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Review

Neuronal excitation/inhibition imbalance: core element of a translational perspective on Alzheimer pathophysiology

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ABSTRACT

Our incomplete understanding of the link between Alzheimer's Disease pathology and symptomatology is a crucial obstacle for therapeutic success. Recently, translational studies have begun to connect the dots between protein alterations and deposition, brain network dysfunction and cognitive deficits. Disturbance of neuronal activity, and in particular an imbalance in underlying excitation/inhibition (E/I), appears early in AD, and can be regarded as forming a central link between structural brain pathology and cognitive dysfunction. While there are emerging (non-)pharmacological options to influence this imbalance, the complexity of human brain dynamics has hindered identification of an optimal approach. We suggest that focusing on the integration of neurophysiological aspects of AD at the micro-, meso- and macroscale, with the support of computational network modeling, can unite fundamental and clinical knowledge, provide a general framework, and suggest rational therapeutic targets.

1. Introduction

Alzheimer's Disease (AD) is a major health problem. The number of cases of AD is estimated to reach ~130 million cases world-wide (according to the World Health Organization) by 2050, imposing enormous societal and economic costs. Despite intensive research efforts, disease-modifying therapies are still lacking, probably because our understanding of the pathophysiological path from cellular damage to brain dysfunction is still incomplete. Furthermore, the challenges associated with the integration of findings from different levels of analysis (micro-meso-macro scale) is delaying the development of a global model of the disease. Classical histopathological findings in AD are the accumulation of the amyloid-beta (Aβ) protein and the abnormal phosphorylation and aggregation of tau protein, but the mechanisms by which they ultimately cause cognitive deficits are still unclear. While AD is often characterized as a synaptic failure disease (Selkoe, 2002), 'loss of neurons and synapses' remains an unsatisfactory and imprecise overarching explanation, because it has to be complemented with the different specific neurophysiological and clinical profiles, particularly at the early stages of the disease. We propose a novel way to establish a link between neuronal structural changes and clinical symptoms, moving up from the synapse to imbalanced neuronal circuits and brain networks. In both AD mice models and human preclinical AD data, neurons show aberrant patterns of cellular and network oscillatory activity, indicating disrupted neuronal processing (Buzsáki and Draguhn, 2004; Fries, 2005; Varela et al., 2001). As we will discuss based on various lines of evidence, neuronal excitation/inhibition (E/I) imbalance is a likely cause of neuronal network malfunctioning in AD.

However, many questions remain unanswered: is E/I imbalance a potential link to integrate pathophysiological findings from different levels of analysis (cell-circuit-network)? Does it play a key role in cognitive impairment? Could it be a robust early clinical biomarker? Is it

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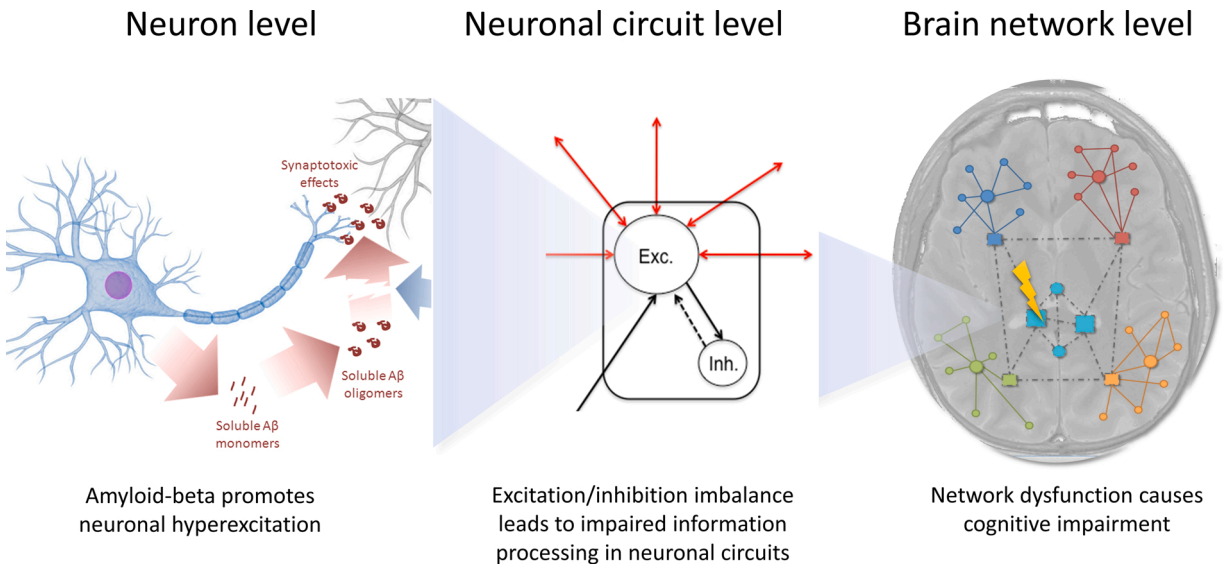

Fig. 1. Simplified multiscale scheme of the neurophysiological disease mechanism of AD, based on the hyperexcitation induced by Aβ.

indeed mainly triggered by abnormal levels of proteins? Is this phenomenon observed in animal models similarly manifest in humans? And, finally, could it contribute to building a better explanatory model for disease progression and cognitive impairment in AD?

The past decade has witnessed a rapid increase in studies investigating how proteinopathies are linked to mechanisms of neuronal miscommunication, functional network dysfunction, and neurodegeneration, and driven partly by the advent of novel advanced recording techniques and theoretical tools. For example, it has been revealed that various toxic effects of Aβ contribute to the development of neuronal hyperexcitability in AD animal models (Busche and Konnerth, 2016). This set of probably parallel occurring mechanisms includes pyramidal neuron hyperexcitability (e.g. by altered postsynaptic inhibitory receptors), impairments of inhibitory neurons (e.g. by excessively activated inhibitory receptors) (Ambrad Giovannetti and Fuhrmann, 2019; Hijazi et al., 2019; Schmid et al., 2016), loss of inhibitory receptors and synapses (Ulrich, 2015; Dorostkar et al., 2015), and blocked synaptic glutamate reuptake (Zott et al., 2019). Besides these reported effects, it is important to realize that non-amyloid-induced damage such as neuromodulatory (e.g. cholinergic deficit) or inflammatory (e.g. microglial) changes are very likely to play a role. An overview of early AD-related disruptive mechanisms can be found in Styr and Slutsky, 2018 (see table 1). It is precisely this partly understood, multifactorial complexity at the cellular level that brings us to a focus on their combined functional higher-level result: neuronal E/I imbalance.

This disruption of neuronal E/I balance may lead to human brain circuit and large-scale network dysfunction and to cognitive impairment (López-Sanz et al., 2017b; Stam et al., 2009). The individual components forming this chain of events have been previously reported using animal models, human neurophysiology recordings and computational models. To date, however, there is no generally accepted framework that bridges these findings in a cohesive and intuitive manner.

In this review, we suggest that the missing link that ties together AD neuronal structural pathology and clinical symptoms is neurophysiology. A neurophysiological framework, where E/I imbalance is a key player, can unite the phenomena found at different levels of analysis in AD (see Fig. 1). We will begin by giving an overview of the available evidence for the direct link between AD pathology and E/I imbalance, as well as the consequences for neuronal (circuit) function. We will then discuss neurophysiological findings at the macro-level in human studies of early AD, that (indirectly) allude to neuronal hyper-/hypoactivity. In the last section, we introduce computational modeling as a powerful tool to not only investigate neurophysiological mechanisms and bridge the gap between the microscale and macroscale level, but also to predict and assess the outcome(s) of activity-targeting interventions. We conclude by summarizing and emphasizing the underestimated, central role of neurophysiology in AD, offer a treatment-oriented research framework focused on E/I balance, and discuss unresolved issues as well as potential future endeavors.

2. Impairment at the synaptic level: the microscale

AD is characterized by two major hallmark lesions: extracellular Aβ plaques and intracellular neurofibrillary tangles (NFT) of filamentous aggregates of hyperphosphorylated tau protein (Paired Helical filament; PHF_{Tau}) (Association, 2020). However, there are numerous studies showing that individuals without cognitive symptoms may accumulate Aβ plaques in their brains and that PHF_{Tau} may also be present in non-demented individuals, and related to normal aging (Ferrer, 2012). Furthermore, Aβ peptides and tau proteins may have a role in the normal functioning of the synapses (see comprehensive review in ref. (Spires-Jones and Hyman, 2014). Thus, one principal question which arises in AD pathology is to what extent do alterations at the synaptic level explain, in of themselves, early cognitive decline in AD, and how can these changes be ameliorated and prevented? At present, one of the most widely accepted hypotheses is that, under certain pathological conditions, Aβ peptides and tau proteins lead to toxic effects at both pre- and post-synaptic elements, leading to synaptic alterations and loss, and which represent a major structural correlate of the cognitive decline observed in AD (Arendt, 2009; Henstridge et al., 2016; Rajmohan and Reddy, 2017; Selkoe, 2002; Spires-Jones and Hyman, 2014; Zhou et al., 2017).

AD is a progressive disease with early symptoms that are typically characterized by the progressive loss of episodic memory and other cognitive functions. The beginning of memory decline is associated with the early, pathological accumulation of PHF_{Tau} and neuronal degeneration in the transentorhinal and entorhinal cortices. However, it is important to note that there is not always a direct relationship between PHF_{Tau} deposition and episodic memory dysfunction as entorhinal PHF_{Tau} is often asymptomatic (reviewed in Ferrer, 2012). Tau-related pathology is thought to then spread progressively to the hippocampal formation and other brain areas as the disease progresses. Since pyramidal cells are the most common cell type and the main projection neurons in the cerebral cortex (neocortex and allocortex), it is thought that these neurons may be responsible for the spread of pathological proteins through their axons (Braak and Del Tredici, 2020, 2019, 2011;

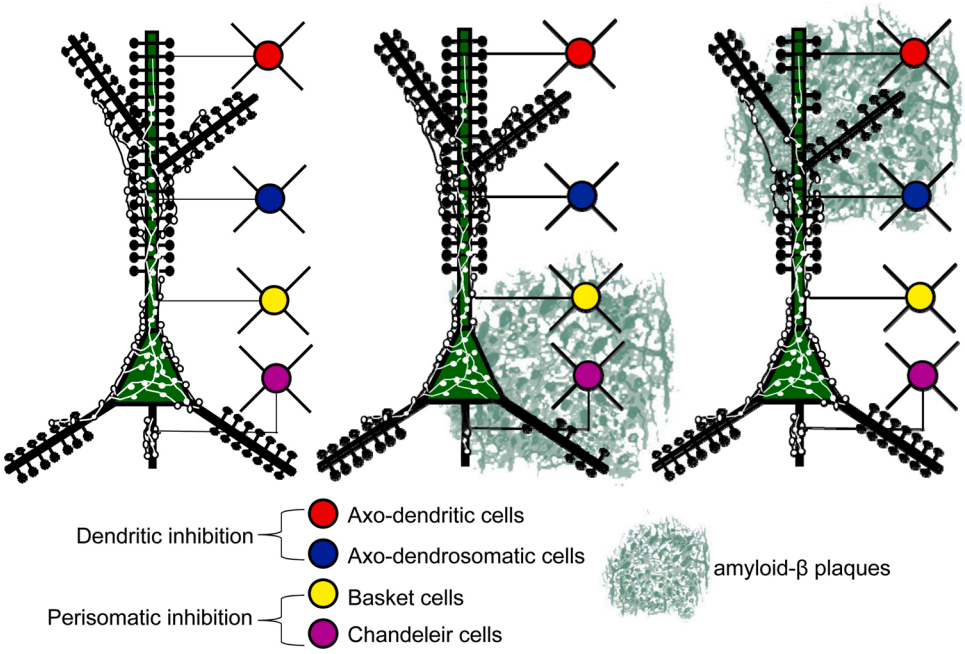

Fig. 2. Aβ plaques may appear in the neuropil or in direct association with neuronal cell bodies, the relative abundance of these two types of plaque configurations is likely to influence the alterations to specific synaptic circuits that may occur in AD. Pyramidal cells are innervated by different axonal systems. In general, all axon terminals forming synapses with the perisomatic region of pyramidal cells are GABAergic and they originate from two main types of interneurons: basket cells and chandelier cells. The dendrites in the neuropil establish synapses with a larger variety of axonal systems, including: glutamatergic axons (mainly originating from pyramidal cells and thalamic afferents); GABAergic/peptidergic axons (originating from various types of axo-dendritic interneurons); and noradrenergic, dopaminergic, serotoninergic and cholinergic axons (arising in the brainstem and basal forebrain). The membrane of neuronal cell bodies in contact with Aβ plaques lack GABAergic perisomatic synapses. This alteration in GABAergic innervation is thought to contribute to the hyperactivity of neurons surrounding Aβ plaques. By contrast, the local loss of dendritic spines may represent a local and partial decrease in the number of excitatory synapses in those regions of the dendritic arbor of the neuron that are in contact with Aβ plaques. This latter alteration would have little impact on the control of the activity of the affected pyramidal cells.

Jucker and Walker, 2013). Furthermore, the dendritic spines of pyramidal cells are the main postsynaptic targets of excitatory glutamatergic synapses, and pyramidal cell axons represent the main source of these synapses in the cerebral cortex (DeFelipe and Fariñas, 1992). Thus, the pyramidal neuron seems to be a key element in AD. These changes may have a variety of functional consequences depending on the alterations of the microanatomy of pyramidal cells and also depending on their GABAergic inputs by inhibitory interneurons.

As stated above, the hippocampus is one of the main brain regions affected in AD and it has been reported that in patients with AD, adult hippocampal neurogenesis is clearly reduced (Moreno-Jiménez et al., 2019). Since newborn neurons represent excitatory, glutamatergic neurons that are integrated in the granule cell layer, the reduction of these newborn neurons in AD patients most likely induces changes in the excitatory connectivity of the hippocampal formation. Moreover, adult neurogenesis has been found not only in the subgranular zone of the dentate gyrus of the hippocampus and in the subventricular zone of the lateral ventricles, but also in other brain regions. As has recently been reviewed by Denoth-Lippuner and Jessberger (2021), neurogenesis has also been observed in the hypothalamus and the brainstem, and possibly in the neocortex, striatum, amygdala and substantia nigra of rodents and other mammals too. Although adult neurogenesis in humans in all these brain regions is still under debate —and consequently we do not know if aberrant neurogenesis occurs in AD— we cannot rule out the possibility that alterations in the connectivity of multiple regions of the brain could also be linked to aberrant neurogenesis.

2.1. *Aβ deposits*

Aβ deposits in the neuropil are thought to be toxic to axons and dendrites, thereby altering specific synaptic circuits. Animal models of AD have shown that Aβ plaques induce local morphological alterations in the dendrites that are in contact with Aβ (e.g., (Knafo et al., 2009; Spires et al., 2005; Tsai et al., 2004)). However, Aβ plaques also come into contact with —or even envelop— neuronal cell bodies (Allsop et al., 1989; Armstrong, 1995; Cummings et al., 1993; Pappolla et al., 1991).

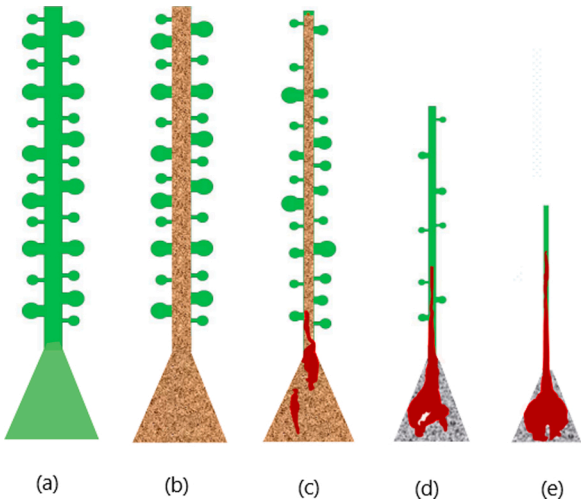

Fig. 3. Scheme representing the changes to pyramidal cell dendrites of that showed different patterns of PHF-tau immunostaining in the human cerebral cortex. For simplicity, dendritic spines were represented as two types: small and large. Normal cell (a); Light red, diffuse phospho-tau (b); Dark red, neurofibrillary tangles (c, d, e). In the so called putative "pre-tangle" stage (light red), the dendritic trees of pyramidal neurons are unchanged (b). In the presence of well-developed neurofibrillary tangles (dark red; in d and e), however, dendritic spines are progressively loss. In cases with an intermediate state of neurofibrillary pathology (c), the loss of dendritic spines is more variable.

Since pyramidal cells are by far the most abundant type of neuron, it seems logical to think that these neurons are the principal population (although see microglia impairment (Saez-Atienzar and Masliah, 2020)) most affected by Aβ deposits. Thus, since plaques may appear in the neuropil —affecting axodendritic connections of pyramidal cells and both excitatory and inhibitory synapses— or in direct association with neuronal cell bodies —affecting inhibitory perisomatic connections

(León-Espinosa et al., 2012; Garcia-Marin et al., 2009)—, the relative abundance of both spatial plaque configurations is likely to differentially influence the alterations of specific synaptic circuits that may occur in AD (see Fig. 2).

2.2. Phosphotau

Abnormal phosphorylation of tau leads to the formation of PHF_{Tau}, which is the main component of the intraneuronal NFTs (Grundke-Iqbal et al., 1986) that are characteristic of AD and other tauopathies (Lee et al., 2001). How tau alterations affect cortical circuits, and how these alterations may be related to the typical cognitive deterioration in AD, is still a matter of debate (Castellani et al., 2008). This is due to the limited data available about synaptic circuits and their relationship with cognition in both the normal human brain and in AD. However, in a previous study assessing the possible alterations in dendritic spines in pyramidal cells from AD patients (Merino-Serrais et al., 2013), significant changes in the number and morphology of dendritic spines were associated with the presence of NFTs (see Fig. 3). Since dendritic spines are fundamental structures in memory, learning and cognition (DeFelipe, 2015), these alterations constitute an important early event in the pathogenesis of AD. However, the presence of PHF_{Tau} in neurons during the pre-tangle stage does not seem to alter the pyramidal neurons. Therefore, the characteristic cognitive impairment in AD is likely to depend on the relative number of neurons that have well-developed tangles. This is in line with the clinicopathologic correlation studies based on data obtained in multiple worldwide research centers concluding that the severity of cognitive impairment correlates strongly with the density of neocortical NFT (Nelson et al., 2012).

Summarizing the microscale data, Aβ plaques, as well as soluble forms of Aβ, induce local alterations in the dendrites and somata that are in contact with Aβ, with such alterations including local loss of dendritic spines and loss of perisomatic GABAergic interneuron terminals. The loss of these perisomatic GABAergic synapses could facilitate the existence of hyperactive neurons that might give rise to epileptiform activity. PHF_{Tau} is likely to be involved in the more general changes that occur in dendritic spines loss that leads to cognitive decline in AD; neurons with NFT show a remarkable loss of dendritic spines —and a consequent loss of synapses— in all dendritic regions of the neuron. Therefore, while Aβ plaques and oligomers could be mainly contributing to neuronal hyperexcitability, PHF_{Tau} could be more related with reduction of neuronal activity and connectivity which may explain the different neurophysiological activity patterns in space and time along the various stages of AD.

3. From cellular to neuronal circuit impairment: the mesoscale

3.1. In vivo neurophysiological recordings in animal models of AD

The loss of GABAergic terminals described above is predictive of increased neuronal activity, while the progressive damage of dendrites could be associated with a silencing of neuronal circuits. These two hypotheses have been tested in neurophysiological recordings in animal models of AD. In vivo cellular-level imaging and electrophysiology of neurons in the direct vicinity of amyloid plaques showed a significant proportion of neurons with abnormally increased activity (Busche et al., 2015, 2012a; Grienberger et al., 2012; Keskin et al., 2017; Liebscher et al., 2016; Maier et al., 2014; Rudinskiy et al., 2012; Scala et al., 2015; Šišková et al., 2014; Xu et al., 2015). Additional support for a role of amyloid-related neuronal hyperexcitability was also provided from long-term video-EEG recordings demonstrating that many Aβ-bearing mouse models exhibit epileptiform discharges as well as spontaneous recurrent seizures (Born, 2015; Palop et al., 2007). Importantly, it is increasingly recognized that many patients with AD exhibit epileptiform and seizure activity (Vossel et al., 2017). Furthermore, recent evidence suggests that hyperexcitability may even precede the formation of amyloid plaques (Bero et al., 2011; Busche et al., 2012b; Cirrito et al., 2008) and drive the propagation of tau pathology from entorhinal cortex to hippocampus and cortex (Rodriguez et al., 2020).

There is now substantial mechanistic evidence that neuronal hyperactivity can be directly mediated by soluble Aβ, which is highly enriched around amyloid plaques (Keskin et al., 2017; Zott et al., 2019). Experimental findings showing that local application of soluble Aβ to neuronal circuits in vivo induces hyperactivity, and that suppression of Aβ production by beta- or gamma-secretase inhibition blocks hyperactivity (Busche et al., 2012a, 2012b; Keskin et al., 2017), strongly support this notion. Mechanistically, the link between Aβ and hyperexcitability has been attributed to an Aβ-dependent shift in E/I balance, favoring excitation, e.g. through inhibition of glutamate reuptake (Zott et al., 2019). Due to the different technical approaches (i.e., single cell action potential firing vs network fluctuations), it remains unclear how neuronal hyperexcitability in animal models and abnormal hyperactivation found in human neuroimaging studies are linked. To have a more complete view of the neurophysiological alterations due to protein-pathology at different stages of the disease, recent work has crucially evaluated the effects of tau-protein and its interaction with Aβ. Busche et al. (Busche et al., 2019) revealed a tau-dependent suppression of activity and silencing of many neurons, dominating over Aβ-dependent neuronal hyperactivity, but also synergistic effects between Aβ and tau (see also Busche and Hyman, 2020 for a recent review on the topic). Importantly, the circuit effects of tau were dependent on soluble tau species rather than NFTs.

There is growing evidence that non-neuronal cell types including microglia and astrocytes, in which most AD risk genes are expressed (Kunkle et al., 2019), play a key role in shaping neural circuit excitability and plasticity in the developing and adult brain, and that disease-associated functional and structural alterations of these cell types may contribute to neural system failure in AD (Harris et al., 2020). Microglia directly communicate with neurons, and recent studies have shown that neuronal hypoactivity activates microglia (Liu et al., 2020; Brawek et al., 2014) and that microglia can in turn reduce neuronal firing (Badimon et al., 2020). Multiple lines of evidence suggest that microglia promote aberrant synapse and neuron loss in AD (Hong et al., 2016; Dejanovic et al., 2018), thereby contributing to impaired synaptic E/I balance. Recent work suggested that astrocytes could play a similar role in synapse removal (Lee et al., 2021). Furthermore, astrocytes become structurally and functionally abnormal in AD (Escartin et al., 2021), and due to their strategic position at synapses these alterations may further impair synaptic and circuit activities. Lastly, recent transcriptomic studies have also heavily implicated oligodendrocytes in the development of AD (Chen et al., 2020), alongside myelin loss both in grey and white matter, but in what manner and to what extent this contributes to AD circuit dysfunction remains a topic of intense research.

3.2. Alterations at the neuronal level related to Aβ and PHF_{Tau}: possible functional implications

These aforementioned studies in animal models of AD have shown that Aβ and tau induce changes in the functional activity of cortical circuits. However, what is the role of cortical layers and brain regions? It is well known that some neuronal populations which reside in cortical regions damaged in AD remain unaffected, whereas others are altered to varying degrees, depending on the cortical area in question. Such differences could indicate different steps in the process of neuronal degeneration. Additionally, it might be possible that the impact of Aβ and tau on neuronal circuits depends on which neuronal compartment (Figs. 2 and 3) is affected or the degree of the pathological alterations. It is also important to note that there are clear differences in the levels of tau alterations and variations in the density of Aβ plaques across cortical areas and layers. Furthermore, at the early stage of AD, amyloid deposits and NFTs are found in different cortical regions: amyloid deposits are located in the neocortex (mainly in the basal regions of the frontal,

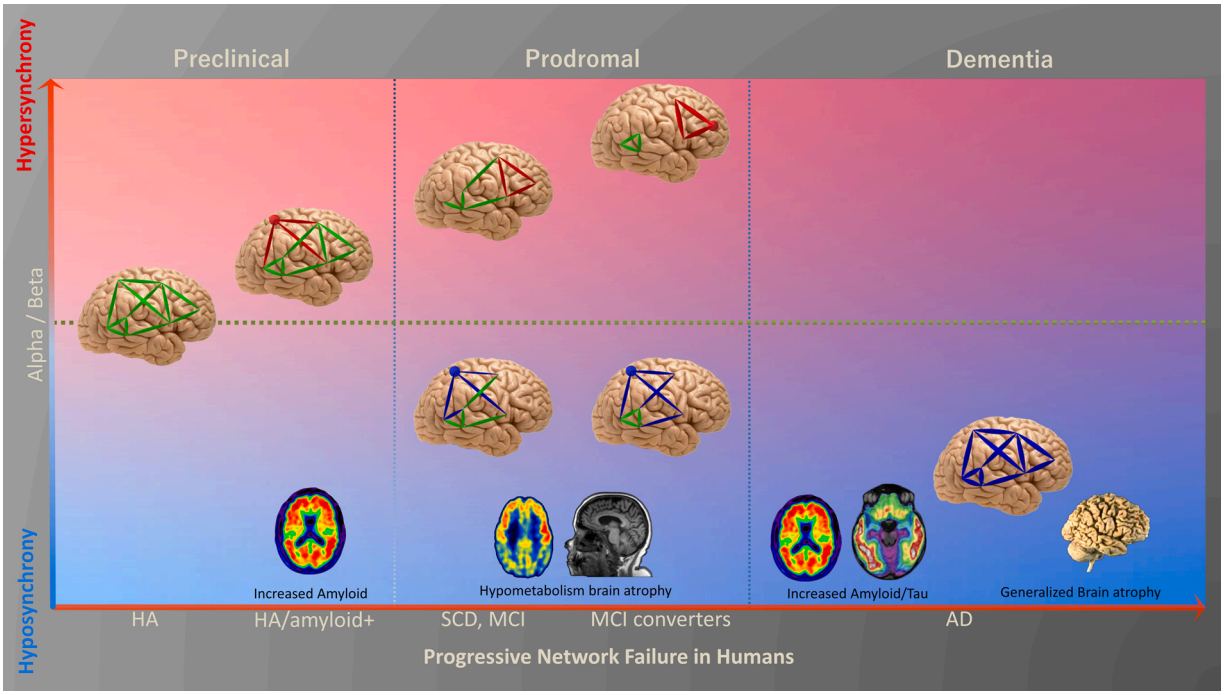

Fig. 4. Neurophysiological profile across different stages of the disease. The ordinate represents the values of phase brain synchrony in alpha/beta frequency bands from hyposynchrony (in blue) to hypersynchrony (in red), in which the synchrony found in controls is represented by a dashed green line. Abscissa represents the progressive network failure at different stages of the disease (preclinical, prodromal, dementia). Typical brain networks found in different studies are depicted where green lines represent links with normal values, as seen in healthy ageing subjects. In turn, red lines represent increased phase synchronization, and blue lines represent links with decreased of brain synchrony with respect to the control group. Note that link thickness represents synchronization value. A dual pattern of hyper/hypo synchrony is seen at SCD and MCI stages. Typical neuropathological findings at different stages of the disease, such as those obtained using a range of imaging modalities (amyloid-PET, glucose-PET, MRI mild atrophy, amyloid-PET, Tau-PET) and consistent with MEG findings, are also shown, as is generalized atrophy in a real brain (bottom right). HA: Healthy aging; HA*amyloid + (healthy aging with an amyloid PET considered +; SCD: subjective Cognitive Decline; MCI: Mild Cognitive Impairment; AD: Alzheimer Disease.

temporal, and parieto-occipital lobes), whereas the hippocampal formation lacks amyloid deposits. In contrast, NFT are found mainly in the transentorhinal and entorhinal cortices, whereas few are located in the CA1 and lacking in the neocortex at initial stages. Thereafter, amyloid deposits and NFT progressively affect multiple cortical areas and subcortical regions (Braak and Braak, 1998, 1991; Braak and Del Tredici, 2015; Thal et al., 2002). Consequently, the alterations of brain circuits become inherently more complex, and it becomes increasingly difficult to interpret the possible functional implications as the disease progresses.

In conclusion, there is growing experimental evidence for pronounced E/I imbalance in early stages of AD. Data suggest that at least part of this imbalance is mediated by the accumulation of Aβ plaques and soluble Aβ oligomers. Additionally, soluble tau promotes the silencing of neuronal activity and therefore the combination of these two effects contributes to alter the functional communication between brain circuits.

Whether this hyper/hypoexcitability dual profile, found in the animal models, is similarly encountered in human neurophysiological recordings and linked or not with cognitive impairment, is still a matter of debate. The next section will aim to cover this gap by describing macroscale functional network failure that might be due to hyper/hyposynchrony.

4. From neuronal circuitry to neurophysiology in humans in the continuum of AD: the macroscale

With the mounting evidence for Aβ- and tau-dependent E/I imbalance at the micro- and mesoscale, it is rational to address the question regarding the specific consequences for large-scale circuits and network processing (Nimmrich et al., 2015; Uhlhaas and Singer, 2010) in humans. Brain network dysfunction (inter-regional communication) is increasingly recognized as the functional representation of the clinical AD phenotype (Deco et al., 2014; Kapogiannis and Mattson, 2011). Functional network changes appear early in the preclinical stage of the disease, are correlated with disease severity, and display disease specificity (Engels et al., 2017; Tijms et al., 2013).

4.1. Regional brain activity: spectral analysis

A typical finding in neurophysiological recordings of AD patients with magnetoencephalography (MEG) and electroencephalography (EEG) (M/EEG), is a progressive (i.e., from MCI to dementia) slowing of brain oscillatory activity (Berger, 1929; Buchan et al., 1997; Soininen et al., 1982) and specifically the reduction of the posterior dominant alpha rhythm (Babiloni et al., 2009). Increased slow delta/theta (0,5 – 4 and 4−8 Hz, respectively) band activity correlates with brain atrophy in the medial temporal lobe (Fernández et al., 2006) and is present in amyloid-positive healthy subjects that later progress to dementia (Gouw et al., 2017). Although oscillatory changes in AD, such as the gradual slowing, are well known from the literature, the underlying mechanisms remain elusive. In turn, early hippocampal activity disruption in AD is an oft observed phenomenon, but how this translates to oscillatory changes is not trivial, despite variations in theta and gamma frequency being often mentioned (Goutagny and Krantic, 2013). An associated sign is increased relative alpha (8−13 Hz) power in regions with high amyloid depositions in preclinical stages (Nakamura et al., 2018), which later decrease at the time of subjective cognitive decline (SCD), mild cognitive impairment (MCI) and dementia (López-Sanz et al., 2016). Furthermore, alpha power decrease is associated with increased levels of phospho-tau (p-tau) in cerebrospinal fluid (Smailovic et al., 2018), constituting a sign for an advanced stage of the disease.

4.2. Interregional communication

One central question pertains to how brain functional networks are altered and coupled to neuropathology and cognitive decline. Functional connectivity represents the statistical dependence between two time series, and this metric provides a means to establish a functional relationship between brain regions based on oscillatory activity at different frequency bands. In this subsection, we describe a series of experiments in which brain interregional communication is disrupted at different stages of the disease (preclinical and prodromal). Nakamura et al. (Nakamura et al., 2017) showed increased phase synchronization (delta and theta frequency bands) between the precuneus and the bilateral inferior parietal lobules in asymptomatic amyloid-positive (preclinical) subjects' relative to amyloid-negative individuals. As these participants did not show the typical metabolic or morphological signs of disease, the long-distance functional network impairment might be a consequence of the toxic effects of underlying protein-pathology. Even earlier in time, relatives of AD patients showed this increased synchronization a decade before the typical age for developing dementia (Ramírez-Toraño et al., 2021). In another study (López-Sanz et al., 2017a) evaluating healthy elderly subjects with SCD, a decrease in synchronization in posterior regions was reported. This disrupted profile in posterior regions is consistent with the "cascading network failure" hypothesis which could be initiated in posterior regions of the brain (Jones et al., 2016) and overloaded hub regions (Stam, 2014). This hyposynchrony in SCD subjects appears in similar brain areas to those in which Nakamura et al. (Nakamura et al., 2017) reported hypersynchrony in younger asymptomatic subjects. Hence, this probably indicates that hypersynchrony precedes hyposynchrony (see Fig. 4 for further explanation). Additionally, subjects with SCD showed hypersynchrony in anterior regions (López-Sanz et al., 2017a). A combination of anterior hypersynchronization and posterior hyposynchrony was also found in patients with MCI, with greater damage of functional networks found over the posterior regions (López-Sanz et al., 2017a). This hypersynchrony of the antero-posterior networks in MCI patients, was also found in an international multicenter blind study (Maestú et al., 2015), predicted the conversion from MCI to dementia (López et al., 2014; Pusil et al., 2019), and was already present in young (Koelewijn et al., 2019) and elderly healthy subjects (Cuesta et al., 2015) carriers of the APOE-ε4. In fact, Najm et al. (Najm et al., 2019) indicated how hippocampal GABA interneurons are especially vulnerable to the neurotoxic effects associated with being APOE-ε4 carrier. Carriers of this genotype have a high probability of Aβ deposition in regions associated with the default mode network (Buckner et al., 2009a) as shown by Nakamura et al. (Nakamura et al., 2018, 2017). This hypersynchrony can be better understood in the framework of the X model (Pusil et al., 2019). This model was developed in a longitudinal design, where MCI patients, who later developed dementia, showed increased synchrony in comparison to those that did not convert to AD during a two year follow up period. However, when MCI patients converted to dementia, they showed a collapse of their brain network synchronization, in the same brain regions which previously exhibited hypersynchrony. Conversely, non-converters showed the opposite pattern, with increased synchrony during the follow-up period and therefore augmenting their risk for developing dementia. This hypersynchrony can be understood within the framework of the neurophysiological basis of epilepsy. As typically happens in some epileptic syndromes, the loss of GABAergic transmission, could induce hyperactivity, increasing the probability of local synchronization of brain oscillatory activity in MEG and EEG recordings. In fact, there is growing clinical evidence for an increased risk of epileptiform activity in individuals with AD (Lam et al., 2017). Furthermore, subclinical epileptogenic activity has been found in about 42 % of AD patients, leading to a faster decline of cognitive abilities (Vossel et al., 2016). Amnestic MCI (aMCI) patients with seizures are associated with earlier cognitive decline about 6.8 years earlier than aMCI individuals without epilepsy (Vossel et al., 2013). Finally, epileptic activity is more common in AD than other dementias, indicating that the link to hyperexcitability may be relatively specific to AD pathophysiology rather than just an unspecific consequence of neurodegeneration. Therefore, hypersynchronization could be a result of cortical hyperexcitability as seen in animal models in the vicinity of the amyloid plaques.

Less is known about the effects of the tau protein in neurophysiological recordings in humans. Canuet et al., (Canuet et al., 2015) showed a reduced synchronization in different regions of the posterior cortex (including the posterior cingulate and orbitofrontal cortex) in the alpha/beta band, and correlated with increased levels of p-tau in the cerebrospinal fluid. This finding is in line with what has been found at the micro- and meso-scales where tau reduces the number of dendrites and contributes to neuronal silencing (Busche et al., 2019; Merino-Serrais et al., 2013). However, p-tau also mediated increased synchronization between the anterior cingulate cortex (ACC) and the medial temporal lobe in the beta frequency band (Canuet et al., 2015), probably due to the interaction with amyloid deposits, which mainly cause neuronal hyperactivation (Busche and Konnerth, 2016). Furthermore, the loss of spine dendrites and number of functional neurons, due to the effects of the PHF_{Tau}, could contribute to slowing of brain oscillatory activity and hyposynchronization of cell assemblies in advanced stages of the disease. In fact, in individuals with dementia, tau deposits (assessed with tau-PET) have been associated with a decrease of alpha band synchronization together with increased synchrony in slow frequency bands, and correlated to cognitive impairment (Ranasinghe et al., 2020). In summary, combined hyper- and hyposynchronization is frequently found in neurophysiological recordings in humans, and is modulated as a function of the different stages of the process of AD (see Fig. 4).

4.3. Network impairment in patients with AD: a graph theory approach

To better understand the consequences of the hyper-/hypersynchronization on network functioning, it is helpful to adopt a network theory approach. Graph theoretical approaches have been particularly successful in characterizing macroscopic functional brain network damage in AD (Pievani et al., 2011; Stam, 2014). AD shows a distinct pattern of gradual network breakdown, and beyond the expected loss of connections and global efficient network topology one striking phenomenon is repeatedly observed: namely that highly connected 'hub' regions in the brain appear to be most vulnerable in AD (Buckner et al., 2009b; Stam, 2014; Yu et al., 2017). The tendency of increased clustering and the loss of brain hubs (de Haan et al., 2012; Engels et al., 2017) reflect a progressive isolation of brain regions which correlates with cognitive impairment. Engels et al. (Engels et al., 2015) found that, alongside decreased functional connectivity values, hubs were mainly damaged in the posterior regions of the brain, with a shift of the center of gravity from the posterior to the anterior areas. This raised the interesting question of whether the damage to hubs at multiple frequency bands were mutually related to each other. In this regard, Yu et al. (Yu et al., 2017), applied multiplex networks analysis and found that several brain hubs (hippocampus, posterior regions of the default mode network and occipital regions), were impaired in AD patients at different frequency bands, indicating a close relationship between the damage across the frequency spectra. This finding could explain why previous hypersynchronization phenomena were found at several frequency bands. This network breakdown seems to be closely linked to the pathophysiological load of the disease (Engels et al., 2017; Yu et al., 2017) as well as cognitive impairment (Stam et al., 2006).

What, then, is the cause of hub vulnerability? One simple explanation could be that these regions are more prone to gradual wear-and-tear (accelerated by AD pathology) due to chronic high levels of metabolic demand and plasticity. Indeed, several groups have recently suggested such a mechanism, and have considered how it would better explain age as chief risk factor for AD as well as pathological spread patterns

(Hasselmo, 1997; Mesulam, 2006). Notwithstanding, how does this hypothesis relate to the abnormal neuronal dynamics in AD described earlier? Modern network analysis is well suited to address this question, as it aims to relate brain structure to function (Bassett et al., 2018; Breakspear, 2017). For example, network modeling allows for lesion simulation studies and exploring the relationship between structural network damage and system dysfunction (Alstott et al., 2009; Honey and Sporns, 2008), as well as simulations of more general system-level damage.

While interesting, these results only provide new insights at the macroscopic scale pertaining to the collective behavior of millions of interconnected cells. As such, can they be linked to the abnormal patterns of underlying, microscale neuronal activity and synchronization? And are these signs of regional hyper-/hyposynchronization and hyper-/hypoactivity faithfully representative of an underlying neuronal E/I disturbance? To answer these essential questions, micro-, meso- and macroscales require integration in a robust, causal, multi-level framework.

5. Computational neurophysiology in AD across spatial scales

In this section, we will look at computational modeling studies investigating altered neuronal dynamics in AD, focusing on the aim to bridge different levels of detail in order to achieve a multiscale perspective of AD pathophysiology. With the accumulating evidence for a pivotal role of abnormal brain dynamics in AD, at and between different spatial scales, the development of a single unifying framework is a tempting endeavor. In what way is neuronal hyperactivity in early AD reflected in patient data? Can activity-targeting interventions perhaps preserve or restore normal network function by countering E/I imbalance? If so, how do we select and monitor specific interventions in individual patients? Addressing these open questions will present new avenues for early detection and more effective treatments in AD, but also represent a sizable challenge. Intuitively, human data indicating early increased regional activity and large-scale synchronization appear to reflect the underlying neuronal hyperactivity previously described at the microscale. However, the direct translation from the cellular to the macroscopic level is still incompletely understood. Ideally, brain-wide activity and connectivity changes at various levels of detail should be captured simultaneously over longer time periods and related to structural AD pathology. The elaborate and invasive nature of the techniques required for this purpose currently precludes their use in humans and more realistic alternatives are therefore needed. Traditional non-invasive methods to capture brain activity such as M/EEG and fMRI are sensitive to early changes in AD, but have not yet produced a specific, generally accepted, signature of underlying neuronal hyperactivity in early stage AD (Horváth et al., 2018; Li et al., 2015; Maestú et al., 2019). Relatively recent approaches based on source localization or non-invasive brain stimulation show promise, but need further validation (Cassani et al., 2018; Ferreri et al., 2003; Guerra et al., 2011; Mandal et al., 2018). Moreover, while these techniques may eventually enable direct detection neuronal hyperactivity, they do not necessarily enhance our understanding of the underlying mechanisms. To attain a more complete theory of AD pathophysiology, a tighter mechanistic description and validation from cell to network malfunction is required. To this end, how best may we proceed?

In the past decades, modern network analysis methods have substantially improved our understanding of brain organization, as already illustrated in the section dealing with network impairment in AD patients above (Bassett and Sporns, 2017). Besides providing an analytic framework to explain brain connectivity changes, one of the critical benefits of network analysis is the ability to reveal large-scale system effects of low-level phenomena. Due to the complexity of distributed brain dynamics over space and time, the brain-wide effects of local changes can become nearly impossible to predict. For this reason, network modeling is common practice in many other complex system research fields, and is increasingly applied to brain disorders (Bassett and Sporns, 2017; Newman et al., 2006). Computational brain network modeling (BNM) can help to link neuronal hyperactivity across scales to altered brain network function (Bassett et al., 2018). Note that at large-scale levels, models become less physiological and more abstract, as the (sub)cellular detail of the lower levels is gradually lost. This may initially feel as an artificial step away from biological reality, but it is in fact crucial to adequately describe high-level phenomena. For example, inhibitory interneuron dysfunction may be a main driver of AD pathophysiology, but it has no meaning on a system-level, where larger patterns of communication between brain regions are investigated.

5.1. *Integrating scales to understand: Alzheimer's disease simulation*

Recent attempts to bridge the gap between cellular and macroscale brain dynamics have been made using coupled networks of so-called 'neural mass models'. These describe oscillatory neuronal activity in cortical regions, and provide realistic descriptions of, for example, the human alpha rhythm, most prominent in eyes-closed resting state M/EEG data (David and Friston, 2003; Lopes da Silva et al., 1974; Zetterberg et al., 1978). Neuronal properties such as membrane potential of both excitatory and inhibitory neurons are defined, but also their interaction, which leads to firing patterns and the typical observed oscillatory behavior (Sotero et al., 2007). These models can then be coupled according to human structural connectivity (e.g. DTI-based). This dynamic network then generates emerging system-level activity and outputs neurophysiological, EEG-like data. An example of a state-of-the-art, user-friendly simulator of brain dynamics is "The Virtual Brain" (Ritter et al., 2013; Sanzleon et al., 2013). With this simulator, optimal E/I balance and coupling in individual models was associated with cognitive performance in AD in various cognitive domains (Zimmermann et al., 2018).

Assuming that this type of high-level modeling of human brain network dynamics allows meaningful deductions, low-level effects on large-scale networks can be explored. The general approach is to see if observed abnormal neuronal behavior leads to the observed large-scale level network deterioration. By implementing a 'disease' algorithm in the model, a presumed pathological effect of hyperactivity over time can be investigated. For example, in a recent study, the Virtual Brain model was used to investigate the link between amyloid deposition and network-level changes in AD (Stefanovski et al., 2019). By assuming an amyloid-dependent effect on E/I imbalance, AD-resembling EEG findings, such as slowing and hub vulnerability, were found. However, no disease development or structural damage took place in this model. To account for this, structural connections between neural masses at each timestep can be impaired based on their recent peak levels of activity. Such an 'activity-dependent degeneration' (ADD) model reproduces all main neurophysiological hallmarks of AD, including, importantly, an initial transient phase of global hyperactivity and connectivity (de Haan et al., 2012). This suggests it to be a good model for explaining the development of brain dysfunction based on pathological activity levels, and while this may be a general aging effect, AD can accelerate this by introducing extra hyperexcitability. While this result is in line with the aforementioned hyperactivation/hypersynchronization in human functional imaging data, spatial patterns were not investigated. It seems contradictory that hyperactivity and oscillatory slowing are both present in AD, but increased activity is found primarily in lower (theta, 4−8 Hz) frequency ranges, and results echo the modeling results at the mesoscale. This is in line with the well-known early theta power increases in AD, later accompanied by decreases in higher frequency bands, together interpreted as oscillatory slowing, structural and functional connectivity loss, and breakdown of network topology (Engels et al., 2017). The finding that a single straightforward assumption ("hyperactivity damages structural connections") simulates AD suggests that this general mechanism may play a key role. Also, it should be noted that increased neuronal activity arises without any compensating mechanisms

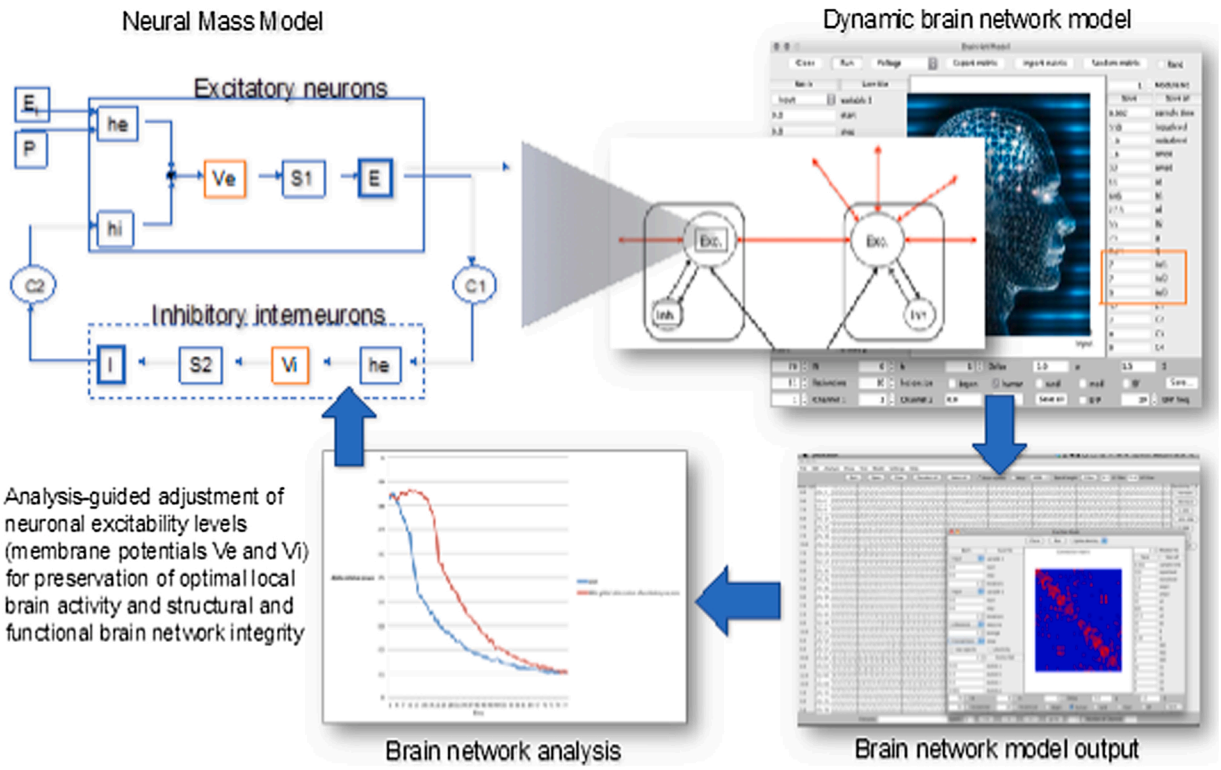

Fig. 5. Model guided intervention development, from neuronal activity to brain network function and back. Abbreviations in the upper left panel (eg, E, Ve, S1, C1) describe neuronal parameters such as membrane potential, spike rate and post-synaptic potentials. Exc = excitatory; inh = inhibitory.

implemented, supporting the idea that hyperactivity is not compensatory.

5.2. *Integrating scales to treat: therapy simulation*

If disease can be represented in the model, so can treatment: if abnormal brain activity can cause cognitive impairment and even structural damage, then it may also be invoked to counter pathophysiological mechanisms, by targeted 'fine-tuning' of neuronal activity (Cantero et al., 2016; Palop and Mucke, 2016). This bottom-up 'virtual therapy' approach has been investigated using computational models at various scales. For example, Rowan et al. present a mesoscale explanation of how directed brain stimulation might be theoretically expected to slow AD progression based on computational simulations in a model of a neocortical column (Rowan et al., 2014). As cells die and synapses lose their drive in AD, neuronal homeostatic synaptic scaling adjusts neuronal firing activity. However, this effect can itself become pathological, as it produces increased imbalance between excitatory and inhibitory circuits, leading to greater calcium-mediated excitotoxicity. The simulations demonstrate that the addition of low-intensity electrostimulation to a network undergoing AD-like cell death can raise global activity and break this homeostatic-excitotoxic cascade. The increase in activity within the remaining cells in the column results in reduced imbalances in excitatory and inhibitory circuits, and lower susceptibility to ongoing damage. Any in vivo treatment that could accomplish this would have a substantial clinical impact.

In silico modification of E/I balance has suggested specific treatment strategies to counter hyperactivity and preserve functional network integrity (de Haan et al., 2017). Neuronal excitability levels were varied in different ways to mimic the effect of medication or brain stimulation techniques (for a schematic workflow see Fig. 5). Here, the best strategy was the global, selective stimulation of excitatory neurons. This seems contradictory in a hyperactive network, but it underscores the counterintuitive forces acting in multiscale systems, and echoes the results of Rowan et al. (Rowan et al., 2014) and the effect of cholinesterase inhibitors. Recently, specific AD medication (Memantine, NMDA antagonist) was simulated, countering amyloid-induced hyperexcitation (Stefanovski et al., 2019). Ultimately, these theoretical predictions should be validated using clinical studies (de Haan, 2017).

In summary, computational modeling studies support the view that (amyloid-induced) neuronal hyperactivity is an early pathological sign of AD, that it disrupts brain circuit function leading to oscillatory slowing and impairs network connectivity, and that it can be modified to counter AD effects. On a more general level, these studies illustrate the potential of computational modeling to integrate empirical findings into a meaningful common framework, rather than a summation of separate findings. Further systematic exploration and validation of multiscale pathophysiology modeling of AD mechanisms is needed.

6. Discussion

In this review, we place a special emphasis on the role of E/I imbalance in AD pathophysiology for three main reasons. First, as a functionally relevant outcome of underlying protein-driven synaptic failure on the one hand, and as a main cause of larger neural network dysfunction on the other, it represents a central element for integrating neurophysiological evidence obtained at different scales into a coherent framework. Second, E/I imbalance may be directly associated with neurodegeneration and cognitive decline. Third, recent studies implicate E/I imbalance as a potential novel therapeutic target in AD. The multiscale scope of neurophysiology, and its natural relationship with computational network modeling, will drive the development of integrative pathophysiological models and greatly improve treatment predictions.

6.1. *A spotlight on E/I (im)balance*

In a multiscale pathophysiological cascade, encompassing toxic

protein deposition and brain network dysfunction, it seems inappropriate to label a single element as 'central feature'. However, specific elements in such a cascade can represent a common pathway or important bottleneck of special interest for diagnostic or therapeutic purposes. In AD, synaptic failure has traditionally been labeled as a core feature, based on the abundant evidence for amyloid/tau-driven synaptic pathology. However, the pathological significance of synaptic dysfunction primarily depends on the extent to which related neurons can still exhibit their normal range of behavior. E/I imbalance could therefore be a key complement, able to underpin a 'central feature' of AD (linking the micro-meso-macro levels of analysis) since it is directly tied to the basic element of brain function, namely neuronal firing. The brain can tolerate a surprising amount of pathological protein deposition or even atrophy before cognitive deficits become apparent. The reason for this is that it can adapt to damage by altering neuronal connectivity and firing patterns due to its structural and dynamic plasticity. However, when the core fundamentals of information transfer, i.e. adaptive, balanced neuronal communication, become impaired, cognition will inexorably and immediately suffer, as is demonstrated by reversible conditions such as delirium based on metabolic/toxic encephalopathy, or epileptic seizures.

6.2. E/I imbalance as a driver of neurodegeneration, network dysfunction and cognitive impairment in AD

E/I imbalance is implicated in both cellular and network disruption. Long-term neuronal hyperexcitability leads to neuronal death caused by excitotoxicity (Canter et al., 2016). Hence, E/I imbalance is theoretically directly linked to neurodegenerative mechanisms. What, then, is the evidence for E/I imbalance in changing the dynamics of the disease process? Neurophysiological studies in humans demonstrate increased synchronization at preclinical stages in young subjects APOE-ε4 carriers (Koelewijn et al., 2019) or healthy adults with a positive amyloid-PET (Nakamura et al., 2017). Posterior regions with Aβ plaques and hypersynchrony were also shown to be the same as those exhibiting network breakdown in SCD or MCI stages (López-Sanz et al., 2017a) and typically exhibit hypometabolism, slow waves, and atrophy. Furthermore, longitudinal studies indicate that MCI patients showing hypersynchronization converted faster to dementia (López et al., 2014). Those networks hypersynchronized at MCI stages later became hyposynchronized at the dementia stage, as explained by the "X model" (Pusil et al., 2019). This model, endorses the hypersynchronization phenomenon as a potential mechanism for accelerating the dementia process as proposed in previous studies (Buldú et al., 2011; de Haan et al., 2012; Styr and Slutsky, 2018). Why are certain brain regions more prone to phenomenon than others? The hubs of the default mode network are brain areas with high metabolic demands and increased neuronal activity. In fact, these regions show higher presence of Aβ plaques (Buckner et al., 2009b). These higher demands of neuronal activity may increase the release of amyloid species into the interstitial fluid (Cirrito et al., 2008), exerting toxicity to inhibitory terminals (Garcia-Marin et al., 2009) and hyperexcitability (Busche and Konnerth, 2016), entering into a vicious-circle ending in network failure and cognitive impairment.

How are cognitive functions affected by the E/I imbalance? Cognitive abilities are supported by large-scale brain systems, reflected in particular functional networks. A tuned, flexible, and balanced synchrony between brain regions is a fundamental mechanism to support rapid and efficient information processing. If cortical hyperexcitability, due to Aβ plaques, dominates neuronal activity, the mechanisms of brain communication became disrupted leading to cognitive impairment. Furthermore, the impairment exerted by the PHFtau on neuronal dendrites, especially in the medial temporal lobe, would reduce neuronal activity altering the normal functioning of neuronal networks. Therefore, typical episodic memory and executive functions impairment in MCI patients, can be seen as a consequence of the toxicity of Aβ plaques and PHFtau in certain hubs of functional networks altering normal dynamics of information processing. Key hubs for episodic memory network are the medial temporal lobe, the prefrontal regions and the precuneus, which are among the areas more severely affected by PHFtau and Aβ plaques. Their already discussed toxic effects, on inhibitory terminals and dendrites, disrupt the local activity of these hub regions, creating a progressive global scale network failure and subsequently cognitive impairment.

6.3. E/I balance-targeting treatment strategies

Since synaptic failure in AD research plays a prominent role, a common strategy in clinical trials has been to 'improve synaptic function'. However, results from neurophysiological studies now point towards a complementary perspective: that recovering network function by improving the E/I balance may have a direct influence on cognitive decline. Treatment strategies aimed at a single pathophysiological phenomenon (e.g. glutamatergic toxicity) may diminish that specific negative effect, but not necessarily improve synaptic or neuronal performance in general. Effective therapy need not necessarily be aimed at the root cause, and this notion may be particularly true for multifactorial disease. Acting on one of the presumed 'causal factors' of synaptic dysfunction may not be sufficient to prevent E/I imbalance and obstruct the deleterious cascade. If we are blind to the functional outcome of synaptic performance, i.e. adequate signal processing, we mislead ourselves. The multitude of mechanistic factors leading to E/I imbalance, and the incompletely understood inter-relationships between these, make it difficult to decide on an effective strategy, and may explain why many recent efforts have yielded no success.

Although E/I imbalance is only a single step in the larger cascade of pathophysiological events in AD, its central position in this cascade makes it a promising therapeutic target; where we may be able to successfully block the effects of pathology on cognition, and possibly also the spread of pathology across the brain. One might contend that neuronal firing (and E/I imbalance) is not an AD-specific feature since other types of brain pathology can cause similar dysfunction. However, there is no *a priori* reason to believe that a singular AD-specific treatment will be most effective. Indeed, this consideration may underpin why fairly general, 'downstream', treatments such as cholinesterase inhibitors have been the most effective symptomatic AD treatment to date. Other highly successful examples of this notion are corticosteroids and antibiotics. However, the general excitatory effect that present cholinesterase inhibitors manifest is a rather blunt way of influencing brain activity, and more subtle activity-targeting treatment regimens (e.g. in terms of location, intensity, timing, personalization) might result in more evident cognitive improvement.

Besides cholinesterase inhibitors, antiepileptic drugs are potent activity modifiers, and could help in re-establishing a healthy E/I balance. In fact, animal models of AD have shown how the diminishing of hyperexcitability by levetiracetam improves their cognitive abilities (Sanchez et al., 2012). Pharmacological compounds are the traditional first choice, and while the non-localized nature of medication may limit its potential, they can be very specific for certain processes, e.g. neurotransmitter or ion channel function.

Alternatively, (non-)invasive techniques such as transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and deep brain stimulation (DBS) have shown promising results in various conditions, including neurodegenerative disease (Kuo et al., 2014; Limousin and Foltynie, 2019). Presumed beneficial effects range from altering neuronal firing to promoting plasticity. In AD, DBS is under investigation (Laxton et al., 2013; Ponce et al., 2016). The theoretical advantage of direct brain stimulation is localized, highly tunable treatment intensity, but positive results in AD have yet to come.

Furthermore, general lifestyle factors could also increase synaptic density and promote a more efficient organization of functional networks. This may engender a better basic environment for defense against

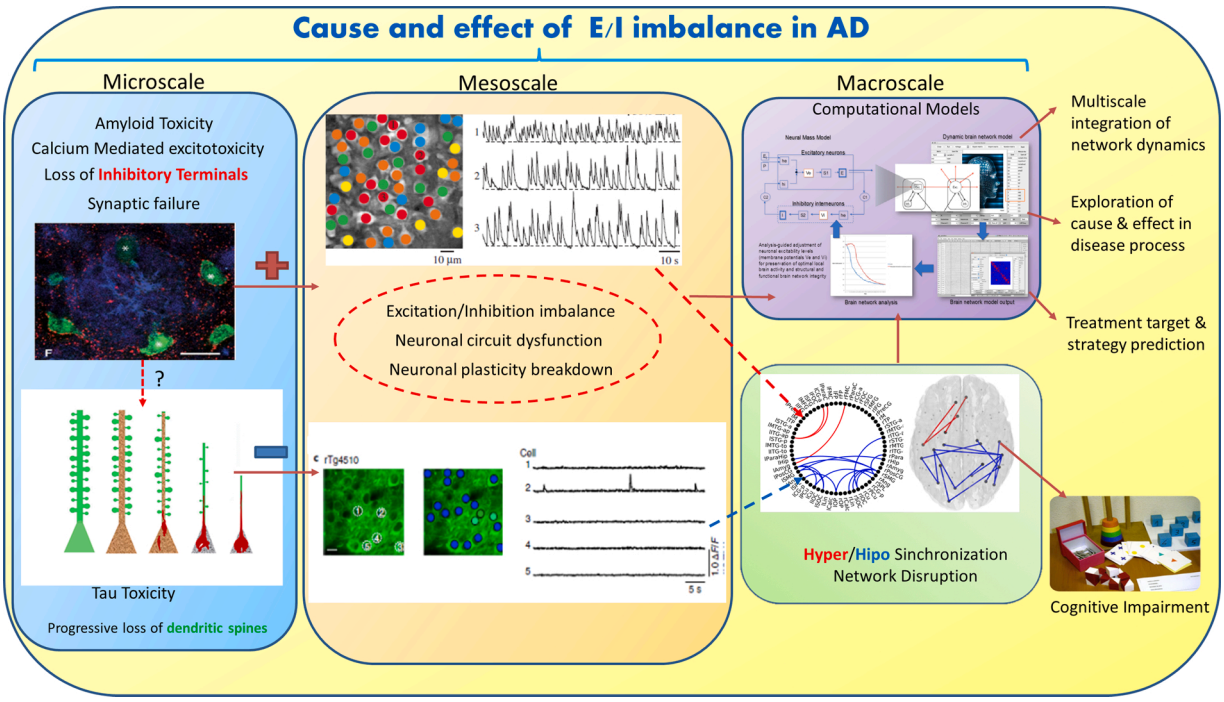

Fig. 6. A proposed model to integrate different phenomena found at different levels of analysis. At the microscale level (upper panel), inhibitory terminals (in red) are diminished in the vicinity of an amyloid plaque (blue) leading to a situation where pyramidal neurons (green) have a reduced inhibition power. Dendrites became progressively atrophic as a consequence of tau phosphorylation among other factors (lower panel). This could also be caused by amyloid plaques (dashed line between upper and lower panels). At the mesoscale level two phenomena are depicted. In the upper panel the electrical activity of a number of hyperactive neurons (electrical trace showed in the right side) close to the amyloid plaque in an animal model of AD. In the lower panel the local electrical fields of an animal model for tau exhibiting silencing of neuronal activity. At the macrolevel, the typical dual connectivity pattern found in MCI patients with posterior hyposynchrony and anterior hypersynchrony leading to the alteration of functional networks and cognitive impairment (lower panel). A pipeline for computational models which could lead to multiscale integration of network dynamics, exploration of cause & effect in disease process as well as treatment strategy is represented in the upper panel. Red arrows represent the upstream consequences of a single phenomenon at one spatial level on those overlying it; e.g. loss of inhibitory terminals at the microscale level could induce neuronal hyperactivity at the mesoscale level and probably hypersynchronization at the macroscale level. Arrows connecting the mesoscale level and that from the lower panel of the macroscale level to the computational models indicate how information from different levels of analysis can feed into these models and generate new tests and strategies. The link between all levels of analysis is the E/I imbalance as indicated with a square bracket at the top of the figure.

disease. Physical activity, cognitive training and diet have been proposed as the main protective factors for delaying AD process (Kivipelto et al., 2018). Animal models (Azambuja et al., 2018) and research on humans revealed reduced brain hypersynchrony by physical activity (de Frutos et al., 2020). Similarly, those individuals with high cognitive reserve showed reduced brain hypersynchrony (López et al., 2014). Therefore, seems that pharmacological and non-pharmacological interventions could reverse this E/I imbalance early in time.

Even gene therapy may play a role: there is a novel and promising aim to influence neuronal hyperexcitability by the regulation of REST, a repressor protein of genes involved in neuronal excitation. REST prevents hyperexcitability and protects neurons over time from oxidative stress (Zullo et al., 2019). Therefore, increased REST activity in populations at risk of developing dementia could reduce the tendency toward hyperexcitability by recovering the E/I imbalance, restoring functional network activity, and preventing cognitive decline.

An adequate test environment to predict treatment effects is needed. True mechanistic understanding, and the prediction of specific treatment strategies, is compromised by the complex interplay between pathological brain dysfunction, added treatments, and the brain's adaptive response (homeostasis, plasticity) to both. With computational brain network modeling, we have a valuable potent tool to address this complexity, and to generate and test falsifiable hypotheses. Recently, intervention studies employing brain network connectivity as an outcome measure in AD have emerged (Briels et al., 2020; De Waal et al., 2014). Needless to say, more intervention modeling work is needed to find reliable, individualized ways to improve neural network organization and cognitive function. Nevertheless, while its application to AD shows great promise, like every technique, it also comes with its own frailties. Near-limitless modeling options introduce new dilemmas regarding which parameters to focus on, and which questions to answer (it is easy to get lost in 'model space'). In this regard, having clinically inspired specific hypotheses and data constrained-model parameters will help to avoid misinterpretation. Further validation of model predictions can be achieved using simulated control conditions, different models for the same analysis, or an integrated modeling-guided experiment setup, such as simultaneous tDCS-MEG (Hanley et al., 2016).

Finally, a natural reversibility of the E/I imbalance should not be ruled out. However, majority of the literature agree on the idea that the aging process implies this tendency, and this process it is just exacerbated in the AD process. Actually, the Aβ deposits increases with age (Jack et al. 2017). Therefore, it is unlikely that this progressive loss of the E/I balance would reverse without intervention.

6.4. *Limitations and challenges*

First, we recognize that our present perspective is neurophysiology-centered, and we acknowledge that it does not tell the whole story and does not currently encompass well-established pathophysiological phenomena in AD, such as role of (epi)genetics, inflammatory processes, or vascular damage. Notwithstanding, much emphasis is habitually placed on the cellular pathology in AD while the *functional performance*, which is the main 'outcome measure' of the brain, often remains neglected or only indirectly evaluated by assessing neuropsychological test performance.

Second, providing direct, multi-level empirical evidence to support

our translational view is technically challenging. Summarizing the lines of evidence from previous sections, we can revisit the schematic neurophysiological mechanism of AD (see Fig. 1). Rich neurophysiological data is present at all scales. However, the integration of different scales is challenged by technical limits and the inherent non-linearity of the brain as a complex system. In particular, the gaps between neuronal circuit function, large-scale network integrity and cognitive function need to be addressed. We have therefore reviewed computational modeling as an upcoming integrative tool to test and explore translational hypotheses based on empirical data in AD. Third, we have tried to link neurophysiological phenomena, from different levels of analysis, in a common space E/I imbalance. While they can be considered as epiphenomena from each level, computational modeling offers a promising and valuable framework to test their direct relationship (de Haan, 2017; de Haan et al., 2017).

7. Conclusion

The essence of our working brain is information processing: a highly dynamical process. To understand cognitive decline in a proteinopathy like AD, neurophysiology has emerged as a prime candidate to tie different scales together by linking protein-induced neuronal hyperactivity to brain network dysfunction. In this review we have highlighted the importance of neurophysiological phenomena, and E/I imbalance in particular, to establish a mechanistic integration of the findings from the micro-meso-macro levels of analysis in AD pathophysiology, in order to understand brain network dysfunction and cognitive impairment (Fig. 6). While Aβ accumulation tends to drive neuronal hyperactivity, emerging evidence suggest that tau dampens activity. Vice versa, neuronal activity influences protein deposition rates, thwarting a simple unidirectional cascade hypothesis of AD. However, regardless of their exact contribution, these phenomena affect normal neuronal homeostasis in an imbalanced manner, and a reduction of this imbalance may benefit cognitive function.

Since E/I imbalance occurs early in preclinical AD and influences the accumulation rate and spread patterns of protein deposition, its correction may have disease-modifying effects. Pursuing diagnostic and therapeutic approaches that focus on the early detection and neutralization of E/I imbalance seems imperative.

Advances in the characterization, modeling and manipulation of multiscale brain dynamics provide an unprecedented opportunity to significantly advance our understanding of AD. Clinical trials have already started to include neurophysiological outcome measures, and neurophysiology-based treatment is receiving more and more attention within the AD research community. Future work, at different levels of analysis, should incorporate the notion of E/I imbalance as one of the essential physiological phenomena of AD, and test how its normalization improves neuronal functioning, network organization and cognitive performance.

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Glossary

Abeta peptides (Beta Amyloid peptides): are the main component of amyloid peptide plaques in the brain of patients with Alzheimer's disease
Neurofibrillary tangles (NFTs): are aggregates of hyperphosphorylated tau protein typically found in Alzheimer's Disease but as well as in other neurodegenerative diseases
Cellular-level imaging: record neural dynamics in behaving mammals, including the means to monitor hundreds of cells targeted by genetic type or connectivity
Homeostatic-excitotoxic cascade: process from E/I balanced to imbalanced activity. It is a cascade of toxic effects due to protein pathology causing cell hyper excitability and calcium toxicity due to neuronal hyperactivity
Functional connectivity: statistical dependency between two time series, typically used for the definition of a brain network
Magnetoencephalography: Non-invasive neurophysiological technique able to record the magnetic fields generated by the electrical activity of neurons
Graph theory: branch of mathematics that has increasingly been applied to brain network data. A functional brain network can be represented as a collection (a graph) of regions ("nodes" or "vertices") and their pairwise interconnections ("edges" or "links")
Computational Neuroscience: employs mathematical models of the brain to understand the principles that govern the development, structure, physiology and cognitive abilities