From genes to network models of Alzheimer's disease: Biological framework for multi-scale brain simulation with The Virtual Brain

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ABSTRACT

While the knowledge in neuroscience and the possibilities in clinical neurology have improved for many years, neurodegenerative diseases and associated dementia remain a growing problem. Alzheimer's Disease (AD) is the most common cause of dementia and also represents the most prevalent type of neurodegenerative diseases. For AD, disease-modifying treatments are presently lacking and the understanding of disease mechanisms remain incomplete. In the present review, we consider candidate contributing factors leading to AD and we evaluate novel computational brain simulation methods to further disentangle their potential roles. We first discuss existing computational models of AD that aim to provide a mechanistic understanding of the disease. Next, we outline the potential to link molecular aspects of neurodegeneration in AD with large-scale brain network modeling using The Virtual Brain (TVB, www.thevirtualbrain.org), an open-source, multi-scale, whole-brain simulation neuroinformatics platform. Finally, we discuss how this methodological approach may contribute to the understanding, improved diagnostics and treatment of AD.

REVIEW

Introduction

Every second senior with an age above 90 years suffers from Alzheimer's disease (AD) or another dementia (1). The mortality rate in the US for people with this neurodegenerative disease (NDD) exceeds that of breast cancer and prostate cancer combined (2). Beyond the impact on individual life circumstances of patients and their families, NDD has an enormous economic impact and hence poses a massive societal burden. The Alzheimer's Association's latest report estimates the annual medical and care costs attributed to AD in the U.S. at \$290 billion in 2019 (2). By 2050, this number is expected to rise as high as \$1.1 trillion (3). It is estimated in the same report, that early diagnosis at the stage of mild cognitive impairment (MCI) could save up to \$7.9 trillion in cumulated medical and care costs by the year 2050. While the prevalence of AD, the most common type of NDD (1, 2), increases, the underlying disease mechanisms are still not understood. No disease modifying treatment does exist. Despite the collection of large data sets and major advances in high throughput computational methods, what is lacking are theoretical frameworks that link the many pieces observations to infer the underlying causes. The brain has multiple levels of organization (e.g., molecular, cellular, ensemble- and region-level) including both feedback and feedforward interactions between and within those different levels. These dependences are nonlinear, leading to emergent phenomena — features of the system that cannot be understood by the simple “sum” of its parts. Small perturbations in such nonlinear systems can have large unexpected consequences. In the brain, interactions traverse many spatial and temporal scales, thus focusing on one scale can underestimate the emergent phenomena at other scales.

A mechanistic understanding of AD opens new horizons for early diagnostics and cause-targeting treatments. Recent pharmacological clinical trials testing substances such as anti-Amyloid-beta (Abeta), tau-protein targeting (4) and immune-modulating substances used for rheumatoid arthritis, have experienced major setbacks. The development of novel therapeutics would clearly benefit from theoretical and computational approaches (5).

We hypothesize that the key to both understanding and curing AD lies in the characterization of the features and processes that control emergent phenomena in the brain. To reach this goal, a deep understanding of state-of-the-art biological research on AD and detailed knowledge of the tools offered by computational brain modeling are required. In this review, we summarize current findings of AD pathogenesis from genomics to connectomics – describing the contribution of the classic hallmark proteins as well as current research on the Notch-1 pathway, neurotransmitters, polygenetic factors, neuroinflammation and neuroplasticity. In the second part, we present various approaches of computational modeling of AD disease mechanisms and discuss their benefits and disadvantages. In the last part, we describe The Virtual Brain (TVB, www.thevirtualbrain.org) as a multi-scale brain simulation platform that enables linking molecular signaling cascades with large-scale brain simulation. An overview about the structure of this article is given by the flowchart in **Figure 1**.

PART I: Alzheimer's Disease Research. Background

I.1: Historical considerations

While nowadays dementia is a descriptive term for (acquired) severely impaired cognitive function due to a brain disease, dementia has historically been understood as a mainly physiological loss of mental function in the elderly (6). Psychiatrists have therefore contrasted the cognitive disorders of the young (*'dementia praecox'*), today classified e.g. as schizophrenia, against dementia in the old, *'dementia senilis'* – i.e. the classification of dementia was dependent on the age at which the cognitive impairment occurred (7). A profound challenge to this concept was posed in 1907 by the observation of Alois Alzheimer when his patient, Auguste D., had a characteristic psychopathology of *dementia* rapidly progressing - at an early age of 56 years (8, 9). Based on his observations of an “unusual disease”, a new field of neurologic and psychiatric research emerged. Various mechanisms, risk factors, etiologic components (i.e. underlying causes such as for example neurotoxic proteins, risk-modifying genes, etc.) and comprehensive classifications of cognitive disorders were developed. Interestingly much later in 2013 (10), it was shown that Auguste D. suffered from an early-onset variant of Alzheimer's dementia. A truly “unusual” and rare disease, which is one of the monogenetic forms with a mutation in the presenilin gene *PSEN1* (10). Yet the primary cause of AD and also criteria for its diagnosis still remain unclear. Even the disease-defining biochemical findings of the pathology in AD, represented by *amyloid beta* ($A\beta_{40}$ and $A\beta_{42}$, in the following *Abeta*) and the phosphorylation of the τ protein (*TAU* for *tubulin-associated unit* or by the Greek letter τ , in the following *Tau*; for a review, see (11)), remained controversial as causative of the disease trajectory and cognitive symptoms. Nevertheless, their presence during pathogenesis is undisputable (12-14).

I.2: Definition and diagnostic criteria

Nosology is the discipline of disease classification based on the underlying disease mechanisms. A disease classification in this sense can only be assigned if the underlying etiology of the respective disease has been established. Otherwise, we speak of a “syndrome” or “disorder” (15). The dementia syndrome encompasses a broad array of different possible etiologies of cerebral or systemic origin (1, 16). Clinically it presents as a set of signs and symptoms. The affected neurocognitive domains are the higher cortical functions, namely: Memory, language, attentional processing, executive functions and visuo-spatial domains. Different diagnostic criteria are being used for the diagnosis of AD.

Amongst the most used diagnostic criteria is the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association) definition of 1984, where possible and probable AD are defined purely by clinical (e.g. daily life impairments) and neuropsychological criteria in the absence of further diagnostic evaluation with technical means (17). At the core of this definition is the presence and slow progression of cognitive decline in two or more cognitive domains including memory, as well as the absence of alternative causes of dementia. In the revision of these criteria in 2011, it was further specified that impairment in activities of daily living (ADLs) is necessary for the diagnosis of the dementia syndrome (18).

In clinical practice, a diagnosis is mainly established based on the definition of probable AD according to NINCDS-ADRDA and through the exclusion of potential other causes of dementia (19). One challenge with this purely symptomatic definition of AD is posed by the various phenomenological forms of AD (16). Clinical symptoms and neurodegeneration occur on a continuum. They can vary tremendous across individuals. The most common phenotype of AD is the slowly progressive amnesic variant. However, it is not uncommon that dysfunction of language, disorientation, apraxia or neuropsychiatric signs like affective symptoms appear first, while memory deficits seem not to be predominant. This heterogeneity in phenotypes can have various causes, such as educational and social factors, structural vulnerability of the brain or the individual cognitive “reserve” of each patient (20). The clinical definition of AD gets further complicated due to an overlap in symptoms with those of other dementias and comorbidities that can influence the clinical presentation. For example, if the patient suffers also from depression, possibly caused by the beginning cognitive decline, this mood disorder itself can impact memory. And if patients also suffer from Parkinson’s disease – do they then necessarily have Parkinson’s dementia? Or AD and Parkinson’s at the same time? Or has the neurodegeneration caused by the Parkinson’s disease diminished the cognitive reserve, which lead to the clinical onset of AD?

In contrast to the original NINCDS-ADRDA classification, the current diagnostic definition from the NIA-AA (National Institute of Aging and Alzheimer’s Association) in 2018 is based on the presence of Abeta and Tau proteins in cerebrospinal fluid (CSF) or positron emission tomography (PET) and atrophy signifying neurodegeneration in brain imaging. The NIA-AA definition introduces the AT(N) classification to standardize biomarker findings in AD: therein A stands for positive Abeta biomarkers, T for phospho-Tau biomarkers, and N for Neurodegeneration markers in cerebrospinal fluid (total Tau burden) or atrophy shown in magnetic resonance imaging (MRI). The cognitive dimension of the disease is handled separately (and can be added to the classification as the letter C in its extension ATNC). This definition is primarily intended for application in research and not used in clinical routine practice (15). It is debated whether this definition may prevent shifting scientific attention to other important candidate factors contributing to AD – which might lead to missing mechanistic cascades beyond Abeta and Tau proteins (21).

While the NINCDS-ADRDA definition only considers cognitive symptoms, the NIA-AA definition does not consider cognitive symptoms in the core AT(N) classification at all (15). Therefore, possible more specific classifications could be “Alzheimer’s disease with dementia” or “Alzheimer’s disease with mild cognitive impairment” instead of the currently used term “Alzheimer’s dementia”, which merges both, AD pathologic changes and dementia syndromes (15).

Despite clinical classifications for probable AD (17) or research frameworks as the definition of AD by dementia with A+T+N+ biomarkers (15), only the exploration of invasively obtained tissue samples either in the living person through biopsy or post-mortem at autopsy can provide definitive diagnosis of AD – by proofing the presence of neuritic plaques (with Abeta) or neurofibrillary tangles (with Tau). Autopsy is the more likely course of action as highly invasive interventions that could secure a diagnosis *in vivo* are rarely performed because of the lack of causal disease-modifying treatment options. The rate of confirmation of clinically diagnosed AD by autopsy was calculated in a meta-analysis with a sensitivity of 85.4% and specificity of 77.7% (22). However, even the neuropathological examination of brain tissue as the state-of-the-art gold standard method for AD diagnosis often reveals several protein-related pathologies, i.e. those represented by the typical picture for AD plus others that have been associated with other neurodegenerative diseases (23).

Possible prodromal stages of dementia, e.g. mild cognitive impairment (MCI) and subjective cognitive decline (SCD), do not meet the clinical criteria for a dementia syndrome because the patients have no deficits in the ADLs. In MCI, cognitive deficits are measurable, but still do not affect ADLs (24). In SCD, it is not objectively possible to measure the deficits in neuropsychological examinations, but patients complain about cognitive deficits they notice (25). These states may in some cases be critical phase transitions of the disease trajectory to dementia. In combination with other factors, they may help assessing the risk of an individual to develop manifest dementia (26).

Diagnosis is often an important question for the patient and the patients' families – even in the absence of helpful therapeutic interventions because this provides more certainty regarding the prognosis of disease and the development of care plans. The consequence of not knowing the diagnosis for the individual patient, especially for the elderly with potential comorbidities, is that it is often not clear to what extent distinct types of dementia and related disorders actually contribute to the cognitive impairment (27, 28).

I.3: Epidemiology

Neurodegeneration is a continuum where several factors, such as proteinopathies, vascular and immunological changes likely interact (23). Within the spectrum of dementias, the most common dementia is AD, followed by vascular dementia (VD) and mixed dementia that is a combination of AD and VD (29) (**Figure 2**, data from (1)). Frontotemporal dementias and Parkinsonian syndromes, in particular the Lewy-body dementia and the Parkinson dementia, occur with lower prevalence than AD. A systematic overview of the most common and clinically important dementias is presented in **Figure 3**. The diagnosis of dementia-underlying diseases is challenging. Dementias can occur due to primary NDDs, i.e. AD, mixed dementia, frontotemporal and Lewy-body dementia, and secondary dementias linked to vascular changes (VD), immunology, infections and other diseases (**Figure 3**). Yet this differentiation is a simplification, as many secondary dementias arise from neurodegenerative processes during the disease course of primarily non-neurodegenerative diseases, . A well-known example is the neurodegenerative course in late stages of multiple sclerosis (30).

The relevance of correct diagnoses results from the different treatment strategies and prognoses as they relate to different types of dementia. Some of the possible causes of dementia are curable such as normal pressure hydrocephalus, metabolic disorders, and immunologic or infectious causes. While presently no disease-modifying therapy for any primary neurodegenerative disease exists (2), future therapies as well as ongoing symptomatic and more experimental studies may benefit from a careful patient stratification. This is in particular important for approaches that aim to model AD mechanisms with patient data, as the resulting model will only be as specific to AD as the patients were assigned to the correct (and strict) diagnosis. An overview about the experimental therapies that are in development for AD can be found in **Table 1**. For the established treatments for other dementia causes, see **Table 2**.

The population above 80 years is the group where the prevalence of dementia is increasing the most (31). While different pathogenic pathways have been hypothesized for AD and VD, it is

increasingly acknowledged that both syndromes share many risk factors (32). However, interactions of Abeta in AD with vascular factors (e.g. altered blood-brain barrier permeability caused both by microvascular changes and Abeta deposition (33)) and can be differentiated from cerebral amyloid angiopathy (34), a distinct vascular disease caused by amyloid, which we will not discuss further here.

An increased rate of cerebrovascular disease manifestations and thus a higher incidence of VD correlates with lifestyle and atherogenic risk factors such as physical activity (35, 36), diabetes mellitus (37) and hypercholesterinemia (38, 39), which are also risk factors for AD (32, 40). However, mechanisms whereby these factors mediate their impact has been debated (41). One hypothesis is that microvascular lesions remain undiscovered leading to a failure to diagnose a vascular or mixed dementia. Another possibility is an involvement of metabolic pathways in the pathogenesis. Notably, the most important genetic risk factor in the whole population, APO-E ϵ -4 hetero- or homozygotic, is an allele of a metabolic gene, which also modulates the atherosclerotic risk (42, 43). Especially in the elderly, the prevalence of both etiologies, atherosclerosis and neurodegeneration, increase exponentially and could therefore likely affect the same individuals (44). Although the role of metabolic factors is not clear, epidemiological approaches have shown that up to one third of cases attributed to AD might be preventable by addressing these modifiable risk factors (45). However, this evidence comes from a mere observational method using the population-attributable risk. This statistical method describes the fraction of the incidence of a disease that can be attributed to one particular risk factor. While this index allows an estimation of the effect that might follow on the removal of the risk factor, as a result from an observational study it precludes establishing a clear causal relation between observed risk factors and the disease (46). For example, if the definition of AD in the underlying observational study is inconsistent and therefore contains also other disease entities as mixed dementia, the population-attributable risk would be related to mixed dementia as well as to AD itself. A reduction of atherosclerotic risk factors might therefore affect the mixed dementia patients instead of “pure” AD cases.

PART II: Brain Alterations in Alzheimer’s Disease: from Genes to Brain Networks

II.1: Genetics

Early-onset AD can be a familial disease with rare structural variants or copy number variants in genes that regulate Abeta production and clearance. For example, structural variants in the Amyloid precursor protein (*APP*) gene affect post-translational processing of *APP* by secretases leading to excess Abeta in early-onset AD. The presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes form the active component of the γ -secretase complex. It is critical for processing APP as well as other type-I integral membrane proteins, including members of the Notch signaling pathway and receptor tyrosine-protein kinase erbB-4 (*ErbB4*) (47). There are autosomal dominant mutations of *PSEN1* and *PSEN2* that affect endopeptidase and carboxypeptidase activity leading to longer and more toxic forms of Abeta peptides (48, 49). Other environmental and genetic factors may contribute to the etiology of early-onset AD (50).

In contrast, late-onset AD is a complex genetic disease in which rare structural variants and common variants, mostly identified by genome-wide association studies (GWAS), play an

important role in etiology. The heritability of late-onset AD is estimated to be high with approximately 50% (51, 52) – yet environmental factors are likely to be additionally important (53, 54). The single nucleotide polymorphism (SNP)-based heritability estimates are usually high in AD, at approximately 25-30% (55), compared to other complex genetic brain disorders (56, 57). Apolipoprotein E (*APOE*) $\epsilon 2/\epsilon 4$ polymorphisms alone explain approximately 25% of the SNP-based heritability with common SNPs explaining the remaining 5-7% (52, 55, 58). The most recent three GWAS have identified 40 independent risk loci (58-60). The majority of these loci have functions in three main pathways: lipid metabolism, microglial activation, and APP processing (61). Importantly, many of these loci contain functionally relevant SNPs that impact expression in AD-associated cortical tissues and correlate with the expression of quantitative trait loci (eQTL) (58).

II.2: Protein level

Two most relevant proteins are associated with the pathogenesis of AD: Abeta and phosphorylated Tau. Abeta is a human protein which - due to an abnormally cleaved configuration - aggregates in neuritic plaques leading to its (neuro-)toxic effects (62-64). It can be found both intra- and extracellularly (5, 65, 66). The hyperphosphorylation of the Tau protein has been suggested, develops as a consequence of the aggregation of Abeta (19). However, phosphorylated Tau is present in other neurodegenerative diseases not associated with Abeta deposition. Immunohistochemical analysis of brain tissue, which is more sensitive than standard microscopical tissue examination, reveals up to 92 - 100% of Tau in people who died with neurodegenerative disorders at a mean age of 71 years, in contrast to Abeta with 20 - 57% (67)). All subjects which fulfilled the official clinicopathological criteria for AD (ADNPC, defined as the presence of Abeta plaques, neurofibrillary tangles, and neuritic plaques (68)) in standard microscopy also showed Abeta and Tau by immunohistochemistry. But in the same group of ADNPC patients, two other protein pathologies could be measured; in 41 – 55% alpha-synuclein (associated to several diseases of the Parkinson spectrum) and in 33 – 40% TAR-DNA-binding protein 43 kDa (TDP-43, associated to amyotrophic lateral sclerosis and frontotemporal dementia; see also **Figure 3**). Therefore, ‘pure’ AD was a rare case in this cohort as 65 – 70% of confirmed AD patients suffered at least from one other neurodegenerative co-morbidity (67).

Neurodegeneration involving Tau has been characterized as primary and secondary tauopathies (69). A major argument in favor of the more prominent involvement of Abeta in driving the neurodegenerative process in AD is its higher specificity and its appearance in the early familial variants of AD, where the pathway is better understood (19, 62, 63). In the past, most therapeutic strategies were aimed at Abeta (70-82).

II.2.1: Amyloid Beta

The deposition of Abeta typically follows a particular spatiotemporal pattern in the progression of AD. An illustration of this distribution can be seen in **Figure 4**. The course can be divided into three general stages (83-85): Stage A develops along the perirhinal and entorhinal cortices. Stage B involves the hippocampus proper and neighboring regions like the posterior gyrus parahippocampalis. Stage C involves also a wide distribution of neocortical areas. **Table 3** provides the list of brain regions that are specific to each amyloid stage.

One possible explanation of the pathogenic deposition of A β is a maladaptive change in its processing, regulated by a group of secretases and other enzymes. We give only a short overview here. APP is a transmembrane protein whose function has been associated with neural development and synaptic plasticity (86). It can be processed to different subdomains. One possible way is the procession by the α -secretase and subsequently the γ -secretase, which is called the non-amyloidogenic pathway (19). This “physiological” pathway does not lead to A β fragments (with β -helix), which can later aggregate to plaques, but APP gets transformed into a protein subdomain with α -helix configuration (19). In another “pathological” pathway, by the β -secretase (and afterwards again the γ -secretase) APP is processed to soluble A β with β -helix configuration. The β -helices allow the molecules to aggregate together and build first A β oligomers and afterwards polymers, that become insoluble and deposit in the extracellular space, where they form the so-called beta amyloid plaques. The activation of this pathway leads to a decreased concentration of A β in CSF, because its insoluble configuration cannot be measured therein (19, 87). The imbalance between these two pathways, represented by the activity of α - and the β -secretase, is suggested to play a major role in the pathogenesis of AD and is currently, the target of various experimental treatment strategies (80, 82, 88-90) (**Table 1** and **Figure 5**).

Another important feature, which is linked not only to the protein metabolism of A β , but also to neural development, is the Notch-1 pathway (91-93). Notch-1 is a membrane protein that plays a major role as the transcription factor for both, the NICD (Notch intracellular domain), and its extracellular domain NECD (94). The processing of Notch-1 to its subdomains is performed by the γ -secretase – the same secretase that is involved both in the amyloidogenic and non-amyloidogenic pathway of APP processing (94). APP and Notch-1 are co-substrates in the extracellular domain of the γ -secretase (91, 94). Notch-1 is found in A β plaques and its intracellular signaling is reduced in AD (94).

II.2.2: Tau protein

In the absence of any additional neuropathological factors in several dementias, phosphorylated Tau may play a major role in the degenerative process of primary tauopathies, including progressive supranuclear palsy (95), corticobasal degeneration and the spectrum of frontotemporal dementia (including Pick’s disease) (69). In contrast, in secondary tauopathies, Tau seems to be involved in the pathogenesis only when other factors are present, as e.g. in prion diseases and chronic traumatic encephalopathy (69) (**Figure 3**). From this point of view, AD has a unique context because it is neither classified as a primary tauopathy (due to the concomitant presence of A β) nor is the amyloid pathology completely linked to Tau’s hyperphosphorylation. However, the density of phosphorylated tau correlates better with the severity of cognitive decline than the accumulation of A β itself (96, 97). Hence, there is controversy on the role of the Tau protein in AD as either an independent disease factor or an indicator of general neurodegeneration derived from the neurotoxic effects of amyloid deposition. Clinical trials, based on anti-Tau-antibodies and vaccines, modulators of Tau aggregation and antisense oligonucleotides targeting its gene *MAPT*, are currently ongoing for AD patients (98, 99) (**Table 1**).

The pathology of Tau protein is complex and involved in several neurodegenerative processes (69, 95, 100). Different forms of neurodegeneration lead to a deposition of Tau (101), that can be measured in the cerebrospinal fluid (CSF) (102). In general, the phosphorylation homeostasis of the Tau protein is maintained by a series of kinases. A turn of this equilibrium towards a hyperphosphorylation of Tau protein shows two consequential effects: First, Tau loses its natural function of microtubule stabilization followed by a disturbed axonal transportation of vesicles,

which leads consecutively to a disturbed axonal signal transmission. Second, the hyperphosphorylated Tau protein polymerizes to insoluble filaments and big tubular aggregates, the so-called neurofibrillary tangles (NFT). The brain's clearance system is unable to eliminate these aggregates leading to inflammatory processes and eventual neuronal death (19). These phenomena have been observed by using three methods: (i) microscopy of neuronal tissue with neurofibrillary tangles, (ii) observing an increased concentration of the hyperphosphorylated Tau section in the CSF, and (iii) non-invasive nuclear imaging methods that trace Tau protein (^{18}F -AV-14-51 PET) (95). Because of its two main effects, namely neuronal death and axonal dysfunction, Tau leads to a disconnection of the affected regions in brain networks. This has been measured in regions with high binding of ^{18}F -AV-14-51 PET tracing the Tau protein (95). The Tau protein is however a better marker in diagnostics for the severity of cognitive dysfunction than Abeta in AD (103). The local neurotoxic effects of Tau can be linked to network disruption as well as to an increased clinical score of apathy symptoms (104). The stages of Tau deposition (defined by *post mortem* histopathological criteria), similar to Abeta stages are called Braak and Braak Tau deposition stages (83, 84, 105), show a characteristic spatio-temporal pattern formation in the course of typical AD (**Figure 4**). For this reason, most patients with a 'typical' AD show early tau depositions years before the onset of symptoms in the transentorhinal (perirhinal cortex, BA35) and entorhinal (BA28) cortices (stages I and II). This prodromal stage is followed by a further spreading into the limbic lobule (stages III and IV) and finally into the neocortex (stages V and VI) (83, 84, 105). The phases of this dissemination process are separated in the six stages of tau deposition falling into three functional categories (i.e., transentorhinal/entorhinal, limbic, and neocortical), and have a good correlation to the cognitive decline of an individual AD patient (96, 97). Only the transentorhinal and entorhinal cortices are affected in the first stage of tau deposition, that is, the first functional category, where often only few amyloid plaques and no clinical symptoms can be observed. In detail, the non-obligatory prodromal stage of AD is characterized by an MCI, which often converts to the full clinical presentation of dementia and has, thus, a significant correlation to higher Braak Tau deposition stages (96, 97). In the limbic category, the findings are strongly associated with clinical symptoms of MCI stage (e.g. memory function, verbal fluency, impairments of daily life activities) (96). In the highest functional category, which concerns the neocortex, most patients have amnesic impairments (83-85). Similarly, the deposition of the Tau protein traced by ^{18}F -AV-1451 PET correlates with the clinical presence of MCI as well as AD and also with cognitive performances (106).

The patterns of *post mortem* neuropathological and nuclear imaging findings are illustrated in **Table 4**. We can describe the six Tau deposition stages as follows: Transentorhinal category consists of stages I and II and concerns the transentorhinal cortex in the ventromedial temporal lobe, and later the entorhinal cortex in the lamina granularis externa (Lamina II). Limbic category consists of stages III and IV, and involves mainly the hippocampus and the temporal allocortex (**Figure 4**). The neocortical category consists of stage V and VI and concerns the spreading of Tau deposition to dorsolateral areas and primary functional areas of the whole neocortex. There seem to be a high correlation in general of the Tau deposition pattern and the pattern of amyloid deposition described above; however, it is worth mentioning that the three stages of amyloid deposition described by Braak and Braak, A, B, and C, do not strictly coincide with the tau deposition stages I to VI. The six stages of tau deposition follow a stricter distribution course and show some overlap with the amyloid deposition stages, in particular, within the ventromedial temporal allocortices and pro-isocortices and later temporoparietal neocortices (**Tables 3 and 4** and **Figure 4**). The effects of both pathologies differ to a larger extend, for instance, in the specificity to AD, to neurodegeneration in general, or to cognitive functions (107). However, the 'macro sequence' of archicortex – mesiotemporal cortex – temporoparietal neocortex is the same as well as the impaired cognitive domains in AD (memory and visuoconstruction) are associated with those regions.

II.3: Neurotransmitters

Of interest in the pathogenesis of AD are especially two transmitter systems: the cholinergic and the glutamatergic systems. Acetylcholine is one of the essential neurotransmitters in the brain. Its functions are pleiotropic: Acetylcholine is fundamental of the peripheral vegetative nervous system and of the neuro-muscular transmission. In the brain, acetylcholine is involved in many functional systems, but particularly expressed in the synaptic signaling of interneurons (108). The dysfunction of the cholinergic system is relevant in the pathogenesis of AD, as acetylcholine is essential for memory consolidation (109). Anti-dementia drugs work as inhibitors of the acetylcholine esterase, increasing the concentration of Acetylcholine in the synaptic gap, and thus leading to a slightly improved memory function (109).

Considering the other relevant transmitter, that is, glutamate, the concept of excitotoxicity is essential. Excitotoxicity refers to calcium-mediated toxic effects due to a sudden increase in glutamatergic transmission. Anti-dementia drugs that are no inhibitors of the acetylcholine esterase – mainly the N-methyl-D-aspartate (NMDA) receptor antagonist memantine – decrease the glutamatergic transmission in the synaptic cleft. Glutamatergic dysfunction is also related to neuroinflammation and plasticity.

II.4: Neuroimmunology

Beside the cascades of Abeta and Tau, the second hallmark in AD pathogenesis is the role of neuroinflammation and autoimmunity. One of the difficulties in understanding the pathogenesis of AD is that intrinsic proteinopathic dysfunction alone does not necessarily lead to neurodegeneration and cognitive decline in the sense of losing brain function. Such impairments are more likely to be caused by various toxic intermediate mechanisms as discussed before. One potentially important but poorly understood mechanism is neuroinflammation. Neuroinflammation is a relevant factor in the pathogenesis of dementia, because it is in each case the last part of the pathogenic cascade and leads directly to neuronal death (110). However, it is not clear how the modulation of inflammation can affect the process of neurodegeneration. Clinical trials have shown contradictory results. For instance, the long-term administration of nonsteroidal anti-inflammatory drugs (NSAIDs) showed positive preventive effects and can hence reduce the *a priori* risk for AD (111). However, in contrast to those observational studies, prospective trials with steroids and other immunosuppressive drugs have shown no significant effects, as have randomized controlled studies with NSAIDs (112). A case-control study in patients with rheumatoid arthritis (who have a slightly higher risk for AD) showed significant reduction of AD incidence by 70% (adjusted OR of 0.30, $p=0.02$) if the patients were treated with the tumor necrosis factor α inhibitor etanercept (113), while it was well tolerable (114). As the etiology and differential diagnosis of dementia is often unclear, the label of AD could cover up a relevant percentage of autoimmunological neural phenomena that could be actually treated with high-dose and long-time corticosteroid therapies (115). The immunology of the brain is very complex, as it involves e.g. the organ-specific immunological cell type of microglia. An appropriate discussion would go beyond the scope of this review and we would like to refer the interested reader to the following review on neuroimmunology and AD (116).

II.5: Imaging

II.5.1: Anatomical MRI

MRI offers a commonly used technique to screen for some of the before-mentioned biomarkers *in vivo*. As mentioned, the pathogenetic pattern of AD consists of the accumulation of amyloid plaques and NFTs. Volumetric assessment of grey matter loss in MRI has been identified to correlate with the distribution and degree of neurofibrillary tangles accumulation (117, 118). Therefore, volumetric MRI can provide a proxy measurement for regional NFT load (119).

The atrophy of memory-related structures has been consistently reported for AD patients, including the hippocampus and other mesiotemporal regions as well as the precuneus, cingulate and prefrontal areas (120-124). However, non-amnesic symptoms like e.g. aphasia, visuospatial problems or behavior predominant dysfunction are initially present in up to 30% of AD patients (125, 126). The distribution of NFTs in those patients with atypical clinical presentation is either limbic-predominant, hippocampal-sparing or not reported, which is also referred to as the no-atrophy or minimal-atrophy AD variant (119, 127). A correlation between those phenomenological subtypes of AD and volumetric MRI has already been demonstrated (128) and multiple studies explored MRI as an *in vivo* marker of these AD subtypes (119, 129-131). Besides the atrophy patterns of syndrome variants in AD morphology, a few of single-region-based volume reductions have also been identified as potential biomarkers for AD. A detailed overview of these features is provided in **Table 5**.

As a non-invasive *in vivo* measurement, MRI opens up the possibility of longitudinal tracking of atrophy and disease progression of AD. Recent studies investigated volume loss in AD patients longitudinally (132-134). Regions with reduced baseline grey matter volume also have a trend to show more atrophy over time and the highest atrophy rates in the temporoparietal regions (134).

Besides grey matter atrophy, white matter hyperintensities, which appear on T2-weighted or fluid attenuated inversion recovery (FLAIR) MRI scans, have a high prevalence among AD patients (135). White matter hyperintensities in general can be morphological correlates of microvascular lesions as well as inflammatory or unspecific changes in aging. An increase of the volume of these hyperintensities has already been observed in *PSEN1*, *PSEN2* and *APP* mutation carriers approximately six to 22 years before estimated symptom onset of AD (136). The relationship between white matter hyperintensities and AD pathology is still an active research field (137).

II.5.2: Positron Emission Tomography

Nuclear imaging methods allow *in vivo* acquisition of metabolic features of the brain by the usage of various radioactively marked tracer molecules, so-called radionuclides. In neuroscience, in particular PET offers the possibility of different functional assessments of the brain. The underlying physics make use of β^+ -emitters – the emitted positrons of β -decay react with electrons of the tissue in a so-called annihilation, which leads to the emission of photons. The photons can be measured by specific sensors (138).

Both Abeta and Tau deposits can be measured indirectly by PET and correspond well to the underlying pathologic changes at autopsy (139, 140). Tau tracer binding in AD is higher in regions that are known to be affected in early Braak stages (104, 106, 132, 139, 141), as well as globally in the cortex (106, 133). However, Tau binding is also increased in healthy controls, predominantly located in areas with atrophic changes (132). Similarly, Abeta tracers show increased global deposition in the brain (140, 142) and in early Braak stage regions (143) (144). Although the partition of “Abeta-positive” healthy controls seems to be higher than for Tau (145-147).

Another important PET measurement is the assessment of energy metabolism by the usage of marked glucose molecules. Multiple studies suggest temporoparietal hypometabolism in AD (148-152), which is already established in unclear cases for the differential diagnosis to other dementias in clinical practice. Interestingly, as atrophy patterns (117, 118), hypometabolism has a strong association to Tau deposits (153). The usage of glucose PET in clinical routine is limited by high costs, exposure to ionizing radiation and low sensitivity in the detection of MCI patients that will convert to AD (154).

An overview of PET findings in AD is provided in **Table 5**.

II.5.3: Connectomics

After discussing the recent advances researching the microscopic molecular level in AD, a whole-brain perspective can be considered at the macroscopic level of brain regions. Connectomic research is also an important aspect in understanding the development of cognition and its decline in dementia. There are various hypotheses highlighting aspects of the degeneration and, in general, network changes in dementia (155). One global idea refers to the hypothesis of disconnection syndromes (156). It states that in dementia very generally all anatomical connections (the structural connectivity *SC*, e.g. measured with diffusion-weighted MRI) are weakened, while in particular specific regions and their sub-networks disconnect, with a focus on the default mode network (DMN), a large-scale network of regions strongly interconnected in resting state) (157-163). Although this is a phenomenon we can also observe in aging (164), the degree of DMN disruption allows in parts the distinction between healthy aging and AD (165).

The connectomic approach is a neuroscientific discipline that analyzes, describes and uses (axonal) connectivity measures of the brain (166). It provides an overview of the disease effects in AD and identifies global phenomena beyond the impairment of single regions. In the general framework of brain networks, brain regions are represented by nodes and connections between them (either structural or functional) are denoted as links or edges (**Figure 6** shows an abstract example network). At this level of abstraction, it is possible to calculate graph-theoretic measures for the connectome, the network metrics (167). There exists a plethora of different – partly interdependent – metrics of which many are showing changes in AD networks compared to healthy controls. An overview of these findings is provided in **Table 5**. Heterogenous findings for different measurement modalities exist, which point towards a widely spanned network disruption in AD on different scales (168, 169). This heterogeneity can also be explained by different methodological choices for network construction, e.g. setting different thresholds for filtering out the most important connections (170-172). In general, however, converging evidence suggests aberrant functional connectivity (FC, measured by functional MRI) and white matter SC in AD compared to healthy aging. We review and align the recent literature on this topic showing multiple local network changes in AD resulting in the global phenomena of less efficient network communication for AD patients compared to healthy controls.

AD has been viewed as a disconnection syndrome, where the loss of neurons and small-scale connectivity influences the macro-scale in the form of (structurally and functionally) disconnected brain areas (169, 173). This disconnection correlated with cognitive and behavioral decline (169) and white matter pathology in certain areas could be used as a biomarker for disease progression (174). This view on AD as a disconnection syndrome was able to bridge multiple scales of disease pathology in a coherent way. In recent years, however, network science studies on AD patients expanded this picture: widespread increases and decreases of connectivity within the brain network were observed, pointing towards compensatory mechanisms or reactions of the network beyond disconnection (169). Even an early but seminal study conveying the importance of “small networks studies” specially related to the initial disease stages showed isolation of the hippocampus from its cortical network connections via initial entorhinal cortex degeneration via the perforant pathway (175).

In network science, brain regions with high connectivity to other regions are called *hubs*. For both structural as well as functional connectivity studies, hub regions have consistently been shown as the most affected areas by AD (176-178). De Brier et al. show that even in preclinical stages of AD hubs are disrupted - in the form of two centrality measurements, the highest betweenness centrality nodes and high participation coefficient nodes (179). This vulnerability of hubs correlates with higher Abeta burden in these hub regions (160). For the functional network, especially the DMN is targeted by the AD-caused neurodegeneration (157-159, 161-163), where the highest Abeta deposition is also located. The extent of hub disruption correlates significantly with the cognitive status of a patient (162). Thus, it can be hypothesized that hubs - with their high Abeta deposition and central role in the overall information flow of the brain network - facilitate the spreading of the pathological cascade within the brains of AD patients (180). Aberrant or decreased FC has also been observed in the insula (181), posteromedial cortex (182), medial temporal cortex (183), and amygdala (184, 185).

Next to the vulnerability of hubs, a decreased global clustering coefficient has been reported showing a loss of connectedness and important redundancy structures for brain communication in FC, which consequently also alters the modular structure of AD patients (161, 179, 186, 187). Probably as a global effect of these “local attacks” on the network (**Figure 6**), decreased global efficiency in SC as well as FC networks is often observed in AD patients, which correlates with cognitive and behavioral decline (161, 188, 189). Global efficiency is in network science defined as the inverse of the characteristic path length – with shorter pathways between the nodes, the information flow within the network is more efficient. A less efficient network can still provide connections between nodes, but they are longer and with more nodes and edges in-between (190).

Recent work analyzed a multimodal perspective on AD, combining diffusion tensor imaging (DTI), functional MRI and magnetoencephalography (MEG) measurements in a multilayer network (191). They found that for the combination of different modalities, the core of the network, which is likely to contain the hubs, has been most affected, which confirms the vulnerability of hubs across modalities. Together, these changes were able to predict the cognitive and memory impairment of patients (191).

Emerging evidence suggest that in the pre-clinical stage of AD, network changes are present in the form of a disconnection on a large scale (179, 192, 193). Indeed, FC and SC are now being investigated to better differentiate AD patients, MCI, and controls moving towards the goal of identifying prodromal AD patients and the possibility of developing early intervention strategies (187, 194-196). A recent study suggests altered FC corresponding to accelerated aging in preclinical AD (197).

To sum up, both altered global and local connectivity have been associated with AD. Converging evidence from white matter diffusion tensor imaging and resting-state fMRI studies point towards less efficient network communication in AD patients compared to healthy aging, especially in the DMN.

PART III: Modeling of Alzheimer's Disease

Mathematical modeling is an adaptive and creative scientific concept and a core technique of computational neuroscience. As AD is a complex disease that takes place on various scales, a wide range of models have been developed for its research: e.g. animal disease models (198, 199), cognitive models (200) or disease progression / classification models (201-205). In general, one can differentiate between approaches focusing on single aspects of the disease, e.g. biochemical Abeta modeling (206), and integrative models incorporating several biomarkers while using multiple scales (205). The latter might be able to provide a more comprehensive, multi-modal view on the disease with its interacting mechanisms and might be therefore more suitable to reflect disease pathogenesis. This approach - also called "integrative disease modeling" (207) - combines functional and structural neuroimaging techniques, CSF sampling and/or genomic data and analyzes them and their intercorrelations using computational algorithms (202).

A comprehensive understanding of both the underlying biological processes of AD and the computational framework of high-performance modeling approaches is necessary to develop novel models for AD that integrate multiple scales, modalities, and research disciplines. With increasing technical possibilities for supercomputing and growing hierarchically organized knowledge architectures, this cross-disciplinary approach holds the potential to overcome some of the enigmas in AD pathogenesis that might not be revealed on a single scale with a single method.

Therefore, in the following sections, we will describe existing computational (brain) models of different scales and outline in how far they can be linked to the biological concepts presented before.

III.1: Statistical disease prediction models

Although statistical models are mainly of descriptive character, their criteria can also be of interest in the understanding of underlying disease mechanisms - beside their practical translational usage as diagnostic tools. A further discrimination of statistical AD models can be made between rather simplistic linear models (208) and more elaborate ones using advanced methods, such as machine learning tools. Both exhibit individual challenges and advantages regarding data analysis and model interpretation. Moreover, with regards to the more complex machine learning (ML) approaches, two major fields of use are present in the literature: prediction of disease trajectories (predictive

modeling) and classification of subjects into groups with highly similar data points (discriminative modeling). The latter can be reached by (supervised) *a priori* labelling of the training data (e.g. as two classes AD and non-AD, or as three-class problem with AD, MCI or HC). Clustering is possible without labelling, solely relying on statistical proximity measures (unsupervised discriminative models, (202)).

Structural T1-weighted MRI in conjunction with other biomarkers have been considered as features with classic ML techniques, e.g. support vector machines - often combined with other machine learning methods, such as linear discrimination analysis. Pellegrini et al. (209) reported that among 111 studies included in their review, AD was only successfully differentiated from healthy controls (HC) with satisfactory accuracy. The performance of classifiers differentiating MCI from healthy controls or AD, as well as the risk prediction of a conversion from MCI to AD was lacking (209). Thus, the clinical relevance of those classifiers remains rather low, given that - in practice - it is already possible to distinguish between HC and AD on the basis of cognitive performance. A diagnosis before clinically-noticed AD onset is therefore still missing.

An improvement could be achieved here by aiming at a deeper mechanistic understanding of AD beside its diagnosis. The relation of such a 'mechanistic biomarker', which is associated to the disease inside a complex knowledge system, is different from the purely associative character of a biomarker that is only related to the disease by correlation. In order to achieve a more accurate risk prediction of a transition from asymptomatic stages or MCI conditions into AD, biological mechanisms of this conversion have been computationally reconstructed. This was done with a predictive time-to-event model incorporating multimodal data ranging from genetic variants to neuroimaging and neuro-psychological assessments. Using a Bayesian Network model together with a literature-based validation, several biological risk factors and their interaction could be extracted (205). As the model makes use of a graph-like organization, it opens new horizons for the integration of multi-scale and multi-modal information and holds the potential to obtain information from biological knowledge bases like e.g. NeuroMMSig (<https://neurommsig.scai.fraunhofer.de>, (210)). In the hierarchical form of an ontology, it integrates chemical compounds, genes, proteins, medical terms and imaging features into a network of knowledge. This allowed to identify 125 sub-networks of pathways that are related to AD (210).

When adding longitudinal patient data to the models, further information about disease progression can be extracted and used to increase accuracy for subsequent predictions. For example, a combination of MRI measures of cortical thickness and clinical assessment scores (MMSE and ADAS-13) at two timepoints together with genetic information (ApoE ϵ 4 status) can be used to predict symptom trajectories in patients with different cognitive performance levels at baseline. Comparing different algorithms trained on multimodal data from two timepoints, a longitudinal Siamese neural-network showed highest performance, even after validation with another data set (203).

This longitudinal and multi-modal approach of predicting the individual risk and disease trajectories could thus represent promising new paths in personalized medicine. Modelling structural and metabolic changes in different areas of the brain in relation to the decline in cognitive functions can yield more sophisticated information about disease progression and its influencing factors on individual level (201). Future approaches could also incorporate a wider range of data modalities, such as is provided by the graph theoretically organized database EBRAINS of the Human Brain Project (<https://ebrains.eu>, (211)).

III.2: Sub-cellular models

Brain simulation can take place on many different scales, as the complex topological hierarchy of the brain consist of many essential components: cortical and subcortical regions, networks, columns, ensembles, circuits, neurons, synapses, vesicles, molecules and genes (compare **Figure 5**).

Sub-cellular features of AD provide promising surrogates for computational modeling based on protein interaction and gene expression. AD mechanisms have therefore been modeled focusing on different aspects such as the deposition process of Abeta (89, 212-214). Biochemical models account for interaction between numerous of the interacting factors like Abeta, Tau, inflammation, different proteases and probable interventions (215-219) and are therefore quite complex.

Early studies have used computational modeling to assess the kinetics of aggregation for synthetic Abeta-like peptides (220). Comparably simple biochemical models allowed a mathematical description of the aggregation process – as the temporal evolution of Abeta in form of monomers, micelles and fibrils (221). Subsequently, the theory of Abeta aggregation could be enhanced by including more detailed interactions between different forms of Abeta fibrils and by fitting the model to empirical data (222). While the experimental findings on Abeta's toxicity increased, a particular model was developed that describes disrupted Ca^{2+} homeostasis and Abeta aggregation as a positive feedback loop that describes how both processes are interacting in a vicious circle (223). In the last decade, more specific models have included connections of AD to important gene transcription factors as p53 (224), possible intervention strategies (225) and genetic risk factors (217).

Concepts of sub-cellular modeling are valuable for the integration to multi-scale models as they describe the molecular hallmarks of AD in a computationally accessible manner. By means of computational linguistics and semantic frameworks, molecular pathways can be “coded” as a network of relations. One possible tool for this approach is the Biological Expression Language (BEL), which enables to describe the interaction between proteins, genes and other chemical compounds with means of first-order logics (226).

III.3. Single-neuron and neural-circuit models

Beside the subcellular scope, models of AD span over different microscopic scales, ranging from single cell models (227-230) to neural networks (227, 231-233).

Single-neuron models are often inspired by an experimental approach, such as a patch-clamp experiment (234), to reproduce the observed data (228). Underlying mathematics for those single-cell simulations may refer to general formulations for neural oscillation models, as it is the case for Hindmarsh-Rose neurons (235). This early model uses three coupled differential equations to simulate basic neural behaviors as oscillatory bursts (235).

To integrate more complex systems of more than just a few neurons, the mean-field theory can be used (236). The simplification of the mean-field has its origin in physics to describe the behavior of fluid or gas without taking into account individual molecules – in the brain, it allows to simplify the behavior of a spatially distinct group of neurons with a similar function (237). This group of neurons is called a neural mass and can be defined on various scales – e.g. as a brain region, a column or an ensemble. Neural mass models (235, 238-243) have been widely used to define local dynamics in a large-scale brain network model.

III.4: Large-scale brain network models

The evolution of large-scale computational brain modeling considering the whole brain has been developed over the past decade. De Haan and colleagues (244) have built a model to test the hypothesis that excessive neural activity leads to neurodegeneration. This model is a large-scale brain network derived from diffusion MRI, where each network node holds a neural mass model by Zetterberg et al. (241) as its local dynamic model. De Haan and colleagues simplified the synaptic strength as a function of neural activity over time (244). As a result, those connections that were more frequented became weakened after a certain period of time. The purpose for the implementation of this specific mechanism was to describe a form of excitotoxicity that leads to degeneration. Here, after a certain period of time, one could consecutively observe degeneration in the functional and structural network topology using graph theoretical measures. The authors also observed a loss of spectral power and an increased sensitivity of hubs, defined by highly connected brain regions (incoming and outgoing ties) (244). The authors observed in the model an increase of brain activity and an increase of FC, similar to empirical findings in MCI or mild AD stages (244). In a subsequent study de Haan et al. (245) tested different “therapeutic” strategies like increasing or decreasing excitability of excitatory and inhibitory subpopulations of the neural masses to prevent neurodegeneration in the excitotoxic model. The most convincing strategy, which could maintain healthy network features over a long period of time, was an increased excitability of excitatory neurons that was followed by increased inhibition of inhibitory neurons. At a first glance, this might seem contradictory but it suggests the reversal of hyperexcitability by more excitation or less inhibition, respectively. The authors could however not provide a clear explanation for this effect but speculated that the reason lies in the network topology. The best strategies suppress the network hubs, which in return may lead to decreased disease propagation. According to this prediction, neurodegeneration spreads along the network infrastructure as a kind of ‘pro-degenerative’ signaling pattern.

Pons and colleagues used another brain network model for AD (246). This model uses at each cortical network node the neural mass model by Jansen and Rit (247), which is related to the Zetterberg model (241). The authors used EEG recordings that showed a slowing down of the alpha rhythm as well as an increase in FC (using phase lag index) in MCI patients with age, i.e. the FC increased from young to old subjects. Pons et al. were able to describe these observations by decreasing the maximum postsynaptic potential and increasing the thalamo-cortical SCs during the simulations.

In another modeling study, Demirtaş and colleagues have investigated the changes in BOLD signal due to AD in their recent modeling study (248). This study included 109 subjects from different groups (healthy controls, preclinical AD, MCI and AD). In empirical BOLD, one could observe a decrease in global interactions evaluating the first-order circular statistics, that is, Kuramoto order parameter, between healthy controls and AD as well as regional differences in the FC strengths. At the same time, FC strength differences were correlated to CSF biomarkers like Aβeta, total Tau and phospho-Tau (248). Estimating an individual effective connectivity (EC) from subject-specific SC and FC with a heuristic approach, the brain model was able to replicate those changes in the network interactions. Local dynamics were described by a supercritical Andronov-Hopf bifurcation. In an *in silico* experiment using brain network models based on healthy subject's EC, they varied the order parameter of the model systematically (248). In this way, they were able to observe the progress of FC degeneration. An optimal order parameter was individually found for each disease stage / group, replicating best the empirical observed degeneration. This study showed how changes in the dynamics at each brain area can lead to disintegration of activity within the anatomical large-scale brain network. At the same time, simulations also replicated the finding that the interaction

(measured by Kuramoto order parameter) between BOLD signals declines with disease progression.

III.5. The Virtual Brain platform

In the following, we will focus on TVB, a multimodal and multiscale virtual brain simulation framework (238, 249-252) that holds the potential to combine different modeling scales for AD research. The open source platform of TVB is available under www.thevirtualbrain.org. TVB is a standardized and established framework that enables large-scale modeling approaches (as mentioned in the last section) on individual patient data and with a wide range of underlying dynamics.

TVB uses the structural connectome as its underlying basis (238). Most of the neural mass models (representing the region activity) implemented in TVB started as a network model for smaller, distinct networks – initially well-known entities like the motor network, the visual system or the Papez circuit, but with the development of connectomics, the networks included were more complex and elaborate (253). Likewise, the local dynamic models used in TVB were in principle composed for smaller or even single neuron systems (235, 238-243). Eventhough TVB was designed to simulate whole brain network dynamics, it can also model and simulate separate subnetworks ranging from regional level down to a few neurons (see (254) for hierarchy of integration in TVB).

The second important feature of TVB that can assist in the future of AD research is the multi-scale character. This term has been coined to describe the fluid transition of brain scales, ranging from the macroscale, at which brain regions interact intra- and inter-hemispherically via long-range connections, to the microscale of myriads of single neurons, where we have knowledge, on their electrophysiological properties, receptors, transmitters, position and wiring in cortical layers etc. In vivo measurement techniques at the macroscale offer information about individual brains, whereas measurements at the micro-scale are more specific to cell membrane and structure but cannot sample an entire individual brain. The concept of TVB addresses both scales: on the one hand, the SC of the whole brain is the scaffold of TVB and, on the other hand, the characteristics on the neural level are represented in the local dynamic models and its biophysiological parameters (e.g. the Jansen-Rit model). Modeling the large-scale brain may not comprise microscopical elements, but modeling the entire brain based on each single neuron may be computationally infeasible. For this reason, the mesoscale has been established (255, 256) and comprises different components: First, neural masses, which can cover the anatomical extent of a functional region or cover the neural mass in a voxel sampled by an MRI scanner. Depending on the neural mass model, they can refer to excitatory and inhibitory populations interacting with each other and through the large-scale network, that is, the connectome, with distant regions. The interplay of this local circuitry in the large-scale brain network can produce physiologically plausible brain activity at a large scale (238, 249, 257-262). Second, another feature of the mesoscale is the spatial influence on neighboring regions through the evolvment of the electromagnetic field of the neural tissue and the temporal aspect of delay in the transmission along the white matter fiber tracts.

The prospect of TVB as an interdisciplinary research framework is that clinical applications and ensuing technologies may benefit and build on theoretical and computational predictions, as it has already shown success in epileptic surgery (263). TVB has already been used in a wide range of

research topics, from the modeling of physiological brain phenomena in healthy participants (249, 251, 254, 264), mouse brain models (265), to clinical approaches of AD (266, 267), epilepsy (263, 268), stroke (269, 270) and brain tumors (271).

A recent study of Zimmermann et al. modeled AD using TVB (267). By fitting the model to predict individual FC from the underlying SC, the authors could show significant correlation between cognitive state of AD patients and the fitted model parameters of TVB (267). As the parameters are surrogates of biophysically relevant entities such as long-range coupling factors and local interactions between inhibitory and excitatory neuronal populations, this enables the non-invasive estimation of intrinsic brain features.

For the field of AD, multi-modal data could include e.g. structural MRI, the SC out of DTI, and PET imaging data of Glucose metabolism, Amyloid and Tau. Our previous study (266) used one of these features, namely Abeta PET, to explore the mechanisms behind another prominent phenomenon in AD: the slowing in EEG (266). As a pilot study in this field, we modeled local Abeta-mediated hyperexcitability using brain network modeling where regional Abeta burden was derived from PET data. By defining the local Excitation-Inhibition balance as a function of local Abeta burden from PET, fundamental differences between the AD patients and controls were established in the absence of other differing factors than the Abeta distribution. We showed that few regions with moderate or high Abeta burdens are transferred into an altered dynamic state, wherein their activity oscillates slower. These slowing mainly presented as a shift from alpha to theta rhythms and was propagated throughout the network and focused to the hubs. Interestingly, local hyperexcitation as well took place in the central parts of the network. Therefore, with this approach, we were able to reveal a possible pathomechanism behind electroencephalographic slowing in AD (266).

Conclusions and future directions

Although our knowledge about the contributing factors in the pathogenesis of AD is increasing, it is still a major challenge in neuroscience to understand their distinct meaning and interaction. Moreover, the translation of these combined novel findings to clinical research is lagging behind. Rather than exploring isolated mechanisms, a goal is to integrate multi-modal datasets to reveal complex interactions underlying AD (272, 273) (**Figure 7**).

The main reasons for the development of precise and early diagnosis tools for dementia can be summarized as follows:

1. Future treatments. If a disease-modifying treatment for degenerative dementia would be available, it is very probable that it has to be performed many years before the clinical and behavioral manifestation of the disease. This is because we know that pathway changes in the brain begin decades before the onset of dementia and lead to irreversible cellular death of neurons. However, one has to expect of such a treatment that it will have to be taken for many years and might have severe adverse reactions – therefore not only a high sensitivity for the screening, but also a high specificity of the diagnosis will be of highest importance. Moreover, future trends of personalized treatments can only be outperformed with personalized biomarker-profiled patient ‘fingerprints’. For example, a recent analysis has shown that the multimodal dataset from the Alzheimer’s Disease Neuroimaging Database (ADNI) can predict the genetic expression pattern (as a potential individualized treatment target) better than the clinical presentation does (274)

2. Differential diagnosis. A more precise diagnosis of AD will lead to the possibility to clarify those cases that seem to be atypical. Some etiologies could be identified with prospective treatments. Moreover, in the future, subtypes of disease entities could be identified, which are currently subsumed under AD, and which could possibly get assessed by a specific treatment, e.g. autoimmunity phenomena with immunosuppression or early-onset AD with anti-Abeta drugs.
3. Study diagnosis. It is necessary to identify the right population to test new treatments. If the diagnosis is not clear enough, possible effects could be overlaid because of too many patients with other disease causes, in which the treatment does not show an effect. In the end, an approach of individualized medicine should be the goal.
4. Study monitoring. Because the clinical trajectories of the disease are slow and not easy to measure objectively, it is useful to use biomarkers for the monitoring of drug effects in study settings.

Using computational models for multi-scale brain simulations in future research may lead to improved diagnostics in early stages of dementia, to a more precise prognostic prediction and differential diagnosis as the fundamentals of rational medical treatment of AD patients.

FIGURES

Figure 1. Flowchart for the structure of this article.

Figure 2. Basic epidemiology of different types of dementia. Data and p-values from (1). Shown is a an elderly cohort (n=185) with mean age of 97.7 years in an autopsy study. On the left, we see the prevalence of the cognitive states within this cohort at time of death. In this age group, more than half of the people suffered of dementia, while a quarter suffered of mild cognitive impairment (MCI), and another quarter had no cognitive disturbances. On the right, the clinical diagnosis (*ante mortem*) for the subpopulation that suffered from dementia is shown. Alzheimer's Disease (AD) is the most prevalent form of dementia, however, mixed forms and other primary neurodegenerative dementias as synucleinopathies or frontotemporal lobar degeneration (FTLD) spectrum also play a role as well as vascular dementia (VD). In the *post mortem* analysis, the full cohort showed at least partial AD-related pathologic changes: 100% had neurofibrillary tangles of at least Braak stage I, and 63% had neuritic plaques. The mean Braak stage was in the dementia group 4.1, in the non-dementia group 3.2 (p<0.001). However, the dementia group also showed a significant higher Lewy-body pathology (p=0.018) and TAR-DNA-binding protein 43 kDa (TDP-43) pathology (p<0.001) as well as higher rate of definitive cerebrovascular disease (p=0.016). These findings indicate that in particular in the “super old”, different neuropathologic changes are probably concomitant and contribute to the development of cognitive decline in dementia – in contrast to the concept of ‘pure’ AD as an isolated neurodegenerative disease.

Figure 3. Mind map of the dementia syndrome and its differential diagnoses. The possible etiologies are widely spread across cerebral and systemic diseases. It is important to mention that Alzheimer's Disease (AD) may be the most common form of dementia but AD is not trivial to diagnose, in particular, if it may be indicated to forgo some invasive tests in the elderly. The exact diagnosis is however of enormous relevance because some of the possible causes of dementia are curable such as normal pressure hydrocephalus, metabolic disorders, and immunologic or infectious causes. In the clinic, most patients are diagnosed with AD, vascular dementia (VD), Lewy-body dementia, frontotemporal dementia or a mixed form thereof (**Figure 2**). None of the primary neurodegenerative diseases can be treated in a causal and disease-modifying way, besides the treatment of vascular dementia with general atherosclerosis therapy. The neurodegenerative diseases are sorted by their leading proteinopathy – caused by Abeta, Tau, prion protein, transactive response DNA binding protein 43 kDa (TDP-43), and alpha synuclein (16). Protein images modified from <http://www.ebi.ac.uk/>. Abbreviations: FTD-TDP – frontotemporal degeneration caused by TDP-43; PPA – primary progressive aphasia; FTD-ALS – frontotemporal degeneration with amyotrophic lateral sclerosis; LATE – limbic-predominant age-related TDP-43 encephalopathy; CJD – Creutzfeldt-Jakob's disease; GSS – Gerstmann-Sträußler-Scheinker; CAA – cerebral amyloid angiopathy; PCA – posterior cortical atrophy

Figure 4. Visual representation of Abeta and Braak (Tau) stages (83, 84, 105). The darker color indicates a higher load of this protein in the colored brain area. Highlighted in different colors are the regions listed in **Tables 3 and 4**.

Figure 5. Overview of contributing factors in AD and potential intervention strategies. Shown are only the most important factors, which are also enlightened in more detail in the main text of this article. In the upper left corner, we see the neurovascular system. Both characteristics of blood vessels (e.g. atherosclerosis and endothelial dysfunction) (32) as well as aspects of the blood-brain barrier (275) play a role in AD. A particular aspect here is the role of neural immunity, both with the brain-own microglia cells as well as the effect of systemic immune cells, e.g. mediated by antibodies (110, 116). On the upper right corner, we see an illustration of the multi-scale network structure of the brain. Stimulation approaches as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) act on the larger scale of a network level, nevertheless the actual changes happen on the level of synapses. Also transmitter interventions develop their effects mainly at the micro-scale of synapses. In the lower right corner, basic molecular pathways in the extra- and intracellular space of a neuron are shown. We focused here on the processing of the two hallmark proteins Abeta and Tau as well as the Notch-1 pathway, which is involved in memory (91) and plasticity (92). We illustrate the APP procession by the amyloidogenic or non-amyloidogenic way and its interaction with Notch-1 processing and, second, in the axon, the hyperphosphorylation and aggregation of Tau. A more detailed description of the named treatment strategies that are presently under development is provided in **Table 1**.

Figure 6. Neurodegeneration in Alzheimer’s Disease (AD) from a network perspective. In this schematic example network, the red links (edges) are being weakened and progressively disconnected by AD. Preferentially, edges attached to nodes with high degree (hubs) are being targeted (here node A) (176-178). In addition, lower clustering in AD has repeatedly been observed (161, 179, 186, 187), i.e. links involved in triangles are broken off (here e.g. the link between nodes B and C forming the triangle A-B-C). These two “attacks” of AD on the network, lead not only to a lower clustering coefficient but also evoke a lower efficiency, defined here as the inverse of path lengths, an estimate of short and efficient connections. This lower efficiency is demonstrated in the example network by the shortest path length between the blue nodes D and E before and after the deletion of the red links (before: 4 links, after: 6 links).

Figure 7. Potential applications of The Virtual Brain in the investigation of Alzheimer’s Disease (AD). As we outline in this article, computational modeling provides a powerful tool to link empirical findings from different scales and disciplines to new insights for improved diagnostics and treatments. Abbreviations: PET – positron emission tomography; DBS – deep brain stimulation; tDCS – transcranial direct current stimulation; TMS – transcranial magnetic stimulation.

TABLES

Table 1. Ongoing developments for AD treatment and therapies. Parts of the table are modified from (276-278).

Possible disease-modifying treatment	Substance example	Results	References
α secretase activators	Etazolate, Epigallocatechin gallate	Safety, A β aggregation↓	(276, 279)
β secretase inhibitors	Pioglitazone, rosiglitazone, AZD3293	Safety, Plasma A β concentration↓cognitive benefit for diabetical patients in observational study, until now no prospective clinical effect	(110, 276, 280-284)
γ secretase modulators	Tarenflurbil, <i>EVP-0962</i>	No clinical effect	(276, 285, 286)
γ secretase inhibitors	Semagacestat, Avagacestat	Skin cancer↑, infections↑, no clinical effect	(88, 90, 276)
A β aggregation inhibitors	PBT2, Tramiprosat, Scylloinositol	CSF A β ↓, PiB PET↓, no clinical effect	(73, 276, 287)
A β active immunotherapy	Anti-A β vaccines AN1792, CAD-106	Meningoencephalitis (AN1792), positive antibody response, no clinical effect	(71, 72, 75, 76, 276)
A β passive immunotherapy	Solanezumab, Bapineuzumab	Safety, questionable cognitive effect of Solanezumab	(79, 276, 288, 289)
τ phosphorylation inhibitors	Lithium, valproat	High toxicity, CSF τ ↓ and questionable cognitive effect of Lithium	(276, 290, 291)
τ fibrillization inhibitors	Methylene blue, davunetide	τ production ↓, possible cognitive effect of davunetide	(276, 292)
Macro-/Micronutrients	Polyunsaturated fatty acids	No clinical effect	(276, 293-295)
Phosphodiesterase inhibitors	Cilostazol	Possible cognitive effect	(276, 296)
Tyrosine kinase inhibitors	Mastinib	unclear	(276, 297)
Statines	Simvastatine, atorvastatine	Unclear cognitive effects, CSF phosphor τ ↓	(276, 298, 299)

Insulin	Intranasal insulin	FDG PET effect, possible cognitive effect	(276, 300)
NGF intracerebral application	Neurotrophic growth factor	CSF effects, gene expression effects, possible cognitive effect in subgroup	(301-303)
Deep brain stimulation	n.a.	Possible cognitive effects, highly invasive, ethical issues	(304-308)
Trancranial brain stimulation	n.a.	Unclear effects	(232, 305, 309-312)

Table 2. Potentially curable causes of dementia syndromes (16, 313).

Curable dementia cause	Diagnostic tool	Therapy
Major Depression	Clinical	Psychotherapy, anti-depressive pharmacotherapy
Nutritive deficiency (Vitamine B12, D, folic acid)	Blood	Substitution
Infections (Lues, borreliosis, viral)	CSF, Blood, clinical, imaging	Anti-infectious
Normal pressure hydrocephalus	Imaging, tab test	Ventriculoperitoneal shunt
Autoimmune encephalitis	CSF, imaging	Immunosuppression, plasmapheresis
Vasculitis	CSF, imaging, angiography	Immunosuppression
Macroangiopathy	Imaging	Risk factor management, thrombendarterectomy
Microangiopathy	Imaging	Risk factor management
Hypothyreosis	Blood	Substitution
Niemann-Pick type C	Blood (genetics, oxysterols)	Enzyme substitution
Epileptic encephalopathy	EEG, ex juvantibus	Anticonvulsive drugs

Table 3. Stages of amyloid deposition (83, 84, 105).

Amyloid deposition – Stage A	Stage B	Stage C
polar and orbitofrontal prefrontal cortex; polar, inferior, central and ventral temporal cortex	As stage A, additional: hippocampus and gyrus parahippocampalis, Amygdala, posterior and anterior insula, subgenual and retrosplenial cingulum, ventrolateral prefrontal cortex	As stage B, additional global neocortical dissemination

Table 4. Braak stages of Tau deposition (83-85).

Tau deposition stage		Anatomic region	¹⁸ F-AV-14-51 PET	Diagnosis (PET)
I	Trans-entorhinal	transentorhinal cortex (medial temporal lobe= perirhinal cortex	Entorhinal cortex, Hippocampus, Parahippocampal cortex, (106)	MCI
II		entorhinal cortex (lamina II)		
III	limbic	hippocampus, temporal allocortex		
IV		neocortical association fields next to hippocampus	Isocortical spreading, particular differences to MCI in precuneus, prefrontal, temporal and inferior parietal cortex (106)	AD
V		Neocortex, spreading to dorsolateral		
VI		Primary sensory and motor areas		

Table 5: Overview of brain imaging studies and their results in Alzheimer's disease for the different modalities EEG, MEG, (f)MRI and PET.

Changes in AD imaging compared to healthy controls		Imaging modality	Reference for evidence	Contradicting evidence
global connectome changes	decreased global efficiency / longer characteristic path length	EEG	(314, 315)	
		MEG	(316)	
		fMRI	Amnestic MCI: (186); AD: (317, 318)	similar characteristic path length as controls (319)
		sMRI	(188, 189, 192, 193) (not significant); (320, 321)	
	decreased averaged local efficiency	sMRI	(189)	increased averaged local efficiency in fMRI (318)
	decreased global clustering	EEG	(314)	
		MEG	(176)	preserved clustering coefficient in EEG (315)
		fMRI	Amnestic MCI: (186); AD: (161, 319)	increased global clustering in fMRI (318); unchanged global clustering in fMRI (317)
		sMRI	(161, 187, 189)(not significant)	increased clustering coefficient in structural MRI (320, 321);
	decreased network robustness	MEG	(244)	
	altered modular structure	fMRI	Amnestic MCI: (186); AD: (161, 181)	
		sMRI	(161, 187)	
	rich club organization affected	sMRI	(161, 177, 187)	
network changes	DMN is attacked by AD	fMRI	(157-163)	increased local efficiency in the DMN in fMRI (318)
		sMRI	(161, 163, 193)	
	core of the network is most affected	sMRI, MEG and fMRI	(191)	predominantly low-degree regions outside the core loose connectivity in structural MRI (192)

	increased connectivity for sensorimotor system	sMRI, MEG and fMRI	(191)	
Regional connectome changes	decreased connectivity in the insula	fMRI	(181)	
	decreased connectivity in the posteromedial cortex	fMRI	(182)	
	decreased connectivity in the medial temporal cortex	fMRI	(183)	
	decreased connectivity in the amygdala	fMRI	(184, 185)	
	decreased connectivity in the parahippocampal area	sMRI	(174)	
	decreased connectivity in frontal regions	sMRI	(188)	increased connectivity within frontal areas in fMRI (319)
	disconnection of the precuneus, parietal and temporal areas	fMRI	Amnesic MC: (186)	
	reduced local clustering for hippocampus	fMRI	(319)	
	decreased connectivity within the temporal lobe	fMRI	(319)	

regional atrophy	Atrophy in the hippocampus	sMRI	Mild dementia stage of AD: (322, 323); amnesic MCI: (324)	
	Atrophy and thinning of the entorhinal cortex	sMRI	(325-329)	
	Reduction of amygdala volume	sMRI	(330, 331)	
	Volume loss in the thalamus	sMRI	(332, 333)	
	Reduction in caudate nucleus volume	sMRI	(334, 335)	
	Atrophy in the nucleus accumbens	sMRI	(333, 336)	
Tau PET	Global neocortical Tau binding increased	¹⁸ F-AV-1451	(106, 133)	
	Early Braak stage Tau binding increased	¹⁸ F-AV-1451, ¹¹ C-PBB3	Entorhinal cortex in MCI: (106); Precuneus and lateral parietal in inherited AD: (141); lateral and medial frontal cortex in AD: (132); orbitofrontal cortex in AD (¹¹ C-PBB3): (104); middle to high Braak stages (139)	Increased Tau binding in older healthy controls' temporal and retrosplenial cortex (132)
	Tau in network hubs	¹⁸ F-AV-1451, ¹¹ C-PBB3	(95, 104)	Low consistency between atrophy and Tau deposition in atypical AD (¹⁸ F-AV-1451) (134)
Abeta PET	Global Abeta binding increased	¹⁸ F-AV-45 (Florbeta pir)	Visual rating: (140, 142)	
	Early Braak stage Abeta binding increased	Florbetaben (¹⁸ F), ¹¹ C-PIB	Inferior frontal cortex and precuneus (144); striatum in hereditary <i>PSEN1</i> patients (62) and <i>PSEN1/APP</i> patients (63); (143)	middle to high Braak stages in HC, but age-related and associated with ApoE: with ¹¹ C-PIB : (145), meta-analysis: (146); medial temporal lobe in HC: (147)

	Abeta binding increased in DMN	¹⁸ F-AV-45 (Florbeta pir)	Hubs of DMN including hippocampus: (337)	
Glucose PET	(left) temporoparietal hypometabolism	¹⁸ -FDG	Left precuneus, posterior cingulate and superior parietal cortex in MCI-to-AD converters (148), bilaterally in (149), and ApoE ε4 carriers (150); temporal, angular and posterior cingular areas (151); frontal, posterior temporal, and parietal cortex (152)	Age-related temporal hypometabolism in HC (145); low sensitivity in meta-analysis for differentiation of MCI converters (154)
	Hypometabolism associated to Tau	¹⁸ -FDG	Hypometabolism only in presence of Abeta in Tau-positive regions (153)	Hypermetabolism caused by low Tau burden in absence of Abeta (153)

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have made substantial intellectual contributions to this work and approved it for publication. LS and PR developed the idea and concept for this article. LS wrote the manuscript with contribution of JMM, RKP, PT, TL, LM, KB and PR. MH, AS, ARM and PR contributed to the interpretation of the results, figure development, and revision of the manuscript.

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