1 immunostaining (Focke et al., 2019). Conducting multi-modal analyses help in defining a more precise relationship between cognitive outcomes and morphological changes of the brain. Moreover, *in vivo* 2-photon calcium imaging evaluation of APP23xPS45 mice has shown neuronal hyperactivity near Aβ plaques. With this information, a correlation was observed between the formation of amyloid plaques, the appearance of hyperactive neurons, and the age-related impairment of the spatial learning capability (Busche et al., 2008). Further studies investigating neuronal hyperactivity revealed that the function of hippocampal neurons is altered long before that of cortical neurons (Busche et al., 2012).

Moving beyond comparisons between imaging measures and behavior, the field is turning towards probing neuroimaging-omics interactions in mice (Liu and Liu, 2011). For example, genetic mapping of phenotypes derived from imaging data using the BXD panel revealed significant quantitative trait loci associated with traits such as hippocampal volume (Ashbrook et al., 2014). Cellular and pathology loads calculated using brain-wide immunohistochemistry can also be integrated with bulk RNA sequencing data to evaluate associations between regional cell counts, gene expression, and biological, molecular, or cellular pathways (Gurdon et al., 2020). Moreover, spatial transcriptomics offers the ability

to survey regional transcriptional changes in mice. Using this method, molecular changes occurring in cells in the vicinity of amyloid plaques can be investigated by characterizing gene co-expression networks that appeared to be highly responsive to Aβ deposition. The plaque-induced genes (PIGs) are a response in multiple cell types across the brain and are implicated to involve the complement system, oxidative stress, lysosomes, and inflammation, all of which are more prominent in the later phases of the disease (Chen et al., 2020). Furthermore, regions vulnerable to AD-related changes can be honed in on to uncover molecular targets, such as those that may contribute to early hippocampal synaptic deficits and olfactory dysfunction in AD mice (Navarro et al., 2020). Ultimately, these studies and many more incorporate select aspects of systems biology and imaging methods to tie together genotype and phenotype; however, many studies that employ imaging techniques are lacking complementary omics and behavioral data to achieve a comprehensive analysis of brain changes with AD.

4. Refining AD diagnosis with the establishment of subtypes

There is a novel opportunity to more optimally segregate AD into subtypes by combining *in vivo* depictions of AD progression (collected via imaging) with omics data. By refining AD diagnoses beyond typical, resilient, or susceptible, researchers will be able to better understand the heterogeneity of AD symptoms, manifestation, and causal influences, which will be crucial for executing precision medicine approaches and developing successful treatments for AD.

Noticing that not all human AD cases neatly follow Braak staging, researchers have begun to classify subtypes of AD based on the detection of regional pathology in conjunction with clinical data. Early approaches to tackle this discrepancy evaluated cases that had severe Braak scores and subdivided them by NFT density and location. Three postmortem classifications of typical, hippocampal sparing, or limbic predominant AD were derived and further characterized in terms of prevalence in the experimental population, age demographics, and rate of cognitive decline exhibited within each subtype (Murray et al., 2011). Building on this concept, tau-PET in combination with demographic data, clinical outcome measures, and APOE e4 frequency was used to refine these subtypes into pathology driven region-specific subtypes prior to death (Armstrong and Wood, 1994; Charil et al., 2019; Ossenkoppele et al., 2020; Vogel et al., 2021; Whitwell et al., 2018). Recent approaches that further evaluated these subtypes found that there is largely a consensus between subtyping based on tau-PET and regional atrophy measured using structural MRI methods (Kolanko and Malhotra, 2018; Park et al., 2017; Ten Kate et al., 2018). Differential patterns of brain atrophy revealed general and reproducible subtypes of AD, including typical, limbic-predominant, hippocampal-sparing, mild atrophy, and no atrophy (Byun et al., 2015; Ferreira et al., 2017; Karkkainen et al., 2020; Whitwell et al., 2012; Zhang et al., 2016). FDG-PET has been implemented as an additional measure correlated with regional atrophy to enhance subtype specificity (Huang et al., 2017; Levin et al., 2021). Such studies link individuals with hippocampal sparing AD, greater global hypometabolism, and reduced executive functioning (Risacher et al., 2017). Importantly, while these classifications are beneficial for appreciating the heterogeneity of AD, there are

methodological inconsistencies, and unbiased, multi-modal approaches are needed to better explore disease mechanism (Mohanty et al., 2020).

With the capacity to combine imaging data with genetic information, unique subtypes rooted in clinical phenotypes, omics, and known regions vulnerable to dysregulation can be classified. Understanding subtypes of AD can allow researchers to develop targeted treatments and clinicians to better predict disease course in patients. By clustering differentially expressed genes and conducting weighted network analyses, tau-mediated neurodegeneration, amyloid-β neuroinflammation, and synaptic signaling subtypes were developed (Neff et al., 2021). These subtypes are well represented in complementary mouse models, including the AD-BXD mouse panel (Philip et al., 2021, unpublished personal communication). Since these subtypes were identified as independent of age and disease severity, there is potential for supplemental data types to be incorporated to promote the identification of predictive factors that can then be tested longitudinally. More specially, studying *in vivo* functional neuroimaging outcomes in combination with other systems biology approaches in transgenic mice may yield important insights regarding the mechanisms that underlie the development of different AD subtypes (Fig. 2).

Precision medicine is driven by the application of high-throughput systems biology, powerful computational and statistical modeling tools, and the integration of asymptomatic, preclinical, and clinical datasets to identify and connect novel causal mechanisms of AD (Castrillo et al., 2018; Hampel et al., 2016; Hampel et al., 2018). The resulting subtypes and networks identified foster precise early preclinical detection, effective prevention, and personalized disease modifying treatments (Collins and Varmus, 2015; Hampel et al., 2019b; Uddin et al., 2019). To attain this level of understanding of AD mechanism and manifestation, large-scale model organism experiments that survey translatable AD biomarkers need to be performed (Fig. 2).

5. Future directions of systems biology and use of imaging modalities to evaluate AD progression

Systems biology has the potential to change how AD is defined and translated from bench to bedside. Human studies have demonstrated that identifying structural and functional relationships using *in vivo* imaging data combined with clinical outcomes has increased our understanding of disease outcomes. Expanding and building upon these studies using model mouse populations will allow researchers better control and the ability to manipulate mechanistic networks across various scales of biology and environmental exposures. Applying systems biology approaches to large reproducible cohorts will be a crucial step toward identifying predictive AD biomarkers, establishing predictive models, and creating precision medicine solutions.

While the benefits of these approaches are clear, there are current challenges to applying imaging modalities and systems biology. Taking a systems biology approach to investigating precision medicine solutions to AD necessitates large sample sizes. Current human studies require hundreds to thousands of individuals to map genetic risk loci or correlate biomarkers with clinical outcomes (Ard and Edland, 2011; Brookmeyer and Abdalla, 2019; Ederer et

al., 1993; Grill et al., 2013). To achieve more confident results from genetic mapping, the same is also needed in mouse studies. Large sample sizes are essential to pursue multimodal analyses of varying biological systems and scales. Monetary and time investments can also greatly influence the feasibility to complete these studies, but a well powered study in an appropriate model has the potential to significantly contribute to the understanding and mechanisms of AD. Moreover, applying imaging modalities to large systems biology datasets requires a significant amount of data processing, which presents the opportunity to introduce user bias. To combat this, the field is pushing towards standardization of imaging acquisition and processing methods (Mueller et al., 2005; Whitesell et al., 2019). Even when using identical mouse models and similar imaging approaches, independent labs can achieve varying results for measures like rate of amyloid plaque accumulation or regional levels of atrophy (Kolinger et al., 2021; Mannheim et al., 2018; Morbelli and Bauckneht, 2018; Osborne et al., 2017). This lack of consistency makes it difficult to combine and compare results, and for these reasons, all processing parameters should be disclosed to promote reproducibility (Eisenstein, 2020). The creation of centralized data portals and collaborative efforts have promoted this type of synchronicity (Hodes and Buckholtz, 2016; Kitano, 2002a). These sites provide researchers a platform to collaborate, contribute their own data, or to analyze data from other groups (Table 3). Furthermore, another area the AD imaging field can improve upon is in the analysis of subjective regions of interest (Simpson et al., 2021). Manual stereology or delineation is based on the user's experience and anatomical knowledge. Even the scope and use of machine learning and artificial intelligence guided methods is biased by users as they set training parameters. Use of more automated pipelines and standard brain atlases aid in reducing the subjectivism of quantifying and reporting region specific measures (Bjerke et al., 2018; Boline et al., 2008; Hawrylycz et al., 2011; Hjornevik et al., 2007; Johnson et al., 2010; Wang et al., 2020). High throughput studies including many regions of interest or brain-wide approaches can give a more comprehensive large-scale look at the changes that occur with disease status.

6. Conclusion

Integrating multiple imaging modalities with the various omics of systems biology permits a thorough investigation of AD and its interacting components across various biological systems and scales. The need to incorporate many imaging and omics methods to study individual humans or mouse strains pays tribute to the complexity of this disease. Modelling AD in mice offers the advantage of parsing out the interacting components underlying AD manifestation in a controlled fashion. Evaluating a wide variety of strains, samples, and methods within translationally relevant mouse panels enables researchers to untangle the mechanisms perturbed in the different subtypes of AD. AD progression is viewed as a spectrum, but patterns of interacting levels of systems biology (e.g. genomic, transcriptomic, or metabolomics relationship to neural connectivity) are evident and are the foundation for classifying mouse models and human individuals into AD subtypes. Categorizing individuals' disease subtypes paves the way towards fully understanding the complexity of AD, how it manifests differently among individuals, and eventually, precision medicine solutions.

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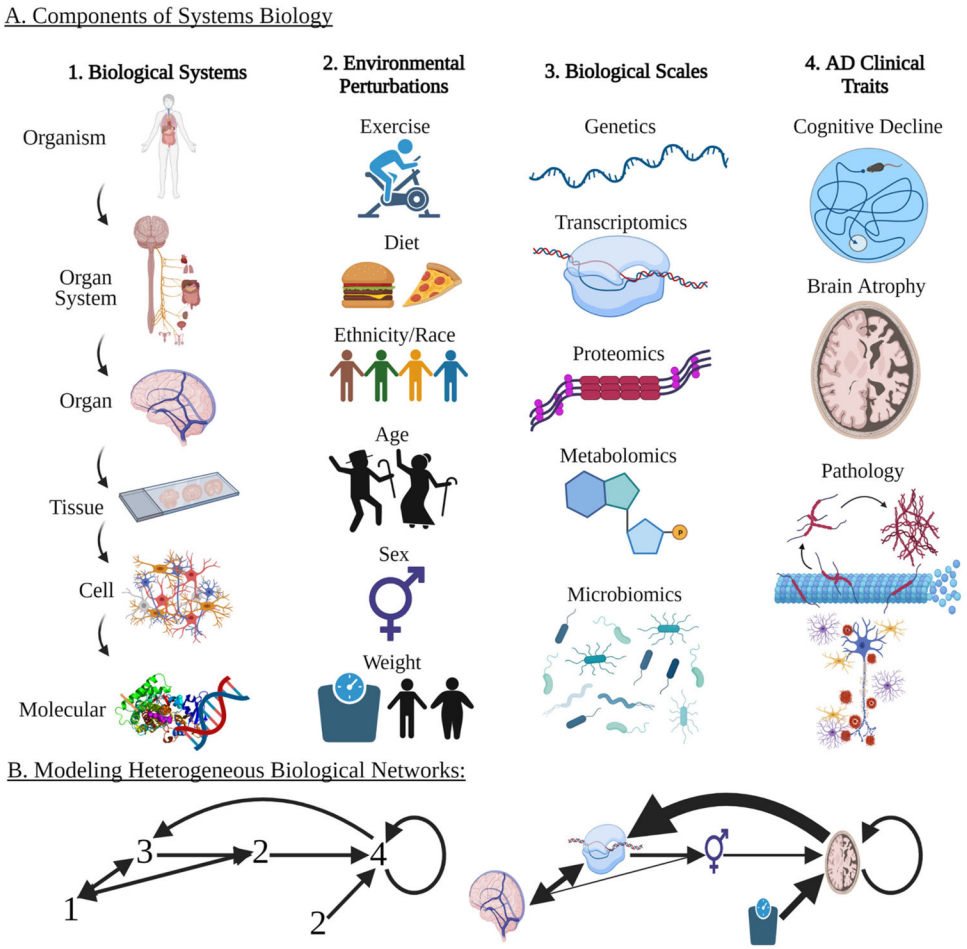

Fig. 1.

Analyzing the Interacting Components of System Biology in the Study of Alzheimer's Disease (A) The study of systems biology and the discovery of genotype to phenotype relationships involves the interaction of multiple levels: 1. biological systems, 2. environmental perturbations, 3. biological scales, and 4. clinical traits. (B) Because AD is a complex disease, modeling of biological networks is required to test and discover the relationship between factors and mechanisms. Combinations of single or multiple factors from each biological and environmental scale (A:1–4) should be included in models to determine the correlation between data types and resulting clinical outcomes. (B) shows a hypothetical model of how the factors from (A) could interact. Each factor can impact others with varying weights of influence indicated by the width of the arrows. (Created with BioRender.com).

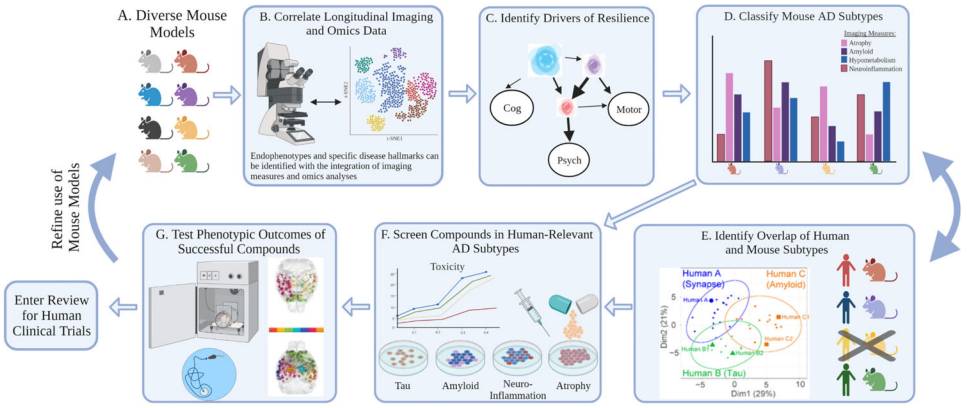

Fig. 2.

Utility of animal models and systems biology approaches for precision medicine solutions (A) Using a translationally relevant and diverse model mouse population, (B) a vast amount of longitudinal imaging and omics data can and has been collected to develop predictive networks and (C) identify drivers of resilience. (D) These identified modulators can guide the classification of AD subtypes. Subtypes reflect a pattern or prevalence of the collected imaging and omics endophenotypes measures. Single or groups of mouse strains can then be classified into these subtypes based on the display of similar traits, and if available, compared to established human subtypes. Mice sorted into these subtypes can then directly enter the precision medicine discovery drug cycle. (E) We recently tested AD-BXD strains against established human AD subtypes to define human relevant subtypes from hippocampal RNAseq data. (F) Mouse subtypes that appropriately align with human subtypes will then proceed through the pipeline. In vitro models that recapitulate the cellular and molecular profiles of each subtype can be create and implemented to conduct compound screens. Measures of neurodegeneration, synapse number and type, axonal degeneration, and neuron excitability can be quantified to assess the result of each compound on the model system. (G) The efficacy of a select compound's ability to alter disease course in mice of certain subtypes can then be assessed in vivo with cognitive phenotyping. Overall outcomes of this pipeline will enable precision medicine solutions to be identified per disease subtype and then potentially applied in clinical trials for humans or to refine the selection of mouse strains in future discovery trials. (Created with BioRender.com).

Table 1

Neuroimaging in AD: modalities and typical findings.

Imaging modality	Brain measurement	Measured changes with relation to AD	Citations
F-fluorodeoxyglucose (FDG) PET	• FDG compound uptake from neurons in the brain is analogous to glucose uptake. Glucose is the main energy substrate of the brain • Glucose uptake and brain metabolism is related to neuronal and synaptic function	• Glucose hypometabolism is commonly observed in the parietotemporal association cortices, posterior cingulate cortex, and the precuneus bilateral temporoparietal. • Hypometabolism highly correlates with the pathological diagnosis of AD	(Brown et al., 2014; De Santi et al., 2001; Foster et al., 1983; Foster et al., 2007; Hoffman et al., 2000; Marcus et al., 2014; Mosconi, 2005; Silverman et al., 2001)
Amyloid PET	• Tracer uptake used to identify Aβ plaque accumulation	• Identify the presence, location, and spread of amyloid throughout the brain • Higher tracer retention found in the frontal cortex parietal cortex, corpus striatum, temporal, and occipital cortex • Not conclusive as a diagnostic factor since amyloid accumulation can greatly vary among those with and without AD	(Agdeppa et al., 2001; Cselényi et al., 2012; Kudo et al., 2007; Landau et al., 2014; Ossenkoppele et al., 2012; Rinne et al., 2012; Rowe et al., 2008; Verhoeff et al., 2004; Wong et al., 2010)
Tau PET	• *In vivo* tracers used to identify tau deposition • Tracers bind to aggregated intracellular and extracellular neurofibrillary tangles	• Tracer retention is higher in those with AD • Accumulation commonly found to spread from inner regions like the medial temporal lobe outward towards the hippocampus, entorhinal cortex, and fusiform gyrus and lastly into the neocortex indicative of disease progression • Tracer binding is negatively correlated with cognitive performance	(Brier et al., 2016; Cho et al., 2016; Jack Jr. et al., 2018; Leuzy et al., 2019; Maass et al., 2017; Mueller et al., 2020; Scholl et al., 2019; Wang et al., 2016a)
Synaptic vesicle glycoprotein 2A (SV2A) PET	• SV2A is ubiquitously expressed in essentially all presynaptic vesicles • Imaging of radioligand tracers to detect SV2A • Detection is used as a biomarker for synaptic density	• Reduced tracer uptake indicates synapse loss in the hippocampus and entorhinal cortex, as well as the parahippocampal cortex, amygdala, lateral temporal cortex, prefrontal cortex, posterior cingulate cortex (PCC)/precuneus, lateral parietal cortex, and pericentral cortex • Negative relationship between global amyloid deposition and SV2A binding • Positive correlation of hippocampal SV2A binding associated with episodic memory	(Bastin et al., 2020; Cai et al., 2019; Chen et al., 2018b; Finnema et al., 2018; Mecca et al., 2020; O'Dell et al., 2021)
Translocator Protein-18 kDa (TSPO) PET	• TSPO is a transmembrane domain protein expressed on the outer mitochondrial membrane of microglia • Tracer binding is a measure of microglial density and neuroinflammation	• Increased TSPO binding is found in regions with high pathology including the hippocampus, striatum, lateral temporal, parietal, anterior cingulate cortex, and medial prefrontal cortex	(Edison et al., 2008; Kreisl et al., 2016; Kreisl et al., 2013; Lagarde et al., 2018; Mirzaei et al., 2016; Tournier et al., 2020; Yasuno et al., 2008)

Imaging modality	Brain measurement	Measured changes with relation to AD	Citations
	• TPSO expression is upregulated in activated microglia and astrocytes	• Increased TSPO tracer binding is associated with greater glial activation and cognitive impairment	
Structural MRI	• Measurement of gray and white matter integrity • Regional volumes assess macrostructural atrophy Identify patterns of neurodegeneration	• Increased atrophy associated with greater risk of converting to Alzheimer's disease (AD) in individuals with mild cognitive impairment (MCI) • Hippocampal and medial temporal lobe volume are related to cognitive score as diagnostic factors	(Cardenas et al., 2011; Hua et al., 2008; Plant et al., 2010; Ridha et al., 2008; Spulber et al., 2013; Vemuri and Jack, 2010)
Functional MRI-resting state or tasks dependent	• Synaptic activity evaluated by changed in blood oxygen level dependent (BOLD) MR signal • Measurement of functional integrity of brain networks • Regional functional connectivity can be assessed at rest or a during relevant cognitive tasks	• Detection of brain regions associated with memory task performance and how connections change with age and disease status • Hypoactivity is noted in some areas while hyperactivity is seen in others; hyperactivity might represent a compensatory mechanism in the setting of early AD pathology Hyperactivity in regions such as the hippocampus or medial temporal lobe are viewed as a biomarker for conversion from MCI to AD	(Bookheimer et al., 2000; Dickerson and Sperling, 2008; Logothetis et al., 2001; Machulda et al., 2003; Ogawa et al., 1990; Rombouts et al., 2000; Sperling et al., 2010; Vemuri et al., 2012)
Diffusion Tensor Imaging (DTI)	• Derive voxel-based measures of the movement of water molecules in the brain to assess tracts and predict structural connectivity • Measurement of white matter integrity and microstructural damage • Common measures: fractional anisotropy (FA): degree of directionality of water diffusion, mean diffusivity (MD): mean water diffusion rate, axial diffusivity (AxD): rate of water diffusion along the longitudinal axis, radial diffusivity (RD): rate of diffusion along the perpendicular axis, free water (FW) • FA and MD provide information about changes to barriers to diffusion Increased AxD is associated with axonal degeneration and increased RD has been linked to demyelination	• AD is associated with reduced white matter integrity (low FA, high MD, AxD, and RD) • Increased free water measure is associated with AD-related neuroinflammation Decreased FA and increased RD is commonly seen in white matter structures (corpus callosum, anterior commissure, fimbria, and internal capsule)	(Alexander et al., 2007; Colon-Perez et al., 2019; Febo et al., 2020; Harrison et al., 2020; Mayo et al., 2019; Ofori et al., 2019; Ouyang et al., 2015; Sahara et al., 2014)

Table 2

Tools for multi-omics integration, viewing, and analysis.Can Table 2 and 3 be widen and displayed as one data frame like Table 1 is formatted in the PDF? Each table is currently split in the proof.

Tools to view and/or analyze multi-omics datasets	Purpose of tool	Platform	Citation
Multi-Omics Factor Analysis (MOFA)	• Statistical method for integrating multiple modalities of omics data in an unsupervised fashion • MOFA disentangles to what extent each factor is unique to a single data modality or is manifested in multiple modalities	Python (mofapy2) and R (MOFA2)	(Argelagu et al., 2018)
MixOmics	• Classify or discriminate sample groups, to identify the most discriminant subset of biological features, and to predict the class of new samples	R Package	(Rohart et al., 2017b)
MixOmics: Multivariate INTegrative method (MINT)	• Integrates independent data sets while simultaneously, accounting for unwanted study variation, classifying samples, and identifying key discriminant variables	R package	(Rohart et al., 2017a)
MixOmics: Data Integration Analysis for Biomarker discovery using Latent cOmponents (DIABLO)	• A multi-omics method that simultaneously identifies key omics variables (mRNA, miRNA, CpGs, proteins, metabolites etc.) during the integration process and discriminates phenotypic groups • DIABLO maximizes the common or correlated information between multiple omics datasets	R package	(Singh et al., 2019)
Similarity network fusion (SNF)	• Similarity network fusion (SNF) constructs networks of samples for each available data type and then efficiently fusing these into one network that represents the full spectrum of underlying data • Uses similarity networks of samples as a basis for integration	R and Matlab Code	(Wang et al., 2014)
Paintomics	• Integrative visualization of multiple omic datasets onto KEGG pathways	Web-based	(Hernandez-de-Diego et al., 2018)
3Omics	• Visualize and rapidly integrate multiple human inter-or intra-transcriptomic, prote-omic, and metabolomic data by combining correlation networking, coexpression, phenotyping, pathway enrichment, and GO (Gene Ontology) enrichment analysis methods	Web-based	(Kuo et al., 2013)
JIVE	• Quantifies the amount of joint variation between data types, reduces the dimensionality of the data, and provides new directions for the visual exploration of joint and individual structure	R Package	(Lock et al., 2013)
MiBiOmics	• Enables the exploration, integration, analysis and visualization of up to three omics datasets. Through the primary exploration of a dataset, the inference of biological networks and the extraction of multi-omics associated features, the application provides a ready-to-use analysis pipeline to interactively explore sources of variability and variables of interest in a given biological dataset, as well as associations between multi-omics features in multi-scale studies	Web-based	(Zoppi et al., 2021)
Multi-Omics Graph cOnvolutional NETworks (MOGONET)	• Explores omics-specific learning and cross-omics correlation learning for effective multi-omics data classification • Supervised multi-omics integrative method that utilizes graph convolution networks for omics data learning to perform effective class prediction on new samples	Python Package	(Wang et al., 2021)

Tools to view and/or analyze multi-omics datasets	Purpose of tool	Platform	Citation
Survival Analysis Learning with Multi-Omics Neural Networks (SALMON)	• Fuses the gene co-expression network analysis, deep learning techniques, feature selection, Cox proportional hazard model, integrative analysis, and module-level enrichment analysis altogether	Python Package	(Huang et al., 2019)
NEMO (NEighborhood based Multi-Omics clustering)	• Algorithm for multi-omics clustering • Can be applied to partial datasets without performing data imputation	R Package	(Rappoport and Shamir, 2019)
Galaxy	• Enables users to perform integrative omics analyses by providing a unified, web-based interface for obtaining genomic data and applying computational tools to analyze the data	Web-based	(Boekel et al., 2015)
Argonaut	• Code-free platform for creating customizable, interactive data-hosting websites • Carries out real-time statistical analyses of the data, Collaborating researchers worldwide can explore the results, visualized through popular plots, and modify them to streamline data interpretation	Web-based	(Brademan et al., 2020)
Alzheimer's Disease Alternative Splicing-Viewer (ADAS)	• Provides researchers with the ability to comprehensively investigate and visualize multi-omics data from multiple brain regions of AD patients	Web-based	(Han et al., 2021)
*G*enome-wide *P*ositioning *S*ystems platform for *Alz*heimer's Drug Discovery (AlzGPS)	• A comprehensive systems biology tool to enable searching, visualizing, and analyzing multi-omics, various types of heterogeneous biological networks, and clinical databases for target identification and development of effective prevention and treatment for AD.	Web-based	(Zhou et al., 2021)

Table 3

General multi-omics and AD specific data portals and platforms.

Data portal	Portal description	Citation
OpenNeuro	• A free and open platform for validating and sharing Brain Imaging Data Structure (BID)S-compliant MRI, PET, MEG, EEG, and iEEG data	https://openneuro.org/
Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA)	• Consortium to bring together researchers in imaging genomics to understand brain structure, function, and disease, based on brain imaging and genetic data	http://enigma.ini.usc.edu/
Encyclopedia of DNA Elements (ENCODE)	• A comprehensive list of functional elements in the human genome, including elements that act at the protein and RNA levels, and regulatory elements that control cells and circumstances in which a gene is active	https://www.encodeproject.org/
Synapse by Sage Bionetworks	• A collaborative, open-source research platform that allows teams to share omics, imaging, and phenotypic data, track analyses, and collaborate	https://www.synapse.org/
	The AD Knowledge Portal, Brain Somatic Mosaicism Network Portal, Cancer Complexity Knowledge Portal, dHealth Digital Health Knowledge Portal, Neurofibromatosis Portal, and Psychencode Knowledge Portal is powered by Synapse	
Accelerating Medicines Partnership Program for Alzheimer's Disease (AMP-AD) Knowledge Portal	• Collection of multi-omics data, methods, and results generated within the network are distributed under FAIR Distribution of data principles from: Accelerating Medicines Partnership in Alzheimer's Disease (AMP-AD), Molecular Mechanisms of the Vascular Etiology of AD (M2OVE-AD) program, Resilience-AD program; (3) the Psych-AD program, Translational Center for Model Development and Evaluation for Late Onset AD (MODEL-AD) program.	https://adknowledgeportal.synapse.org/
AGORA	• Hosts evidence for whether or not genes are associated with AD. Agora also contains a list of close to 100 nascent drug targets for AD that were nominated by AD researchers	https://sagebionetworks.org/tools_resources/agora/
	Partnered with NIH-led Accelerating Medicines Partnership – Alzheimer's Disease (AMP-AD) Target Discovery and Preclinical Validation Project	
Alzheimer's Disease and Healthy Aging Data Portal	• Provides access to national and state level CDC data on a range of key indicators of health and well-being for older adults	https://www.cdc.gov/aging/agingdata/
Single-cell RNA-Seq database for Alzheimer's disease (scREAD)	• A single-cell RNA-Seq database for Alzheimer's Disease scREAD covers 73 datasets from 16 studies, 10 brain regions, 713,640 cells	https://bmbls.bmi.osumc.edu/scread/
Alzheimer's Disease Neuroimaging Initiative (ADNI)	• ADNI researchers collect, validate and utilize data, including MRI and PET images, genetics, cognitive tests, CSF and blood biomarkers as predictors of the disease. Study resources and data from AD patients, mild cognitive impairment subjects, and elderly controls in the North American ADNI study are available	http://adni.loni.usc.edu/
The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)	• NIAGADS provides qualified investigators with access to a national genetics data repository pertaining to late-onset AD. • This site ensures that genotypic data for the study of AD and related dementias (ADRD) are harmonized and shared with the research community at large	https://www.niagads.org/
National Alzheimer's Coordinating Center (NACC)	• Established by the National Institute on Aging/NIH to facilitate collaborative research by collecting data from 29 NLA-funded Alzheimer's Disease Centers. NACC includes approximately 25,000 subjects, roughly equal parts cognitively normal, MCI and demented.	https://www.alz.washington.edu/

Data portal	Portal description	Citation
	• Includes imaging, CSF, and genomic data at autopsy and cross-sectional timepoints	
Global Alzheimer's Association Interactive Network (GAAIN)	• A big-data community for cohort discovery and data exploration that promotes data sharing among a federated, global network of data partners who are studying AD and other dementias. • It is a collaborative project that provides researchers with access to clinical, genetic, and imaging data on Alzheimer's disease from hundreds of thousands of subject participants	http://www.gaain.org/
The Rush Alzheimer's Disease Center (RADC) Research Resource Sharing Hub	• Site for non-RADC investigators to navigate the complex data and biospecimens available for sharing • Provides assistance in identifying data and biospecimens that you can use to support your own projects	https://www.radc.rush.edu/
Alzheimer's Disease Cooperative Study (ADRCS)	• Develop and execute innovative clinical trials focused on interventions that may prevent, delay, or treat the expression of AD and related dementias • Committed to sharing resources and tools including data, biospecimens, trial designs, outcome and analysis measures	https://www.adcs.org/