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Research Article,

Scale-Bridging In Alzheimer's disease: Biological Underpinnings for Brain Simulation Using the Virtual Brain

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Abstract:

Despite the recent acceleration in the collection of information and data in the field of neuroscience, the very widespread neurodegenerative illness of Alzheimer's disease (AD) continues to be a major issue. The most frequent cause of dementia and the most common neurodegenerative illness is Alzheimer's disease (AD). There are currently no disease-modifying AD medications available, and our knowledge of the disease's causes is still limited. In the current study, we examine probable causes of AD and assess cutting-edge computational brain modelling techniques to better elucidate their potential involvement. In order to provide a mechanistic explanation of the illness, we first give an overview of the computational models for AD that are currently in use. We next discuss the possibility to use The Virtual Brain, an open-source, multiscale, whole-brain simulation neuroinformatics platform, to connect biochemical elements of neurodegeneration in AD with large-scale brain network modelling. Finally, we talk about how this analytical approach can help us better understand AD and enhance AD diagnosis and therapy.

Key Words: Alzheimer's Disease, Neurological Degeneration, Brain Simulation, Virtual Brain, Artificial Inelegance, Deep Learning, Machine Learning.

Introduction:

Alzheimer's disease (AD) or similar dementia affects one senior over the age of 90 every two minutes (Robinson et al., 2018a). This neurodegenerative illness has a death rate in the US that is higher than the combined rates of breast and prostate cancer (Alzheimer's Association, 2019). Beyond the effects on the quality of life for patients and their families, neurodegenerative disorders have a significant economic cost and thus place a heavy burden on society. The most recent research from the Alzheimer's Association pegs the US yearly medical and care expenditures associated with AD at $290 billion in 2019 (Alzheimer's Association, 2019). This amount is predicted to increase to $1.1 trillion by the year 2050 (Alzheimer's Association, 2018). The same analysis claims that by the year 2050, early detection at the stage of moderate cognitive impairment (MCI) might prevent up to $7.9 trillion in total medical and care expenses. The most prevalent form of neurodegenerative illness, Alzheimer's disease (AD), is becoming more prevalent, yet the underlying disease processes are still unknown (Robinson et al., 2018a; Alzheimer's Association, 2019). For AD, there is no disease-modifying medication. Despite significant improvements in high throughput computing tools and the collecting of enormous data sets, theoretical frameworks that connect the many bits of observation might attempt to derive unique insights about the underlying causes (Ritter et al., 2013; Schirner et al., 2018; Solodkin et al., 2018; McIntosh and Jirsa, 2019). The molecular, cellular, ensemble, and region levels of the brain's organisation are only a few examples. These levels of organisation in the brain also include interactions that are both feedforward and

feedback between and within each level (Solodkin et al., 2018). These dependencies produce emergent phenomena—features of the system that cannot be comprehended by the mere "total" of their parts—because they are nonlinear (Ritter et al., 2013). Such non-linear systems are capable of producing large, broad effects from little disturbances. Focusing on one scale might undervalue the emerging phenomena at other scales because interactions in the brain span many different spatial and temporal domains. While computational neuroscience offers mathematical tools for the study of organised flows on manifolds (McIntosh and Jirsa, 2019), integrative brain modelling enables the examination of these several scales in tandem (Schirner et al., 2018). A molecular knowledge of AD may provide new opportunities for early detection and cause-specific therapies. Recent pharmacological clinical trials testing medications such as anti-Amyloid-beta (Gilman et al., 2005; Lannfelt et al., 2008; Winblad et al., 2012; Farlow et al., 2015; Sevigny et al., 2016; Vandenberghe et al., 2017; Panza et al., 2019), tau-protein targeting (Yanamandra et al (Panza et al., 2019). The use of theoretical and computational methods would aid in the creation of innovative treatments (Hofmann-Apitius et al., 2015; Selkoe and Hardy, 2016; Solodkin et al., 2018). Characterizing the traits and mechanisms that govern emergent brain events will be crucial to understanding and treating AD, according to our hypothesis. To do this, a thorough understanding of current biology studies on AD and in-depth familiarity with computational brain modelling methods are required. The contribution of the traditional hallmark proteins as well as recent results on the Notch-1 pathway, neurotransmitters, polygenetic variables, neuroinflammation, and neuroplasticity are described in this review, which summarises current findings of AD pathogenesis from genomes to connectomics. In the second section, we review different prior methods for computational modelling of the systems underlying AD illness and analyse their pros and shortcomings. The Virtual Brain (www.thevirtualbrain.org), which permits integrating molecular signalling cascades with large-scale brain simulation, is described as a multiscale brain simulation platform in the last section.

Rationale:

While dementia is today a word used to describe someone who has (acquired) substantially reduced cognitive function as a result of a brain disorder, dementia was previously thought of as an ageing person's primarily physiological loss of mental function (Schorer, 1985). Psychiatrists had so compared cognitive abnormalities in young people (dementia praecox), which are now classed as schizophrenia, with dementia in elderly people (dementia senilis), i.e., the definition of dementia was based on the age at which the cognitive impairment developed (Kendler, 2009). Alois Alzheimer's finding from 1907 posed a significant objection to this idea. At the young age of 56, his patient Auguste D. exhibited the typical psychopathology of dementia senilis that was advancing quickly (Alzheimer, 1907, 1911). His findings of a "unique sickness" led to the emergence of a brand-new area of neurologic and psychiatric study. Comprehensive classifications of cognitive diseases were produced, as well as a variety of processes, risk factors, etiologic elements (i.e., underlying causes such neurotoxic proteins, risk-modifying genes, etc.), and risk factors.It was interestingly discovered much later in 2013 (Müller et al., 2013) that Auguste D. had an early-onset variation of Alzheimer's dementia, one of the monogenetic variants with a mutation in the presenilin gene 1 (PSEN1)—a really "strange" and uncommon illness. However, it is still unknown what the root cause of AD is and what the diagnostic criteria are. Even the pathology-defining biochemical findings of AD, represented by Amyloid-beta (A40 and A42, hereafter Abeta) and phosphorylation of Tau protein (TAU for tubulin-associated unit or by the Greek letter, hereafter Tau; for a review, see Bloom, 2014), are debatable as causes of disease trajectory and cognitive symptoms. However, it is undeniable that they were present throughout pathogenesis (Jellinger, 1997; Hyman et al., 2012; Nelson et al., 2012).

Defined and Diagnostic Standards

Nosology is the scientific field that categorises diseases according to their underlying processes. In this sense, a disease class may only be determined when the underlying aetiology of the specific disease has been determined. The underlying aetiology of AD and the diagnostic standards, however, are yet unclear. Even the

pathology-defining biochemical signs of AD, represented by amyloid-beta (A40 and A42, hereafter Abeta) and phosphorylation of tau protein (TAU for tubulin-associated unit or by the Greek letter, hereafter Tau; for a review, see Bloom, 2014), are disputed as contributors to the course of the disease and cognitive symptoms. But there is no denying that they existed throughout pathogenesis (Jellinger, 1997; Hyman et al., 2012; Nelson et al., 2012).

Standards That Are Outlined and Diagnostic:

The scientific area of nosology classifies illnesses based on the underlying mechanisms. In this respect, a disease class can only be established when the root cause of a certain condition has been identified. Disorders Association (NINCDS-ADRDA) diagnosis of potential and probable AD only based on clinical (such as daily-life deficits) and cognitive criteria without further diagnostic examination by technology methods (McKhann et al., 1984). The existence and gradual course of cognitive impairment in two or more cognitive domains, including memory, as well as the lack of other dementia-causing factors, form the basis of this description. The 2011 amendment of these criteria added that the diagnosis of dementia requires impairment in daily life activities (McKhann et al., 2011).

In clinical practise, a diagnosis is mostly done using the NINCDS-ADRDA criteria of probable AD and by ruling out any other possible dementia causes (Blennow et al., 2006). The many phenomenological manifestations of AD present a problem with this strictly symptomatic description (Wallesch and Förstl, 2012). Neurodegeneration and clinical symptoms coexist continuously. They might be very different from patient to patient. The slowly progressing amnestic variety of AD is the most prevalent manifestation. While memory problems do not appear to be predominate, it is very unusual for language difficulties, disorientation, apraxia, or neuropsychiatric indicators such affective symptoms to show initially. The anatomical susceptibility of the individual brain, the patient's cognitive "reserve," educational and social variables, and other factors can all contribute to this variation in phenotypes (Stern, 2012). The symptoms of AD and those of other dementias overlap, and comorbidities that might affect the clinical presentation further confound the clinical diagnosis of AD. The 2018 National Institute of Aging and Alzheimer's classification differs from the original NINCDS-ADRDA classification. The diagnostic criteria for association (NIA-AA) are based on the detection of Abeta and Tau proteins in CSF fluid or by positron emission tomography (PET), as well as atrophy, which is a sign of neurodegeneration during brain imaging. To standardise biomarker findings in AD, the NIA-AA definition introduces the so-called AT(N) classification, wherein A stands for positive Abeta biomarkers, T for phospho-Tau biomarkers, and N for neurodegeneration markers in cerebrospinal fluid (total Tau burden) or atrophy seen on magnetic resonance imaging (MRI). Positive biomarkers are denoted with a plus sign (+). Since AD is not the only cause of neurodegeneration, N is typically included in parenthesis. The cognitive component of the illness is described separately and can be included in the categorization by adding the letter C to its extension AT(N) (C). It is not common clinical practise to adopt this definition; it is mostly meant for research (Jack et al., 2018). It is debatable if this definition might restrict the scientific community from focusing on other important potential variables contributing to AD, which could result in the absence of additional molecular cascades except those involving Abeta and Tau proteins (Gauthier et al., 2018).

The NIA-AA definition does not take cognition symptoms into account in its core AT(N) classification, in contrast to the NINCDS-ADRDA definition, which solely takes cognition symptoms into account (Jack et al., 2018). Instead of the phrase "Alzheimer's dementia," which combines both AD pathologic alterations and dementia syndromes, potential, more precise classifications may be "Alzheimer's disease with dementia" or "Alzheimer's disease with moderate cognitive impairment" (Jack et al., 2018). Despite the existence of research frameworks such as the definition of AD by dementia with A+T+N+ biomarkers (Jack et al., 2018) and clinical classification for probable AD (McKhann et al., 1984), only examination of invasively obtained tissue samples from either living individuals by biopsy or post-mortem at autopsy can provide a definitive diagnosis of AD—by demonstrating the presence of neuritic plaques (with Abeta) or neurofibrill (with Tau). Due to the paucity of possibilities for treating the underlying cause of the disease, autopsy is preferable over more intrusive in vivo procedures for a conclusive

diagnosis of AD. In a meta-analysis, the rate of clinically confirmed AD by autopsy was determined with a sensitivity of 85.4% and a specificity of 77.7%. (Cure et al., 2014). However, even the most advanced, gold-standard approach for diagnosing AD, neuropathological analysis of brain tissue, frequently identifies many protein-related pathologies, including both those that are characteristic of AD and those that have been linked to other neurodegenerative illnesses (Robinson et al., 2018b). Due to the lack of abnormalities in patients' activities of daily living, possible prodromal phases of dementia, such as moderate cognitive impairment (MCI) and subjective cognitive decline, do not match the clinical requirements for a dementia syndrome. Although quantifiable in MCI, cognitive abnormalities do not yet interfere with daily activities (Petersen et al., 2014). Neuropsychological tests cannot objectively assess cognitive impairments in cases of subjective cognitive decline, yet patients report cognitive abnormalities (Rabin et al., 2004). In certain situations, these conditions might represent stages in the transition from an illness to dementia. They might be used in conjunction with other elements to determine a person's likelihood of experiencing manifest dementia (Cheng et al., 2017). Even in the absence of beneficial treatment approaches, the diagnosis is frequently a crucial question for patients and their families since it increases the predictability of the disease's prognosis and the creation of care plans. However, it is frequently unclear how much certain dementias and associated illnesses affect cognitive function (Ashraf et al., 2016; Leyhe et al., 2017).

Prevelance & Pathophysiology:

Numerous variables, including proteinopathies, vascular, and immunological alterations, are believed to interact in the progression of neurodegeneration (Robinson et al., 2018b). According to the American Psychiatric Association (2013), AD is the most prevalent cause of dementia, followed by vascular dementia and mixed dementia, which is a mixture of AD and vascular dementia . Lewy-body dementia and Parkinson's disease, in particular, are more common than AD in frontotemporal dementias and Parkinsonian syndromes (Robinson et al., 2018aSecondary dementias connected to vascular alterations, immunology, infections, and other diseases can also cause dementia. However, this distinction is oversimplified because many secondary dementias develop as a result of neurodegenerative processes throughout the course of largely non-neurodegenerative illnesses. The neurodegenerative trajectory of multiple sclerosis in its latter stages is a well-known example (Bermel, 2017).

Because there are various treatment options and prognoses associated with various forms of dementia, it is important to identify the precise kind of dementia. Some potential dementia causes, such normal pressure hydrocephalus, metabolic conditions, immunologic or viral causes, are treatable. While there are currently no disease-modifying treatments for any primary neurodegenerative diseases, future treatments as well as existing symptomatic and more experimental research may benefit from appropriate patient stratification. This is crucial for techniques that use patient data to simulate AD processes since the final model will only be as specific to AD as the patients' actual (strict) diagnoses. The group in which the prevalence of dementia is rising the fastest is those over 80 years old (Fiest et al., 2016). Although alternative pathogenesis routes for AD and vascular dementia have been theorised, it is becoming increasingly clear that both illnesses share a number of risk factors (Love and Miners, 2016). The interactions of Abeta in AD with vascular factors, such as altered blood-brain barrier permeability brought on by both microvascular changes and Abeta deposition (Santos et al., 2017), can, however, be distinguished from cerebral amyloid angiopathy (Banerjee et al., 2020), a distinct vascular disease brought on by amyloid, which we will not discuss further here. Increased physical activity, diabetes mellitus, and hypercholesterinemia, which are risk factors for AD as well as cerebrovascular disease, are associated with a higher incidence of vascular dementia and an increased rate of cerebrovascular disease manifestations. (Lindsay et al., 2002; Larson et al., 2006) (Reitz et al., 2011; Love and Miners, 2016). However, it has been disputed how these elements moderate their effects (Santos et al., 2017). One theory is that vascular or mixed dementia is not diagnosed because microvascular lesions go undetected. The involvement of

metabolic pathways in the aetiology is another potential. Notably, apolipoprotein E (APOE) E4 hetero- or monozygotic, an allele of a metabolic gene that also influences atherosclerosis risk, is the most significant genetic risk factor in the general population (Suri et al., 2013; Mahley, 2016). Atherosclerosis and neurodegeneration are more common than ever, particularly in the elderly, and are likely to impact the same people (Rohn, 2014). Epidemiological methods have demonstrated that up to one-third of cases of AD may be prevented by addressing these modifiable risk factors, even though the impact of metabolic variables is unclear (Norton et al., 2014). However, this proof is based only on observation and population-attributable risk. This statistical technique identifies the percentage of a disease's occurrence that may be linked to a certain risk factor. As a consequence of an observational research, this index permits an evaluation of the effect that could follow the removal of the risk factor, but it prevents establishing a clear causal relationship between identified risk variables and the disease (Siegerink and Rohmann, 2018). The population-attributable risk would be associated to both mixed dementia and AD itself, for instance, if the definition of AD in the underlying observational research is unclear and includes other disease entities as well as AD, such as mixed dementia. Reducing atherosclerotic risk factors may therefore have an impact on people with mixed dementia rather than "pure" AD cases.

Alzheimer's Disease-Related Brain Changes: From Genetic To Brain Network & Changes In Proteins:

Rare structural polymorphisms or copy number variations in the genes that control Abeta synthesis and clearance can cause early-onset AD in a family. For instance, structural variations in the gene for the precursor protein for amyloid beta (APP) influence how secretases process APP after it has been translated, which results in an excess of beta-amyloid in AD with early start. The active element of the beta-secretase complex is made up of the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes. Processing type-I integral membrane proteins such as the Notch signalling pathway's components and the receptor tyrosine-protein kinase erbB-4 (ERBB4) depends on it (Sannerud et al., 2016). Longer and more toxic versions of Abeta peptides result from autosomal dominant mutations of PSEN1 and PSEN2, which alter endopeptidase and carboxypeptidase activity (Ertekin-Taner, 2007; Lanoiselée et al., 2017). The pathogenesis of early-onset AD may also be influenced by other environmental and genetic variables (Sun et al., 2017).

Contrarily, late-onset Alzheimer's disease (AD) is a complicated genetic condition in which both common and uncommon genetic variants—the majority of which were discovered through genome-wide association studies—play a significant etiological role. According to estimates, late-onset AD heritability is substantial, at around 50% (Pedersen et al., 2004; Ridge et al., 2016); however, environmental influences are likely to be much more significant (Grant et al., 2002; Wainaina et al., 2014). When compared to other complicated hereditary brain illnesses, AD's single nucleotide polymorphism-based heritability estimates are typically high, at about 25–30% (Cuyvers and Sleegers, 2016). Common single nucleotide polymorphisms account for the remaining 5-7% of the single nucleotide polymorphism-based heritability, whereas APOE E2/E4 polymorphisms alone account for about 25%. (Cuyvers and Sleegers, 2016; Ridge et al., 2016; Kunkle et al., 2019). In the last three genome-wide association analyses, 40 distinct risk loci have been found (Marioni et al., 2018; Jansen et al., 2019; Kunkle et al., 2019). The bulk of these loci have roles in the APP processing, microglial activation, and lipid metabolism pathways (Andrews et al., 2020). Notably, several of these loci have functionally important single nucleotide variations that affect how these loci are expressed in AD-associated cortical regions and are correlated with the so-called expression of quantitative trait loci (Kunkle et al., 2019).

Protein Level Two Phosphorylated Tau and Abeta are two of the most important proteins connected to the pathophysiology of AD. Human protein beta clumps in neuritic plaques because of an improperly cleaved structure, which causes it to have (neuro-)toxic effects (Klunk et al., 2007; Jack et al., 2009; Villemagne et al., 2009). Both intracellularly and extracellularly, it is present

(Hardy and Selkoe, 2002; Walsh and Selkoe, 2007; Selkoe and Hardy, 2016). It has been proposed that the aggregation of Abeta results in the hyperphosphorylation of Tau protein (Blennow et al., 2006). But other neurodegenerative conditions that are not linked to a buildup of a protein called abeta called phosphorylated Tau are also seen (Kovacs, 2015). In individuals who died of neurodegenerative illnesses at a mean age of 71 years, immunohistochemical analysis of brain tissue, which is more sensitive than conventional microscopical tissue inspection, showed up to 92-100% of Tau, in contrast to Abeta with 20-57%. (Robinson et al., 2018b). Each participant who met the Standard microscopy also revealed Abeta and Tau in immunohistochemistry, which is an established clinicopathological criterion for AD (ADNPC, defined as the presence of Abeta plaques, neurofibrillary tangles, and neuritic plaques) (Montine et al., 2012). (Robinson et al., 2018b). Alpha-synuclein (SNCA, linked to a number of Parkinson's disorders) was found in 41–55% of patients, whereas transactive response DNA-binding protein (TDP-43, linked to amyotrophic lateral sclerosis and frontotemporal dementia) was found in 33–40% of patients in the same group of patients. (Robinson et al., 2018b). Therefore, "pure" AD was uncommon in this group since at least one additional neurodegenerative disease affected 65-70% of diagnosed AD patients (Robinson et al., 2018b). In the development of AD, the deposition of Abeta generally follows a certain spatiotemporal pattern. There are three general stages to the course (Braak and Braak, 1991, 1997; Taylor and Probst, 2008). Along the perirhinal and entorhinal cortices, stage A develops. The hippocampus itself, as well as surrounding areas such the posterior gyrus parahippocampalis, are involved in stage B. Neocortical regions in Stage C are distributed widely as well. An unsui modification in the processing of Abeta, controlled by, is one explanation for the pathogenic deposition of Abeta. a collection of enzymes, including secretases. Here, we merely provide a quick summary. A transmembrane protein called APP has been linked to synaptic plasticity and neuronal development (Korte, 2019). It may be broken down into many subdomains. The following procession by the -secretase and the -secretase, often known as the non-amyloidogenic route, is one possibility (Blennow et al., 2006). Instead of transforming APP into Abeta fragments (with a helix), which may then combine to form plaques, this "physiological" process transforms APP into a protein subdomain with a helix structure (Blennow et al., 2006). Another "pathological" mechanism involves the conversion of APP to soluble Abeta with a -helix shape by the -secretase (and subsequently by the -secretase once again). Molecules can cluster into Abeta oligomers and then polymers, which become insoluble and deposit in the extracellular space to create what are known as Abeta plaques, thanks to the -helices. Because Abeta's insoluble form cannot be quantified in cerebrospinal fluid, this pathway's activation lowers the concentration of Abeta there (Blennow et al., 2006; Olsson et al., 2016). The activity of - and -secretase, which represents the imbalance between these two pathways, is thought to be a key factor in the pathophysiology of AD and is the subject of several experimental therapeutic approaches at the moment (Coric et al., 2012; Tong et al., 2012; Ortega et al., 2013; Hsiao et al., 2019; Xia, 2019). The notch receptor 1 (NOTCH1) pathway is another crucial component that is connected to both brain development and the protein metabolism of Abeta. As a transcription factor for both its intracellular and external domains, NOTCH1 is a membrane protein that has a significant impact (Brai et al., 2016). The -secretase, which is also engaged in the amyloidogenic and non-amyloidogenic pathways of APP processing, processes NOTCH1 to its subdomains (Brai et al., 2016). Co-substrates in the extracellular domain of the -secretase are APP and NOTCH1 (Marathe and Alberi, 2015; Brai et al., 2016). Abeta plaques include NOTCH1, and AD patients have decreased intracellular signalling of this protein (Brai et al., 2016).

The degenerative process of so-called primary tauopathies may be significantly influenced by phosphorylated Tau in the absence of any other neuropathological variables in a number of dementias. This category consists of conditions such as Pick's disease, corticobasal degeneration,

and progressive supranuclear palsy (Cope et al., 2018). (Kovacs, 2015). In contrast, Tau appears to be implicated in the development of secondary tauopathies only in the presence of additional variables, such as in prion disorders and chronic traumatic encephalopathy (Kovacs, 2015). From this perspective, AD is special because it neither qualifies as a primary tauopathy (since Abeta is present concurrently) nor does the amyloid pathology finally result from hyperphosphorylation of Tau. But phosphorylated Tau density rather than Abeta buildup is a stronger predictor of the degree of cognitive impairment (Riley et al., 2002; Bennett et al., 2005). As a result, there is debate about Tau protein's significance in AD as either a cause of the illness on its own or as a sign of general neurodegeneration brought on by the neurotoxic effects of amyloid accumulation. There are now active clinical studies for AD patients using anti-Tau antibodies and vaccinations, modulators of Tau aggregation, and antisense oligonucleotides targeting its gene, the microtubule associated protein tau (MAPT). The pathophysiology of tau protein is complex and connected to several neurodegenerative disorders (Kovacs, 2015; Guo et al., 2017; Cope et al., 2018). According to Spires-Jones et al. (2017), certain types of neurodegeneration cause Tau to accumulate and be detectable in the cerebrospinal fluid (Ossenkoppele et al., 2015). A number of kinases generally keep the phosphorylation homeostasis of the Tau protein in check. Tau loses its natural ability to stabilise microtubules as a result of a shift in this balance toward hyperphosphorylation, which is followed by altered vesicle transport in the axons, which disrupts axonal signal transmission. Second, the hyperphosphorylated Tau protein polymerizes to form the so-called neurofibrillary tangles, which are large tubular aggregates and intractable filaments. These aggregates cannot be removed by the brain's clearing mechanism, which causes inflammatory reactions and, eventually, neuronal death (Blennow et al., 2006). Three techniques have been used to observe these phenomena: I nuclear imaging techniques that track Tau protein (flortaucipir PET), (ii) an increase in the concentration of the hyperphosphorylated Tau section in the cerebrospinal fluid, and (iii) microscopy of neuronal tissue with neurofibrillary tangles (Cope et al.,2018). Tau causes the two primary impacts of neuronal death and axonal malfunction, which cause the damaged areas of the brain network to become disconnected. This has been determined in areas where flortaucipir PET tracking the Tau protein has strong binding (Cope et al., 2018). Nevertheless, the Tau protein is a more accurate diagnostic marker for the degree of cognitive loss in AD than Abeta (Degerman Gunnarsson et al., 2014). Network disruption and a rise in the clinical score of the apathetic symptoms are two factors that the local neurotoxic effects of Tau are associated with (Kitamura et al., 2018). Similar to Abeta stages, the phases of Tau deposition (determined by post-mortem histological criteria) are known as Braak Tau deposition stages (Braak and Braak, 1991, 1997; Braak et al., 2006). They constitute a distinctive spatiotemporal pattern throughout typical AD. Due to this, early Tau depositions in the medial temporal lobe are present in the majority of people with "classic" AD years before symptoms appear. Stages I and II make up the so-called transentorhinal stage, which is concerned with the entorhinal cortex in the lamina granularis externa and the transentorhinal cortex in the ventromedial temporal lobe (Lamina II). Following this prodromal stage, the disease spreads deeper into the limbic lobule (stages III and IV, mostly affecting the hippocampus and temporal allocortex), and then into the neocortex (stages V and VI) (Braak and Braak, 1991, 1997; Braak et al., 2006). There is a strong association between the six phases of this Tau deposition diffusion process, which are divided into three functional stages (transentorhinal/entorhinal, limbic, and neocortical), and the individual cognitive deterioration of an AD patient (Riley et al., 2002; Bennett et al., 2005). In this first functional group, there are just a few amyloid plaques and frequently no clinical signs. A MCI, which frequently progresses to the complete clinical manifestation of dementia and, as a result, has a substantial link to higher Braak Tau deposition stages, characterises the non-obligatory prodromal stage of AD (Riley et al., 2002; Bennett et al., 2005). Memory function, verbal fluency,

and deficits in daily living activities are only a few examples of the clinical symptoms of MCI stage that are closely correlated with Tau deposition in the limbic stage (Riley et al., 2002). The majority of patients exhibit amnestic impairment at the highest functional stage, which is related to the neocortex (Braak and Braak, 1991, 1997;Taylor and Probst, 2008). The accumulation of Tau proteins detected by flortaucipir PET also corresponds with the clinical presence of MCI, AD, and cognitive function (Cho et al., 2016).

Although there appears to be a strong correlation between the above-described patterns of amyloid and tau deposition, it is important to note that the three stages of amyloid deposition identified by Braak and Braak (Braak and Braak, 1991, 1997; Taylor and Probst, 2008)—A, B, and C—do not exactly correspond to the stages I–VI of tau deposition. The ventromedial temporal allocortices, pro-isocortices, and later temporoparietal neocortices are among areas where the six phases of Tau deposition overlap with the stages of amyloid deposition and follow a tighter distribution pattern The consequences of both illnesses vary more dramatically, for example, in how specific they are to Alzheimer's disease, neurodegeneration in general, or cognitive abilities (Van Hoesen and Solodkin, 1994). However, the damaged cognitive domains of AD (memory and visuoconstruction) are connected to those regions because of the same "macro sequence" of the archicortex—mesiotemporal cortex—temporoparietal neocortex.

The cholinergic and glutamatergic transmitter systems are of particular relevance in the pathophysiology of AD. One of the vital neurotransmitters in the brain is acetylcholine. A basic transmitter in the peripheral vegetative nervous system and neuromuscular transmission, acetylcholine has a variety of multifaceted activities. A lot of functioning systems in the brain use acetylcholine, but it plays a key role in modulating synaptic communication (Van der Zee et al., 2011). Because acetylcholine is necessary for memory consolidation, the malfunctioning of the cholinergic system is related to the aetiology of AD (Ferreira-Vieira et al., 2016). Anti-dementia medications act as acetylcholine esterase inhibitors, increasing the amount of acetylcholine in the synaptic gap and resulting in marginally enhanced memory performance (Ferreira-Vieira et al., 2016). Through the augmentation of synaptic modification and the selective presynaptic regulation of synaptic transmission in various locations and layers, cholinergic effects have been demonstrated to be involved in learning processes in the hippocampus formation (Hasselmo and Schnell, 1994). Acetylcholine's positive effects on memory encoding are likely mediated by enhanced afferent input, spiking activity, and synaptic change (Hasselmo, 2006). Working memory for new stimuli has been connected to cholinergic modulation on a functional level (Hasselmo and Stern, 2006). According to a theory (Hasselmo and Stern, 2006), previously familiar stimuli (such words or numbers) have synaptic connections, which renders working memory of these stimuli independent of cholinergic regulation (Crow and Grove-White, 1973; Broks et al., 1988). Additionally, acetylcholine has a role in AD excitability modulation. While medial temporal lobe areas such as the hippocampus and gyrus parahippocampalis can be activated during task functional MRI to correlate with memory performance, it has been demonstrated that greater recruitment of such regions is linked with cognitive deterioration in MCI patients (Dickerson et al., 2004). The underlying theory proposed that hippocampus shrinkage might have a compensating impact on hyperactivation (Dickerson et al., 2004). Similar to this, several years before the expected disease onset of familial AD, task functional MRI in PSEN1 mutant carriers who were cognitively still unimpaired showed greater activity in the right anterior hippocampus relative to non-carrier controls (Quiroz et al., 2010). This may be understood in light of how cholinergic suppression affects learning. The phenomenon of exponential growth in the strength of synaptic connections, brought on by activity developing across previously stronger synapses, is known as runaway synaptic modification (Hasselmo, 1994). Although it may be viewed as a natural outcome of Hebbian principles (Morris, 1999), it interferes with learning processes since only a certain subset of

connections should be reinforced (the pattern to learn), and other existing strong connections should stay stable (Hasselmo, 1994). During learning, cholinergic presynaptic regulation of transmission along associative fibres provides a defence against runaway synaptic alteration (Hasselmo and Bower, 1992). However, the introduction of hyperactivity in AD causes more uncontrolled synaptic remodelling. In turn, the strengthening of undesirable networks can also cause additional hyperactivity, creating a vicious cycle (Hasselmo, 1994). Additionally, the ongoing presence of hyperactivation may have excitotoxic consequences (Hynd et al., 2004). Excitotoxicity is the term used to describe the harmful effects of calcium brought on by an abrupt increase in glutamatergic transmission. A wide range of genetic and environmental AD risk variables that are linked to greater plasticity have further bolstered Ashford and Jarvik's hypothesis from 1985 that highly neuroplastic connections have a preferential affinity for neurofibrillary tangles (Mesulam, 2000). Additionally, the idea of excitotoxicity is crucial for other transmitter systems, like as glutamate. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, and other anti-dementia medications that do not block acetylcholine esterase diminish glutamatergic transmission in the synaptic cleft. Neuroinflammation and plasticity are also connected to glutamatergic dysfunction.

Neuroimmunology:

Neuroinflammation and autoimmunity have a significant role in AD pathogenesis in addition to the cascades of Abeta and Tau. The fact that intrinsic proteinopathic malfunction alone does not always result in neurodegeneration and cognitive loss is one of the challenges in understanding AD pathophysiology. As was previously said, several hazardous intermediate pathways are more likely to be the source of such deficits. Neuroinflammation is one potentially significant but poorly understood process. Because it always comes last in the pathogenic cascade and directly causes neuronal death, neuroinflammation is an important element in the pathophysiology of dementia (Heneka et al., 2015a). The control of inflammation's potential impact on the neurodegenerative process is unclear, though. Contradictory findings have been found in clinical trials. For instance, long-term use of non-steroidal anti-inflammatory medications shown beneficial preventative benefits, hence lowering the a priori risk for AD (Wang et al., 2015). However, unlike those observational studies, prospective trials using steroids and other immunosuppressive medications, as well as randomised controlled trials using non-steroidal anti-inflammatory medicines, failed to demonstrate any appreciable effects (Jaturapatporn et al., 2012). As long as the tumour necrosis factor inhibitor etanercept was well tolerated, a case-control study in patients with rheumatoid arthritis (who have a slightly higher risk for AD) revealed a significant reduction of AD incidence by 70% (adjusted Odds ratio of 0.30, $p = 0.02$) if the patients received treatment (Butchart et al., 2015). The label of AD may conceal a significant portion of autoimmunological brain events that may be treated with high-dose and prolonged corticosteroid therapy since the cause of dementia and its differential diagnosis are frequently uncertain (Pruss and Lennox, 2016). Microglia, an immune cell type with organ-specificity, play a key role in the complicated field of cerebral immunology. A suitable discussion would be outside the scope of this study, thus we would like to direct the interested reader to the review on neuroimmunology and AD below (Heneka et al., 2015c).

Magnetic resonance imaging of the human body

An approach that is frequently used to search for biomarkers in vivo is imaging MRI. According to what has been said, the pathogenetic pattern of AD is characterised by the buildup of amyloid plaques and neurofibrillary tangles. The location and degree of neurofibrillary tangle buildup have been found to correlate with the volumetric evaluation of grey matter loss in MRI (Csernansky et al., 2004; Whitwell et al., 2008). Consequently, a proxy assessment for the regional neurofibrillary tangle burden may be obtained using volumetric MRI (Persson et al., 2017). Memory-related tissues, including as the hippocampus and other mesiotemporal regions, as well as the precuneus, cingulate, and the prefrontal areas, have repeatedly been observed to atrophy in AD patients (Braak and Braak, 1991; Frisoni et al., 2002; Karas et al., 2004; Shiino et al., 2006; Rosenbloom et al., 2011). However, up to 30% of

AD patients first exhibit non-amnestic symptoms such aphasia, visuospatial issues, or behavior-predominant dysfunction (Koedam et al., 2010; Dickerson et al., 2017). In individuals with an unusual clinical presentation, the distribution of neurofibrillary tangles is either limbic-predominant, hippocampal-sparing, or not documented, which is also known as the no-atrophy or minimal-atrophy AD variation (Murray et al., 2011; Persson et al., 2017). These phenomenological categories of AD and volumetric MRI have already been shown to be correlated (Whitwell et al., 2012). MRI was investigated in several studies as an in vivo marker of different AD subgroups (Byun et al., 2015; Hwang et al., 2016; Ferreira et al., 2017; Persson et al., 2017).Additional to the atrophy patterns. A few single-region-based volume decreases have also been discovered as possible biomarkers for AD, in addition to phenotypic variations in AD morphology. The use of MRI as a non-invasive in vivo assessment allows for the longitudinal monitoring of AD atrophy and disease development. Volume loss in AD patients was the subject of recent longitudinal research (Harrison et al., 2019; Pontecorvo et al., 2019; Sintini et al., 2019). The temporoparietal areas have the highest rates of atrophy, which are also regions with lower baseline grey matter volume (Sintini et al., 2019).

White matter hyperintensities, which show up on T2-weighted or fluid-attenuated inversion recovery MRI scans, are also quite common in AD patients in addition to grey matter atrophy (Brickman, 2013). Generally speaking, white matter hyperintensities can be morphological indicators of microvascular lesions as well as inflammatory or general ageing alterations. Prior to the expected start of AD symptoms, an increased total hyperintensity volume has been noted between 6 and 22 years (Lee et al., 2016). Research on the connection between white matter hyperintensities and AD pathogenesis is still ongoing (Graff-Radford et al., 2019). Tomography using positron emission Nuclear imaging techniques enable the in vivo collection of the brain's metabolic characteristics using a variety of radioactively labelled tracer molecules, or radionuclides. A unique opportunity for various functional evaluations of the brain is provided by PET. The underlying process takes use of +-emitters: the tissue's electrons and the positrons released during -decay engage in a reaction known as annihilation. Photons are emitted as a result, and they may be monitored by certain sensors (Phelps, 2000). According to Clark et al. (2011) and Schöll et al. (2016), both Abeta and Tau deposits may be indirectly identified by PET and match the underlying pathologic alterations at autopsy well. Tau tracer binding is up in the cortex generally in AD, in addition to being elevated in areas that are known to be impacted in the early stages of the disease (Cho et al., 2016; Schöll et al., 2016; Kitamura et al., 2018; Gordon et al., 2019; Harrison et al., 2019). (Cho et al., 2016; Pontecorvo et al., 2019). Tau binding, however, is additionally detectable in healthy individuals and is mostly seen in regions that have undergone atrophic alterations (Harrison et al., 2019). Similar to this, Abeta tracers demonstrate greater global deposition throughout the whole brain (Clark et al., 2011; de Wilde et al., 2018) and in areas of the early Braak stage (Murray et al., 2015). (Alongi et al., 2019). However, compared to Tau, the proportion of "Abeta-positive" healthy controls appears to be larger. The evaluation of energy metabolism using tagged glucose molecules is a crucial PET test. Numerous investigations (Meltzer et al., 1996; Langbaum et al., 2010; Morbelli et al., 2010; Fukai et al., 2018; Ou et al., 2019) imply temporoparietal hypometabolism in AD, which is already a recognised marker for ambiguous instances of various dementias in clinical practise. Interestingly, hypometabolism strongly correlates with Tau deposits, resembling atrophy patterns (Csernansky et al., 2004; Whitwell et al., 2008). (Adams et al., 2018). Due to its high price, exposure to ionising radiation, and poor sensitivity in identifying MCI patients who would develop AD, glucose PET has a limited role in ordinary clinical practise (Smailagic et al., 2015).

Connectomics:

Following a discussion of current developments in AD molecular research at the microscopic level, we take a look at a whole-brain viewpoint at the macroscopic level of brain regions. The connectomic method is a branch of neuroscience that examines, characterises, and employs measurements of the brain's (axonal) connection (Fornito et al., 2015). It gives an overview of the symptoms of AD and reveals universal phenomena that go beyond localised impairment.

Brain networks often consist of nodes that represent areas and links or edges that signify relationships between them (either structural or functionalThe degree of abstraction here is The connectome may be measured using graph-theoretic metrics, or network metrics (Bullmore and Sporns, 2009). The AD networks differ from healthy controls in a variety of various—and sometimes interdependent—metrics. There are heterogeneous results for several measuring modalities, suggesting that AD disrupts networks on a variety of scales (Dennis and Thompson, 2014; Stam, 2014). Additionally, differing network creation methodologies, such as varying criteria for filtering out the most crucial links, might explain this variation (van Wijk et al., 2010; Tijms et al., 2013; van den Heuvel et al., 2017). In contrast to healthy ageing, however, convergent evidence points to aberrant white matter structural connectivity and aberrant functional connectivity in AD. Reviewing and comparing the most recent research on the subject, we find that AD patients' networks communicate less effectively than those of healthy controls due to a variety of local network alterations. The viewpoint offered by connectomic research is crucial for comprehending how cognition grows and how it deteriorates in dementia. Numerous theories concerning the network alterations in dementia that emphasise distinct elements of neurodegeneration are available (Dennis and Thompson, 2014). The loss of neurons and small-scale connectivity affects the macro-scale in the form of (structurally and functionally) disconnected brain regions, according to one line of study on dementia (Brier et al., 2014a) (Delbeuck et al., 2003; Stam, 2014). According to Stam (2014), this gap was associated with behavioural and cognitive deterioration, and white matter pathology in some regions may serve as a biomarker for the development of the illness (Solodkin et al., 2013). This understanding of AD as a disconnection syndrome was able to coherently connect several disease pathology scales. However, in recent years, network science research on AD patients have broadened this picture. These studies have seen extensive increases and reductions in connectivity within the brain network, suggesting compensating mechanisms or network responses beyond disconnection (Stam, 2014). Even a pioneering research that stressed the significance of "small networks studies," particularly in relation to the early stages of illness, demonstrated how the entorhinal cortex degeneration that precedes the onset of hippocampal detachment from its cortical network connections. Hubs are brain areas that have a high degree of connection to other regions, according to network science. Hub regions have consistently been identified as the areas most impacted by AD for both structural and functional connectivity investigations (Stam et al., 2009; Lo et al., 2010; Yan et al., 2018). Hubs were defined as nodes with the highest betweenness centrality (a measure for involvement in important pathways) and the highest participation coefficient (in how far the node is connected to different modules or subnetworks), and De Brier et al. demonstrated that hubs are disrupted even in preclinical stages of AD (Brier et al., 2014b). The increased Abeta load in certain hub locations is correlated with the vulnerability of hubs (Cope et al., 2018). The default mode network, a massive network of densely linked areas in resting state, is the centre of the disconnection in AD (iftçi, 2011; Hahn et al., 2013; Dai et al., 2014, 2019; Bernard et al., 2015; Chen et al., 2016; Cope et al., 2018). The degree of default mode network disruption allows for some differentiation between AD and healthy ageing, even if this phenomena is also seen in ageing (Perry et al., 2015). (Greicius et al., 2004). Regarding the functional network, AD-related neurodegeneration specifically targets the default mode network, which is also where the most Abeta is deposited (iftçi, 2011; Hahn et al., 2013; Dai et al., 2014, 2019; Bernard et al., 2015; Chen et al., 2016). The degree of hub disruption is highly correlated with a patient's level of cognitive function (Dai et al., 2014). The propagation of the degenerative cascade within the brains of AD patients is thus anticipated to be facilitated by hubs, given their high Abeta deposition and crucial location in the overall information flow of the brain network (Buckner et al., 2009). The insula (Chen et al., 2013), posteromedial cortex (Xia et al., 2014), medial temporal cortex (Burggren and Brown, 2014), and amygdala (Burggren and Brown, 2014) have all shown abnormal or impaired functional connectivity (Yao et al., 2013; Wang et al., 2016). In addition to the hubs' susceptibility, a lower global clustering coefficient has also been observed, indicating a loss of connectivity and significant redundancy structures for brain communication in

FC, which therefore changes the modular structure of AD patients (Brier et al., 2014b; Minati et al., 2014; Pereira et al., 2016; Dai et al., 2019). Decreased global efficiency in structural connection as well as functional connectivity networks is frequently seen in AD patients, which corresponds with cognitive and behavioural deterioration. This is likely a global impact of these "local attacks" on the network (Lo et al., 2010; Reijmer et al., 2013; Dai et al., 2019). In network science, global efficiency is described as the inverse of the typical path length; the information flow inside a network is more efficient when there are fewer paths connecting the nodes. Although they are longer and have more nodes and edges in between, connections between nodes in a less efficient network are still possible (Bullmore and Sporns, 2009). Recent research examined the effects of AD using many imaging modalities, including magnetoencephalography, functional MRI, and diffusion tensor imaging (Guillon et al., 2019). They discovered that the hubs, which are most likely to be situated in the centre of this multilayer network, have been most negatively impacted, demonstrating the susceptibility of hubs across modalities. Together, these alterations allowed researchers to forecast patients' cognitive and memory decline (Guillon et al., 2019). Recent research indicates that network alterations, such as widespread disconnection, are prevalent in the preclinical stage of AD (Brier et al., 2014b; Daianu et al., 2015; Zhao et al., 2017). To better distinguish between AD patients, MCI, and controls, functional connectivity and structural connectivity are now being studied. This is a step toward the objective of identifying prodromal AD patients and the potential for early intervention techniques (Phillips et al., 2015; Pereira et al., 2016; de Vos et al., 2018; Ye et al., 2019). According to a new study, preclinical AD has disrupted functional connectivity that corresponds to accelerated ageing (Gonneaud et al., 2020). White matter diffusion tensor imaging and resting-state functional MRI studies have found that AD patients had less effective network connectivity than healthy older adults, particularly in the default mode network.

Alzheimer's disease Modelling:

Numerous models have been created for the analysis of AD since it is a complex disease that affects many different scales, including animal disease models (Saito et al., 2014; Weintraub et al., 2014), cognitive models (Sevush et al., 2003), and disease progression and classification models (Bhagwat et al., 2018; Khanna et al., 2018; Koval et al., 2018; Pellegrini et al., 2018; Golriz Khatami et al., 2019). An innovative and adaptable scientific idea, mathematical modelling is a key computational neuroscience tool. In general, one may distinguish between methods that concentrate on certain components of the illness, such as biochemical Abeta modelling (George and Howlett, 1999), and integrated models that include various biomarkers while concurrently employing several scales (Khanna et al., 2018). The latter may offer a more thorough, multimodal perspective on the illness and its interrelated mechanisms, and may be more suited to capture disease aetiology. This multiscale strategy, also known as "integrative disease modelling" (Younesi and Hofmann-Apitius, 2013), combines genetic data analysis with cerebrospinal fluid collection and functional and structural neuroimaging approaches (Golriz Khatami et al., 2019). To create innovative models for AD that incorporate many dimensions, modalities, and study fields, a thorough grasp of both the underlying biological processes of AD and the computational framework of high-performance modelling techniques is required. This cross-disciplinary approach has the potential to resolve some of the mysteries surrounding AD pathogenesis that might not be revealed on a single scale using a single method due to the growing technical possibilities for high-performance computing and hierarchically organised knowledge architectures. As a result, we discuss current computational (brain) models at various dimensions in the parts that follow and explain how they relate to the biological ideas we've just covered.

When used to linear classification problems, statistical prediction models serve primarily as descriptive tools. Based on the input data, subjects are categorised into one of three diagnostic groups (HC, MCI, or AD). But in addition to their usefulness in clinical translation as diagnostic tools, prediction models offer some decision criteria that may also be useful for comprehending

the underlying illness processes (Jack and Holtzman, 2013). There are techniques like machine learning (Moradi et al., 2015; Pellegrini et al., 2018) or Bayesian modelling in addition to those somewhat oversimplified linear models (Khanna et al., 2018). Regarding data analysis and model interpretation, each person has unique difficulties and benefits (Poil et al., 2013). In order to anticipate illness trajectories (predictive modelling) or categorise people into groups with a large number of extremely comparable data points, machine learning techniques are used (discriminative modelling or clustering). The second objective can be accomplished either by unsupervised clustering without labelling or by supervised a priori labelling of the training data (e.g., as two classes AD and non-AD or as a three-class issue with AD, MCI, and healthy controls) (Golriz Khatami et al., 2019). These unsupervised discriminative models group individuals according to how closely related or dissimilar two parameters are. Statistical proximity metrics can be used to quantify this (Bock, 2005; Golriz Khatami et al., 2019). Structural T1-weighted MRI has been regarded a feature for traditional machine learning methods like support vector machines—often paired with linear discrimination analysis—along with other biomarkers. While patients with AD could be distinguished from controls with success, Pellegrini et al. (2018) revealed in a review that the categorization of participants with MCI remained inadequate (Pellegrini et al., 2018). This was equally true for the risk assessment of MCI to AD conversion. Because it is already possible to differentiate between controls and AD based on cognitive ability in practise, the therapeutic value of the classifiers remains comparatively low. Therefore, a diagnosis before the start of clinically apparent AD is currently lacking. Building biologically informed models that provide "mechanistic biomarkers" in an effort to facilitate early AD prediction involves a greater knowledge of AD pathomechanisms (Selkoe, 2004). To do so, physiologically plausible predictions are derived and a comprehensive illness knowledge system (i.e., ontology) may be constructed from various data sources. This is in contrast to the methods mentioned above, which rely the selection of biomarkers mostly on statistical reliance (e.g., correlations). However, mechanistic biomarkers resemble physiologically viable notions rather than only correlating with the illness. Biological causes of the change from asymptomatic phases of MCI to AD have been computationally recreated using this method to produce a more precise risk prediction (Khanna et al., 2018). Several biological risk variables and their interactions might be retrieved by employing a predictive time-to-event model that includes multimodal data including genetic variations, neuroimaging, and neuropsychological tests (Khanna et al., 2018). The model (Khanna et al., 2018) uses a graph-like Bayesian network architecture, which creates new opportunities for the integration of multiscale and multimodal data to find additional potential mechanistic biomarkers. Additionally, longitudinal patient data may be used to extract information regarding illness development to improve the precision of future forecasts. For instance, Bhagwat et al. (2018) used longitudinal data from MRI brain volumetry (cortical thickness), clinical evaluations, and genetic information (ApoE 4 status) to estimate the progression of AD illness in patients with variable baseline cognitive ability. Even after being validated with a second untrained data set, a longitudinal predictive neural-network outperformed other algorithms when tested on multimodal data from two time points (Bhagwat et al., 2018). This multimodal, longitudinal method to forecasting individual risk and disease trajectories may thus open up new, exciting possibilities for customised therapy. Modeling structural and metabolic changes in various brain regions in relation to the deterioration of cognitive abilities can provide more complex information on the course of the disease and the factors that influence it on an individual level (Koval et al., 2018). The European Brain Research Infrastructures (EBRAINS) of the Human Brain Project (https:// ebrains.eu, Markram et al., 2011), a graph-theoretically organised database, is one example of a data source that might be included into future techniques. Palomero-Gallagher and Zilles (2018) note that EBRAINS has comprehensive data for several brain regions from a number of modalities, such as receptor density

or gene expressions (Yetman et al., 2016). In addition, the Multimodal Mechanistic Signatures Database for Neurodegenerative Diseases (NeuroMMSig; Domingo-Fernández et al., 2017) offers considerable promise for mechanistic models. A mechanistic pathway representation of AD is created by combining chemical substances, genes, proteins, medical terminology, and imaging data in NeuroMMSig, a hierarchically structured ontology. These pathways, which are causal chains of biological ideas or processes, were found using literature mining techniques and distilled into 125 sub-networks that each have a unique function in the pathophysiology of AD (Domingo-Fernández et al., 2017). Promising new techniques for the forecasts of individual illness trajectories using mechanistic cause-and-effect models are offered by merging large databases like those outlined.

Cellular-level models

For computer modelling that relies on protein interaction and gene expression, sub-cellular characteristics of AD offer interesting input. Early AD modelling efforts, for instance, concentrated on the Abeta deposition process (Jarrett et al., 1993; Lomakin et al., 1997; Pallitto and Murphy, 2001; Ortega et al., 2013). Additionally, biochemical models take into consideration potential therapies along the course of the illness as well as interactions between several variables including Abeta, Tau, inflammation, and other proteases (Proctor and Gray, 2010; Anastasio, 2013, 2014; Kyrtsos and Baras, 2013; Proctor et al., 2013). Early research evaluated the aggregation kinetics of artificial Abeta-like peptides using computer modelling (Tomski and Murphy, 1992). A mathematical description of the aggregation process—as the temporal development of Abeta in the form of monomers, micelles, and fibrils—was made possible by comparably straightforward biological models (Lomakin et al., 1997). The Abeta aggregation hypothesis was further improved by incorporating more thorough interactions between various Abeta fibril types and adapting the model to empirical evidence (Pallitto and Murphy, 2001). A specific model that represents impaired Ca2+ homeostasis and Abeta aggregation as a positive feedback loop and their interaction in a vicious circle was devised as experimental evidence of Abeta's toxicity grew (De Caluwé et Dupont, 2013). More detailed models have been developed over the past ten years, and now incorporate genetic risk factors, potential therapeutic options, and connections between AD and crucial gene transcription factors like p53 (Proctor and Gray, 2010; Proctor et al., 2013). (Kyrtsos and Baras, 2013). Sub-cellular modelling ideas are helpful for merging multiscale models because they clearly define the molecular characteristics of AD from a computational standpoint. Computational linguistics and semantic frameworks can be used to "code" molecular pathways as a network of relationships. The Biological Expression Language (BEL), which enables the use of first-order logic to describe the interactions between proteins, genes, and other chemical molecules, is one potential tool for this method (Madan et al., 2019).

Models of a single neuron and a neural circuit

Aside from the subcellular level, AD models may be applied to a variety of tiny sizes, from single cells to brain circuits (Morse et al., 2010; Romani et al., 2013; Bianchi et al., 2014; Perez et al., 2016). (Zou et al., 2011; Abuhassan et al., 2012; Bianchi et al., 2014; Rowan et al., 2014). In an effort to replicate the observed data, single-neuron models are frequently motivated by an experimental strategy, such as a patch-clamp experiment (Chen, 2005). (Morse et al., 2010). These single-cell simulations' underlying mathematics may make use of more generic formulations for brain oscillation models, as with the Hodgkin-Huxley model (Hodgkin and Huxley, 1952). In a model of a neuron, Hodgkin and Huxley provided the first influential mathematical description in 1952. (Hodgkin and Huxley, 1952). The Hodgkin-Huxley model is based on research records made on the axons of squid: It makes it possible to approximate membrane potentials over time realistically by specifying the capacitance of the phospholipid membrane and the conductance of leak and voltage-gated ion channels (Hodgkin and Huxley, 1952). The model, however, requires a lot of processing, making it best suited for

simulations with a limited number of neurons or a short simulation time (Izhikevich, 2004). Models like those proposed by Hodgkin and Huxley (1952), Morris and Lecar (1981), Rose and Hindmarsh (1989), and Wilson (1999) that are biologically realistic yet relatively inefficient seem to be caught in a catch-22 since they only suggest a small number of alternative behaviours (e.g., the integrate-and-fire or integrate-and-fire-or-burst model; Smith et al., 2000; Izhikevich, 2004). Izhikevich offered a computationally effective model that could create emergent biological phenomena like as tonic and phasic spiking and bursting, frequency adaptation, and accommodation as a potential solution (Izhikevich, 2003, 2004). The mean-field theory may incorporate intricate neural networks with many neurons (Spiegler et al., 2011). The use of the mean field to explain fluid or gas dynamics without taking individual molecules into account has its roots in physics. It permits simplification of a geographically different set of neurons with a similar function in the brain (Liley et al., 2002). The term "neural mass" refers to a collection of neurons that can be characterised on several spatial scales, such as a brain area, a column, or a neuronal ensemble. A large-scale brain network model has frequently employed neural mass models to specify local dynamics (Wilson and Cowan, 1972; Zetterberg et al., 1978; Hindmarsh and Rose, 1984; Jansen and Rit, 1995; Wong and Wang, 2006; Stefanescu and Jirsa, 2008; Sanz-Leon et al., 2015).

Brain Network Models At A Large Scale:

Over the past ten years, large-scale computer brain modelling has advanced more quickly. In order to test the idea that excessive brain activity causes neurodegeneration, de Haan et al. (2012) developed a model. The neural mass model by Zetterberg et al. (1978) is each network node's local dynamic model in this model, which is a large-scale brain network generated from diffusion MRI. The synaptic strength as a function of brain activity across time was condensed by De Haan and colleagues (de Haan et al., 2012). As a result, after a while, the links that were sending more activity started to degrade. This particular pathway was used to characterise a kind of excitotoxicity that causes degeneration. Here, using graph-theoretical measurements, one could successively see degradation in the functional and structural network topology over time. Hubs, which are classified as densely linked brain areas (through incoming and outgoing links), also showed a decrease of spectral power and an increase in sensitivity, according to the scientists (de Haan et al., 2012). According to the authors' observations, the model's increased brain activity and functional connections are consistent with real data from MCI or moderate stages of AD (de Haan et al., 2012). In a later investigation, de Haan et al. (2017) experimented with several "therapeutic" ways to stop neurodegeneration in the excitotoxic model, such as modifying the excitability of the excitatory and inhibitory subpopulations of the neuronal masses. The most effective method for maintaining healthy network characteristics over an extended period of time was raising excitability of excitatory neurons and then increasing inhibition of inhibitory neurons. This can appear paradoxical at first, but it implies that hyperexcitability can be reversed by increasing either excitation or decreasing inhibition. The authors hypothesised that the network architecture could be to blame for this phenomena. The most effective tactics stifle network hub activity, which may in turn slow the spread of illness. This hypothesis postulates that neurodegeneration propagates through network architecture as a sort of "pro-degenerative" signalling pattern. This is connected to a previous account of Hasselmo in 1994. The spatiotemporal pattern of disease progression along significant fibre tracts, early memory deficits, and neurodegeneration brought on by excessive demands on synaptic plasticity rather than excitotoxicity can all be explained by this model (Hasselmo, 1994), which offers a descriptive model of runaway synaptic modification, learning, and cholinergic suppression. The Hasselmo model (Hasselmo, 1994) explains an earlier stage of the same process, where hyperactivation induces undesirable neuroplasticity through extensive runaway synaptic modification and through this mechanism results in neurodegeneration. This is in contrast to the work by de Haan et al. (2012), which assumes that neurodegeneration is a

consequence of hyperactivation. The neural mass model of Jansen and Rit (1995), which is connected to the Zetterberg model, was used at each node of the cortical network by Pons and colleagues in their other brain network model for AD (Pons et al., 2010). (Zetterberg et al., 1978). The electroencephalography recordings utilised by the authors demonstrated a slowing of the alpha rhythm and an increase in functional connectivity (measured by the phase lag index) in MCI patients as they aged, i.e., functional connectivity increased from young to elderly participants. In their simulations, Pons et al. were able to explain these data by lowering the maximal postsynaptic potential and raising the thalamocortical SCs. Demirtas and colleagues examined the blood-oxygen-level-dependent (BOLD) signal alterations brought on by AD in another recent modelling work (Demirtas et al., 2017). There were 109 participants in this study from various categories (healthy controls, preclinical AD, MCI, and AD). Regarding their empirical BOLD signal, it was possible to see a decline in global interactions of AD patients when evaluating first-order circular statistics, or in the Kuramoto order parameter, as well as regional variations in the strengths of the functional connectivity, in comparison to controls (Demirta's et al., 2017). Additionally, variations in functional connectivity were linked to Abeta, total Tau, and phospho-Tau levels in cerebrospinal fluid (Demirtas et al., 2017). The brain model may mimic these observed changes by estimating individual effective connectivity using subject-specific structural connectivity and functional connectivity using a heuristic method (Demirtas et al., 2017). Its local dynamics were represented by a supercritical Andronov-Hopf bifurcation. Demirtas et al. systematically changed the model's order parameter in an in silico experiment employing brain network models based on the effective connectivity of healthy people (Demirtas et al., 2017). They were able to track the development of functional connection degradation in this way. For each illness stage and group, an ideal order parameter was identified that best replicated the degeneration that had been empirically observed. This study demonstrated how changes in regional dynamics might cause activity within the anatomically large-scale brain network to fragment. Additionally, simulations confirmed the observation that the interaction between BOLD signals decreases with illness development as shown by the Kuramoto order parameter.

Platform for the virtual brain:

In the sections that follow, we concentrate on The Virtual Brain, a multimodal and multiscale virtual brain simulation framework that has the potential to integrate various modelling scales of AD research (Ritter et al., 2013; Sanz Leon et al., 2013; Sanz-Leon et al., 2015; Stefanovski et al., 2016; Solodkin et al., 2018). The Virtual Brain's open-source platform is accessible at www.thevirtualbrain.org. The Virtual Brain is a standardised and well-established framework that permits large-scale modelling techniques on individual patient data, encompassing a variety of underlying dynamics (as indicated in the preceding section, Large-scale Brain Network Models). The structural connectome serves as the foundation for the Virtual Brain (Sanz-Leon et al., 2015). The majority of the neural mass models used in The Virtual Brain—which depict regional activity—had their roots in network models for smaller, more distinct networks. However, as connectomics evolved, the included networks became more intricate and complicated (Dipasquale and Cercignani, 2016). In The Virtual Brain, smaller or even single-neuron systems were employed to create the local dynamic models (Wilson and Cowan, 1972; Zetterberg et al., 1978; Hindmarsh and Rose, 1984; Jansen and Rit, 1995; Wong and Wang, 2006; Stefanescu and Jirsa, 2008; Sanz-Leon et al., 2015). The Virtual Brain can model and simulate distinct subnetworks spanning from a regional level to a few neurons, although it was developed to replicate whole-brain network dynamics (see Spiegler and Jirsa, 2013). The multiscale aspect of The Virtual Brain is its second crucial component that can help with AD research. This term was developed to describe the fluid transition between the various brain scales, from the macroscale, where long-range connections between brain regions allow for intra- and inter-hemispheric interaction, to the microscale, where countless single neurons are

present and their electrophysiological characteristics, receptors, transmitters, locations within cortical layers, etc. are known. While measurements at the microscale are more focused on cell membranes and structures but are unable to sample a full human brain, measurements at the macroscale provide information on individual brains. The Virtual Brain idea takes into account both scales: on the one hand, the scaffold of The Virtual Brain is the structural connection of the entire brain, and on the other hand, the neural properties are represented in local dynamic models and their biophysiological parameters (e.g., the Jansen-Rit model). Both modelling the complete brain based on every single neuron and modelling the large-scale brain alone could not include microscopical components. As a result, the mesoscale has been formed and is made up of many components (Deco et al., 2008; Wright and Liley, 2010). First of all, nearby electromagnetic fields have a direct bearing on one another. Additionally, there are neural masses, which can either cover the neuronal mass in a voxel captured by an MRI scanner or the anatomical area of a functional region. They may relate to interactions between excitatory and inhibitory populations as well as through the connectome, a large-scale network connecting distant areas, depending on the brain mass model. This small circuitry's interaction with the larger brain network can result in widespread, physiologically realistic brain activity (Honey et al., 2007; Ghosh et al., 2008; Sotero and Trujillo-Barreto, 2008; Bojak et al., 2010; Jirsa et al., 2010; Ritter et al., 2013; Sanz-Leon et al., 2015; Kunze et al., 2016). Clinical applications and consequent technologies may benefit from and expand on theoretical and computational predictions, as The Virtual Brain has already demonstrated success in epileptic surgery. The Virtual Brain is an integrative research platform (Jirsa et al., 2017; Proix et al., 2017). The Virtual Brain has already been utilised for a variety of research topics, including the modelling of physiological brain phenomena in healthy participants (Ritter et al., 2013; Sanz Leon et al., 2013; Spiegler and Jirsa, 2013; Roy et al., 2014); mouse brain models (Melozzi et al., 2017); clinical approaches of AD (Zimmermann et al., 2018; Stefanovski et al., 2019); (Aerts et al., 2018). In a research, Zimmermann et al. used The Virtual Brain to simulate Alzheimer's (Zimmermann et al., 2018). The authors were able to demonstrate a statistically significant link between the cognitive status of AD patients and the fitted model parameters of The Virtual Brain by fitting the model to predict individual functional connectivity from the underlying structural connectivity (Zimmermann et al., 2018). This allows for the non-invasive assessment of intrinsic brain properties since the parameters serve as substitutes for biophysically significant entities like long-range coupling factors and local interactions between inhibitory and excitatory neuronal populations. Multimodal data for the study of AD can comprise, for instance, structural connectivity from diffusion tensor imaging, anatomical MRI, and PET imaging data of glucose metabolism, amyloid, and tau. One of these characteristics, Abeta PET, was employed in our prior work (Stefanovski et al., 2019), which examined the processes behind the slowing of electroencephalography, another well-known AD symptom (Stefanovski et al., 2019). We modelled local Abeta-mediated hyperexcitability utilising brain network modelling with The Virtual Brain as a pilot research in the field of molecularly-driven large-scale brain simulations, where regional Abeta load was acquired from PET data. Fundamental differences between AD patients and controls were found by characterising the local excitation-inhibition balance as a function of local Abeta load from PET. We demonstrated that a few areas with a moderate or high Abeta load are switched into a different dynamic state, resulting in slower activity oscillations. The major manifestation of this slowdown is a change in rhythm from alpha to theta. It spread over the whole network and concentrated on the hubs. It's interesting to note that local hyperexcitation also occurred in the network's core areas. As a result, we were able to identify a potential pathomechanism for the electroencephalographic slowing in AD utilising this technique (Stefanovski et al., 2019).

Conclusions and Suggested Further Research:

Although our understanding of the mechanisms that contribute to AD pathogenesis expands, it remains a significant challenge for neuroscience to comprehend their unique significance and interplay. Additionally, clinical research is being translated slowly. The objective should be to combine multiscale information to show complex relationships underlying AD rather than examining separate processes (Hofmann-Apitius et al., 2015; Iyappan et al., 2016). When a disease-modifying therapy for degenerative dementia becomes available, it must most likely be started several years before the disease's clinical and behavioural symptoms appear. This is because pathways in the brain start to shift decades before dementia manifests and cause permanent neuronal loss. However, one should be prepared with the fact that such a treatment may need to be used for many years and may have serious bad effects. High screening sensitivity and diagnostic specificity will thus be of utmost significance. Furthermore, individual biomarker profiles of patients' "fingerprints" are the sole way to conduct future trends of tailored therapies. As an illustration, recent research has demonstrated that the multimodal dataset from the Alzheimer's Disease Neuroimaging Database (ADNI) may predict the gene expression pattern (as a prospective individual therapeutic target) better than the clinical presentation does (Iturria-Medina et al., 2018). It will be possible to explain situations that initially seem out of the ordinary with a more accurate AD diagnosis. Prospective therapies may help identify some etiologies. Additionally, in the future, subtypes of disease entities that are now included under AD may be created and evaluated using a particular therapy, such as immunosuppression for autoimmune phenomena or anti-Abeta medications for early-onset AD. The appropriate population must be chosen. Too many patients with various illness reasons, where the therapy has no impact, might lead probable consequences to be superimposed if the diagnosis is not precise enough. The use of biomarkers to track treatment effects in research settings is advantageous because the disease's clinical trajectories are sluggish and difficult to evaluate objectively. Future research utilising computer models for multiscale brain simulations may result in better early detection of dementia, more accurate prognostic prediction, and differential diagnosis, which are the cornerstones of rational medical treatment of AD patients.

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