

**Revolution of Alzheimer Precision Neurology
Passageway of Systems Biology and Neurophysiology**

By Harald Hampel, Nicola Toschi, Claudio Babiloni, Filippo Baldacci, Keith L. Black, Arun L.W. Bokde, Rene S. Bun, Francesco Cacciola, Enrica Cavedo, Patrizia A. Chiesa, Olivier Colliot, Cristina-Maria Coman, Bruno Dubois, Andrea Duggento, Stanley Durrleman, Maria-Teresa Ferretti, Nathalie George, Remy Genthon, Marie-Odile Habert, Karl Herholz, Yosef Koronyo, Maya Koronyo-Hamaoui, Foudil Lamari, Todd Langevina, Stephane Lehericy, Jean Lorceau, Christian Neri, Robert Nistico, Francis Nyasse-Messene, Craig Ritchie, Simone Rossi, Emiliano Santarnecchi, Olaf Sporns, Steven R. Verdooner, Andrea Vergallo, Nicolas Villain, Erfan Younesi, Francesco Garaci, and Simone Lista for the Alzheimer Precision Medicine Initiative (APMI)

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Perspective

Revolution of Alzheimer Precision Neurology. Passageway of Systems Biology and Neurophysiology

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Abstract. The Precision Neurology development process implements systems theory with system biology and neurophysiology in a *parallel, bidirectional research path*: a combined hypothesis-driven investigation of systems dysfunction within distinct molecular, cellular, and large-scale neural network systems in both animal models as well as through tests for the usefulness of these candidate dynamic systems biomarkers in different diseases and subgroups at different stages of pathophysiological progression. This translational research path is paralleled by an “omics”-based, hypothesis-free, exploratory research pathway, which will collect multimodal data from progressing asymptomatic, preclinical, and clinical neurodegenerative disease (ND) populations, within the wide continuous biological and clinical spectrum of ND, applying high-throughput and high-content technologies combined with powerful computational and statistical modeling tools, aimed at identifying novel dysfunctional systems and predictive marker signatures associated with ND. The goals are to identify common biological

denominators or differentiating classifiers across the *continuum* of ND during detectable stages of pathophysiological progression, characterize systems-based intermediate endophenotypes, validate multi-modal novel diagnostic systems biomarkers, and advance clinical intervention trial designs by utilizing systems-based intermediate endophenotypes and candidate surrogate markers. Achieving these goals is key to the ultimate development of early and effective individualized treatment of ND, such as Alzheimer's disease. The Alzheimer Precision Medicine Initiative (APMI) and cohort program (APMI-CP), as well as the Paris based core of the Sorbonne University Clinical Research Group "Alzheimer Precision Medicine" (GRC-APM) were recently launched to facilitate the passageway from conventional clinical diagnostic and drug development toward breakthrough innovation based on the investigation of the comprehensive biological nature of aging individuals. The APMI movement is gaining momentum to systematically apply both systems neurophysiology and systems biology in exploratory translational neuroscience research on ND.

Keywords: Alzheimer's disease, biomarkers, integrative disease modeling, pathophysiology, precision medicine, precision neurology, systems biology, systems neurophysiology, systems pharmacology, systems theory

Abbreviations: ^{18}F -FDG-PET, ^{18}F -2-fluoro-2-deoxy-D-glucose PET; $\text{A}\beta_{42}$, 42-amino acid-long amyloid beta peptide; AD, Alzheimer's disease; ADD, Alzheimer's disease dementia; ADNI, Alzheimer's Disease Neuroimaging Initiative; ADO, Alzheimer's disease ontology; APMI, Alzheimer Precision Medicine Initiative; APMI-CP, Alzheimer Precision Medicine Initiative Cohort Program; APP, amyloid precursor protein; BFCS, basal forebrain cholinergic system; CSF, cerebrospinal fluid; DBS, deep brain stimulation; DLB, Dementia with Lewy bodies; DTI, diffusion tensor imaging; EEG, electroencephalography; EHRs, electronic health records; EPAD, European Prevention of Alzheimer's Dementia consortium; EPAD LCS, EPAD Longitudinal Cohort Study; EPI, echo planar imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; FTD, frontotemporal dementia; ICNs, intrinsic coherent networks; IDM, integrative disease modeling; MCI, mild cognitive impairment; MD, mean diffusivity; MEG, magnetoencephalography; MMN, mismatch negativity; MRI, magnetic resonance imaging; ND, neurodegenerative diseases; NFL, nerve fiber layer; p-tau, hyperphosphorylated tau; Nold, normal elderly subjects; PDD, dementia due to Parkinson's; PET, Positron Emission Tomography; PM, Precision medicine; PMI, Precision Medicine Initiative; PoC, Proof-of-Concept; RGC, retinal ganglion cell; ROI, region of interest; rTMS, repetitive transcranial magnetic stimulation; SBML, Systems Biology Markup Language; SPECT, Single Photon Emission Computed Tomography; t-tau, total tau; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; WB-MRI, whole-body magnetic resonance imaging; WES, whole-exome sequencing; WGS, whole-genome sequencing; WM, white matter.

INTRODUCTION

A dementia syndrome is caused by a range of neurological disorders; Alzheimer's disease (AD) is the most common disease-causing dementia, accounting for 50–70% of cases. Increasing age is the most important risk factor for AD and other dementias, and as life expectancy increases and demographic aging occurs in populations around the world, the number of people with dementia is expected to continue to exponentially grow. In 2015, almost 47 million people worldwide were estimated to be affected by dementia, and the numbers are expected to reach 75 million by 2030, and 131 million by 2050, with the greatest increase expected in low-income and middle-income countries [1].

On May 29, 2017, at the 70th session of the World Health Assembly in Geneva, the World Health Organization (WHO) has unanimously adopted a

global plan on dementia—the Global Plan of Action on the Public Health Response to Dementia 2017–2025—that includes targets for the advancement of dementia awareness, risk reduction, diagnosis, care and treatment, support for care partners, and research (available at <https://www.alz.co.uk/news/global-plan-on-dementia-adopted-by-who>).

Recent years have witnessed an increasing understanding of the molecular mechanisms related to AD. The pathogenesis of this complex polygenic neurodegenerative disease (ND) involves sequentially interacting pathophysiological cascades, including both core events, i.e., accumulation of the 42-amino acid-long amyloid- β ($\text{A}\beta_{42}$) peptide into amyloid plaques and self-aggregation of hyperphosphorylated tau protein to form intraneuronal neurofibrillary tangles, and downstream processes, such as generalized neuroinflammation [2, 3]. These events induce axonal degeneration [4–6] and disruption of synaptic integrity [7, 8], thus leading to synaptic dysfunction

and, ultimately, deterioration of physiological neural connectivity [9].

In spite of such advancements in understanding the disease, AD is characterized by a high degree of heterogeneity in its manifestation, progression, and response to treatment, as well as susceptibility to risk factors. Phenotypic variability is currently considered one of the biggest challenges in clinical science and clinical trial design [10]. On the one hand, the same syndrome can be caused by substantially different pathophysiological mechanisms. In order to ensure more precise and definitive AD diagnosis, biomarkers are crucially needed to detect and track disease processes in the brain. On the other hand, similar pathophysiology can present itself with distinct symptomatology across patients, suggesting that additional factors can influence disease manifestation and progression. The identity and impact of such additional factors (including genetic, epigenetic, lifestyle, and phenotypic traits) deserve further investigation. Particularly, a growing body of evidence demonstrated that a factor such as an individual's sex can modulate disease phenotype and drug response [11], thus substantially contributing to clinical heterogeneity. In AD patients, sex differences have been reported in the rate of cognitive deterioration [12, 13] and brain atrophy [14], in the absence of clear differences in amyloid or tau burden [15]. In addition, sex-genotype interaction in AD have been shown to affect both risk of onset and conversion [16] as well as response to pharmacological treatment [17, 18]. The socio-economic construct associated with the female and male position in the society (i.e., gender) can also influence disease onset and progression, as it affects education, salary, pension plans, and caregiving burden [19]. Therefore, sex and gender appear to be central drivers of phenotypic variability in AD and their role should be carefully considered when designing strategies for prevention, detection and treatment of the disease. Analysis of sex and gender effects, both alone and in combination with a variety of genetic, epigenetic, and phenotypic traits, should be the first step toward a more personalized and patient-centered approach to AD.

THE PRECISION NEUROLOGY PARADIGM IN ALZHEIMER'S DISEASE

Breakthrough conceptual shifts have recently commenced to emerge in the field of AD and other ND, highlighting the presence of risk and protection factors and the non-linear dynamic continuum of complex pathophysiology along a wide spectrum

of multi-factorial brain proteinopathies. Substantial advancements in detecting, treating, and preventing AD are expected to evolve through the generation and the systematic implementation of a strategy based on the precision medicine (PM) paradigm [20, 21], whose establishment requires the implementation of an array of integrated disciplines and technological developments such as the "omics" approaches, neuroimaging modalities, cognitive assessment tests, and clinical characteristics. These converge to several domains that need to be analyzed according to the systems theory paradigm [22]. This allows for the conceptualization of novel and original models to elucidate all systems levels, assessed by systems biology and systems neurophysiology (Fig. 1), and the different types of spatiotemporal data characterizing the genetically, biologically, pathologically, and clinically heterogeneous construct of "AD" [21]. Thus, systems biology and systems neurophysiology permit to delineate the multivariate and combinatorial profiles of genetic, biological, pathophysiological, and clinical markers reflecting the heterogeneity of this condition. Thanks to fundamental advances in research technology, we got new and better performing analysis tools to register and create comprehensive brains maps and record dynamic patterns across different systems: from molecules, neurons to brain areas. Particularly, systems neurophysiology will aim at showing how computational network models can elucidate the relationship between structure and dynamic function in brain networks, as demonstrated by recent findings in time-dependent functional connectivity measured with non-invasive neuroimaging techniques.

The transition to PM from the traditional model does not occur overnight. But the more we build innovative and interdisciplinary networks with partners, the faster and more effectively we can see the changes happening. To fulfill on the promise of PM, there needs to be a new ecosystem with partnerships of multiple stakeholders who collaborate to find creative and novel solutions. Such a new ecosystem, comprised of academic and community providers, industry, professional societies, government, consumers, and patient advocacy groups, could advance the following pilot initiatives on a local, national and potentially international scale.

In order to advance the development of the PM paradigm in AD, the international Alzheimer PM Initiative (APMI) and its planned Cohort Program (APMI-CP) (Fig. 2) have been recently launched by our consortium and thematically linked to the U.S. Precision Medicine Initiative (PMI) (available

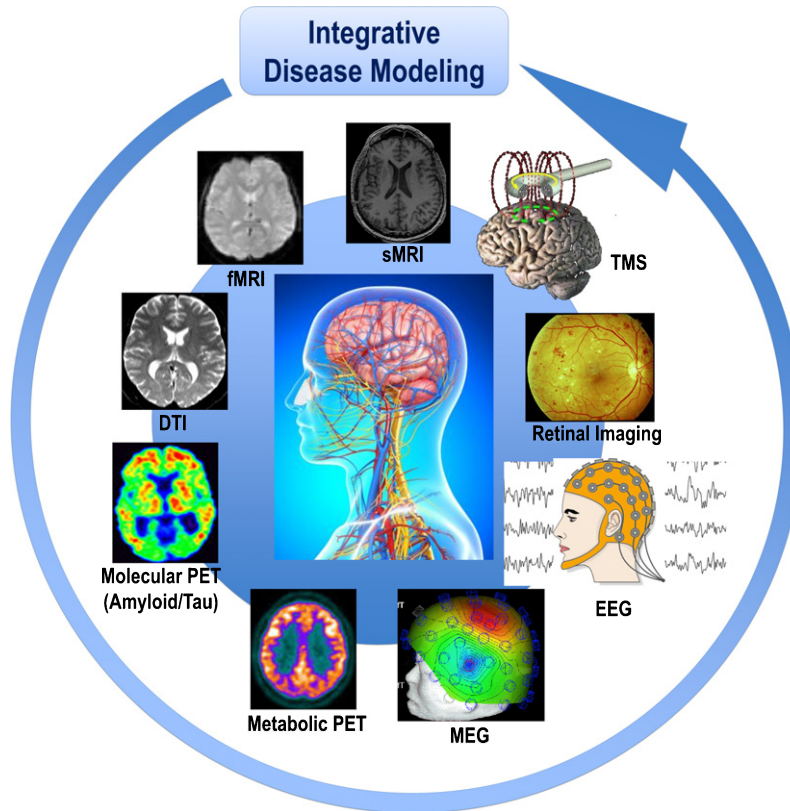


Fig. 1. Cohorts stratified according to different neuroimaging modalities and methods are integrated in the disease modeling for classification and prediction of subsets of AD and other ND patients. The paradigm of systems neurophysiology aims at studying the fundamental principles of integrated neural systems functioning by integrating and analyzing neural information recorded in multimodal fashion through computational modeling and combining data-mining methods. This paradigm may be used to decode the information contained in experimentally-recorded neural activity using analysis methods that are able to integrate the recordings of simultaneous, single-modality brain cell activity such as fMRI or EEG to generate synergistic insight and possibly infer hidden neurophysiological variables. The ultimate goal of systems neurophysiology is to clarify how signals are represented within neocortical networks and the specific roles played by the multitude of different neuronal components. AD, Alzheimer's disease; DTI, diffusion tensor imaging; EEG, electroencephalography; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging; ND, neurodegenerative diseases; PET, positron emission tomography; TMS, transcranial magnetic stimulation

at <https://www.whitehouse.gov/precision-medicine>) and the U.S. "All of Us Research Program", evolved from the U.S. PMI Cohort Program (available at <https://www.nih.gov/research-training/all-of-us-research-program>) (Table 1). Four pioneering translational neuroscience research programs—"MIDAS", "PHOENIX", "POSEIDON", and "VISION"—have been developed and launched in an interdisciplinary local network by our group at the APMI and APMI-CP initiation site Paris, France, at the Sorbonne University (*Sorbonne Université*) and at the Pitié-Salpêtrière University Hospital, Institute for Memory and Alzheimer's Disease (*Institut de la Mémoire et de la Maladie d'Alzheimer*, IM2A) and the Brain and Spine Institute (*Institut du Cerveau et de la Moelle Épinière*, ICM) in Paris to organize, combine, and integrate the components of systems

biology and neurophysiology in order to facilitate the development of PM in AD, a model approach for other proteinopathies/ND of the brain. In this regard, following the APMI conceptual framework, mono-center pilot APMI subcohorts spanning from early asymptomatic preclinical populations to prodromal to dementia late stage populations, namely *INSIGHT-preAD*, *Predict-MA PHRC*, *RESPIR*, and *SOCRATES*, have been established at our central clinical recruitment site, the IM2A. These pilot APMI cohorts allow for the standardized academic university-based expert center inclusion of both cognitively intact individuals at risk for AD and patients with a full range of ND and provide an assortment of unique heterogeneous and multidimensional data. The research using these pilot APMI cohorts is performed under the structural framework of the

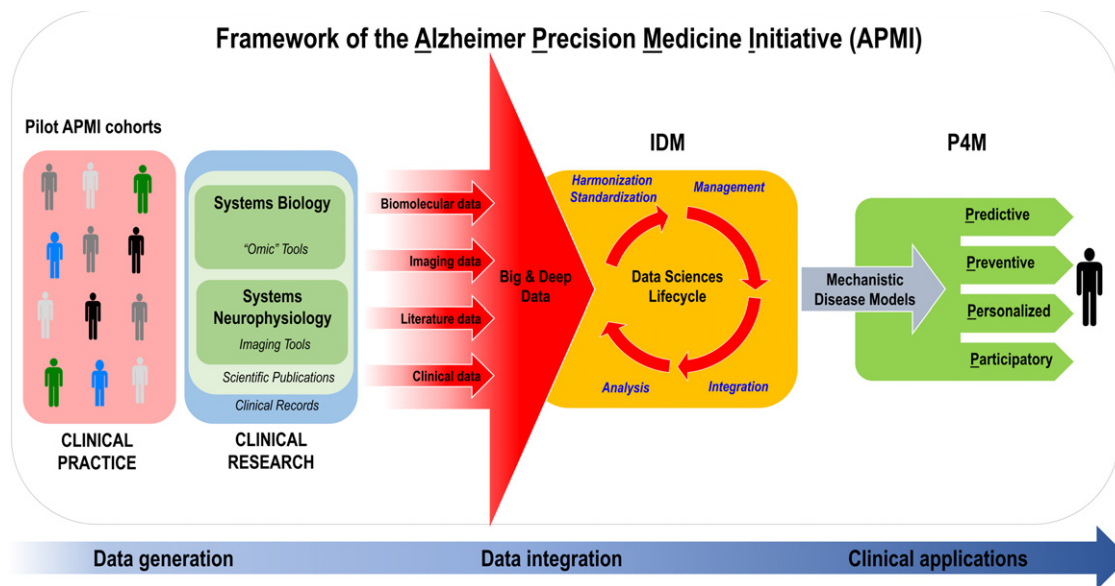


Fig. 2. Translational bench-to-bedside data flow within the conceptual framework of the Alzheimer Precision Medicine Initiative (APMI). The IDM-based “Data Sciences Lifecycle” takes advantage of both data-driven and knowledge-driven approaches so that both quantitative data (biomolecular, neuroimaging/neurophysiological, and clinical data) and qualitative data (collected from scientific literature and on-line media)—generated through the application of systems biology and systems neurophysiology paradigms—are represented in a harmonized, standardized format to be prepared for proper management within an integrative computational infrastructure. Indeed, the resulting heterogeneous, multidimensional big and deep data are harmonized, standardized, and integrated via computational and data science methods in the form of mechanistic disease models, according to the IDM conception. Disease-specific integrative computational models play a key role in the IDM paradigm and represent the foundations for “actionable” P4M measures in the area of AD and other ND. As a result, the integrative disease models are anticipated to support decision making for: 1) early diagnosis of brain disease progression with mechanistic biomarkers (predictive), 2) screening populations and stratifying individuals at high risk of developing ND based on mechanistic co-morbidities in order to reduce the likelihood of disease and disability (preventive), 3) tailoring treatment to the right patient population at the right time (personalized), and 4) optimizing “actionable” plans for the benefit of patients based on patient-oriented information gathered in EHRs and on patients’ feedback reported in social media. Internet has greatly enabled the participation of individual patients in the healthcare through sharing their experiences in various social media and other online resources (participatory). The output is anticipated to be an “actionable” model that permits the prediction of the trajectory of individual patient-centric detection or treatment within the implementation of the P4M paradigm. APMI, Alzheimer Precision Medicine Initiative; EHRs, electronic health records; IDM, integrative disease modeling; ND, neurodegenerative diseases; P4M, Predictive, Preventive, Personalized, Participatory Medicine. Modified from [21].

newly established Sorbonne University – “Clinical Research Group in Alzheimer Precision Medicine” (GRC n° 21), Sorbonne Université – “Groupe de Recherche Clinique – Alzheimer Precision Medicine” (GRC-APM). The major objective of the Sorbonne Université GRC-APM is to accelerate the reformation of traditional Neurology, Psychiatry, and Neuroscience embracing the PM paradigm, based on complex systems theory, using systems biology and systems neurophysiology, big data science, and biomarker-guided integrative disease modeling (IDM) to improve detection, classification, and therapy development in AD and other ND.

The implementation of PM in AD is expected to result into a novel, original scientific taxonomy and a distinguished working lexicon and terminology (see Table 2) for reality-based medicine, which detects evidence from real-life scenarios.

An appropriately integrative understanding of AD will be propelled by advances in molecular technology and data processing that will allow generating, analyzing, interpreting, and storing huge amounts of heterogeneous and multidimensional data, termed big data. Big data in AD can be used to improve our current mechanistic understanding of the disease through the application of different computational and data science methods, under the theoretical framework of IDM [23]. Multimodal big data integration is essential to understand the link between elements from large-scale neurobiological systems such as protein interaction and genetic regulatory networks, synaptic connections and anatomical projections among brain areas. Usually, these data come from multiple levels of organizations or involve different domains of biology and data types (Fig. 3).

Table 1

The five pillars of the Alzheimer Precision Medicine Initiative (APMI). The mission of APMI is to transform Neurology and Neuroscience embracing Precision Medicine (or Precision Neurology) based on complex systems theory using integrative disease modeling (IDM) to facilitate health care solutions for brain proteinopathies, protein misfolding disorders, and neurodegenerative diseases, such as Alzheimer's disease (AD). This is facilitated through five breakthrough theoretical scientific advances, as follows:

Concept	Comment
(1) The emergence of the “precision medicine” paradigm	Discovery and development of treatments targeted to the needs of individuals on the basis of <i>systems biology technology</i> using genomic biomarker, phenotypic, or psychosocial characteristics that distinguish a given individual from others. Inherent in this definition is the goal of impacting pathophysiological progression at early disease stages and clinical outcomes at later stages and minimizing unnecessary side effects for those less likely to have a response to a particular treatment supported by pharmacogenomics. The <i>convergence of genetics/genomics/transcriptomics, bioinformatics, neurodynamics, neuroimaging, and connectomics along with other technologies such as cell sorting, epigenetics, proteomics, lipidomics and metabolomics</i> , is rapidly expanding the scope of precision medicine by refining the staging and classification of disease, often with important prognostic and treatment implications. Among these new technologies, genetics and next-generation DNA sequencing methods are having the greatest effect.
(2) The emergence of the “systems biology” paradigm	Systems biology represents an integrated and deeper investigation of interacting biomolecules within cells or organisms. This approach has only recently become feasible as <i>high-throughput technologies</i> including cDNA microarrays, mass spectrometric analyses of proteins and lipids together with rigorous bioinformatics have evolved. High-content data point to convergent pathways among diseases, which transcend descriptive studies to reach a more integrated understanding of neurodegenerative disease pathogenesis and, in some instances, highlighting ‘druggable’ network nodes.
(3) The emergence of the “systems neurophysiology and complex network” paradigm	This is due in large part to advances in mathematics, computer science and statistical methods applied to neuroimaging and neurophysiology; instead of thinking of the brain as a set of modules (i.e., individual brain regions) that perform specific cognitive functions, the network paradigm argues that cognitive functions are performed by dynamic interactions among different brain areas, i.e., by <i>dynamically formed complex structural and functional networks</i> of brain regions.
(4) the emergence of “neural modeling” paradigm	This paradigm is required by the <i>complex network paradigm</i> , since, in order to deal with the large complexity of the dynamic interactions among multiple brain regions, one must employ advanced mathematical and computational methods.
(5) The emergence of “integrative disease modeling” (IDM) paradigm	This is an evolving knowledge-based paradigm in translational research that exploits the power of advanced computational methods to collect, store, integrate, model, and interpret accumulated disease information across different biological scales, i.e., from molecules to phenotypes. IDM is a new paradigm at the core of translational research, which prepares the ground for transitioning from descriptive to mechanistic representation of disease processes. Given the tremendous potential of IDM in supporting translation of biomarker and drug research into clinically applicable diagnostic, preventive, prognostic, and therapeutic strategies, it is anticipated that <i>computer-readable disease models</i> will be an indispensable part of future efforts in the P4 medicine research area.

To be effective, PM needs to exploit advanced tools for collecting/managing/examining big data. Particularly, thanks to outstanding progresses in information technology, the development and implementation of electronic health records (EHRs) enable gathering/preserving longitudinal health-care records and clinical data at highly limited costs. Furthermore, the adoption of personal mobile technologies, namely phones, apps, wearables, in-home devices, as innovative ways to collect health information (mobile health or “m-health”) is becoming a common practice. These devices allow the accumulation of clinically relevant information in a more ecological/natural environment and the improvement of patient care. High-volume and dense data generated from progressively more sophisticated software applications can enrich self-reported information on both lifestyle and environment, thus providing researchers with a well-defined vision of these factors, previously difficult to obtain.

Being rooted in a multidimensional data-driven approach, PM is expected to upgrade the prevention and treatment of AD to a higher level of individualization, promoting a shift toward every single preclinical participant at risk rather than late stage patients and disease in general. This goal will be achieved mainly through the identification and validation of reliable biomarkers, which will allow better classifying patients by their probable disease risk, prognosis, and/or response to preventive measures and treatment [20, 21]. To date, PM (in general) and biomarker-guided therapeutic strategies (in particular) have witnessed their broadest applications in the field of oncology. The Food and Drug Administration (FDA) has recently approved for the first time a cancer treatment based on the presence of specific molecular aberrations rather than on the tumor's anatomical origin. Pembrolizumab (a humanized antibody used in cancer immunotherapy) has been

Table 2
Evolving lexicon and terminology within the Alzheimer Precision Medicine Initiative (APMI) framework

Concept	Abbreviation	Definition
Big Data		A repository of large amounts of data sets generated by data mining tools. Big Data includes information obtained through systems theory- and, knowledge-based approaches and clinical records.
Biomarkers	BMs	A defined characteristic that is measured as an indicator of normal biological processes, pathogenic process, or response to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiological characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives. Categories of biomarkers include: susceptibility/risk biomarker, diagnostic biomarker, monitoring biomarker, prognostic biomarker, predictive biomarker, pharmacodynamics/response biomarker and safety biomarker.
Data Science		Interdisciplinary field about processes and systems to extract knowledge from data in different forms – either structured or unstructured – which is a continuation of some of the data analysis fields including statistics, artificial intelligence, machine learning, data mining, and predictive analytics.
e-Health		Term indicating healthcare practice supported by electronic processes and communication. It can also include health applications and links on mobile phones, referred to as mobile health (“m-health” : smart personal mobile devices, such as phones, wearables, in-home devices and Apps, collecting health information aimed at improving patient care). The term can also encompass a range of services or systems that are at the edge of medicine/healthcare and information technology, including: electronic health records (EHRs). These indicate a systematized gathering of population electronically-stored health information and clinical data in a digital format. These registries can be shared across different health care settings through network systems.
European Prevention of Alzheimer’s Dementia Consortium	EPAD	Pan-European initiative whose objective is to establish a shared platform to design and conduct phase II Proof-of-Concept (PoC) clinical trials specifically aimed at developing novel treatments for the secondary prevention of AD.
Genomic Medicine		Discipline utilizing personal genomic information (see also the definition of “Personal Genomics”) for diagnostic characterization and the development of therapeutic plans.
Integrative Disease Modeling	IDM	Multidisciplinary approach to standardize, manage, integrate, and interpret multiple sources of structured and unstructured quantitative and qualitative data across biological scales using computational models that assist decision making for translation of patient-specific molecular mechanisms into tailored clinical applications.
“Omics” or “Omic” disciplines		High-throughput screening tools aimed at fully collecting, characterizing and quantifying pools of biological molecules (DNA sequences, transcripts, miRNAs, proteins/peptides, metabolites/lipids) that translate into the structure, function, and dynamics of an organism and/or whole organisms.
“One-size-fits-all” approach		Traditional approach used for the development of early detection, intervention, and prevention options, where biomarker candidates are being validated against the plethora of heterogeneous clinical operationalized syndromes, rather than against genetically (risk profile) and biologically (i.e., based on molecular mechanisms and cellular pathways) determined entities.
Ontology		Formal naming and designation of the types, properties, and interactions of the entities that really or fundamentally exist for a specific domain of discourse.
P4 (Predictive, Preventive, Personalized, and Participatory) Medicine	P4M	Translational medicine component of the Precision Medicine paradigm. It is a clinical practice model aimed at applying knowledge, tools, and strategies of systems medicine. It involves generation, mining, and integration of enormous amounts of data on individual patients to produce predictive and “actionable” models of wellness and disease.
Personal Genomics		Branch of genomics that provides support in predicting the likelihood that an individual will be affected by a disease. It helps personalize drug selection and treatment delivery to get the best care, thus playing a crucial role both in predictive and personalized medicine, according to the PM paradigm.
Personalized Medicine		Component of the P4M aiming at tailoring treatment for individual patients in contrast with “one-size-fits-all” or traditional “magic bullet drug” approach.

(Continued)

Table 2
(Continued)

Concept	Abbreviation	Definition
Precision Medicine	PM	Translational science paradigm related to both health and disease. PM is a biomarker-guided medicine on systems-levels taking into account methodological advancements and discoveries of the comprehensive pathophysiological profiles of complex polygenic, multi-factorial neurodegenerative diseases (proteinopathies of the brain). It aims at optimizing the effectiveness of disease prevention and therapy, by considering (customized) an individual's specific "biological make-up" (e.g., genetic, biochemical, phenotypic, lifestyle, and psychosocial characteristics) for targeted interventions through P4M implementation.
Systems Biology	SB	Evolving hypothesis-free, exploratory, holistic (non-reductionistic), global, integrative, and interdisciplinary paradigm using advances in multimodal high-throughput technological platforms that enable the examination of networks of biological pathways where elevated amounts of structurally and functionally different molecules are simultaneously explored over time at a system level (i.e., at the level of cells, group of cells, tissues, organs, apparatuses, or even whole organisms).
Systems Medicine	SM	Holistic paradigm applying systems biology-based strategies to medical research. It aims at integrating a variety of considerable biomedical data at all levels of the cellular organization (by employing global, integrative, and statistical/mathematical/computational modeling) to explicate the pathophysiological mechanisms, prognosis, diagnosis, and treatment of diseases.
Systems Neurophysiology	SN	Paradigm aimed at studying the fundamental principles of integrated neural systems functioning by integrating and analyzing neural information recorded in multimodal fashion through computational modeling and combining data-mining methods. This paradigm may be used to decode the information contained in experimentally-recorded neural activity using analysis methods that are able to integrate the recordings of simultaneous, single-modality brain cell activity such as functional magnetic resonance imaging or electroencephalography to generate synergistic insight and possibly infer hidden neurophysiological variables. The ultimate goal of systems neurophysiology is to clarify how signals are represented within neocortical networks and the specific roles played by the multitude of different neuronal components.
Systems Pharmacology	SP	Science of advancing knowledge about drug action at the molecular, cellular, tissue, organ, organism, and population levels" (http://www.aaps.org/Systems_Pharmacology/).
Systems Theory	ST	Translational research theory of the Precision Medicine paradigm. It is an interdisciplinary conceptual framework allowing for the conceptualization of novel/original models to extract and explicate all systems levels and different spatiotemporal data types of complex polygenic diseases.

Modified from [21].

granted approval for adult and pediatric patients with metastatic or unresectable, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors [24]. The implementation of PM in ND currently impels researchers to envision a cross-trans-fertilization from such more advanced fields of medicine. In this setting, the repurposing of some previously approved mechanistic anticancer drugs for ND may offer the potential to reduce both the cost and time to achieve licensed approval status. For instance, tyrosine kinase inhibitors like bosutinib [25] and masitinib [26] (which represent a standard approach for anticancer treatment) have shown promising clinical results in patients with amyotrophic lateral sclerosis and can also exert neuroprotective actions in other ND through the activation of autophagy. The search basin for anticancer drugs repositionable

for neurodegeneration will ultimately require data-driven approaches grounded on specific biomarker data; such a strategy is aimed at identifying pathophysiological commonalities, potentially common molecular alterations between cancer and ND [26].

Apart from treatment, another important aim of PM in AD will be the preclinical detection of pathophysiology at its earliest stage and related early disease initiation and the implementation of preventive interventions at the individual level. This goal may be achieved through an integrated analysis of genetic, biomarker, imaging, and clinical characteristics that distinguish one individual from others. To achieve this goal, the availability of reliable multimodal biological indicators—biomarkers—will be required [27–34]. In this regard, several potential biological markers have been identified

level [74]. To target “individual variability” will ultimately require analyzing multiple biological pathways inexpensively, quickly, and sensitively. The increasing adoption of next generation sequencing in clinical practice has been recently driven by reducing costs and high-throughput analytical methods. In this setting, unbiased whole-genome sequencing (WGS) and whole-exome sequencing (WES) represent major milestones in the area of genomic medicine since they allow the complete elucidation of the genomic determinants of a specific AD patient’s heritable make-up, and thus are among the most comprehensive tools for future clinical applications [74, 75]. Moreover, upcoming commercially available genetic tests, e.g., gene-based assays, implementing polygenic risk scoring for assessing AD onset risk, are currently in late stage clinical development. In particular, a 90% maximum prediction accuracy via polygenic risk scoring can be accomplished by predictors of genetic risk based on genomic profiles [76]. It is generally acknowledged that an individual’s health, response to environmental and lifestyle factors, susceptibility to pathophysiology/syndromes/diseases, and tolerability/response to treatments are indeed impacted to a varying degree by their own unique biological (genetic/genomic/molecular) profile. Thanks to progress in the area of personal genomics, it is possible to identify the genetic/genomic predisposition of an individual for some common diseases, carrier status for inherited diseases, and adverse reactions to common drugs. Personal genomics provides support in predicting the likelihood that an individual will be affected by a disease and may help personalize drug selection and treatment delivery to get the best possible care, thus playing a key role in predictive and personalized medicine, in the framework of the PM paradigm [77]. In this regard, the 23andMe Personal Genome Service (PGS) Test (available at <https://www.23andme.com/en-gb/>) uses a qualitative *in vitro* molecular diagnostic system used for detecting variants in genomic DNA isolated from human adults specimens (saliva) that will provide information, i.e., delivering and interpreting genetic health risk (GHR) reports, to users about their genetic risk of developing a disease to inform lifestyle choices and/or conversations with a healthcare professional. Specifically, GHR reports have already been authorized by the FDA for late-onset AD and Parkinson’s disease and the following diseases: hereditary thrombophilia, alpha-1 antitrypsin deficiency, Gaucher disease, Factor XI deficiency, celiac disease, G6PD deficiency, hereditary

hemochromatosis, and early-onset primary dystonia (available at https://www.accessdata.fda.gov/cdrh_docs/pdf16/DEN160026.pdf). Based on the gene expression profiles generated by GenomeDx Biosciences Decipher Genomics Resource Information Database (Decipher GRID[®]), a recent analysis showed that the genomic signature PAM50, normally applied to breast cancer patients to determine their risk of reappearance, can be used in prostate cancer as well for predicting which individual may take advantage from early initiation of post-operative androgen deprivation therapy, thus delivering a potential clinical tool to customize the treatment of prostate cancer. This personalized selection of patients will ameliorate treatment outcomes and prevent many patients from unnecessary risks of toxicity [78].

Differently from the invariable genetic/genomic information, an individual’s proteomics/peptidomics and metabolomics/lipidomics profile may be modified and vary over time. Figure 4 provides an up-to-date summary of currently available “omics” technologies (genomics, transcriptomics, miRNomics, proteomics, metabolomics) and how they can be used to disentangle different systems biomarker categories [79]. At present, the majority of the documented candidate biomarkers originate from genomic and proteomic disciplines. This might be due to the higher stability of the signal and standardization achieved by using genomic and proteomic tools compared to other available “omic” methodologies. In addition, the better stability of proteins *versus* mRNAs might account for the greater availability and progress in discovery and validation of proteomic markers compared to, e.g., transcriptomic approaches [79]. The appropriate interpretation of the obtained high-throughput data in the context of the disease molecular pathophysiology and its specific treatment is considered the rate-limiting step in the biomarker discovery and validation process. As a result, “omics” data sets need to be rigorously identified, extracted, and interpreted in order to deliver valuable biological information [79].

Within the PM framework, it has been proposed to screen and detect unsuspected age-related neurodegenerative diseases as early as possible in cognitively healthy potentially preclinical affected adults. As far as AD is concerned, it has been hypothesized that such a screening program—based on WGS combined with whole-body magnetic resonance imaging (WB-MRI), metabolomics screening, constant heart monitoring, pedigree analysis, microbiome sequencing, and standard laboratory tests—could identify people at risk of developing clinical AD decades in

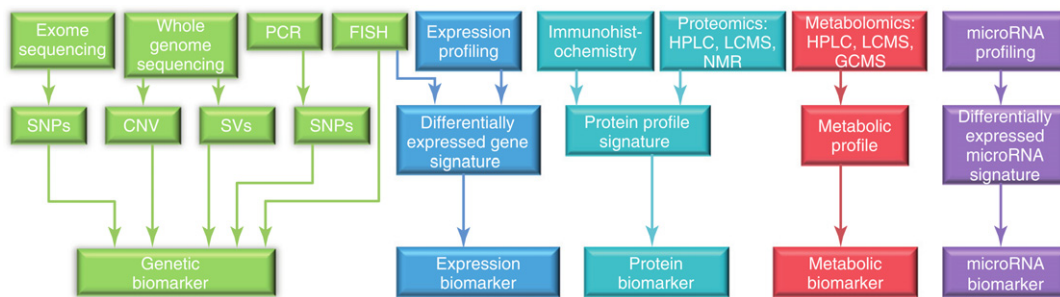


Fig. 4. Overview of the currently available technologies and the resulting biological marker categories used for biomarker discovery in preclinical and clinical research. CNV, copy number variations; FISH, fluorescence in situ hybridization; GCMS, gas chromatography mass spectrometry; HPLC, high-performance liquid chromatography; LCMS, liquid chromatography–mass spectrometry; NMR, nuclear magnetic resonance; PCR, polymerase chain reaction; SNPs, single nucleotide polymorphisms; SVs, structural variations. Reproduced with permission from [79].

advance. Controversies still exist, however, regarding both the high costs inherent to this approach and the potential risks of false-positive results and overdiagnosis [80].

Very recently, a pilot study has been conducted to investigate the impact of WGS in healthy subjects examined within a primary care context. Although several potentially pathogenetic variants were identified, only a fraction of the carriers demonstrated overt clinical signs or symptoms, indicating that the expected clinical phenotype would develop later during progression of pathophysiology. Although integrating genome sequencing and other sequencing methods into the day-to-day practice will undoubtedly provide unprecedented preventive opportunities, a careful sample size determination will be necessary for achieving a sufficient statistical power to detect a clinically meaningful effect size [81].

To aid PM fully coming to life in the field of ND, the interplay of “omics”-based techniques and sequencing methods is paramount, since the availability and increasing standardization of high-throughput big data will, through adequate IDM supported by advances in data science, allow creating new biomarker-guided targeted preventive and therapeutic opportunities [20, 21]. Therefore, the use of advanced sequencing methods and of “omics”-based screening of pathophysiological disease states is anticipated to result in enhanced personalized and precise, both preventive and therapeutic, interventions by disclosing accurate patterns of pathophysiological biomarkers and molecular signatures underlying the biological mechanisms progressing non-linear dynamic in specific disease states in individual patients [82]. Extensive efforts are

presently performed to explicate gene-protein links, key molecular pathways functions, protein-protein and signaling network organization, and organism-level responses *via* high-throughput biological data at different time points (e.g., global gene expression and comprehensive proteomic data) [83].

In this context, it is important to note that, so far, a major obstacle to our understanding and to the development of possibly novel stratification approaches for AD is, as mentioned, the fragmentation of previous research (single-center, single-method studies). Neuroscience has been highly productive, but its progress can also be somewhat unsystematic and remote to clinical practice. That said, so far conventional “big data” analytics techniques have failed to provide the qualitative change which is indispensable to provide a mechanistic (and not only statistical) understanding of AD pathophysiology, which in turn is instrumental to formulating personalized treatment strategies. A first step, as mentioned above, is the integration of complex and high-dimensional information from hundreds or thousands of patients contained in “big data” repositories. However, this alone is not sufficient; “big data” need to be turned into “smart data” by injecting not only novel methodologies but also expert knowledge and targeted clinical hypotheses. This poses a major analytics challenge, as neither single national-level studies nor single biomedical or technical disciplines can tackle the problem on their own. A number of potentially disease-modifying clinical development programs in AD have failed so far [84], and in addition we are in serious need of novel out-of-the box preclinical models that can generate actionable knowledge, either in research or, eventually, therapy. This is why, while computational and statistical modeling are increasingly invaluable

in AD research, it is necessary to go beyond purely descriptive data-analysis techniques (e.g., techniques that identify associations between certain data and phenotypes). Additional efforts are needed to inject specific domain competencies which can be formalized mathematically into predictive models that can disclose how specific components of pathogenic pathways interact within complex brain networks, across molecular to cellular and systems scales. Such predictive models should, as far as possible, include realistic representations of neurobiological processes and mechanisms that allow direct comparison to experimental settings and, ultimately, pave the way to discover new strategies for targeted control and intervention. In this respect, it is also essential to form additional private-public partnerships with a strong focus on data sharing and pathway-based analysis. With this type of integrative approach, successful real-world examples of advanced simulation have already generated tangible support for clinical trials in AD.

SYSTEMS BIOLOGY OF ALZHEIMER'S DISEASE

The polygenic multifactorial nature of AD and other complex proteinopathies of the brain with progression to ND is widely recognized. Although several mechanisms have been identified that may have a role in the pathogenesis of AD and other ND, the molecular and temporal dynamics of the biological processes that lead to onset and progression of diseases such as AD remain to be well-understood on a system level. Complex chronic diseases such as AD are thought to result from an interplay between environmental, genetic, and epigenetic factors. State-of-the-art “omics” techniques such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics offer remarkable promise as research tools to decipher the dynamics and biological nature of the pathogenesis ultimately leading to neurodegeneration and a spectrum of clinical neurological phenotypes for which predictive markers and selective therapeutic tools are needed. Breakthrough advances in genetic and genomic technologies are making global genome sequencing possible, affordable, and clinically practical through advanced NGS technologies. New genetic technologies, however, provide a crucial basis to the understanding of the complex pathophysiological pathways involved in proteinopathies/ND.

The concept of complex multiscale systems (consisting of macromolecules that reciprocally interact with each other in dynamic modular complexes and networks) as the underlying foundations of life has been first proposed more than 50 years ago [85]. Over the past decades, we have gained detailed insights into the structure, regulation, and function of different molecular and cellular systems, which are currently viewed as building blocks or inventories of working parts. However, the main challenge ahead is to clarify how these single agents are reciprocally associated by multiple interactions across distinct system levels and networks of structural and functional organization (e.g., DNA-protein, RNA-protein, protein-protein, protein-metabolite networks, interactomics). Major challenges exist for the development of reliable holistic models that are based on unbiased data-integration workflows and that could highlight the properties of complex biological structures, for which the whole is often greater than the sum of their parts. In this context, the main goals of systems biology in the field of ND research are as follows: 1) to characterize complex systems and/or networks in a straightforward, viable manner, by probing key layers of molecular regulation and expression on a genome-wide level and 2) to integrate different genome-wide data sets in a multidimensional manner—that is, across different layers of molecular regulation, timescales, cell types and so on—in order to generate comprehensive *in silico* models of ND that show the best balance between coverage and selectivity, reduce model space down to manageable numbers of highly-prioritized testable hypotheses, and are biologically precise. This will shed more light on how complex diseases may be conceptualized as a result of altered networks states [86] caused by multifactorial perturbations, which is expected to foster marker and target discovery. Under this theoretical framework, the dynamics and biology of ND processes scrutinized by systems modeling and systems biology can be more comprehensively understood. This may be achieved via a two-step approach consisting of initial animal studies followed by confirmation and validation in clinical cohort programs [87] or via an approach consisting of molecular and clinical studies in cohorts, for example the search for predictive marker signatures, followed by studies in experimental models of ND of biological and therapeutic significance associated with such marker signatures. Numerous disease conditions in humans (including proteinopathies/ND, cardiovascular disorders, malignancies, the metabolic syndrome, and diabetes) have

a highly complex biological nature that cannot be entirely and adequately captured through the investigation of single linear molecular alterations. Besides being multifactorial, such diseases are primarily caused by altered essential networks required for the correct functioning of basic physiological pathways. Such disease processes are fundamentally non-linear dynamic, being the results of an evolving interplay between homeostatic defense mechanisms and impaired physiological networks through space and time [88]. Since cell survival mechanisms under the control of stress response factors may also be those that trigger cell death depending on the pathophysiological context in which they operate [89] identifying the critical phases that, at the molecular, cellular, or system levels, are associated with the dynamics of ND processes and could modify the capacity of individuals to maintain function and resist ND is essential for clinical discovery and therapeutic developments, especially in the context of the growing needs for PM.

Recent years have witnessed significant advances in our understanding of how human diseases are routed in altered molecular and cellular networks. Several genetic alterations and pathophysiological mechanisms, mainly involving the amyloid- β protein precursor (A β PP) processing and tau related networks, are considered to be significant aspects in the pathogenesis of AD [90]. Such network derangements can cause either loss or gain of specific molecular functions and an increased formation of neurotoxic molecular species (e.g., toxic amyloid or protein aggregates) that can in turn adversely affect supra-cellular levels. Another important factor that should not be overlooked in the conceptualization of complex diseases is the crucial counteracting role of homeostatic networks. In this regard, the interest into the potential protective role of resilience factors against neurodegeneration (e.g., autophagy, proteostasis, endolysosomal networks, protein folding chaperone networks, disaggregates, and other stress-protective and clearance networks) is currently gaining momentum [90].

The causative pathways that lead to the onset of AD and its clinical phenotypes at the individual level are thought to consist of genetic/epigenetic susceptibility and/or protection coupled with a continuing dynamic interplay between altered brain networks and counteracting neural mechanisms of resilience. Integrative systems biology-based approaches are crucial to disentangling this intricate interplay. First, simple model organisms mimicking the main features of AD need to be developed in order to extensively apply dif-

ferent “omics” techniques. This approach may offer invaluable data to shed more light on the conserved pathways that modulate the onset and progression of AD, being ultimately useful for testing potential strategies that could delay and/or modify the natural course of disease [90]. However, the regulation of gene expression and pathway activity might differ between simple model organisms and humans, which calls for integrated use of simple model organisms and higher-order models such as mouse models and human cell models, e.g., induced-pluripotent-stem-cells coaxed into neurons or neurons obtained by direct conversion of fibroblasts [91].

New evidence from preclinical models needs to be duly replicated, with a special focus on subtle initial network alterations that can be visualized by neuroimaging, which could potentially become the targets of early therapeutic interventions [92–95]. Neuroimaging and biomarker data should be fully integrated and analyzed in a longitudinal manner through computational and integrative network biology tools within a systems biology-based framework. The increasing trend toward high-throughput techniques in AD research will generate multifactorial data that will require integration in a standardized, efficient, cost-effective, and secure manner. The vast amount of data generated will cause new challenges for data science, mainly in terms of data storage, processing, and mining. As we are entering into the “era of big and deep data” in AD, computational systems biology approaches are continuously being optimized in order to support the approximate modeling of biological systems [90].

A holistic systems biology-based research strategy in AD research will likely rely on generating large and rich data sets, applying multi-layer network approaches for integration and comparative assessments of different datasets, and reckoning on the information generated for discovery of novel disease markers and targets. A translational approach from preclinical studies to bedside (complemented by reverse translational approaches) will be required to integrate and implement fundamental aspects of the systems theory and the systems biology concept into clinical practice, i.e., translational systems medicine, in the upcoming future [96–99]. Key to the success of these approaches is the use of robust data integration methods. There is a large array of methods that enable complex data sets collected in experimental models of ND or human cohorts to be analyzed and integrated on a system level [100, 101]. Methods based on graph theory (that is net-

work approaches) such as spectral decomposition of the signal [102] weighted gene co-expression network analysis [103] and Bayesian causal inference [104] and those based on formal concept analysis [105] and tree induction [106, 107] likely hold strong promises for generating comprehensive *in silico* models that accurately select for biological rules, disease targets, and risk factors with potential for clinical exploitation.

APPLICATION OF SYSTEMS BIOLOGY IN AD COHORTS: THE EXAMPLE OF THE EUROPEAN PREVENTION OF ALZHEIMER'S DEMENTIA (EPAD) CONSORTIUM

Implementation of systems biology into clinical and research practice requires a number of steps. First, molecular tests and biomarkers for matching individuals/patients to clinical trials and/or targeted therapies will require continuous refinements and validation of high-throughput techniques, systems-level approaches, and computational tools. Second, all molecular tests to be used for AD, as well as all patient care-related molecular analyses, need to be performed using assays that are highly reproducible, accurate, and satisfy the FDA clinical trials guidelines, with adherence to principles of Good Clinical Practice (GCP) (available at <http://www.fda.gov/regulatoryinformation/guidances/ucm122046.htm>), the European Medicines Agency (EMA) (<http://www.ema.europa.eu/ema/>), and the European Clinical Trials Database (EudraCT) (<https://eudract.ema.europa.eu/>). In this scenario, the Alzheimer's disease neuroimaging initiative (ADNI) and the Dominantly Inherited Alzheimer Network (DIAN) will provide collaborative large-scale longitudinal data on AD associated autosomal dominant mutation carriers that will be invaluable to systematize and make explicit the translation of neuroimaging and biochemical markers into clinical guidelines. Third, the era of big and deep data generation and the availability of comprehensive repositories has brought the need for collaboration, sharing, integration, normalization, and analysis of both data and metadata, with the ultimate goal to make effective translational use of this new knowledge. In this scenario, several clinical trials may benefit from the holistic approach provided by systems biology. Among them, interest in the European Prevention of Alzheimer's Dementia (EPAD) program is gaining momentum.

The EPAD program [108] is a pan-European initiative that will establish a shared platform to design and conduct phase II Proof-of-Concept (PoC) clinical trials specifically aimed at developing new treatments for the secondary prevention of AD. To investigate different agents in the pre-AD population in the most efficient manner, a Bayesian adaptive design that learns from data accrued as the trial progresses will be used. Clearly disappointing results of recently completed phase III AD therapy trials may be explained by their exploratory (rather than confirmatory) nature, mostly caused by an incomplete exploration phase throughout phase II [109]. Hopefully, the EPAD program will be helpful to overcome previous pitfalls in the field by assuming that a correctly designed phase II trial can take several years to be completed. Other common issues that the EPAD Longitudinal Cohort Study (LCS) (available at <https://clinicaltrials.gov/ct2/show/NCT02804789>) will address include: 1) the high screen failure rates, 2) the unwillingness or inability to implement an adequate patient stratification, and 3) the lack of a pre-randomization run-in period. The EPAD LCS is expected to provide reliable disease models of the preclinical and prodromal periods of AD before the final implementation of a clinical trial. The EPAD LCS will be conducted in a large cohort of 5,000 subjects who had undergone a thorough assessment in terms of cognition [110, 111], neuroimaging, core CSF biomarkers ($A\beta_{42}$, total tau [t-tau], and hyperphosphorylated tau [p-tau]), clinical outcomes, and genotyping. Annual assessments will be performed with the goal of identifying different disease trajectories to provide an optimal stratification for trial inclusion. Risk stratification groups with similar biological underpinnings will be helpful to identify specific classes of subjects to be included (or excluded) from the clinical trial according to the PM paradigm.

The development of an EPAD site network across the European Trial Delivery Centers will be critical to the initiative success. Site certifications, continuing training, and commitment to the EPAD program is expected to reduce study site heterogeneity and will hopefully provide highly accurate estimates of treatment effects. Each TDC will assess approximately 200 research participants, of whom 100 will be included in the clinical trial. This effort is unprecedented, as previous clinical trials involved numerous centers (up to 200), each enrolling a handful of patients. Conversely, the traditional methodology will be overturned by EPAD, inasmuch as a few centers will enroll numerous patients.

In general, the correct implementation of phase III trials preliminary requires more robust phase II outcomes. The EPAD program will improve the study methodology, ultimately favoring an optimal disease modeling and a better patient stratification before embarking on phase III confirmatory trials. The EPAD LCS was started in May 2016 at six sites, with a total of 400 participants having already been recruited. Disease modeling work is expected to be introduced as soon as an enrolment goal of 500 subjects will be achieved. It is anticipated that the EPAD PoC Study Platform trial will begin in 2018.

SYSTEMS NEUROPHYSIOLOGY OF ALZHEIMER’S DISEASE: UNDERSTANDING NEUROPHYSIOLOGY AND NEURODYNAMICS BEHIND ETIOLOGY

During the last two decades, the neuroscience field has entered a rapid phase of expansion characterized by the development of a large proportion of method-

ologies allowing the recording of neural data obtained from a wide range of modalities, from metabolic pathways to optical imaging to functional magnetic resonance imaging (fMRI). These data are collected through different spatiotemporal domains (Fig. 5). Most of these techniques have been so far used one at a time [112, 113]. Recently, there is an attempt toward data integration in order to create comprehensive maps and record dynamic patterns across multiple levels of organization (neurons, circuits, systems, whole brain) and involving different domains of biology and data types (such as anatomical and functional connectivity, genetic/genomic patterns [112, 114]). This effort is in line with the new paradigm of systems neurophysiology aiming at integrating “big neuroscience data” recorded in a multimodal fashion to understand the role of the complex web of interconnections among several elements of large-scale neurobiological systems [115–118]. The ultimate goal of systems neurophysiology is to clarify how signals are represented within neocortical networks and the specific roles played by the multitude of the

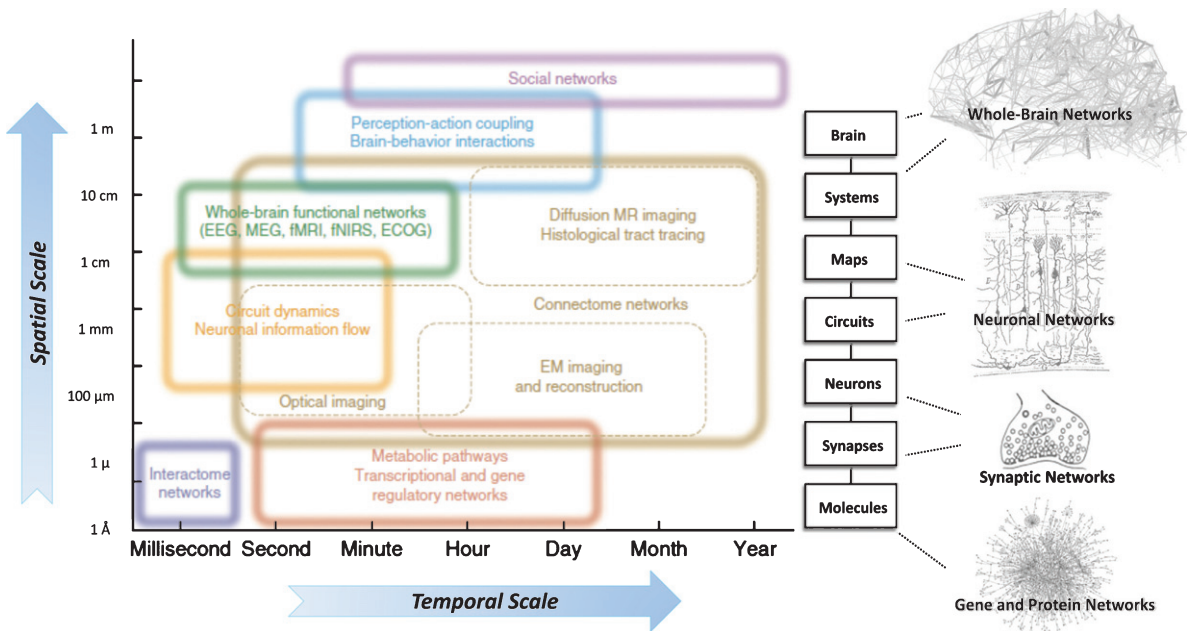


Fig. 5. Systems neurophysiology and network neuroscience: schematic representation of how structural levels within the nervous system integrate over multiple spatial and temporal scales. Network neuroscience encompasses the study of very different networks encountered across many spatial and temporal scales; however, the network ideas clearly extend down to the level of neuronal circuits and populations, individual neurons and synapses, as well as genetic regulatory and protein interaction networks. In network neuroscience and systems neurophysiology in general, the overall aim is to bridge information encoded in the relationships between genes and biomolecules to the information shared between neurons across to the brain level while integrating the additional information provided from the time dimension. This could eventually allow access to mechanistic understanding and models which faithfully reproduce and possibly predict both brain structure and function. Interestingly, above the single brain level, the social network level should still be considered a network neuroscience domain and, albeit with different measurement techniques, can be studied with the same paradigms with the aim to understand the larger “brain” that interacting brains give rise to (i.e., economies and cultures). Adapted from [112] and [609].

heterogeneous neuronal components. The new interdisciplinary field of network neuroscience proposes to overcome these enduring challenges by approaching brain structures and functions via an explicitly integrative perspective [112]. Here, we will present scientific advancements related to single methodologies utilized by system neurophysiology, within wider context of the PM paradigm in AD.

An increasingly important integrative component in this endeavor is connectomics the emerging science of brain networks, which comprises studies of both anatomical and functional brain connectivity, across modalities and methodologies. The rise of connectomics has triggered several national and international consortia devoted to mapping patterns of brain connectivity across large subject cohorts, including the Human Connectome Project funded by the U.S. National Institutes of Health [119]. These projects have pushed the boundaries of data sharing, neuroinformatics and computational analysis. Similar connectomics efforts are underway to track lifespan development [120] as well as address patient populations, including people with ND. To deal with the mounting volume of connectome data, the field is developing basic network science tools and methodology that can be applied to brain data [121]. So far, broad exploratory analysis has revealed a number of architectural principles that underpin macro- and meso-scale maps of brain connectivity, including modular organization and the existence of prominent hub regions. Much is still to be learned about the contributions of connectome architecture to human brain function and its role in pathophysiological processes. Systems neurophysiology in combination with connectomics and computational network models has great promise to illuminate the relation of structure to dynamics in brain networks as shown, for example, in recent findings on time-dependent functional connectivity as measured with non-invasive neuroimaging techniques.

CONTRIBUTION AND ROLE OF STRUCTURAL MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is a widely, non-invasive, relatively non-expensive and versatile technology. Among MRI modalities, structural or anatomical MRI, using three-dimensional T1-weighted sequences, is the most widely used [122, 123] and validated [124, 125]. Structural MRI allows

visualization and measurement of atrophy which is a macroscopic correlate of neurodegeneration, in particular of neuronal and dendritic loss. The progression of atrophy in AD approximately follows that of neurofibrillary tangles found in postmortem AD cases and described by Braak and colleagues [126] and Delacourte and colleagues [127]. Moreover, previous studies showed that structural MRI alterations correlate with tau deposition, as described by Braak stages, and CSF tau biomarkers [128]. On the contrary, not all structural MRI measures are well correlated to measures of A β deposition, and atrophy patterns do not follow those of amyloid deposition [129, 130]. Due to these reasons, it should be noted that brain atrophy in AD is descriptive of brain structural changes but not specific for underlying AD pathophysiology. Indeed, a given atrophy pattern can be associated with different pathophysiological processes. However, MRI atrophy measures are well correlated with cognitive and clinical functions [131, 132], and highly correlated with the concurrent rate of clinical decline [133–135]. Therefore, they constitute attractive tools to track disease progression and to monitor the effect of treatment.

Automated image analysis approaches allow measuring distributed patterns of atrophy across the whole brain, using either region-of-interest measurements, voxel-based maps of gray-matter or cortical thickness measurements [136, 137]. Machine learning algorithms applied to whole-brain atrophy maps can automatically identify patients with AD and thereby support diagnosis [138–141].

The most widely studied and accepted structural MRI marker of AD is atrophy of the medial temporal lobe [142, 143]. Assessment of medial temporal atrophy can be performed in clinical routine using visual scales [144]. However, such approach is observer-dependent and only semi-quantitative. On the other hand, fully-automated segmentation approaches provide objective, quantitative, volumetric measurement of hippocampal atrophy [145–149]. Hippocampal volumetry can discriminate AD patients from controls with high sensitivity and specificity [150]. Moreover, numerous studies have shown that patients with higher hippocampal atrophy are at higher risk of rapid cognitive decline [151–155]. However, atrophy of the hippocampus was found in other types of dementia, suggesting low specificity of this marker for the identification of AD [156, 157]. Recent developments of ultra-high field MRI (7 Tesla and higher) allow the study of anatomical alterations with an unprecedented level of detail. In particular, using

7T MRI, it is possible to distinguish between different cellular layers and anatomical subregions within the hippocampus. Its application in AD has demonstrated that hippocampal subregions and layers are differentially affected by atrophy [158, 159]. These advanced techniques have the potential to provide more sensitive measures than global hippocampal volumetry.

Another region of interest for AD is the basal forebrain cholinergic system (BFCS) since it represents the region with the majority of cholinergic nuclei efferent to the cerebral cortex [160, 161]. The measurement of BFCS nuclei has been developed and validated as a highly relevant and robust region of interest for automatic structural MRI assessment of atrophy rate of change from the preclinical to the clinical AD stages [160, 162–167]. Evidence indicates that the BFCS may even degenerate before medio-temporal lobe structures, as early as at the preclinical stage [163, 168]. In contrast to the hippocampal volume, the atrophy of BFCS was significantly correlated to *in vivo* brain amyloid load in AD and non-demented elderly individuals [169, 170]. Machine learning approaches based on whole brain atrophy patterns have been developed to predict the evolution of patients, in particular the progression to dementia of individuals with mild cognitive impairment (MCI) [171–173]. Nevertheless, most of these approaches have been validated on a single research dataset, most often provided by the ADNI. Therefore, their ability to generalize across datasets as well as their performance in a clinical routine context remain unclear and larger-scale validation studies are needed.

Its ability to track progression makes structural MRI also attractive to monitor the effect of treatment [29]. Of all outcome measures (including clinical, cognitive, and fluid biomarkers), structural MRI measures seem to have the highest measurement precision [135]. They are thus an attractive outcome measure for clinical trials, as well as to monitor the effect of treatment in a clinical context. It should be noted that different types of treatment seem to result in different effects on atrophy measures. In a randomized placebo-controlled trial, patients treated with donepezil, an acetylcholinesterase inhibitor, have a significantly lower rate of annual hippocampal atrophy and cortical thickness compared to those receiving placebo [174, 175]. Moreover, the treatment group demonstrated a significantly decreased annual rate of atrophy of the BFCS compared to MCI individuals that received placebo [176]. The BFCS complements hippocampal volumetry in assessing

structural progression in AD and provides a promising outcome measure for clinical trials. Anti-amyloid therapies, however, seem to result in increased rate of atrophy [177]. Nevertheless, it may be hypothesized that such accelerated atrophy only occurs at the beginning of treatment, perhaps caused by a reduction in microglial activation associated with plaques, and that a reduction of atrophy may occur in the longer term. Overall, structural MRI remains an attractive tool to study the morphological effects of treatment, in particular if new molecules targeting other aspects of AD pathophysiology (e.g., anti-tau or neuroprotective treatments) become available. Furthermore, structural MRI plays an important role in monitoring safety of treatments. Indeed, microbleeds and transient cerebral edema (respectively called ARIAH and ARIAE) occur in some patients treated with active A β immunization [178].

In summary, structural MRI is an attractive marker for tailoring therapeutic interventions. Its most attractive features are its ability to precisely track cognitive decline, its potential for monitoring the effect of treatment and to predict the evolution of patients. For prediction, the most promising avenue is that of machine learning approaches from whole-brain measurements. Such approaches require larger scale validation using multiple clinical routine cohorts. The integration of structural MRI analysis tools with other techniques such as those from functional MRI, electroencephalography (EEG), magnetoencephalography (MEG) or diffusion tensor imaging (DTI), in a multimodal fashion, will enable the investigation of temporal and topographical relationships between numerous pathological alterations and neurobiological systems related to AD. Such big data integration, will improve our understanding of the *in vivo* interacting pathophysiological mechanisms across brain related systems characterizing AD, as envisioned by the PM concept.

CONTRIBUTION AND ROLE OF DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI), which employs a Gaussian approximation to model the MR signal attenuation due to net water molecule displacements in a *de facto* restricted cellular environment. This technique has become the mainstream strategy for examining white matter (WM) microarchitecture, connectivity as well as integrity both in an investigative and in a clinical setting, and it has been

widely employed in studies focused on AD and MCI [179–181] as well as several other pathologies [182–185]. The apparent water diffusion tensor (which is termed *apparent* precisely because intracellular water diffusion is not truly free) can be estimated in brain parenchyma based on relatively fast echo planar imaging (EPI) techniques [186] which only pose moderate demand in terms of in-scanner subject time. From these tensor estimates, WM tract-specific orientation information can be obtained through deterministic (based on the orientation of the main DT eigenvector) or probabilistic approaches [187]. Also, model free tractography approaches exist, a promising development of which is constrained spherical deconvolution [188–191], which has lately been extended to incorporate multi-tissue models anatomically based filtering [188, 189] (Fig. 6). Further, scalar indices derived from the diffusion tensor are rotationally invariant and are well known to be sensitive, albeit not specific, indicators of microstructural alterations. The single tensor eigenvalues as well as mean diffusivity (MD – mean of eigenvalues) and fractional anisotropy (FA – normalized variance of eigenvalues [192]) can aid in quantifying fiber integrity through region of interest (ROI), voxel- or Tract-Based Spatial Statistics based approaches [180]. A decrease in FA (possibly accompanied by an increase of MD or other directional diffusivities) is typically the hallmark of unspecific bundle degeneration, as seen in AD and MCI [193, 194]. Importantly, correlations between DTI-derived indices in WM and AD disease severity have been reported [195, 196], suggesting that DTI measures may be used as indexes of disease progression. DTI may therefore provide unique information about WM integrity [66] in AD patients and MCI subjects. Indeed, several studies have demonstrated early WM changes within the parahippocampus, hippocampus, posterior cingulum, and splenium already at the MCI stage [197–200]. However, the majority of DTI studies indicate that the uncinate fasciculus, the entire corpus callosum and the cingulum tract are most involved in pathogenesis in both MCI and AD. In a recent study on AD and MCI subjects [201] the interpretation of a selective increase in FA in the MCI group was aided by the introduction tensor mode (MO) [202], a third invariant which distinguishes the type of anisotropy (planar, e.g., in regions of crossing or kissing fibers versus linear, in regions which exhibit one predominant orientation). This, in turn, led to the detection of a relative preservation of motor-related projection fibers crossing the

association fibers of the superior longitudinal fasciculus in the early-stage MCI subjects before they degenerated to AD. Also, recent DTI data seems to point toward a reconstruction of the trajectory of progressive WM degeneration in AD as it spreads with aging. In agreement with this so called retrogenesis model (cortical regions that mature earliest in infancy tend to degenerate last in AD) it has been shown that WM abnormalities in specific brain regions such as prefrontal cortex WM, inferior longitudinal fasciculus, and temporo-parietal areas [180, 197, 203, 204] appear earlier. Also, DTI has been able to offer insight into asymptomatic “preclinical” at risk stages such as subjective cognitive decline, where DTI based scalar markers of diffusion properties were significantly associated with rates of cognitive decline and hippocampus atrophy at clinical follow up, with odds ratios up to 3 [205], and DTI indexes invariants were seen to be more sensitive than CSF biomarkers in predicting cognitive decline and medial temporal atrophy in subjective cognitive decline and MCI subjects [205].

Nevertheless, a recent meta-analysis indicates high variability in both the anatomy of regions studied and DTI-derived metrics [206], a partial contribution to which may be the intrinsic limits of the DTI techniques. Determining the most robust acquisition parameters and processing strategies for DTI for a multicenter setting is still an active area of research, and initial clinical and physical phantom data, i.e., scans obtained from a volunteer as well as a physical object with defined diffusion properties, suggest that the variability of DTI-based diffusion metrics across a range of MRI scanners is at least 50% higher than that of volumetric measures [207]. For prediction of conversion from MCI into AD dementia, DTI reached an accuracy of about 77%–95% at 2 to 3 years follow up [205, 208, 209] in monocenter studies, prediction accuracy for multicenter studies still needs to be studied. Also, all diffusion weighted imaging protocols suffer from the relatively low signal-to-noise ratio inherent in the necessarily fast EPI techniques. In this respect, the increase in signal-to-noise ratio afforded by moving to ultra-high field imaging (at, e.g., 7T) is somewhat counteracted by the rapid shortening of transverse (T2) relaxation times with increasing field strength and consequent signal loss. Nevertheless, while ultra-high field diffusion weighted imaging therefore poses significant challenges, improved distortion correction techniques [210] coupled with monopolar acquisition schemes which allow a significant (about 30%) shortening of echo times, and the

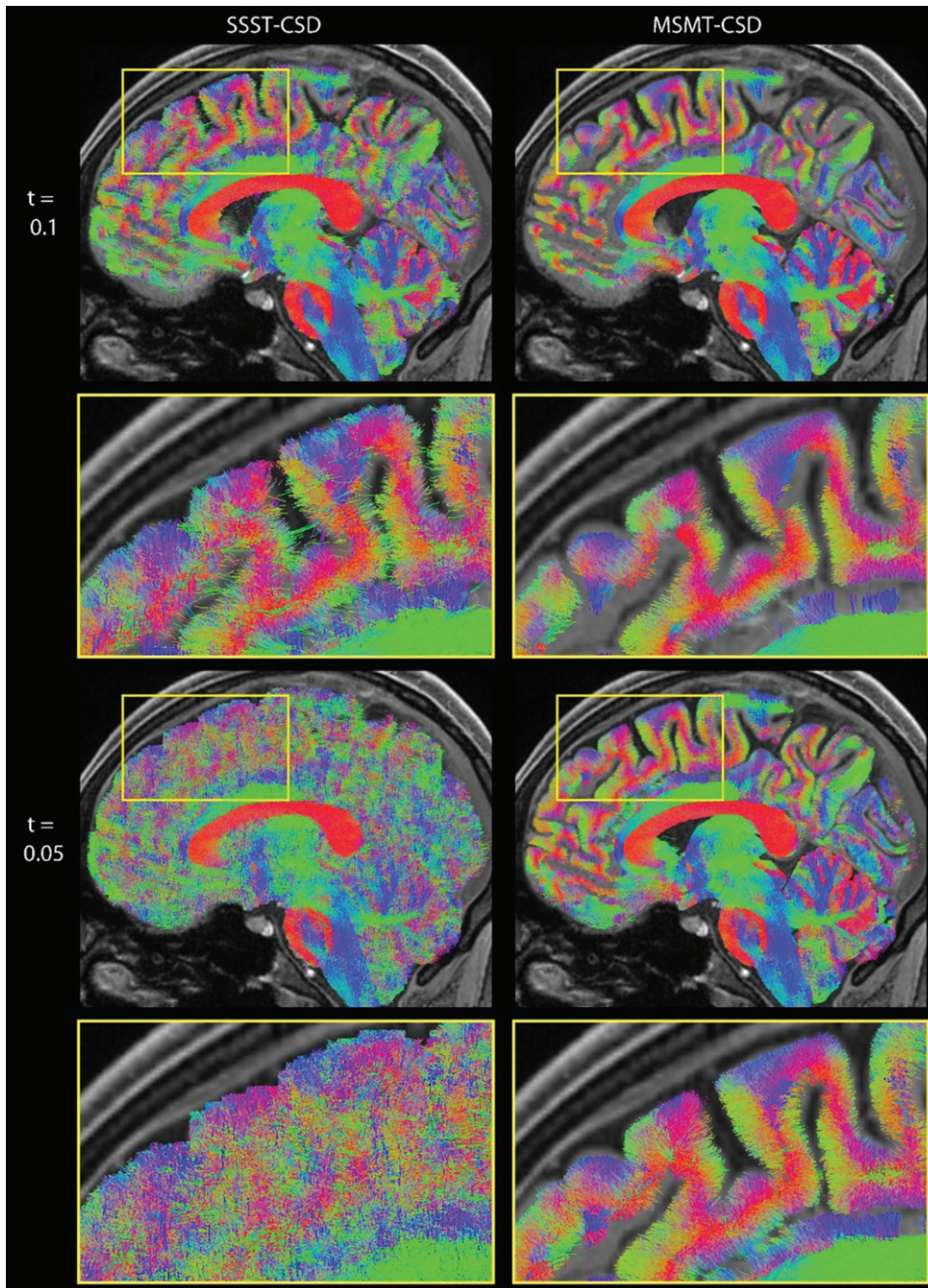


Fig. 6. Sagittal slab visualization of a fiber tractogram obtained from WM fODFs estimated with SSST-CSD (left) and MSMT-CSD (right) with different fODF amplitude thresholds (top, bottom). fODF, fiber orientation distribution function; MSMT-CSD, multi-shell, multi-tissue constrained spherical deconvolution; SSST-CSD, state-of-the-art single-shell, single-tissue constrained spherical deconvolution; WM, white matter. Reproduced with permission from [188].

additional use of simultaneous multislice excitation strategies [211] may allow *in vivo* diffusion-weighted imaging to finally advance toward sub-millimeter imaging at ultra-high field. Accordingly, *ex-vivo* studies have already defined WM lesions in aging and

AD at 11.4T [212], and 7T imaging has been helpful in discriminating Parkinson's disease [213] and amyotrophic lateral sclerosis [214]. Finally, it is well known that the assumption of a Gaussian propagator (which is at the root of DTI) is insufficient in

regions with more intricate fiber architecture such as mixed tissue types and/or kissing or crossing fibers [215]. To this end, more advanced protocols such as Diffusion Spectrum Imaging [216], Diffusional Kurtosis Imaging [217–221], higher order tensor models [222], compartment models [223–225], and anomalous diffusion [226, 227], which can be optimized in order to enhance their suitability in a clinical setting [228], have been already been successfully employed in augmenting information about tissue degeneration in several ND, including AD [229–232].

Another avenue for DTI-based methodology is the construction and subsequent analysis of brain-wide maps of anatomical connections that can be summarized as structural networks or graphs [115]. Basically, these efforts proceed by first dividing the brain into a set of internally coherent gray matter parcels or regions (the nodes of the network) and then estimating the strengths of anatomical projections between these nodes (the edges of the network). While the reconstruction of such maps faces significant methodological issues, the resulting structural networks have been validated against classical histological techniques in non-human species. Human structural networks capture individual differences that relate to genetics [233] and various phenotypic variables, including indices of cognitive performance [234]. They also exhibit characteristic changes across the lifespan [120], during normal aging [235], and in the course of brain disorders [236]. For example, the loss of connectivity associated with the progression of AD results a loss of links between dense clusters of functionally-related regions and hence a decreased capacity for integration [237, 238].

CONTRIBUTION AND ROLE OF FUNCTIONAL MAGNETIC RESONANCE IMAGING

Using fMRI in a PM-based paradigm to tailoring therapeutics for patient treatment would be a very innovative approach from current methods to developing therapeutics for patients. The diagnosis and classification of patients would be based on clinical criteria, where a patient would be classified according to predetermined criteria. Implementation of a PM paradigm would use fMRI as a biomarker of functional brain changes that would be part of defining the patient's phenotype in combination with the other modalities. Thus, it would seek to integrate fMRI-based biomarkers within a systems neurophys-

iology context to provide an integrated picture of the patient's status [21]. The biomarkers within a systems neurophysiology approach would inform the treatment approach that a patient would receive. Given the complexity of AD and the other ND, the fMRI-based biomarkers would be integrated within a systems biology and neurophysiology approach with the other modalities (genetic, clinical, behavioral, cognitive, etc.) where the different biomarkers would reflect disease mechanisms, pathophysiology, clinical history and permit patient stratification for treatment [20, 21].

fMRI can be used to measure the vascular response to local neuronal activation due to stimuli or a cognitive task [239]. There are two broad approaches that may be utilized with fMRI data in defining PM-based biomarkers for AD detection and diagnosis—one would examine brain activation data in response to a stimulus or cognitive paradigm whereas another approach would examine the intrinsic connectivity networks measured using resting state fMRI. The first approach would lead to biomarkers that would be associated with the cognitive paradigm or stimulus class whereas examination of the intrinsic connectivity networks would provide a search for biomarkers over all brain networks.

In terms of a PM approach with tailoring therapeutics, the use of a cognitive task or stimulus would be a form of 'stress test' to a specific network, for example in asymptomatic at risk stages for preclinical and clinical AD, a memory task would typically activate the hippocampus, ventral- and dorsal-prefrontal regions, posterior cingulate regions [240–249], and a working memory task would primarily activate dorsal and ventral frontal regions and inferior and superior parietal regions [250–255]. A limitation of the cognitive paradigm approach is that the patient must be able to perform the task, and variability in task performance would alter the activation pattern [256–261]. An alternative approach in AD would be to implement cognitive paradigms outside of the memory domain that individuals may still be able to perform such as visual perception, attentional tasks, or passive stimuli [262–273]. The changes found using this approach would be applicable to patients that may be clinically more advanced, but also provides an approach to measure the 'downstream' effects of the pattern of disease-related neuropathology. Current studies examined the differences between patients and healthy controls or among different risk groups by quantifying the average difference between the groups, where the groups are defined by clinical-descriptive phenotypes or risk groups

based on genetics or family history. The proposed PM paradigm would instead examine the variability among the subjects to define phenotypes that are data-driven and may not necessarily reflect the underlying pathophysiology and clinical phenotypes. There is evidence of significant variability in brain activation from healthy status to MCI to mild AD stage, for example a using a face-name association paradigm, there was a nonlinear response in hippocampus, with higher activation in MCI subjects compared to healthy controls and AD dementia patients [242, 249, 274]. Similarly with the visual perception task the activation levels varied along the dorsal visual pathway as disease severity increased [262].

In addition to measuring brain function, one would need to integrate the above biomarkers with results from fMRI studies of the mechanisms of action of the potential therapeutics; most studies have examined cholinergic drugs over an extended treatment period in either MCI subjects or mild AD patients (see for example [273, 275–278]). Another potential approach to be used within a PM paradigm is to measure the effects of a single dose [279–282] and investigate the predictive power of the single dose over the effectiveness of the therapeutic strategy for the biomarkers-characterized patient. The single dose approach has the potential to inform the tailoring of the therapeutic intervention by providing information about potential medium to long term effects of any treatment.

The various fMRI-based paradigms described above would provide information about a specific brain network or set of brain regions and any data-driven approach would be limited to data from the brain network or regions activated during the task. An alternative approach utilizing fMRI would be to use whole-brain resting state fMRI to measure so-called resting-state networks or intrinsic connectivity networks (ICNs) [283–286]. These ICNs have been shown to be highly reproducible across individuals [287], exhibit characteristic dynamic fluctuations [288] as well as patterns of change across development, life span and in the course of brain disorders [236]. The topography of ICNs resembles other networks, such as those engaged during human behavior and cognition (for example, see [289–293]), derived from gene co-expression [294, 295], disease phenotypes and disease progression (for example [246, 296–303]), as well as brain activation level and cognitive performance (for example [293, 304–306]). The structure of ICN networks can be probed with a variety of network tools to reveal individual differences

in their internal coherence and their mutual interactions. In combination with these advanced analytics, ICNs can potentially provide a rich set of biomarkers of brain function, including insights into which ICNs are specifically disturbed as a result of pathophysiology, and thus yield a more integrated perspective on system-wide changes within a patient. The tailoring of therapeutics could benefit from associations between biomarkers and the presence of the disease pathophysiology. Given the variability that is present in AD patients and MCI subjects, the ICN-based biomarkers and their relation to genetic profiles [68] may be able to provide an improved systems biology characterization of brain function. The use of ICNs for tailoring therapeutics still needs considerable development work, and there is currently only limited work on the effects of an AD-related drug on ICNs [307]. It should be noted that while the task-free design of resting fMRI lends itself to application in clinical cohorts, the sensitivity to motion artifacts and ongoing temporal fluctuations in the network structure of ICNs entail greater reproducibility as scan lengths are increased (for example, see [308]).

The potential of fMRI to assist in the PM-oriented targeting of therapeutics for AD patients is strong but also will require very significant development work. The integration of fMRI with the other domains such as genetics, cognition, clinical measures has so far mostly been attempted within a group analysis context, and a PM paradigm would need development of new statistical models to define potential therapeutic strategy on a single individuals basis [309].

CONTRIBUTION AND ROLE OF ELECTROENCEPHALOGRAPHY

Candidate topographic neurophysiological (neurodynamic) biomarkers of AD can be derived from resting state eyes-closed electroencephalographic (rsEEG) rhythms recorded in subjects relaxed in quiet wakefulness (eyes closed, no sleep) with their mind freely wandering [310]. These rsEEG markers are non-invasive, cost-effective, available worldwide, and repeatable even in severe dementia. They may probe the neurophysiological “reserve” in AD patients, as one of the dimensions of the brain reserve [311]. This neurophysiological “reserve” may reflect residual mechanisms for 1) “synchronization” of neural activity in a given cortical region and 2) the coupling of activity between nodes of a given brain

neural networks as a sign of functional cortical “connectivity” [310, 312].

RsEEG markers in AD at the group level reflect the neurophysiological reserve of the disease over time and after cholinergic therapy

Previous rsEEG studies using “synchronization” markers showed that compared with groups of normal elderly (Nold) subjects, AD groups with dementia (ADD) exhibited lower power density in posterior cortical alpha (8–12 Hz) and beta (13–30 Hz) rhythms [313–319]. There was also higher power density in widespread delta (<4 Hz) and theta (4–7 Hz) rhythms [320–325]. Finally, ADD, dementia due to Parkinson’s (PDD), and dementia with Lewy bodies (DLB) groups were characterized by abnormally lower posterior alpha source activities [326]. The effect was dramatic in the ADD, marked in the DLB, and moderate in the PDD [326]. There were also abnormally higher occipital delta source activities with dramatic effects in the PDD group, marked in the DLB group, and moderate in the ADD group [326].

Concerning “connectivity” markers, ADD groups were characterized by abnormally lower spectral coherence in alpha and beta (13–20 Hz) rhythms between posterior electrode pairs [316, 327–339]. These effects were observed in temporo-parieto-occipital electrode pairs in some studies [316, 327, 333, 337] and in frontocentral electrode pairs in others [329, 332, 340]. Other studies reported either a global decrease [327, 334] or increase [337, 341] of delta and theta coherences between electrode pairs in ADD groups. Another investigation pointed to a complex topographical pattern of coherence increase and a decrease in those groups [342]. Alternative techniques of “connectivity” unveiled a decrement of synchronization likelihood between electrode pairs in frontoparietal alpha rhythms in ADD and its prodromal stage of amnesic MCI [319, 343]. Finally, there were reduced cortical connectivity and “small-worldness” in ADD groups as revealed by graph theory indexes [344–347].

RsEEG rhythms deteriorate across time (e.g., about 12–24 months) in groups of aMCI subjects and ADD patients (see for a review [348]): 1) increased delta-theta and increased alpha-beta power density at parieto-occipital electrodes [349]; 2) increased theta power density, decreased beta power density, and decreased mean frequency at the temporal and temporo-occipital electrodes [316, 350, 351]; 3) increased delta and increased alpha 1 in parieto-

occipital sources [352, 353]; and 4) reduced cortical connectivity as revealed by graph theory indexes [347].

In groups of ADD patients, acetylcholinesterase inhibitor drugs (i.e., enhancing the cholinergic tone) showed beneficial or protective effects in delta [320, 354–356], theta [321, 356, 357], and alpha rhythms [355, 358]. When observed at short-term, these effects predicted longer-term therapy efficacy [357, 359, 360] (for a review, see [352]). However, some contradictory findings suggest future more controlled cross-validation studies [361, 362].

Abnormal posterior cortical delta rhythms in ADD patients might reflect an upregulation of their generation mechanisms in quiet wakefulness, possibly due to cortical blood hypoperfusion and synaptic dysfunction in the same regions [363–366] and atrophy in the posterior cortex [312, 352, 367–369]. Furthermore, reduced posterior cortical alpha rhythms in ADD subjects might be due to an unselective tonic cortical excitation in populations of cortical pyramidal, thalamo-cortical, and reticular thalamic neurons generating those rhythms [370–372]. Such cortical over excitation might induce a background noise in the neural information processing interfering with vigilance and cognition [310].

RsEEG markers in AD at the individual level: Classification accuracy and predictions

RsEEG markers allowed the discrimination of ADD patients from Nold individuals and others with neurodegenerative dementing disorders such as PDD and DLB persons. Global delta and alpha coherences between electrode pairs successfully classified ADD compared with DLB people with 0.75–0.80 (e.g., 1 = 100%; [373]). Furthermore, twenty discriminant scalp rsEEG power density and coherence variables showed a classification accuracy of 0.90 in the discrimination of ADD versus Nold and ADD versus PDD subjects [374]. Another study in small populations of ADD, PDD/DLB, and frontotemporal dementia (FTD) patients reached a classification accuracy of 1.0 using 25 discriminant scalp rsEEG power density and functional cortical connectivity (i.e., Granger causality) variables [375]. In another study, combining quantitative rsEEG variables (including those of functional cortical connectivity) with neuropsychological, clinical, neuroimaging, cerebrospinal fluid, and visual EEG data reached “only” a classification accuracy of 0.87 in the discrimination between ADD, PDD, and DLB

persons [376]. Concerning cortical source space, resting state delta and alpha sources classified Nold subjects versus ADD/DLB/PDD patients and ADD versus PDD patients with 0.85–0.90 [326]. Milder classification effects were observed in PDD and ADD individuals with MCI [377]. RsEEG markers predicted cognitive decline in aMCI individuals at about 6–24 months (see [348] for a review). The main effects are summarized as follows: 1) combined alpha-theta power density and mean frequency from left temporal-occipital regions [316]; 2) anterior localization of alpha sources [315]; 3) high temporal delta sources [378]; 4) high theta power density [379]; and 5) low posterior alpha power density [380].

Concluding remarks on EEG implementation

Overall, it is suggested that resting state cortical delta and alpha rhythms might unveil more compromised neurophysiological reserve in AD, at the group and the individual level. These rsEEG markers predicted and tracked the AD progression as neurophysiological endpoints for therapeutic interventions. Future multi-centric longitudinal studies should provide a large open access database for a systematic comparison of rsEEG markers of “synchronization” and “connectivity” markers for a better definition of “neurophysiological reserve” for clinical applications and research.

CONTRIBUTION AND ROLE OF MAGNETOENCEPHALOGRAPHY

Magnetoencephalography (MEG) allows recording the magnetic signals of the order of 10^{-12} Teslas, which are produced at the scalp surface by the activity of neuronal assemblies. It may provide information complementary to EEG for uncovering new neurodynamic biomarkers of AD, particularly in its very early asymptomatic at risk and preclinical stages, therefore before the prodromal and clinical stages.

MEG can be used to investigate cognitive functions in a way very similar to EEG. With this approach, impaired brain functional activities were characterized in AD and MCI stages during memory tasks for instance. Walla and colleagues [381] used a recognition memory task in which they manipulated the depth of encoding of verbal information. They showed alteration of temporo-parietal event-related responses to old—previously encoded—versus new items in AD patients relative to controls, after deep encoding. The mismatch negativity (MMN) was also

shown to be a potential AD marker. The mismatch negativity is a well-known component of the event-related potential response, which is associated with the detection of deviant stimuli in a stream of standard, repeated stimuli—classically in the auditory modality, hence allowing the assessment of the quality of sensory processing, memory, and predictive coding [382, 383]. Its magnetic counterpart, the MMNm, was shown to be delayed in latency in AD compared to healthy elderly controls [384] (see also [385]). Most interestingly, using memory tasks in pre-clinical stages of AD, e.g., in *APOE* $\epsilon 4$ carriers, some studies pointed to the capacity of MEG for revealing neurophysiological markers of subjects’ decline, potentially predictive of pathology emergence [386, 387]. In sum, MEG can be used in the same way as EEG to investigate cognitive functions during various task performance; both these methods provide highly convergent and temporally detailed data on information processing and cognitive functions in normal and pathological aging.

However, the most unique potential of MEG for uncovering pathophysiological mechanisms and providing new neurodynamic biomarkers in the field of AD may lie in the study of functional brain networks, particularly of resting state networks (for review, [388]). As mentioned above, fMRI studies have shown that, in the absence of task demand, the resting brain exhibits spontaneous and highly structured, often oscillatory, fluctuations in activity [389]. MEG and EEG provide a richer view of these networks in the time and frequency domains [390–395]. Resting state networks are usually studied using time-frequency decomposition of MEG (or EEG) signals. This allows identifying a rich set of resting state networks in distinct frequency bands (e.g., [390, 392, 393, 396]). It was shown that AD patients show altered resting state network activity. This was revealed at the level of oscillatory activity characteristics, pointing to an overall slowing of brain rhythms with particular abnormalities in the delta (<4 Hz) and beta (~20 Hz) frequency ranges [397–402]. Moreover, alteration of resting state networks, correlated with memory impairment, was recently shown using a graph-theoretical approach applied to neuromagnetic data [403]. Important questions are: When do these changes emerge in the course of the disease and which changes are predictive of or specific for the development of molecular and clinical AD? There is particular potential in EEG and MEG methods to provide such a surrogate biomarker for clinical outcome. Moreover, there is evidence that some MEG mark-

ers of functional brain networks may be predictive of the conversion from MCI to AD dementia [397, 400, 404].

On a practical note, it is important to underline that resting state studies have the advantage to be particularly adapted for elderly patients, because they require no cognitive effort and require relatively modest data acquisition time. It is worth mentioning that MEG, in comparison to most EEG systems, requires only a short time of subject's preparation for recording. The whole-head MEG systems that are available at present comprise about 300 sensors that are fixed in a rigid helmet. After head shape numeration and the installation of a few reference sensors, individuals are comfortably seated with their head placed in the helmet. The installation time takes as little as 20 minutes. Moreover, the total "innocuity" of MEG allows close follow-up and detailed longitudinal assessment of disease progression.

The recent development and promising results of neuromagnetic imaging methods has led to the Magnetoencephalography International Consortium of Alzheimer's Disease (MAGIC-AD) initiative. This initiative aims at advancing the use of MEG for AD and pre-AD research, combining data from resting state and simple memory and MMN tasks, in a multicentric study [405]. While still in its burgeoning with regard to clinical applications, MEG has the potential to provide new tools for patient stratification, in order to better target patient population for clinical trials, and for treatment evaluation [406, 407], and to shed new light on the neurodynamic pathophysiological mechanisms of AD. It allows to foresee the identification of individualized signatures of disease progression in the form of temporal profiles of early adaptive, compensatory, and decompensatory brain network changes. Moreover, it is clear that the full power of MEG will come from its combination with other methods to allow multimodal assessment of individuals and IDM of multi-modal big data. For example, the combination of genetic data, such as the APOE polymorphism characterization with MEG resting state analysis has revealed promising in identifying MCI subjects at high risk of conversion to AD dementia as well as asymptomatic subjects at high risk of developing significant cognitive deterioration [408]. Multifactorial characterization of MCI subjects, including neuropsychological assessment, structural and functional brain measures, APOE genotyping, demonstrated very high sensitivity and specificity for predicting conversion to AD [409].

In conclusion, the advances in the characterization of the dynamics of functional brain networks based on MEG stands the chance to provide new insights into the pathophysiological mechanisms of AD. In doing so, it shall constitute a powerful tool to bridge the gap between what is known from the cellular and molecular pathways of the disease—its start and its progression—and the cognitive dysfunctions constituting its clinical and behavioral hallmark. This is likely to be key for developing new biomarker-guided targeted treatments and PM, based on the characterization of the individual genetic patterns and pathophysiological pathways towards neurodegeneration and dementia.

CONTRIBUTION AND ROLE OF NEUROMODULATION

Neuromodulation refers to forms of more or less invasive targeted and reversible electrical stimulation of discrete brain regions; it usually assists, but not replaces, traditional pharmacological treatments, with the aim to induce long-lasting changes of firing neural properties, both in the target region and connected networks, thereby modifying behavior or diseases' symptoms. Therefore, neuromodulation fits well with the broad paradigm of PM that is the customization of healthcare tailored on the individual patients' demands and disease's pathophysiology.

Invasive neuromodulation in AD

Neuromodulation through deep brain stimulation (DBS) is an emerging opportunity in AD, being already an established therapy for advanced neurological and psychiatric diseases [410]. Several subcortical and cortical targets of stimulation have experimentally shown improvements in learning and memory, reinforcement of synaptic strength and restoring of physiological patterns of oscillatory brain activity, especially in the theta band, a rhythm that is functional to memorization [411]. DBS of the entorhinal cortex [412] enhanced memory of spatial information when applied during learning. DBS of the nucleus basalis of Meynert was studied in six patients with mild to moderate AD in a 12-month pilot study [413]. DBS was well tolerated and 4 of 6 patients were considered stable or improved at 12 months based on cognitive scores. The fornix, a deep WM tract interconnecting hippocampus with mammillary bodies, and a central node of the Papez circuitry which is integral to memory function [411],

has been the most investigated, human DBS target for AD [414–417].

A 12-month follow-up of the first implanted 6 patients in the bilateral fornix showed a possible slowing of cognitive decline in some of them, accompanied by increase of metabolism in memory-related neural network structures [418], and by a reversal of the usual hippocampal atrophy found in AD [416]. These promising results prompted the first multicenter, 12-month, double-blind, randomized, controlled study of bilateral DBS of bilateral fornix in 42 patients with mild probable AD [419, 420]. The study showed no differences between those patients who received stimulation compared to controls who were not stimulated in cognitive measures. However, patients who received stimulation showed an increase in glucose metabolism in pre-selected brain regions at 6 and 12 months whereas those who were not stimulated showed decreased metabolism as expected. In a *post-hoc* regression analysis age was associated with outcome. Patients with late onset disease (≥ 65 years old) receiving stimulation showed a slowing of decline in cognitive measures when compared to those not stimulated. Improvement in glucose metabolism in this subgroup was greater in magnitude compared to the group as a whole. Stimulation of the fornix appeared to be safe. The overall peri-operative adverse effects of the procedure, despite the cortical atrophy and the trans-ventricular trajectories of the electrodes towards the deep target, were comparable in DBS in other ND and there was no evidence of mortality or neurological morbidity at three months from the implant [419].

Non-invasive neuromodulation in AD

A different, non-invasive yet still experimental in AD, research approach for neuromodulation is the targeting of neocortical regions relevant to AD pathophysiology, through the scalp by applying repetitive transcranial magnetic stimulation (rTMS) or weak currents via transcranial direct current stimulation (tDCS), in repeated daily sessions of stimulation [421]. Mechanisms of action are different, as rTMS makes cortical neurons to fire trans-synaptically [422], while tDCS shifts the level of their firing probability in a polarity-dependent manner [423]. Both stimulation techniques induce controllable excitatory or inhibitory after effects: high-frequency rTMS and anodal tDCS generally increase cortical excitability, while low-frequency rTMS and cathodal tDCS do the opposite [424, 425]; these effects are either local

or involve the cortico-subcortical network to which the targeted region belongs [426]. In case of AD, the mere “stimulation” of a cortical target, even if prolonged for several daily sessions, does not help so much in preventing the decline of memory and other cognitive functions [421]. However, there are few controlled studies for rTMS in AD and even less for tDCS, for a total of a few dozens of patients treated so far [421]. What is emerging as a possible role for non-invasive neuromodulation is the coupling of stimulation with cognitive therapy, with the aim to promote plastic associative learning mechanisms to synergically improve the effects of cognitive rehabilitation only [427–429]. This approach, while still in need of quantitative characterization [430–432] seems promising only in mild AD, when the severity of neurodegeneration makes still available a residual neural substrate to possibly intervene on [433].

From the bench to the patient: A future way of non-invasive neuromodulation?

Physiological cerebral activity is composed of oscillatory activity across a wide range of frequencies, ranging from 0.05 up to 500–600 Hz: oscillations in the 30–80 Hz range are known as “gamma” activity. A relative attenuation of gamma activity is a consistent finding in patients with AD [315]. Moreover, dysregulation of hippocampal theta/gamma coupling may precede amyloid deposit activity in animal models of AD [434]. A seminal recent study in pre-symptomatic and amyloid pre-depositing AD mice, showed that exogenously-induced flickering lights oscillating at 40 Hz reduce A β concentrations and amyloid plaques, as well as tau concentrations, in a mouse model of AD [435], preventing subsequent neurodegeneration and behavioral deficits, thus suggesting that gamma induction may represent a novel therapeutic approach for AD. This opens translational perspectives, as the possibility of modulating gamma activity in humans, potentially leading to the same beneficial effects observed in mouse models. The possibility of modulating brain oscillatory patterns in AD patients has been recently shown, with EEG changes in brain connectivity in the gamma band following the administration of antiepileptic drugs [436].

A viable way to interact with brain oscillations is transcranial alternating current stimulation (tACS), where low intensity (max 2 mA) alternating sinusoidal currents are applied via scalp electrodes. Due to the safety [437] and controllability (in terms of

stimulation frequency and the possibility to target almost any cortical region) of the procedure, tACS has gained consensus as one of the most promising techniques to modulate brain oscillations in the healthy and pathological brains. Empirical evidence using neurophysiological markers, demonstrate that tACS modulates brain oscillatory activity via network resonance, suggesting that a weak stimulation at a resonant frequency could cause large-scale modulation of network activity and amplify endogenous network oscillations in a frequency-specific manner [438–441]. The application of tACS in the gamma band (specifically 40 Hz) has been shown effective in transiently modulating various abilities in humans, including those related to higher-order cognition [442, 443] and sensorimotor performance [444]. The repeated administration of tACS in AD patients, if individually tailored on cortical regions with higher concentration of A β , might constitute a timely, disease-transforming, personalized therapeutic application worth to be tested in patient populations.

CONTRIBUTION AND ROLE OF POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) has the potential to make a major contribution to selection for treatment in AD. This is of particular interest at very early asymptomatic stages of the disease, when clinical symptoms are still absent. In addition, it may also turn out as important at later stages as it is increasingly being recognized that several distinct pathophysiological processes can contribute to the development and manifestation of first symptoms and dementia. They vary considerably among patients, and one would therefore want to target the leading cause in individual patients.

At preclinical or prodromal disease stages identification of fibrillary amyloid deposits by PET currently is of obvious importance as an approved imaging biomarker for clinical trials. Use of a conservative cut-point has been suggested to minimize inclusion of elderly subjects with beginning amyloid deposition but without subsequent worsening [445]. Depending on a positive outcome of trials, amyloid PET might become a theragnostic procedure to select patients for anti-amyloid treatment.

In individuals with manifest dementia, differential diagnosis between AD and other diseases, such as FTD and vascular dementia, is important for selecting symptomatic treatment. ^{18}F -2-fluoro-2-deoxy-

D-glucose PET (^{18}F -FDG-PET) has repeatedly been demonstrated to provide reliable differentiation between AD and FTD [446]. Beyond its relevance in the differential diagnosis, ^{18}F -FDG-PET is a topographic marker of AD that can be used to measure disease progression and help identifying clinical subtypes [447]. Thus, it has a mediational effect between the neuropathological hallmarks of the disease (neurofibrillary tangles and A β) and the cognitive symptoms [448]. It has also been used successfully to study mechanisms underlying cognitive reserve, which delays the onset of dementia [449]. Identification of *in vivo* AD pathology has also proven to be relevant in disease identification. Indeed, some AD clinical phenotypes can be underlain by several neurodegenerative disorders (e.g., primary progressive aphasia, corticobasal syndrome), including the classical amnesic AD [450]. In such cases amyloid PET can identify fibrillary amyloid as an indicator of AD. Fibrillary amyloid can also coexist with other pathologies, which is frequently the case in patients with DLB and vascular dementia (which might be termed mixed dementia), but is also possible with FTD and may possibly contribute to more rapid progression [451, 452]. Thus, if anti-amyloid therapy did eventually show clinical benefit in AD patients, patients with non-AD dementia and positive amyloid PET might also benefit.

Among the large variety of possible pathophysiological contributors to AD, many are accessible by specific PET tracers. The most prominent are fibrillary tau deposits. The current generation of PET tau tracers has been demonstrated to reflect the pathological staging of tau deposits in AD, but there is also evidence of some off-target binding that complicates the interpretation of scans. Next generation tracers are being developed to overcome these limitations [453].

Neuroinflammation is another major factor which has been shown to accelerate disease progression. It is associated with activation of microglia, which can be imaged by PET using the translocator protein (TSPO) tracers. ^{11}C -(R)-PK11195 has been the first of those, and in spite of some limitations due to a relatively high level of non-specific binding is still widely used. A large number of second generation tracers with higher specificity has been developed but their binding is subject to a genetic polymorphisms that blurs the advantage of these tracers [454]. Nonetheless, beyond these limitations, the development of these tracers could provide relevant biomarkers and offer new insights in the variability of evolution of AD [455]. There are also tracers for imaging of

astrogliosis, and markers for cytokines and inflammatory endothelial changes are being developed. Further translational research will investigate the molecular characteristics and the effects of targeted interventions on microglial and astrocytic activation. Deficits in cholinergic transmission play a major role for deficits in memory and attention in patients with dementia. Tracers have been developed for nicotinic and muscarinic receptors, for vesicular transporters and acetylcholinesterase. Clinical studies have provided preliminary evidence that such tracers could be used to identify responders to acetylcholinesterase inhibitor therapy, and further research into this issue is required [456].

There are well established single photon emission computed tomography (SPECT) and PET tracers for identification in dopaminergic transmission, which is most severely affected in DLB. This is providing a useful diagnostic tool for differentiation between AD and DLB, while research is ongoing to identify the cognitive deficits associated with that deficit and potential targeted therapeutic interventions [457].

There is also current research into PET imaging of glucose energy metabolism, mitochondrial damage, glutamatergic and GABAergic dysfunction, blood-brain barrier damage and defects in transcriptional regulation and protein synthesis. They may play an important role in AD pathophysiology and offer windows for targeted intervention.

In conclusion, there is a huge potential of PET to contribute development of the PM paradigm in AD. Currently, amyloid imaging has been progressed most as a biomarker in clinical trials towards that goal. ^{18}F -FDG-PET and tau-PET imaging are also involved in multiple trials, while a large variety of other tracer for specific targets in AD pathophysiology are still at earlier stages of translational research.

CONTRIBUTION AND ROLE OF RETINAL IMAGING

Over the past three decades, growing evidence indicates that AD is not confined to the brain but also affects the eye. Patients with AD and subjects with MCI experience a wide spectrum of visual deficits [458–464], sleep disturbances [465–471], and ocular abnormalities [466, 472–489]. Historically, these visual and circadian rhythm disturbances were attributed to pathology in the brain yet are now being revisited and explored as a potential direct outcome of ocular pathologies. Among ocular tis-

sues, studies have shown that the retina is massively impacted by AD [466, 472, 474–479, 482, 484, 486, 487, 490–507]. The retina of MCI subjects and AD patients displays a host of abnormalities including nerve fiber layer (NFL) thinning, optic nerve and retinal ganglion cell (RGC) degeneration, macular volume changes, retinal angiopathy involving reduced blood flow and vascular structural alterations, astrogliosis, and abnormal electroretinogram patterns [472]. Given these findings, it is no surprise that attention has begun shifting towards the neuroretina as a site of AD manifestation.

As a CNS tissue derived from the embryonic diencephalon, the retina shares many structural and functional features with the brain [508], including the presence of neurons, astroglia, microglia, pericytes, microvasculature with similar morphological and physiological properties, and a blood barrier [509–511]. Axons of the optic nerve directly connect the retina and brain, facilitating vesicular transportation of A β PP synthesized in RGCs [512]. Further, retinal neurons and glia secrete proteins associated with the amyloid cascade including γ -secretase, BACE1, Apolipoprotein E, and clusterin [511, 513, 514]. However, the skull-encased brain is shielded by bone, whereas the retina is accessible for direct, non-invasive high-resolution imaging.

The converging evidence denoting retinal abnormalities related to nerve degeneration and vascular changes, common to various neurological and ocular diseases, have long been described in MCI subjects and AD patients. Yet, the AD-specific pathophysiological hallmark, A β plaques, was only recently identified in postmortem retinas of AD patients and early-stage cases [490]. Subsequent studies corroborated these findings of retinal A β deposits and further indicated the presence of p-tau in retinas of AD patients [466, 485, 489, 515, 516]. These studies provided evidence for elevated retinal A β_{40} and A β_{42} peptides using biochemical assays on whole retinal extracts and revealed diverse retinal A β plaque morphology in flatmounts, often associated with blood vessels or co-localized with sites of cell degeneration (Fig. 7A-H) [466, 485, 489, 490, 515, 516]. Recent data showed that retinal A β deposits were found in clusters and frequently mapped to peripheral regions in the superior quadrant in AD patients (Fig. 7C, F). The load of A β_{42} -containing retinal plaques in the superior quadrant was substantially elevated by 4.7-fold in patients compared to age- and gender-matched controls (Fig. 7C, D) [485]. While two groups were unable to detect A β or p-tau in the

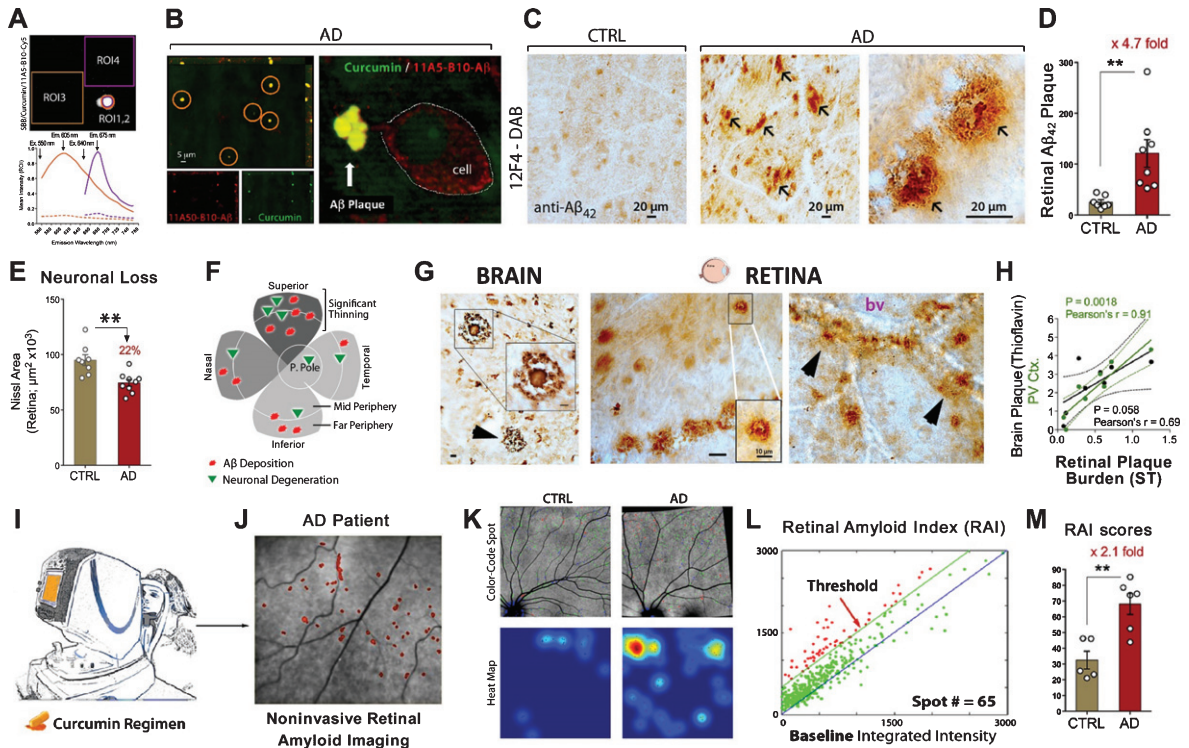


Fig. 7. Retinal amyloid imaging: from histological examination to clinical trials. A) Spectral analysis of A β plaque in AD human flatmount retina via specific curcumin labeling. Representative image and spectra curves of retinal A β plaque double-labeled with curcumin [region of interest (ROI) 1; orange line] and anti-A β_{40} antibody-Cy5 conjugate (ROI2; purple line) and corresponding background areas (ROI3 and ROI4; dashed lines) at excitation wavelengths of 550 nm (for curcumin spectra) and 640 nm (for Ab-Cy5 conjugate). Sudan black B (SBB) was applied to quench autofluorescence. Peak emission wavelengths captured for the same individual A β plaque (605 nm for curcumin when bound to A β plaque and 675 nm for anti-A β Ab conjugated Cy5) are distinct, indicating specific fluorescent signals for each fluorochrome and signifying the detection of A β plaque by curcumin. B) Representative z-axis projection images of flatmount retinas from AD patients. Retinal A β plaques (yellow spots) co-labeled with curcumin (green) and anti-A β_{40} monoclonal antibody (11A50-B10; red) are detected. Analysis included definite AD ($n=8$), probable/possible AD ($n=5$), and age-matched controls ($n=5$). High-magnification image (right) showing an extracellular A β plaque. Images A-B are adopted from [490]. C) Representative microscopic images from flatmount retinas of a healthy control individual (CTRL; 71 years) and a definite AD patient (74 years) stained with anti-A β_{42} C-terminal-specific antibody (12F4) and visualized with peroxidase-based labeling. High-magnification image showing different A β_{42} plaques including classical morphology. Analysis included definite AD patients ($n=5$) and matched controls ($n=5$). Images reproduced from [466, 472]. D) Quantitative analysis of retinal A β_{42} -containing plaques (12F4-immunoreactive area) in the superior quadrant shows a significant increase in AD patients versus matched controls. E) Quantitative Nissl $^{+}$ neuronal area in retinal cross sections indicated a significant reduction in AD patients compared to CTRLs, which is associated with retinal neuronal loss. D, E) Data reprinted from [485] ($n=23$ AD patients and $n=14$ controls). F) Retinal flatmount illustration demonstrating the geometric distribution of pathology in AD retina by quadrant, with more consistent findings of nerve fiber layer thinning, neuronal degeneration and retinal A β deposits mapped to peripheral regions of the superior quadrant. Adopted from [472]. G) Representative images of a frontal cortex section and a flatmount retina from AD patients stained with 12F4 monoclonal antibody (brown) showing different A β_{42} plaque morphology including classical plaques (inserts). Clusters of A β_{42} -containing plaques are often associated with blood vessels (bv; right image). H) Correlation analyses using Pearson's coefficient (r) test between retinal 12F4 $^{+}$ -plaque burden in the superior-temporal (ST) quadrant and cerebral plaque burden (Thioflavin-S staining) in a total of seven brain regions (Brain; black) and in the primary visual cortex alone (PV Ctx.; green) in a subset of AD patients and matched CTRLs. I, J) Illustration displaying non-invasive retinal amyloid imaging using Longvida $^{\circledR}$ curcumin and a modified scanning laser ophthalmoscope in human trials. K-M) *In vivo* retinal imaging in AD patients and age-matched controls. K, L) Increased curcumin fluorescent signal (red dots) in superior hemisphere in AD patient versus CTRL. Color-coded spot overlay images: red spots are above threshold and considered curcumin-positive amyloid deposits; green spots exceed 1:1 reference but not threshold; blue spots fall below reference. Heat map images with red spot centroids (lower panel) showing regions of interest with more amyloid plaques in the retina. L) Automated calculation of retinal amyloid index (RAI). Blue line is 1:1 reference; green line represents the threshold level, determined at 500 counts and above; red spots are above the threshold. The same automated image processing and analysis was applied on all human subjects ($n=16$). M) RAI scores showing significant increase in AD patients compared to age-matched CTRLs. G-M) Republished with permission of American Society for Clinical Investigation from [485]; permission conveyed through Copyright Clearance Center, Inc. Group means and SEMs are shown. $**p < 0.01$, unpaired two-tailed Student's *t*-test.

human AD retina [489, 517], they relied on analysis of cross sections prepared from narrow strips spanning horizontally from nasal to temporal quadrants, regions scarce in A β pathology. In contrast, a recent study provided in-depth characterization of retinal A β deposits in larger cohorts of definite AD patients via scans of large retinal areas in flatmounts and in cross sections derived from geometrical regions abundant with A β pathology [485]. The discovery of classical, dense-core (compact), and neuritic-like plaques in these patients, albeit smaller in average size compared to plaques in the brain, along with neurofibrillary tangles, A β ₄₂ fibrils, protofibrils, and structures resembling oligomers, suggests that the specific signs of AD are shared between the retina and the brain (Fig. 7G). A correlation analysis in a subset of patients has validated positive relationships between retinal and respective cerebral A β plaque burden, with a tighter association to plaques in the primary visual cortex (Fig. 7H) [485]. Notably, retinal regions in AD patients where abundant A β pathology was detected—the periphery of the superior quadrant and the innermost retinal layers—also showed a significant decrease in retinal neuronal cells (Fig. 7E, F), in agreement with previous studies showing a marked RGC loss and NFL thinning in the superior quadrants [466, 476, 484, 491, 498, 502, 518, 519]. A recent clinical study identified circadian abnormalities in AD patients along with a significant loss of melanopsin RGCs (mRGCs), photoreceptors known to drive circadian photoentrainment [520], and discovered A β accumulation within and around these degenerating cells. The loss of mRGCs may therefore result from their increased susceptibility to toxic A β forms and offers a plausible retina-based explanation for sleep disturbances in AD [466].

In line with the above findings, numerous studies examining the retina of transgenic and sporadic animal models of AD have reported A β deposits, vascular A β , p-tau, and paired helical filament-tau (PHF-tau), often in association with RGC degeneration, local inflammation (i.e., microglial activation), and impairments in retinal structure and function [472, 485, 490, 515, 516, 520–537]. These investigations, which included a variety of transgenic rat and mouse models (ADtg) as well as the sporadic rodent model of AD, *O. degus*, demonstrated abundant A β deposits, mainly in the GCL and NFL [490, 516, 521, 525, 528, 530, 533]. Furthermore, several publications have described positive responses to therapies in reducing retinal A β plaque burden in ADtg mice, often reflecting the reactions

observed in the respective brains [490, 524, 527, 528, 532, 536].

To visualize retinal A β pathology in live subjects, a non-invasive retinal amyloid imaging approach was initially developed in ADtg mice, utilizing curcumin as a fluorescent probe [490, 527]. Curcumin is a natural and safe fluorochrome that crosses the blood-brain and -retinal barriers and binds to A β fibrils and oligomers with high affinity [490, 527, 538–551], with the ability for *ex vivo* and *in vivo* visualization when specifically bound to retinal A β plaques (Fig. 7A, B) [485, 490, 527]. This approach enabled non-invasive detection and monitoring of desecrate retinal A β deposits in live animal models of AD [490], including the capability to track the dynamic appearance and clearance of individual plaques and their substantial reduction after glatiramer acetate immunotherapy [527, 552, 553].

In a proof-of-concept clinical trial, the safety and feasibility to non-invasively detect and quantify retinal amyloid deposits in live human patients was demonstrated using a modified scanning laser ophthalmoscope and a proprietary oral curcumin formulation (Longvida[®]) with increased bioavailability (Fig. 7I–M) [485]. Corresponding to the pattern reported in histological examinations, retinal amyloid deposits in living AD patients were frequently concentrated in the mid- and far-periphery of the superior hemisphere (Fig. 7K). A significant 2.1-fold increase in retinal amyloid index, a quantitative measure developed to assess numerical value of amyloid burden in the retina of living patients, was revealed in AD patients versus matched controls (Fig. 7L, M) [485]. Recent studies applying non-invasive retinal imaging in live AD patients, which detected NFL thinning [466, 477], increased inclusion bodies [554, 555], reduced blood flow, microvasculature alterations, and oxygen saturation in arterioles and venules [479, 556, 557], and importantly, hallmark A β deposits [485], are encouraging first steps toward the development of practical tools for predicting disease risk and progression. Since the retina in other ND such as multiple sclerosis, ischemic stroke, and Parkinson's disease also exhibits pathophysiological processes similar to those detected in the brain [501, 558–561], retinal imaging may also facilitate differential diagnosis for different proteinopathies, neurodegenerative and neurological diseases.

As research exploring AD in the brain, the possibility that the easily accessible retina may faithfully reflect AD neuropathology warrants further inves-

tigation. The preliminary evidence of retinal A β accumulation in early-stage cases together with the indication of amyloid-related neurodegeneration in the AD retina [466, 485, 490] suggests that AD is both a cerebral and an ocular disease, and may support retinal imaging as a screening tool even during the asymptomatic at risk stage. Future studies are needed to assess the nature of the relationship between cerebral and retinal amyloid burden in larger cohorts and in specific anatomical regions, and perhaps also to determine the potential link among cerebral amyloid angiopathy and retinal vascular amyloid. Given that retinal amyloid pathology could foretell brain disease and cognitive decline, it may prove essential for early detection of AD, predicting disease progression, and monitoring response to therapy.

In addition, non-invasive functional tests of pupil reactivity to light may complement the characterization of retinal abnormalities with imaging techniques [562]. Indeed, pupil responses to light stimulations are abnormal in AD patients [563], who show hypersensitive pupil-dilation to tropicamide, an acetylcholine receptor antagonist, as well as a diminished pupil light reflex [564, 565]. Although the retinal abnormalities mentioned above could account for these pupillary effects, the Edinger-Westphal nucleus, a major relay involved in pupil control where early signs of AD (cell loss and amyloid plaques) have also been observed, could also contribute to pupillary abnormalities. Conducting focal tests in different regions of the visual field to probe the pupil response can help identifying the functional consequences of the retinal amyloid imaging results. If the results of retinal imaging and functional tests were strongly correlated, pupil reactivity could be used as a proxy for AD severity, with the advantage that functional tests of pupil reactivity are easy, cheap and fast to perform, do not require a strong involvement of the patients, and can routinely be conducted to detect and track the evolution of AD, as well as the response to therapy.

In this regard, the “VISION” pilot translational neuroscience research program, belonging to the previously mentioned Sorbonne Université GRC-APM (GRC n° 21), has been developed and launched in an early asymptomatic preclinical population to assess retinal amyloid imaging for 1) screening of amyloid and tracking its progression as well as 2) predicting pathophysiological disease progression, cognitive decline, and conversion to prodromal AD. The non-invasive nature, easy accessibility and generalizability are appealing features regarding a potential context of use.

SPATIOTEMPORAL MODELING OF MULTIMODAL LONGITUDINAL DATA ANALYSIS

Nowadays, deepening our understanding of AD pathophysiology is made possible by the following biomarkers that can be derived *in vivo* from the subject: “fluid” from blood (e.g., genetic risk factors) and CSF (e.g., abnormal A β ₄₂ and p-tau dosing); “structural” (e.g., brain atrophy as a sign of neurodegeneration) and “functional” (e.g., brain disconnection syndrome) from MRI, “molecular” (e.g., brain hypometabolism and deposition of A β ₄₂ and p-tau) from PET, and “neurophysiological” (e.g., abnormal cortical neural synchronization and coupling). Furthermore, fine neuropsychological and clinical scales allow a detailed measurement of cognitive impairment, self-care, independence in living in a community, and mental disorders (e.g., anxiety, mood, psychosis, and behavior). All these measurements allow a personalized evaluation of cerebral residual capacity and function over time by the repetition of the recording sessions.

Keeping in mind this premise, a major issue is the identification of the best statistical and mathematical procedures, from computational neurosciences, weighting the information value of the above biomarkers and clinical indices for early diagnosis (even in preclinical or prodromal stages preceding dementia), monitoring, therapy response, and prediction of the disease evolution.

To this aim, digital brain models have been developed in recent years, as a way to synthesize a 3D geometrical model summarizing the anatomical invariants in a group of subjects [566–569]. This model has been extended recently to functional data [570, 571]. The main interest of such models is that they do not only illustrate the effects of the AD on brain structure and function at the group level but also include information about individual variability allowing the computation of the difference between a given patient and the reference groups of healthy subjects and patients with other dementing disorders to provide diagnostic information as sensitivity (detection of AD patients), specificity (detection of healthy subjects or patients with other diseases), and global classification accuracy.

These diagnostic models are based on the Bayesian inference of *non-linear* mixed-effects models, which complement the usual *linear* mixed-effects models typically used in biostatistics [569, 572]. This combination of statistical and geometric approaches

accounts for the inherent structure in the data such as the specific organization of the brain anatomy as prior knowledge. It allows the rendering of the inter-individual variability as a realistic and interpretable change of the 3D model. Individual characteristics are summarized by a multivariate descriptor, which may be used in turn to explore the distribution of the individuals in different clusters, to correlate it with external factors, or to use as input in machine learning algorithms to make individual predictions [568].

Ideally, such a static model should be adapted to account for the disease progression over time and provide prognosis of clinical evolution in individual AD patients. Digital models of brain ageing are constructed as dynamical models showing the complex spatiotemporal patterns of changes in the above biomarkers while the disease progresses. Inter-individual variability is expressed in terms of changes in individual spatiotemporal trajectories. The construction of such models of disease progression results from several key components [570, 571, 573–576]: 1) artificial intelligence approaches that are used to combine several short-term data sequences in longitudinal data sets to synthesize a long-term scenario of disease progression; 2) different data modalities that are integrated in the model by converting them into a common abstract mathematical space (called a Riemannian manifold) where statistical distributions of spatiotemporal trajectories may be rigorously defined; 3) variability in trajectories accounting for the direction of the trajectories and the dynamics at which these trajectories are followed.

Each individual disease trajectory is now positioned in a spatiotemporal coordinate system, where a multivariate descriptor encodes the variability in the direction of the trajectory, and dynamical parameters encode for the variability in age at disease onset and pace of disease progression. Given the observation of a new subject at one or few time-points, one may personalize the scenario of disease progression by adjusting model parameters, thus transferring the knowledge gained from the automatic analysis of a longitudinal data set to this new individual. This personalized model may be utilized then to predict the future state of the subject, for instance the time to the onset of a specific symptom. We have employed such an approach to predict the time-to-diagnosis in mild cognitive impaired subjects using a model of cognitive decline from neuropsychological assessments [577], and to predict the future map of cortical thick-

ness for the same subjects using structural imaging [571]. This approach opens up the way to build efficient decision support systems for monitoring disease progression and selecting patients in clinical trials with a specific biomarker-based diagnosis of AD, at a specific disease stage (e.g., preclinical, prodromal, or manifest dementia) and with an expected pattern of progression.

In addition, such a personalized scenario may offer a new way to assess treatment efficacy by evaluating to which extent it changes the disease trajectory, that is the complex non-linear spatiotemporal patterns of changes. This approach evolves the standard procedure based on annual percentage rate of an outcome measure since: 1) it does not assume a linear variation of the outcome at all disease stage but account for the non-linear dynamics of changes across disease stages, and 2) it makes use of a multivariate descriptor of disease trajectory and not only a univariate outcome measure.

THE EMERGING FIELD OF SYSTEMS PHARMACOLOGY IN ALZHEIMER'S DISEASE

The consequences of the highly complexity of AD pathophysiology can be clearly observed in the results of drug development pipeline for the disease: out of 413 clinical trials conducted during the 2002 to 2012 period, 99.6% failed [578]. Moreover, a review of AD drug development pipeline in 2016 showed that although the pipeline has increased in size, it is significantly smaller compared to the cancer field, and that the most common target (76%) is still amyloid, reflecting the urgent need for deeper understanding the pathophysiology of the disease [579]. In fact, disappointing results of anti-amyloid drug candidates can be attributed to three major factors relating to drug discovery and development, namely 1) inter-species mechanistic differences between animal models and human, 2) complex biology of A β in relation to disease staging, and 3) ignorance of non-amyloid pathways. Thus, it is imperative to delineate the complexity of AD pathophysiology using systems biology-based approaches, which take advantage of computational analysis and modeling of both quantitative (e.g., “omics”-based) and qualitative (e.g., literature-based) data. The goal of systems biology methods is to aid researchers develop hypotheses regarding the disease system and gain better mechanistic insights into the

pathophysiology and progression of disease across multiple biological scales and time. Mechanistic systems models are either mathematical representations of pathophysiologic processes or computable cellular networks but the latter has gained more attention for analysis of drug action [580]. Since these models use networks instead of single transduction pathways, complex patterns of drug action within the target biological context can be studied in more details, a field that has emerged as systems pharmacology.

According to the American Association of Pharmaceutical Scientists (AAPS), systems pharmacology is “*the science of advancing knowledge about drug action at the molecular, cellular, tissue, organ, organism, and population levels*” (available at http://www.aaps.org/Systems_Pharmacology/). To obtain full understanding of drug action at the systems level, we need to combine disease mechanism, pharmacodynamics, and pharmacokinetic data into a single model. However, incorporation of quantitative parameters and measurements increases the model complexity so that special mathematical techniques are required to reduce the number of parameters without affecting the behavior of the system; thus, disease mechanistic models are considered as the first substrate for building full-fledged systems pharmacology models [581]. Disease mechanistic models are molecular and cellular networks that aim to elucidate the impact of therapeutics or new drug candidates on impaired biological functions under disease conditions. The key to usefulness of disease models is context-sensitivity, meaning that disease network models should represent the real-world context in terms of cell and tissue type (spatial dimension), disease sub-type (functional dimension), and progression stages (temporal dimension). It is only in the right context that correct inferences, interpretations, and predictions can be made out of the model. The focus of earlier models was to relate drugs to proteins in the form of drug-target networks where protein-protein interaction networks were used as the fundamental model for interpretation of drug mode-of-action [582]. Interestingly, these models also revealed an important aspect of systems pharmacology paradigm, which was conceptualized and coined as “polypharmacology” [583]. This concept changed the single-target approach to designing new drugs in the discovery phase because topological analysis of drug targets in network models demonstrated that a compound binds to multiple targets. As a consequence, a drug hits addi-

tional targets, known as off-targets, which leads to side effects. Campillos and colleagues (2008) used drug-drug and drug-target networks enriched with side-effect phenotype information for all approved drugs across many disease indications and based on side-effect similarities predicted and experimentally validated novel drug-target relations [584]. This approach enables researchers to predict off-targets and thereby probable side effects for candidate drugs in preclinical settings. The so-called structural systems pharmacology aims at modeling energetic and dynamic modifications of genomic macromolecules including proteins, DNA, and RNA by drug candidates [585]. This strategy has been implemented by Nikolic and colleagues (2016) to predict both primary target and off-target profiles of several anti-neurodegenerative compounds based on their chemical structures [586]. Their analysis resulted in identification of novel compounds that hit multiple targets and inhibited acetylcholinesterase, butyrylcholinesterase, monoamine oxidases A and B in the context of AD pathophysiology. Moreover, knowing which drug properties distinguishes CNS drugs from others can help drug designers select those properties in the new drug candidates that confer the least side effects and the best efficacy. To this end, Shahid and colleagues (2013) developed a computational method that identified and classified neurodegenerative drugs from non-neurodegenerative drugs with 80% accuracy [587]. DrugGenEx-Net is a computational platform that predicts disease-specific drug polypharmacology based on multi-tiered network analysis of drug-target, disease-target, pathway-target and target-target interactions [588]; the model revealed that Sunitinib, an approved drug for renal cell carcinoma, hits multiple targets associated with AD pathways and thus can be considered for repurposing.

With advancements in systems biology modeling languages, such as Systems Biology Markup Language (SBML) and Open Biological Expression Language (OpenBEL), drug-mode-of-action can now be investigated in a context-sensitive, rich environment that goes beyond simple representation of protein-protein interactions by including various types of biological entities covering genotype to phenotype scales. For instance, Fujita and colleagues (2014) developed a comprehensive molecular interaction map of Parkinson’s disease that included major signaling pathways in Parkinson’s disease, modeled and presented in SBML format; however, they did not include drug information

in their model [589]. AlzPathway is the result of an early initiative that attempted to systematically collect AD-related signaling pathways from literature and bring them together within the first map of cellular AD signaling pathways, represented in SBML [590]. Recently, Iyappan and colleagues (2016) identified all signaling pathways reportedly involved in the human ND, mapped them back onto their corresponding anatomic sites on the human brain, and used these pathways for explaining the mode-of-action of the AD approved drug, Rasagiline [591].

In the past years, with the availability of increasing amount of data and knowledge on the one hand, and emergence of new computational biology methods on the other, the IDM framework has increasingly drawn more attention by academic and pharmaceutical research groups. The models generated by this approach combine data-driven and knowledge-driven models into a single integrative model and represent signaling pathways with cause and effect relations [23]. However, a major challenge for this approach is integration of heterogeneous datasets and information that come from various data sources. For instance, the ADNI provides big neuroimaging data along with genetic and biomarker data from AD and MCI subjects [592]. If integrated into predictive models, ADNI data will have maximal impact on the AD drug research. But, the first step toward IDM is standardization and harmonization of different datasets so that they are semantically compatible. Ontologies are semantic frameworks that provide a reference for standardization and harmonization of diverse datasets. For instance, AD ontology (ADO) has been developed to provide such a reference for AD knowledge domain [593]. ADO was used by Kodamullil and colleagues (2015) to represent scientific findings in a computable, cause-and-effect model of AD pathology, which was designed and coded in Open Biological Expression Language (available at <http://openbel.org/>) [594]. This model contains causal and correlative relationships between biomolecules, pathways, and clinical readouts and was used for model-guided interpretation of genetic variation data for a comorbidity analysis between AD and type 2 diabetes mellitus. Similarly, drug-target interactions and drug mode-of-action can be investigated and predicted using these models. Indeed, integrative models that encompass data from genome to phenome across biological scales from cells to clinical outcomes, enable us to predict the mode-of-action of candidate drugs within the right

pathophysiological context and in a multidimensional space of human biology. Perhaps one of the most fundamental works in this area is the study by Emon and colleagues (2017) who systematically analyzed the brain chemical space and identified drug candidates for repositioning in AD [595]. They first generated a large model in BEL containing genes, proteins, drugs and chemicals, biological processes, and disease concepts in the context of neurodegeneration. Then, by mechanistic analysis of this model, they not only suggested Donepezil as repurposing candidate for amyotrophic lateral sclerosis, but also found a mechanism of action by which Riluzole, a drug used in amyotrophic lateral sclerosis, could be predicted to interfere with several pathophysiological pathways in AD. Moreover, the mode-of-action analysis of other drugs in the context of AD using this model predicted that Cyclosporine, a drug used for treatment of rheumatoid arthritis, which shares common targets with 5 approved drugs for AD, can exert neuroprotective effects. Several lines of evidence that experimentally proved its anti-AD effects supported this prediction.

Currently, several initiatives have undertaken the effort to facilitate systems pharmacology studies in the field of ND in general and AD in particular. The AETIONOMY project, funded by the Innovative Medicine Initiative (see <http://www.imi.europa.eu/>), has already set up a specialized knowledgebase for ND with focus on AD and Parkinson's diseases, and takes an integrative modeling approach to computationally predict and clinically validate mechanistic signatures that stratify AD and Parkinson's patients (see <http://www.aetionomy.eu/>). The mission of this project is to lay foundation for development of new drugs targeting patient subgroups and thus promoting personalized medicine. The Brain Health Modeling Initiative (BHMI) is another project that takes advantage of integrative mechanism-based computational models and simulations using big data with the aim of matching right targets and biomarkers for optimal drug design in AD [596]. The European commission-funded project SysPharmAD proposes a systems pharmacology approach to the discovery of novel therapeutics in AD using an integrative network model that combines "omics" data with stage-specific clinical data. The aim of this project is to design and validate a systems pharmacology strategy based on AD staging that helps researchers identify synergistic multi-targeting compounds modifying the disease path (available at http://cordis.europa.eu/project/rcn/185567_en.html).

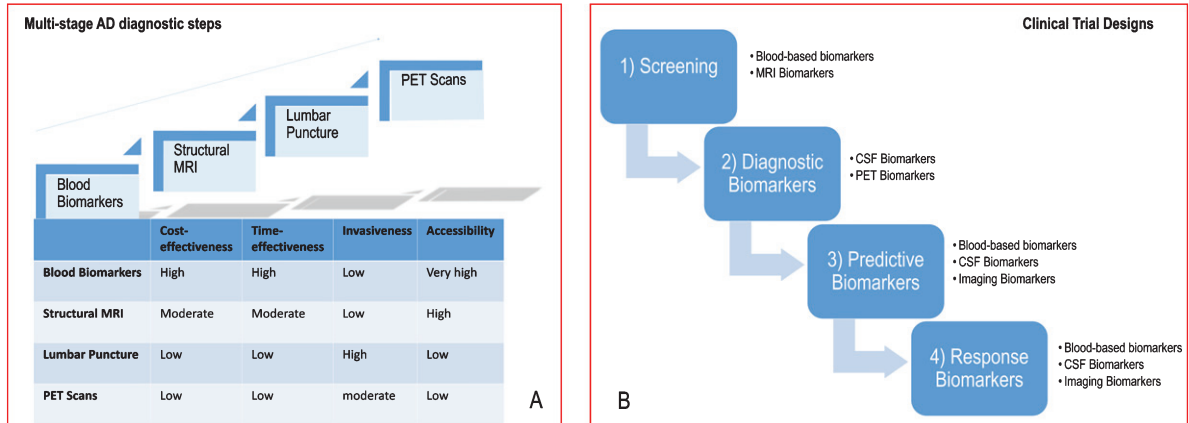


Fig. 8. Evolving spectrum of biomarkers and modalities. A) The ideal biomarker should be minimally-invasive, unexpensive, practical, rapid and reliable with low level of expertise required. Therefore, in the clinical-setting, biomarkers should be assessed in a multi-stage diagnostic workout carried-out along four steps (blood biomarkers, structural MRI, lumbar puncture, PET scans) according to the overall balance among the following factors: cost-effectiveness, time-effectiveness, invasiveness and accessibility. B) Biomarkers represent one strategy to tailor therapy. The idealistic markers for ND would enable their implementation in screening, diagnosis, progression of the disease, and monitoring of the response to therapy. Therefore, in clinical trials, biomarkers can be used for several purposes: 1) to identify people eligible for the trial, i.e., those considered at high risk for ND (screening biomarkers); 2) to guide clinical diagnosis (diagnostic markers); 3) to optimize treatment decisions, providing information on the likelihood of response to a given drug (predictive biomarkers); 4) to detect and quantify the response rate to treatment (response markers). MRI, magnetic resonance imaging; PET, positron emission tomography; ND, neurodegenerative diseases.

CONCLUSIONS

The multidimensional nature of all ND, AD included, is well established to-date, along with the fact that their onset and progression arise from dysregulation processes which evolve at both intracellular and extracellular levels. At the cellular level, ND are characterized by dystrophic neuronal structural changes leading to loss of function and, eventually, cell death. These phenomena spread in a “cell-to-cell” fashion in which intraneuronal protein misfolding affects structural plasticity in a nearby neuron by self-propagation of pathogenic protein aggregates. This, in turn, leads to decreased dendritic spines and synaptic sites density, and, eventually, loss of brain connections.

At the subcellular and molecular level, the core pathophysiological phenomenon is represented by failure of proteostasis cellular pathways [597, 598], from protein misfolding and aggregation to decreased clearance, mitochondrial dysfunction, loss of cell homeostasis, and, consequently, enhanced cell signaling pathways related to apoptosis. Therefore, ND are initially characterized by several alterations of subcellular frameworks, mostly concerning proteostasis, on which both the anatomy and physiology of neurons and glial cells are founded.

The genome, through mutual interactions with endogenous and exogenous factors, leads to a wide spectrum of variations at the level of proteome and metabolome that, incontrovertibly, account for both intracellular and extracellular integrity. As a result, the systems biology and systems neurophysiology paradigms can provide a conceptual model where structural and functional networks are dynamically interconnected across different dimensional levels into accounting a multiscale dynamical system which has already been seen to manifest also into peripheral branches like the autonomic nervous system in health and disease [599, 600].

At present, there is an urgent need to identify a large array of reliable biomarkers to *in vivo* identify the above mentioned interacting multidimensional levels which characterize ND. Such biomarkers need to be able to chart the spatio-temporal trajectories of complex brain pathophysiological mechanisms, at the same time taking into account interindividual variables. Complex, time varying higher order statistics as well as structural model should also be considered within the systems neurophysiology modeling approach [601–604]. Pathophysiological biomarkers are required to track the pathophysiological mechanisms underlying ND (Fig. 8). For instance, cerebral amyloid-PET is commonly considered as a

molecular proxy of the A β metabolism impairment rather than a conventional biomarker of neocortical deposition of neuritic plaques. In this context, biomarkers are the appropriate tools for developing receptor-tailored drugs, as already demonstrated and currently practiced in the field of oncology. Both structural and functional brain markers are expected to elucidate the link between clinical phenotypes and molecular pathophysiological mechanisms.

Notably, cerebral ^{18}F -FDG-PET is commonly used as prognostic indicator in several clinical trials on AD and other ND. Indeed, the early recovery of specific brain functions or networks is crucial to identify downstream effects of disease therapies, even before measuring the clinical benefit. As another example, in the context of identifying brain biomarkers from non-invasive imaging within a more individually tailored, PM-based approach, recent developments have pointed out the concept and added value of “dense sampling of individual brains” [605–607]. This interesting development is based on the realization that, while a large body of research is accustomed to averaging neuroimaging data across individuals and, hence, implicitly assuming a high degree of functional homology, by definition there must be a finer scale at which this homology breaks down, possibly the scale which encodes the individual idiosyncrasies at the base of a unique individual’s disease trajectory and/or therapy response. By sampling relatively few brains for several hours, the authors demonstrate how individual differences in well-known networks, e.g., the default mode and the salience network, are clearly visible. Therefore, it is possible that future developments in neuroimaging will shift more toward longer (several hours/days) sampling of individual brains/patients, thus providing more solid bases for the implementation of the “precision neuroscience” paradigm that will likely be needed to understand ND.

Interestingly, functional and topographic biomarkers could also be employed in identifying the adequate target. In particular, they could be valuable in detecting specific brain areas for potential trials of targeted neuromodulation, thus providing comprehensive information on regional atrophy, impaired connectivity, metabolic alterations, and regional decrease of cerebral blood flow. Finally, both clinical examination and full psychometric evaluation still remain the first-line approach in identifying pathological phenotypes supporting the whole diagnostic workout. For instance, to date, the iden-

tification of hippocampal-like amnesic impairment supports the clinical diagnosis of AD, thus justifying an anticholinesterase inhibitor-based treatment. Notably, in the context of a systems biology- and systems neurophysiology-based interpretation of ND phenotype, clinical markers should be considered the highest level “descriptors” of the disease and represent the ultimate measures to identify effective therapies.

In summary, the future implementation of the systems biology and systems neurophysiology paradigms, based on the integrated analysis of big and deep heterogeneous data sources, will be crucial to reach a deeper understanding of the pathophysiology of AD and other ND. The main challenges ahead will certainly lie in the development of analytical applications capable of processing massive quantities of stored laboratory and clinical data. Against this backdrop, the big data approach should be leveraged to maximize the information that can be extracted from preclinical and clinical records, ultimately augmenting our knowledge regarding the molecular, cellular, and systems processes underlying AD development. As we unravel the dynamic and longitudinal changes of the biomarker landscape in AD, we will make a further step toward a holistic understanding of the natural course of the disease. Integrating different sources of information will enable researchers to obtain a new integrated picture of the pathophysiological process of the disease that will span from molecular alterations to cognitive manifestations. In this scenario, the Big Data Research and Development Initiative (available at <https://obamawhitehouse.archives.gov/blog/2012/03/29/big-data-big-deal>), promoted by the previous Obama Administration under the “Big Data is a Big Deal” motto, is expected to accelerate progress toward a new era of PM in AD. This ultimate mission will be accomplished by assembling, linking, and harmonizing big data to facilitate high-impact, multidisciplinary, and collaborative research efforts. After a decade of failed clinical trials in AD, the adoption of “big data science” within an IDM theoretical framework by the international APMI allowed us to enter into a transformative research scenario. It is currently expected that PM will underpin most, if not all, of the prevention and treatment advances yet to come. Significant breakthroughs in our understanding of the early phases of AD and other ND and the rapid advent of new laboratory technologies are providing unprecedented opportunities to make a major impact on the natural history of AD at the earliest pre-

clinical asymptomatic stage [608]. We are currently standing at the edge of a new frontier that will thoroughly explore the molecular and cellular events that drive the development of the disease before cognitive symptoms are evident. New preventive approaches and therapies developed through PM may improve compliance and increased level of trust and confidence among all stakeholders and reduce the number of failures. In this context, we are expected to move swiftly from the traditional “one-size-fits-all – magic bullet therapies” scenario to a personalized PM-based approach. The unprecedented effort promoted by the APMI is ultimately tailored to implement a paradigm shift in AD research which will be backboned by large, international, and interdisciplinary collaborative academic, private and industry networks. The field of PM does not lack for enthusiastic, dedicated pioneers who are moving forward expeditiously to clinical adoption. As the evidence base supported by the APMI expands, much more can and should be done to accelerate the process for the benefit of individual patients, the healthcare system, and society overall.

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