Chapter 2

Connecting epilepsy and Alzheimer’s Disease: Modeling of normal and pathological rhythmicity and synaptic plasticity related to Amyloid$\beta$ (A$\beta$) effects

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Abstract This paper is motivated by the hidden links between neurodegeneration due to Alzheimer’s disease and temporal lobe epileptic activity. $\beta$-amyloid peptides have multiple effects potentially at molecular, cellular, synaptic, network as well as system levels. To explore these links a computational framework was discussed, and two parts of the framework, i.e pathological rhythm generation and altered bidirectional synaptic plasticity have been constructed and analyzed. By using a skeleton network model of the hippocampal rhythm generation it was demonstrated how A$\beta$ affects the ability of neurons in hippocampal networks to fire in unison at theta frequency resulting in reduced power of the theta rhythm. The dual qualitative effects of elevated A$\beta$ at the synaptic level, i.e LTD facilitation and LTP impairment is studied by a modified calcium control hypothesis. The modification implemented the $\beta$-amyloid effects on the bidirectional synaptic plasticity and explained well the experimental findings of decreased LTP and increased LTD. The analysis of a kinetic model taking into account the phosphorylation and dephosphorylation pathways as-
sociated with potentiation and depression of the AMPA receptor activity supported the biological plausibility of the modification.

2.1 Alzheimer’s Disease and epilepsy: the big picture

2.1.1 General remarks

This paper is motivated by the hidden links between neurodegeneration due to Alzheimer’s disease (AD) and temporal lobe epileptic activity (TLEA).

Alzheimer’s disease is a devastating neurodegenerative disorder likely affecting millions of people. Neurodegeneration in early AD primarily affects the hippocampal formation in the medial temporal lobe, leading to severe memory loss [3]. This region is also the main focus of TLEA. In AD the incidence of convulsive seizures is ten times higher than in age-matched general population [8, 9]. Epilepsy is 87 times more frequent in patients with ‘early onset’ disease and occurs particularly early in familial AD, as an integral part of the pathophysiology [4]. There is accumulating evidence [8, 13, 2] that seizures in the cortico-hippocampal system might contribute to cognitive decline. Cognitive decline starts 5.5 years earlier in AD patients with epilepsy than in those without [10]. In a mouse model of AD, combined video and electroencephalographic (EEG) recordings revealed abundant non-convulsive seizures characterized by cortical and hippocampal spikes and sharp waves [11]. Together these lines of evidence indicate a strong association between the mechanisms of AD and epilepsy, but one that may often be masked by the covert, non-convulsive nature of seizures. Common mechanisms of epilepsy and dementia extend to other neurodegenerative disorders as well. For example, Lewy body dementia (LBD) is the second most frequent cause of dementia in the elderly and often co-exists with both sporadic and familial AD. LBD is characterized by EEG abnormalities, including epileptiform activity, and can sometimes show an overlap of clinical phenotype with epileptic seizures [12]. A better understanding of possible common neural mechanisms underlying AD, LBD and TLEA is crucial for an efficient clinical management of these conditions.

Many facts have been accumulated to support hypotheses that link the elevated level of human amyloid precursor protein (hAPP) related β-amyloid (Aβ) to pre-clinical and clinical observations related to AD [1, 2]. The most significant elements of a working hypothesis assume:

- Aβ alters hippocampal rhythmicity (Sect. 2.1.2.1 and Sect. 2.4.1).
- Aβ alters long term synaptic plasticity by several mechanisms, enhance long-term depression (LTD) and impair long-term potentiation (LTP) (Sect. 2.1.3)
Elevated Aβ implies neuronal dysfunction resulting from an impaired balance between positive and negative feedback loops in modulation of synaptic transmission (Sect. 2.1.3).

Non-convulsive, subclinical partial seizures worsen the memory and behavioral symptoms in AD (Sect. 2.1.4).

Antiepileptic drugs can reduce the deteriorating effects of epileptiform activity in AD (Sect. 2.1.5).

Computational modeling is an appropriate tool to test the hypothesis. Fig. 2.1 summarizes the big picture to explain the multiple and multilevel effects of Aβ: from altered synaptic plasticity via network dysfunction to cognitive deficit. The figure contains three connected columns. The left column is about the relationship between hippocampal structure and normal and pathological rhythms. Based on the classical knowledge going back to Cajal on the morphology and trisynaptic circuit of hippocampal formation a computational model has previously been constructed to simulate the generation of gamma-related theta-frequency resonance and pharmacological control of the septo-hippocampal theta rhythm [19, 20, 21].

Several neuron populations are modeled using individual conductance-based cell models. These biophysically realistic conductance-based single cell models correspond to resistor-capacitor circuits with time and voltage-dependent parallel resistors representing different types of experimentally verified channels in each cell type. A previous study [20] demonstrated a correlation between the effects of experimental and computational manipulations on theta power. With the view that this model is thus validated with respect to physiologically-relevant septo-hippocampal theta rhythm generation, the single compartment models consisting of uniform channel densities for hippocampal basket interneurons, horizontal oriens interneurons, and GABAergic neurons of the medial septum are further used without modification. The multi-compartmental model of a CA1 pyramidal cell, capable of demonstrating the many firing patterns of this neuron, is also used without change unless otherwise specified.

The second column is about altered synaptic plasticity due to the effect of β-amyloid. The starting point of the analysis is the three middle plots, demonstrating the dual qualitative effects of elevated Aβ, i.e LTD facilitation and LTP impairment. The bottom diagram shows a hypothetical relationship between Aβ concentration and synaptic activity, the details will be discussed in Sect. 2.1.3. The top panel shows a computational model of bidirectional plasticity [57]. In this paper we offer an extension of the model to take into account the multiple effects of Aβ to synaptic plasticity.

The third column displays two interconnected sub-processes. Pathologically elevated Aβ and altered synaptic activity implies abnormal synchronized activity exhibiting (maybe subclinical) epileptic seizures. We believe that no computational models have addressed the problem of falsifying/supporting hypotheses on the causal relationship between Aβ-related synaptic depression and aberrant network
activity. There might be a two-way relationship between synaptic activity and network dysfunction. One main hypothesis to be tested assumes that Aβ-induced increases in excitatory network activity lead to synaptic depression by a **homeostatic plasticity** compensatory mechanism. (Homeostatic plasticity is interpreted as “staying the same through change”). Homeostatic plasticity is a neural implementation of a feedback control strategy with the goal of stabilizing the firing rate by changing synaptic parameters such as receptor density and synaptic strength [35, 36]. Homeostatic plasticity is supposed to compensate for the unstable features of Hebbian synapses [?]. Failure of this stabilizing mechanism may imply hyperactivity, hypersynchronization and epileptiform activities. However, we leave this problem for another publication. Altered network activity at least is correlated to cognitive deficit. The main working hypothesis is that seizures amplify the process of AD progression by some positive feedback mechanisms involving Aβ deposition and cell death [8]: both pre- and postsynaptic mechanisms provide the molecular bases for modeling of such kinds of positive feedback mechanisms. The two bottom panels show results of memory tests for mouse and human experiments. In a later phase of this project we will built memory tests of neural networks into the computational platform to model normal and impaired cognitive performance. Behavioral tests used to assess memory functions in AD mouse models are indispensable for characterizing the degree and type of memory deterioration [52]. Memory functions associated with different subregions of the hippocampus, namely dentate gyrus, CA3 and CA1 were tested both experimentally and by computational models. Different subregions may implement different functions, such as spatial and temporal pattern separation, short-term or working memory, pattern association, and temporal pattern completion [53]. These domain-specific memory performance test will be implemented and used.

Our big goal is to provide insight using the tools of computational neuroscience on how cellular and synaptic level effects of Aβ accumulation translate across spatial scales into network level changes in theta and gamma rhythms [32], and aberrant network synchronization leading to cognitive deficits. Our multi-level model considers the brain as a hierarchical dynamical system. To specify a dynamical system, characteristic **state variables** and **evolution equations** governing the change of state must be defined. The dynamic laws at the molecular level can be identified with chemical kinetics, at the channel level with biophysical detailed equations for the membrane potential, and at the synaptic and network levels with learning rules to describe the dynamics of synaptic modifiability, see Tab. 2.1. Overall, our perspective on multi-level hippocampal modeling is summarized here [33].
Table 2.1 The brain as a hierarchical dynamical system. The possible state variables and dynamical equations are shown for different levels in the hierarchy.

<table>
<thead>
<tr>
<th>level</th>
<th>variables</th>
<th>equations</th>
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<tbody>
<tr>
<td>molecule</td>
<td>chemical composition</td>
<td>reaction kinetics</td>
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<tr>
<td>membrane</td>
<td>membrane potential</td>
<td>Hodgkin–Huxley-type equations</td>
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<tr>
<td>cellular</td>
<td>cellular activity</td>
<td>integrate-and-fire neurons</td>
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<tr>
<td>synapse</td>
<td>synaptic efficacy</td>
<td>elementary learning rules (short term and long term plasticity)</td>
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<tr>
<td>network</td>
<td>synaptic weight matrix</td>
<td>Hebbian and homeostatic learning rules</td>
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2.1.2 Modeling Hippocampal Rhythm Generation and Control: Aβ pathology

2.1.2.1 Skeleton network model

The skeleton network model (Fig. 2.2) of the hippocampal CA1 region and the septum introduced in [20] consisted of five cell populations: pyramidal cell, basket cells, two types of horizontal neurons and the septal γ-Aminobutyric acidergic (GABAergic) cells.

Connections within and among cell populations were created by faithfully following the hippocampal structure. The main excitatory input to horizontal neurons is provided by the pyramidal cells via alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) mediated synapses [38]. Synapses of the septally projecting horizontal cells [39] and synapses of the other horizontal cell population, the oriens-lacunosum moleculare (O-LM) cell population innervating distal apical dendrites of pyramidal cells [40] are of the GABA_A type synapses are taken into account. O-LM neurons also innervate parvalbumin containing basket neurons [41]. Basket neurons innervate pyramidal cells at their somatic region and other basket neurons [42] as well. Septal GABAergic cells innervate other septal GABAergic cells and hippocampal interneurons [43, 44] (Fig. 2.2).

The above described model captures several elements of the complex structure of the hippocampal CA1 and can be used to account for very precise interactions within this region. However, when the focus of interest is instead on general phenomena taking place during rhythm generation, modelers might settle for a simpler architecture. In [19] we described gamma related [45] theta oscillation generation in the CA3 region of the hippocampus. The architecture of the model is exceedingly simplified: only an interneuron network is simulated in detail. This simplification, however, allowed the authors to introduce an extrahippocampal input and study its effect on rhythm generation. As a result, the model is able to account for basic phenomena necessary for the generation of gamma related theta oscillation.

We plan to adapt, extend and combine our models of the hippocampal rhythm generation for describing mechanisms not yet studied by computational models.
The extended version will be able to take into account aberrant changes in cellular and synaptic morphology, intrinsic membrane and synaptic parameters to study the causal chains between Aβ induced structural changes and pathological rhythms. Recently, Scott et al [37] observed an age-dependent reduction in the amplitude of a slow oscillation in the extracellular electric potential of the hippocampus of mice overexpressing Aβ, as Fig. 2.3 shows. The goal of our computational model [30] was to demonstrate how Aβ affects the ability of neurons in hippocampal networks to fire in unison at theta frequencies to reduce the amplitude of theta rhythm. For the results see Sect. 2.4.1, also in [46].

2.1.3 Two-way relationship between altered synaptic activity and neuronal dysfunction

In a seminal paper entitled Synaptic Depression and Aberrant Excitatory Network Activity in Alzheimer’s Disease: Two Faces of the Same Coin? Palop and Mucke [47] discusses the intricate (presumably two-way) relationship between altered synaptic activity and network dysfunction. Elevated Aβ implies neuronal dysfunction due to the consequence of the impaired balance between positive and negative feedback loops in modulation of synaptic transmission. Two main possibilities have been suggested: (i) “...depression of excitatory synaptic activity could lead to network disinhibition, if it affected inhibitory interneurons more than principal excitatory cells.”; (ii) “...Aβ–induced increases in excitatory network activity lead to synaptic depression through homeostatic or compensatory mechanisms.”

As suggested by Palop and Mucke [2], Aβ might have a concentration-dependent dual control effect on excitatory synapses: reduced presynaptic efficacy, presynaptic facilitation and postsynaptic depression appear for low, intermediate and high Aβ concentrations, respectively. Since pathologically elevated Aβ impair LTP and enhances LTD related to the partial block of N-Methyl-D-aspartate (NMDA) receptors. It is assumed that slow increases in postsynaptic calcium trigger LTD, whereas large increases induce LTP [56, 57].

2.1.4 Non-convulsive, subclinical partial seizures worsen the memory and behavioral symptoms in AD

There is accumulating evidence [8, 13, 2, 17] that seizures in the cortico-hippocampal systems might contribute to cognitive decline. Seizures in individuals with AD have been described previously and by today there is a robust data-based foundation to support clinical comorbidity. The question now is as it was formulated by Noebels
“Two Disorders or One?” Both mouse models and human data support the structural connection between the two disorders. Impairment of inhibitory mechanisms (the phenomenon called disinhibition) may destabilize network oscillatory activity at early stages of the disease. Hyperexcitability and hypersynchrony in cellular and circuit activities may imply subclinical seizures in the temporal lobe and aggravate memory loss, as it was identified in mouse models of AD. There is a remarkable regional overlap in human AD and TLEA, and it looks to be a testable working hypothesis that subconvulsive seizures due to plasticity within hippocampal circuitry contribute to the memory impairment of AD. Therefore, one might cautiously assume that these animal models of AD may have temporal lobe epilepsy-like syndromes. Similarities and differences between epilepsy and AD from studying mechanisms of hyperexcitability and seizures have been analyzed by Chin and Scharfman [13]. Seizures facilitate production of Aβ and can cause impairments in cognition and behavior in both animals and humans. There seems to be a correlative relationship between duration of epilepsy and degree of impairments in episodic memory.

A recent review [14] on co-morbidity of AD and seizures hypothesizing common pathological mechanism highlights that (i) clinical data from familial and sporadic AD patients reveal increased seizure risk; (ii) many APP-linked AD mouse models develop seizures and other EEG abnormalities; (iii) APP and/or APP-derived peptides may link AD pathology to epileptiform activity; and (iv) epileptiform activity in AD mouse models can be rescued independent of Aβ reduction.

Our longer term plan is to use a computational model to test possible mechanisms, which suggest that high levels of Aβ imply aberrant (epileptiform) activity and the failure of compensatory inhibitory responses contributes to the emergence of cognitive deficits associated with AD.

2.1.5 Antiepileptic drugs can reduce the deteriorating effects of epileptiform activity in AD

There is also growing evidence suggesting that some antiepileptic drugs (such as levetiracetam (LEV)) can reduce abnormally enhanced electrical activity, and slow down or even reverse hippocampal synaptic dysfunction, and cognitive deficits in hAPP mice, or even in human patients [15, 16, 18].

It seems to be convincing that perturbations of brain network activity are observed in AD patients and aberrant network activity might contribute to AD-related cognitive decline. Human APP transgenic mice simulate key aspects of AD, including pathologically elevated levels of Aβ peptides in brain, aberrant neural network activity, remodeling of hippocampal circuits, synaptic deficits, and behavioral abnormalities. Computational modeling seems to be an indispensable tool to study whether there is any causal mechanism to connect these elements.
To explore whether Abeta-induced aberrant network activity contributes to synaptic and cognitive deficits, [18] treated patients with amnestic mild cognitive impairment (aMCI; a condition in which memory impairment is greater than expected for a person’s age and which greatly increases risk for Alzheimer’s dementia) with different antiepileptic drugs. It was shown that very low doses of the drugs calm hyperactivity in patients’ brain. Among the drugs tested, LEV effectively reduced abnormal spike activity detected by electroencephalography. Chronic treatment with LEV also reversed hippocampal remodeling, behavioral abnormalities, synaptic dysfunction, and deficits in learning and memory in hAPP mice. These findings support the hypothesis that aberrant network activity contributes causally to synaptic and cognitive deficits in hAPP mice. Consequently, LEV might also help ameliorate related abnormalities in people who have or are at risk for AD.

There are more and more recent studies [17, 14], which support the view the some antiepileptic drugs also reverse memory deficits at least in aMCI patients, adding further support to the hypothesis that neuronal network hyperactivity may causally contribute to cognitive impairment in both aMCI and AD mouse models. Dynamical system theory helps us to understand the neural mechanisms of temporal and spatio-temporal neural activities. The discipline of computational neuropharmacology [24] emerges as a new tool of drug discovery by constructing biophysically realistic mathematical models of neurological and psychiatric disorders. Nowadays the term “Quantitative Systems Pharmacology” is used and defined as an approach to translational medicine that combines experimental and computational methods to apply new pharmacological concepts to the development of new drugs.

We have adapted methods of computational neuroscience to the emerging field of computational neuropharmacology [20, 22, 23, 24, 25, 26, 27, 28, 29, 30]. The computational framework was developed for testing hypotheses related to pharmacotherapy of anxiety and schizophrenia. Subsequently, based on a similar but extended model of septo-hippocampal theta rhythm generation and control further preliminary results were obtained related to AD [31].

### 2.2 Abeta effects on Synaptic Plasticity: Brief Summary of the Experimental Background

It is well known that glutamtergic synaptic transmission is controlled by the number of active NMDA receptors (NMDARs) and AMPA receptors (AMPARs) at the synapse. NMDAR activation has a central role, as it can induce either LTP or LTD, depending on the intracellular calcium rise in dendritic spines. Activation of synaptic NMDARs and large increases in calcium concentration are required for LTP, whereas internalization of synaptic NMDARs, activation of perisynaptic NMDARs...
and lower increases in intracellular calcium concentration are necessary for LTD. LTP induction implies recruitment of AMPARs and growth of dendritic spines, while LTD induces spine shrinkage and synaptic loss.

The multiple effects of pathologically elevated Aβ on synaptic plasticity are being studied [2, 49]. Generally speaking, it now seems to be accepted that Aβ impairs LTP and enhances LTD. Most likely soluble oligomers rather than plaques are the major cause of synaptic dysfunction and ultimately neurodegeneration [50], for a review see [51].

The detailed mechanism underlying Aβ-induced LTP and LTD are not fully understand. Computational models of normal bidirectional synaptic plasticity could be supplemented with Aβ-induced effects to elaborate on this question. Both phenomenological and more detailed receptor-kinetic models (taking into account receptor internalization, desensitization, etc.) should be studied. This paper makes a step into this direction.

Fig. 2.4 is the reproduction of Figure 2 of [2] (NEEDS permission!)

Below is the list of stylized facts based on [2] to be explained by model studies in a consistent way:

- Aβ suppresses basal excitatory synaptic transmission
- Aβ facilitates LTD after subthreshold LTD inductions
- Aβ occludes LTD
- Aβ facilitates LTD by inducing activation of metabotropic glutamate receptors (mGluRs) and NMDARs
- Aβ-induced facilitation of mGluR-dependent LTD is suppressed by mGluR antagonists
- Aβ-induced facilitation of NMDAR-dependent LTD is suppressed by NMDAR antagonists
- Aβ-induced LTP deficits depend on activation of LTD pathways. Aβ potently inhibits LTP
- Blocking LTD-related signaling cascades with mGluR5 antagonists or an inhibitor of p38 MAP prevents Aβ-induced LTP impairment

2.3 Model construction

We suggest here that the findings and hypotheses should be explained within the framework of calcium dependent models of bidirectional synaptic plasticity [57].
2.3.1 Modeling modulation of synaptic transmission by Aβ

As Shankar and Walls [34] wrote: “How Aβ mediates its effects on synaptic plasticity may take many years to fully understand...”. It seems likely that Aβ influences the feedback loop that controls neuronal excitability. (author?) [2], suggests that reduced presynaptic efficacy, presynaptic facilitation and postsynaptic depression may occur at small, intermediate, and large Aβ concentrations. An often used simple implementation of the calcium control hypothesis [59, 57] is given by Eqn. 2.1:

\[
\frac{dW_i(t)}{dt} = \eta([Ca^{2+}(t)]) \left( \Omega([Ca^{2+}(t)]) - \lambda W_i(t) \right). \tag{2.1}
\]

Here \( W_i \) is the synaptic weight of synapse \( i \), the value of the function \( \Omega \) depends on calcium concentration, and determines both the sign and the magnitude of the change of the synaptic strength. \( \eta \) is the learning rate, and also depends (typically monotonously increasingy) on calcium concentration, \( \lambda \) is a decay constant. To complete the model we need an equation which prescribes calcium dynamics. A simple assumption is that the source of calcium depends on the NMDA current, as Eqn. 2.2 defines:

\[
\frac{d[Ca^{2+}(t)]}{dt} = I_{\text{NMDA}}(t) - \frac{1}{\tau_{\text{Ca}}} [Ca^{2+}(t)], \tag{2.2}
\]

where \([Ca^{2+}(t)]\) is the calcium concentration at the spine, \( I_{\text{NMDA}}(t) \) is the NMDA current, and \( \tau_{\text{Ca}} \) is the decay time constant of calcium in the spine. The details of the calculation of the NMDA currents are given in [59] based on the assumption that NMDA receptors are the primary sources of calcium.

\[
I_{\text{NMDA}} = P_0 G_{\text{NMDA}} \left[ I_f(t) e^{\frac{\theta V}{\tau_f}} + I_s(t) e^{\frac{\theta V}{\tau_s}} \right] H(V) \tag{2.3}
\]

where \( I_f \) and \( I_s \) are the relative magnitude of the slow and fast component of the NMDA receptor current. \( I_f + I_s = 1 \) is assumed. \( H(V) \) is the general form of the voltage dependence. \( \theta = 0 \) if \( t < 0 \) and \( \theta = 1 \) if \( t \geq 0 \). \( P_0 \) is the fraction of NMDARs in the closed state, and set to be 0.5.

The functional form selected for \( \Omega \) function is based on experimental data of [60] (for the underlying mathematical details see also Supporting Information of [57]) and given as

\[
\Omega \left([Ca^{2+}(t)]\right) = \frac{e^{\beta_2([Ca^{2+}(t)]-\alpha_2)}}{1 + e^{\beta_2([Ca^{2+}(t)]-\alpha_2)}} - \frac{\gamma e^{\beta_1([Ca^{2+}(t)]-\alpha_1)}}{1 + e^{\beta_1([Ca^{2+}(t)]-\alpha_1)}} + \gamma \tag{2.4}
\]

The function is visualized with the blue line of Fig. 2.8.
2.3.2 Construction of $\Omega$ Function to Implement $A\beta$ Effects

The $\Omega$ function (Fig. 2.8) plays a crucial role in the calcium control hypothesis, and determines the behavior of the synaptic weight at different calcium concentration. Essentially, the shape of the $\Omega$ function determines when LTP or LTD occurs. This implies that abnormal synaptic plasticity can be modeled by modifying the $\Omega$ function in Eqn. 2.1.

A new $\Omega$ function was constructed to incorporate the effect of $A\beta$. The idea behind the construction of this function was a combination of $\Omega_{\text{LTP}}$ and $\Omega_{\text{LTD}}$. The necessity to separate the $\Omega$ function into these two terms comes from a fact that $A\beta$ affects only the LTD-related pathways and yet impairs the LTP. The new $\Omega$ function assumes competition of LTP and LTD.

$$\Omega_{\text{new}}([Ca^{2+}(t)], A\beta) = \frac{e^{\beta(k_1 LTP - k_2 LTD) - \varepsilon}}{1 + e^{\beta(k_1 LTP - k_2 LTD) - \varepsilon}}$$

$$LTP([Ca^{2+}(t)]) = \frac{e^{\beta_1([Ca^{2+}(t)] - \alpha_1)}}{1 + e^{\beta_1([Ca^{2+}(t)] - \alpha_1)}}$$

$$LTD([Ca^{2+}(t)], A\beta) = \frac{e^{\beta_3([Ca^{2+}(t)] - \alpha_3(A\beta))}}{1 + e^{\beta_3([Ca^{2+}(t)] - \alpha_3(A\beta))}}$$

In Sect. 2.4.2 it will be shown that by using the constructed function the simulations results are in accordance with the experimental data on altered synaptic plasticity. In Sect. 2.5 some explanation is give for the kinetic basis of altered synaptic plasticity.

2.4 Simulation Results

2.4.1 $A\beta$ Overproduction and Hippocampal Network Dysfunction: Modeling the age-dependent effects

The simulations described here have been motivated by Fig. 2.3.
Aβ pathology initially decreases hippocampal theta power with subsequent frequency reduction and power normalization

Age-dependent neurophysiological effects on both cellular and network levels observed in mice models of amyloid pathology approximately between the ages of 2 and 8 months were incorporated to describe what may determine age-dependent reduction of elicited theta power. These age-dependent changes appear in sodium conductance, and in the number and connectivity of O-LM cells. Reduction in theta power and eventual reduction in theta frequency (each determined from a power spectrum) were observed when these progressive effects were applied to the computational model (Fig. 2.5).

Pyramidal Cells Exhibit Reduced Population Synchrony Dependent on Cellular Events

The initially declining LFP theta power suggests further investigation of whether reduced temporal coordination amongst the cells or fewer active cells participating in the rhythm occurs. Since the source of LFP patterns is thought to be synaptic activity acting along pyramidal cells, the population-level spike timing of pyramidal cells can provide clues as to the source of theta rhythm attenuation observed in Fig. 2.5, and can be observed in this computational model. The correlation amongst spike times in pyramidal cells was reduced by the incorporated cellular effects of Aβ accumulation in addition to theta power changes in the local field potential, pointing toward alterations in mutual spike timing regulation mechanisms in the network model.

Average zero time-lag cross-correlations using a synchrony time window of 10 ms for each pair of spike trains in pyramidal cells revealed a significant reduction in this measure of coherence across the simulated mice groups (Fig. 2.6).

Pyramidal Cells Exhibit Increased Spiking Period Variability

To investigate the loss of correlation amongst action potential timings at theta frequency caused by amyloid pathology effects, the time intervals between spikes of individual neurons were analyzed for variability using a Poincaré plot. This plot relates each spike period to its preceding period for all pyramidal cells in representative network instantiations, revealing greater variation around the line-of-identity when amyloid pathology induced effects were implemented (Fig. 2.7).
2 Modeling of normal and pathological rhythmicity and synaptic plasticity

2.4.2 Altered synaptic plasticity

THIS SHOULD BE WRITTEn by my DEAR CO-AUTHORS !!!

Fig. 2.10
$A\beta$ suppresses basal excitatory synaptic transmission and facilitates LTD after subthreshold LTD inductions

Fig. 2.11
$A\beta$ induced occlusion of LTD

Fig. 2.12
The only difference is in the clamp voltage (?? so what ??)

$A\beta$-dependence on NMDAR-induced LTD was also simulated

Fig. 2.13
$A\beta$-induced LTP impairment

2.5 Biophysical backgrounds of the effects of $A\beta$ on $\Omega$ Function

2.5.1 Kinetic models: some remarks

Many kinetic models have been constructed to explain the molecular mechanisms behind bidirectional synaptic plasticity. Since there are many (the order of magnitude is about hundred) molecules involved in the biochemical pathways of synaptic plasticity, a huge number of mathematical models have been suggested (for reviews, see [62, 63, 64]). A subset of these models explain bidirectionality.

In [58] both a phenomenological kinetic model and a biophysical (but simplified) model of the phosphorylation cycle were given to derive the functional form of the $\Omega$ function. The phenomenological model is based on the insertion/removal of postsynaptic AMPARs. Both models paved the road towards the understanding of the molecular basis of the calcium control hypothesis, but did not give a full description.

In our own studies specifically we chose to use three kinetic models with increasing complexity studied by [61]. These models have been constructed to grasp the requirements of calcium-induced bidirectional synaptic plasticity. The models use a signal molecule $S^\ast$ (the Ca$^{2+}$/calmodulin complex), which activates two different pathways to control the production of either the active conformation $R^\ast$ or
the inactive conformation $R$ of a response molecule, respectively. The two pathways can be identified as the phosphorylation and dephosphorylation pathways associated with potentiation and depression of the AMPAR activity, respectively. We chose the most detailed model to incorporate the $A\beta$ effects to explain the molecular basis of the pathological form of the $\Omega$ function and we feel that is a working skeleton model containing some good sausage.

2.5.2 Kinetic modeling of normal and pathological $\Omega$ function

Fig. 2.14 shows the three kinetic models with increasing complexity (from [61]. Takumi’s results...

!! A paragraph explaining a combination of the enhancement of the inhibitory processes and the decrease of $r3/r4$ would achieve both impairment of LTP and the subthreshold LTD induction.

Fig. 2.15

Fig. 2.16 and Fig. 2.17 would demonstrate enhancing inhibitory processes (characterized by $p2/p1$ and $n2/n1$) cause the subthreshold LTD induction. A combination of (increased $r3/r4$ and $p1/p2$) or increased $r3/r4$ and decreased $n1/n2$) would achieve both impairment of LTP and the subthreshold LTD induction.

2.6 Further plans

This paper is a first step to implement the proposal sketched in Sect. 2.1.1. We have a plan to build a two-stage model.

First, the model should connect synaptic events to altered network dynamics. Computational simulations will support the existence of a causal relationship between two $A\beta$ induced phenomena, namely (1) reduced excitatory transmission and plasticity at the synaptic level; (2) epileptiform activity at the network level. According to our best knowledge, no computational models have addressed the problem of falsify/support hypotheses on the causal relationship between synaptic depression and aberrant network activity. One main hypothesis to be tested assumes that $A\beta$-induced increases in excitatory network activity lead to synaptic depression by a homeostatic plasticity compensatory mechanism. (Homeostatic plasticity is interpreted as “staying the same through change”). Homeostatic plasticity is a neural implementation of a feedback control strategy with the goal of stabilizing the firing rate by changing such synaptic parameters as receptor density and synaptic
strength [35, 36]. Homeostatic plasticity is supposed to compensate for the unstable features of Hebbian synapses. Failure of this stabilizing mechanism may imply hyperactivity, hypersynchronization and epileptiform activities.

Second, the model should be extended to explain the transition from altered network activity to cognitive deficit. The main working hypothesis of this second stage is that seizures amplify the process of AD progression by some positive feedback mechanisms involving $A\beta$ deposition and cell death [8]: both pre- and postsynaptic mechanisms provide the molecular bases for modeling of such kinds of positive feedback mechanisms.

### 2.7 Messages for Neurologists and Computer Scientists

A significant amount of data and hypotheses about the neural mechanisms of the interaction of these diseases have been accumulated. Computational models have proved to be efficient tools to test working hypotheses about normal and pathological neural mechanisms. Such kinds of models offer an integrative perspective to organize scattered data obtained by methods of anatomy, electrophysiology, brian imaging, neurochemistry, behavioral studies, etc. into a coherent picture.

Our specific message for neurologists is that computational platform under development is an appropriate tool to test the hypotheses for the potential mechanisms of the **multiple effects** of the level of **elevated human amyloid precursor protein related $\beta$-amyloid** ($A\beta$) [1, 2].

The main specific message for computer (better saying computational) scientists is that there is ample room to combine different neural models, such as compartmental technique, phenomenological and biophysically detailed description of synaptic plasticity including biochemical kinetic models, network models of synchronized activity, memory models to help uncovering the hidden links between epilepsy and Alzheimer’s Disease.

### 2.8 Acknowledgments

PE thanks to the Henry Luce Foundation to let him to serve as a Henry R Luce Professor.
Concentration-dependent plasticity

Fig. 2.1 Hypothetical causal chain to explain the multiple and multilevel effects of Aβ: from altered synaptic plasticity via network dysfunction to cognitive deficit. A skeleton network of the hippocampal system generates gamma and theta rhythms. Aβ concentration-dependent altered synaptic plasticity implies network dysfunction including epileptiform activity. This activity contribute to cognitive deficit by positive feedback cellular mechanisms. The sources of figures: +++ to be added ++

References


Fig. 2.2 Structure of septo-hippocampal network model. Red symbols and black circles indicate inhibitory populations and synapses, respectively; yellow symbols and open triangles indicate excitatory populations and synapses. Representative connectivity specified quantitatively with divergence numbers (blue) defining the number of cells in the target population that each cell in the presynaptic population innervates. Each target cell was chosen from a uniform distribution over the target population cells for each network instantiation. Similarly, convergence numbers (red) define the number of presynaptic neurons innervating each cell in target population. Total simulated cell numbers in each population are given in parentheses.

Fig. 2.3 Age-dependent reduction in the amplitude of nPO-stimulation elicited theta rhythm for transgenic mice (APP/PS1) exhibiting increasing Aβ plaque loads from 2 months to 8 months. No theta power reduction was observed in wildtype (WT) mice, which do not exhibit Aβ plaques. Data from [37].


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Figure 7. Synthetic LFP power spectra timcourse due to integrated age-dependent neurophysiological effects. Progressive reduction in power of theta rhythm at about 4 Hz for 2- and 4-month old simulated transgenic mice networks is followed by reduction in peak frequency to below 4 Hz accompanied by a subsequent increase in power for 6- and 8-month old mice simulated transgenic networks. Error bars denote standard error of the mean.


Fig. 2.6 Left panel represents firing raster plots of the pyramidal cell population in wildtype simulations, and right panel shows firing for 8 month effects exhibiting reduced synchrony. Time windows in which two spikes are considered synchronous was 10 ms. Significantly lower coherence was observed across all simulated transgenic mice group in comparison to wildtype simulations (not showed here)


Fig. 2.7 Greater variation perpendicular to the line of identity representing greater consecutive period variation was observed in addition longer interspike intervals when effects of A\textsubscript{β} at the 8 month stage are implemented (lower) than in the baseline network (upper). Axes of ellipses represent standard deviation in each direction. Points represent spike intervals of eight pyramidal cells in individual representative random network trials.

Fig. 2.8


Fig. 2.12


Fig. 2.14 Permission!


Fig. 2.15


Fig. 2.16 Decreasing $r_3/r_4$ widens the region of LTD, and impairs LTP strength. (This does not explain the subthreshold LTD induction). Increasing $p_1/p_2$ achieves the subthreshold LTD induction.


Fig. 2.17 Decreasing $r3/r4$ widens the region of LTD, and impairs LTP strength. (This does not explain the subthreshold LTD induction). Decreasing $n2/n1$ achieves the subthreshold LTD induction.


