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Review

# Cortical Activity and Rhythmic Patterns in Mouse Models of Aging and Alzheimer's Disease

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**Abstract**

Aging and Alzheimer's disease (AD) have been reported to induce changes in the cerebral cortex circuits. The present review aims to study these alterations by reviewing emergent cortical activity with a focus on the rhythmic patterns. The rationale for this approach was two-fold: (i) emergent rhythmic activity integrates cellular and network properties of these underlying circuits; and (ii) alterations in rhythmic patterns reflect the functional impact of changes on the network induced by the pathophysiology of the disease. We first review the changes in cortical circuits that occur with aging and AD in both humans and animal models of early aging (SAMP8) and AD. We provide experimental evidence in support of earlier studies for understanding the cortical synchrony in these neurodegenerative processes, compatible with previous observations in patients with AD. A comparison of experimental findings in the literature opens up a debate in an attempt to understand paradoxical findings

in different models when analyzing cortical excitability in AD. Finally, we assess the value of sleep and oscillatory activity in understanding circuit impairments and their roles as biomarkers for AD and neurodegeneration for early intervention.

**Keywords**
Alzheimer disease; aging; neurodegeneration; slow oscillation; synchrony; excitability; gamma rhythm; mouse model; cortex

## 1. Introduction

Alzheimer's disease (AD) and other aging-associated pathophysiologies result in changes in cortical circuits, which can be observed in the emergent activity of the cortex. On one hand, brain rhythms serve as links between cellular and network properties, on the other hand, these constitute the cognitive function. This property makes them particularly suitable for studying the cellular and network basis of pathological processes [1-3]. The so-called slow oscillation (<1 Hz), present on the slow side of this rhythmical spectrum, occurs during slow wave sleep and deep anesthesia (Figure 1). This rhythmic pattern could be considered the default activity pattern of the cortical network [4, 5] as it is spontaneously generated during conditions in which the brain is "disconnected" from external stimuli. This could be a functional disconnection such as in the case of slow-wave sleep and under certain kinds of anesthesia, or physical such as in the case of isolated cortical portions of the surrounding tissue, and clinical conditions including stroke or more generally cardiovascular or traumatic lesions that generate "cortical islands." Evidence in support of the theory that slow oscillations can be generated by isolated cortex comes from the finding that they emerge from cortical slabs [6] and cortical slices [7] (Figure 1D). The slow oscillation is a rhythm generated and maintained by the cortex [6, 8, 9] through the interaction between the synaptic reverberation of the network and activity-dependent adaptation mechanisms [7, 10] and/or slow inhibition [11-13]. Furthermore, it is a rhythm of local origin, in which the long-range connectivity that characterizes the wakeful state of the brain is significantly reduced [14-16], slow oscillations being rather similar across different cortical areas [17]. The ability of relatively small circuits to exhibit slow oscillations is a generalized feature of the cerebral cortex, as this rhythm is found in all cortical areas of numerous animal species including humans [18-20]. Therefore, it acts as an appropriate paradigm with which to compare the findings obtained in animal models of diseases with those obtained in patients. Although slow oscillations are not present during vigilance (however, see [21]), persistent activity that occurs during Up states has been considered a model of brain processing during this state [22-24], as in both cases the firing and dynamics of the membrane potential of neurons are considerably similar, although their input resistance is lower during the Up state [25, 26] (for a review see [10]). Another similarity between the two states is the synchronization of activity in the beta-gamma frequency bands (15–100 Hz, also known as fast oscillations), rhythms that constitute the dominant pattern during the active vigil brain state [27-30] (Figure 1C), suggesting that Up states induce network operations that are significantly similar to those present during the awake state [10]. Numerous studies have shown that beta and gamma rhythms are related to higher cognitive processes [31, 32], as well as to

attention [33], language processing [34, 35], learning [36], working memory [37], and both short- and long-term memories [38, 39].

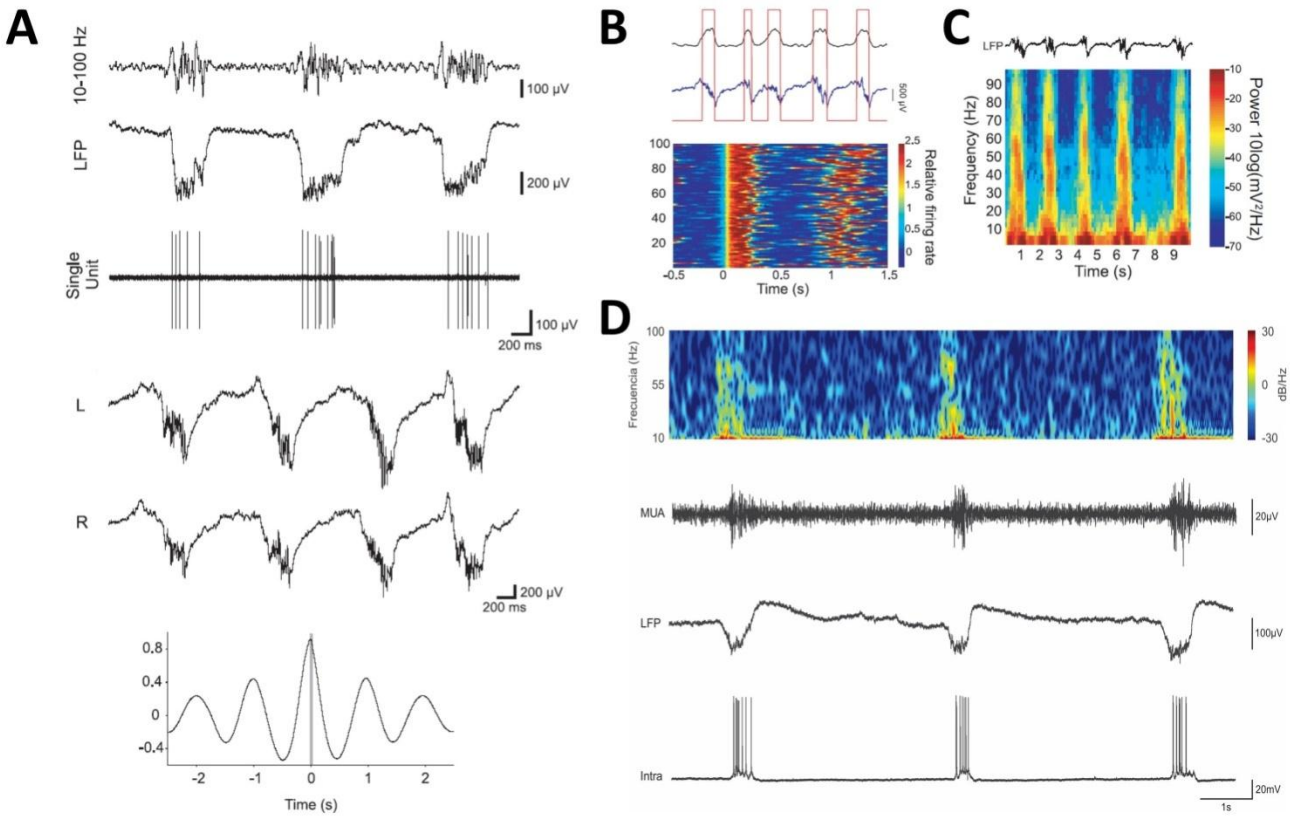


**Figure 1** Slow oscillations in the mouse neocortex *in vivo* and *in vitro*. (A) Oscillatory activity in the mouse cerebral cortex during ketamine anesthesia. (*Top*) filtered signal of the recording (band pass 10–100 Hz) illustrating the occurrence of high frequencies in the up state. (*2nd trace*): local field potential (LFP) in the motor cortex. (*3rd trace*): single-unit recording of a neuron firing in the up states. (*4th trace*): simultaneous bilateral extracellular recording in the prefrontal cortex. L, left hemisphere; R, right hemisphere. (*Bottom*): waveform cross-correlation of the two signals in *L* and *R*. (B) (*Top*) multiunit activity. (*2nd trace*) LFP. (*3rd trace*) raster plots of 100 aligned up states. (C) Spectrogram showing the occurrence of fast rhythms during the up states in the prefrontal cortex. (D) Slow oscillations in cortical slices. (*1st trace*) spectrogram. (*2nd trace*) MUA. (3rd trace) LFP. (4th trace) intracellular recording. A, B, C, taken from Ruiz-Mejias, M., Ciria-Suarez, L., Mattia, M., & Sanchez-Vives, M. V. (2011). Slow and fast rhythms generated in the cerebral cortex of the anesthetized mouse. *Journal of neurophysiology*, *106* (6), 2910–2921. Used with permission.

The observation of slow oscillations is a scenario in which the balance between excitation and inhibition, whose alteration has been linked to several pathological conditions [40-43], can be studied (Figure 2). The intense synaptic activity that occurs during Up states is triggered by the firing of excitatory and inhibitory neurons [7, 25, 44, 45], which are well balanced [10, 11, 13, 46, 47], molding the properties of slow oscillations and determining information processing [26]. Similarly, the gradual blockage of the rapid inhibition mediated by $GABA_A$ receptors results in an

increase in the local network trigger which, before causing epileptic discharge, is offset by the upward regulation of activity-dependent adaptation mechanisms, thereby shortening the duration of Up states and elongating that of Down states, and reducing the frequency of slow oscillations [48]. Therefore, the excitability of the network and susceptibility to activity-dependent adaptation mechanisms are two key factors that could modulate the properties of slow oscillations, thereby creating a large repertoire of dynamic regimes [4, 49-51].

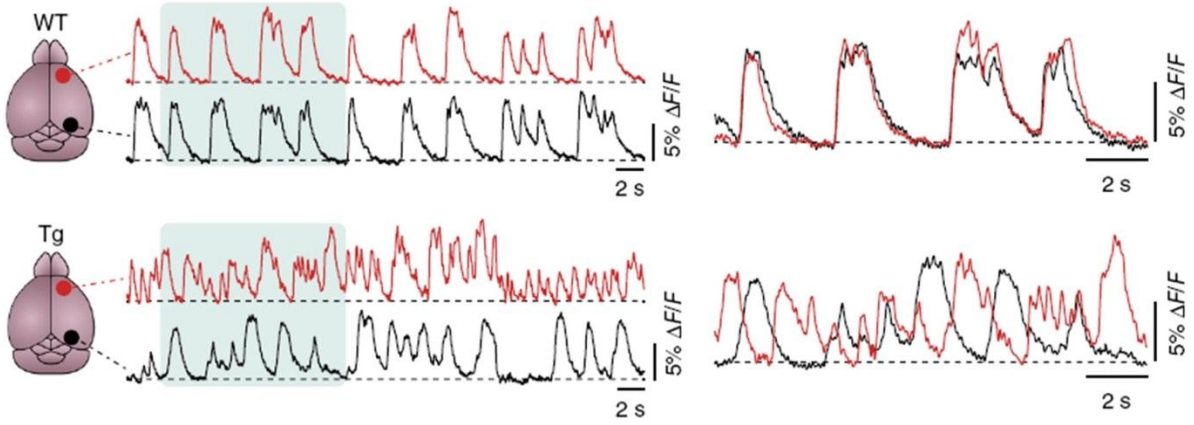


**Figure 2** Impaired cortical slow-wave oscillations in AD transgenic mice. Representative traces of slow oscillations from the frontal (red) and occipital (black) cortex in wild-type (WT) and APP23 x PS45 transgenic (Tg) mouse, respectively. Taken from Busche, M. A., Kekuš, M., Adelsberger, H., Noda, T., Förstl, H., Nelken, I., & Konnerth, A. (2015). Rescue of long-range circuit dysfunction in Alzheimer's disease models. *Nature Neuroscience*, *18* (11), 1623. Used with permission.

The synchronization of neuronal activity is a key element that controls the function of circuits and neural networks. Spectral disturbances in the EEG or MEG that have been consistently described in human AD indicate a gradual slowdown in the spontaneous activity that originates in posterior cortical areas and travels toward anterior areas. This is reflected in the increased power in low-frequency bands (delta 1–4 Hz, theta 4–8 Hz) and decreased power, or a displaced synchronization peak, in high-frequency bands (alpha 9–15 Hz, beta 15–30 Hz, and gamma 30–100 Hz) [52-57]. Moreover, these perturbations have been associated with regional alterations in the blood flow or metabolism and the deterioration of global cognitive function [58-60]. Furthermore, vigil rhythms, such as theta and alpha oscillations, have been reported to propagate across the neocortex as traveling waves [61, 62]. Another alteration characteristic of AD is the lower complexity of the EEG signal, which could reflect a reduction in the transmission of information between cortical areas [59, 63], as well as decreased fast rhythms, which suggests alterations in cortical connectivity [64-69]. This observation has led to the conceptualization of AD as a "disconnection syndrome" [70-73]. In addition, AD has been linked to seizures in 10–22% of patients [74]. Numerous observations have described the presence of epileptogenic activity in patients with AD (reviewed in [75]). Seizures increase with the progression of the disease [76] and are more frequent in cases with early onset [77]. Among the proposed mechanisms underlying the cortical phenotype in AD that could sustain these observations, neuronal hyperexcitability has

been postulated [78-80]. This is in contrast to a previous hypothesis in which AD neocortical activity was described as a synaptic failure as a result of neurodegeneration and connectivity loss [81]. As a human correlate of this hypothesis, AD pathology-related cortical hyperexcitability has been reported in patients with AD following magnetic stimulation of the motor cortex [82].

As previously mentioned, a valuable tool for assessing network properties is the study of slow oscillations in sleep and under anesthesia in AD models, considering the changes observed in slow oscillations in anesthetized disease models correlate with those in awake conditions [83, 84]. Animal models that attempt to reproduce the symptoms, lesions, or causes of neurodegenerative diseases have been extremely useful in understanding the etiology and pathophysiology of AD although, to date, there has been no model that presents all characteristics of the disease. For example, cognitive deficits and Aβ plates are present in almost all models; however, neurofibrillary tangles (NFTs) are only observed when animals express the human Tau protein. Moreover, very few models show a neuronal loss. In this regard, it is better to consider such models as a tool for understanding the effect of genes and proteins associated with AD on brain function [85].

Interestingly, there exists a relationship between sleep, slow wave sleep, and AD [86]. Here, we review studies on models of AD and premature aging that we have been conducting in our laboratory. We provide evidence in support of earlier work in understanding the cortical synchrony in these neurodegenerative processes and, to stimulate debate, consider findings in other models when analyzing cortical excitability. Finally, we highlight the value of sleep and oscillatory activity in mouse models in understanding circuit impairments as well as serving as a biomarker for AD and neurodegeneration.

## 2. Cortical Synchrony in the Gamma Band of AD and Aging Models

A potential tool for studying network synchrony in the neocortex is the analysis of the gamma rhythm, as it recruits excitatory activity, which is reordered by the action of inhibitory synaptic input [30, 87, 88] (Figure 1C). Despite few studies, alterations in cortical gamma patterns in AD have been identified. Furthermore, these alterations have been found across different models of AD and aging, and mimic similar alterations that have been observed in patients with AD [89, 90]. First observed in an *in vivo* model, Nakazono et al. showed that cross-frequency coupling of high-frequency oscillations (30–100 Hz) to theta oscillations (4–12 Hz) was reduced in the medial entorhinal cortex of anesthetized amyloid precursor protein knock-in (APP-KI) mice [91]. Similarly, previous findings in cortical slices provided evidence of the slowing of gamma oscillations (20–60 Hz) in the entorhinal cortex [92]. In addition, a recent study showed that peak gamma oscillations (60–90 Hz) shifted toward lower frequencies within the 15 to 100 Hz band in the neocortex of anesthetized 3xTg-AD mice [93]. Moreover, deregulation of the Up–Down cycle featuring slow oscillations was observed, supporting the desynchronization of the cortical network. Further evidence of alterations in the gamma rhythm is provided in our characterization of the APP/PS1 mouse model [94], where lower activity synchronization in the beta-gamma frequency range (15–90 Hz) is shown (Figure 3). The novelty of this work was that we analyzed excitability and cortical synchrony in the beta-gamma range in the proximity of the amyloid-β (Aβ) plaques (Figure 3A), which was reduced close to the plaques. Stoiljkovic et al. observed that intra-cortical coherence was reduced in TgF344-AD rats, which is also reminiscent of altered synchrony [95]. In contrast with previous observations, Gurevicius et al. reported a general increase in EEG power from 5 to

100 Hz in a mouse model of AD [96]. Furthermore, reduced gamma oscillations have been observed in human aging [97]. Another study provided evidence of reduced gamma oscillations (30–90 Hz) during senescence and in the neurodegeneration SAMP8 mouse model [98] (Figure 4). In this study, we found that the synchronization peak in the gamma range during Up states occurred at lower frequencies in SAMP8 in anesthetized animals than in control mice. Moreover, the mean power spectrum between 0 and 100 Hz presented an overall increase in its lower range together with a decrease in its upper range. Interestingly, the gamma synchronization alterations in SAMP8 mice at seven months of age were consistent with those found in 20-month 3xTg-AD mice, providing evidence in favor of the SAMP8 model displaying premature aging. Additionally, we observed deregulation in the Up-Down cycle, consistent with that observed in the 3xTg-AD model [93, 98]. These findings are substantially reminiscent of those described in human patients with AD, and add to the evidence in support of the suitability of the SAMP8 mouse as a model of AD, given the fact that few reports using mouse models find EEG alterations consistent with human observations [99]. Similar alterations in the gamma rhythm (30–90 Hz) were previously observed in a mouse model of Down syndrome, in which the authors report impaired inhibitory connectivity [83]. This may be of relevance owing to the fact that the development of AD is often present in Down syndrome subjects (for a special issue on the topic, see [100]). In support of this link, Verret et al. found in hAPP mice overexpressing a human precursor of APP gene that a loss of gamma oscillations (20–80 Hz) was related to an inhibitory interneuron deficit [101].

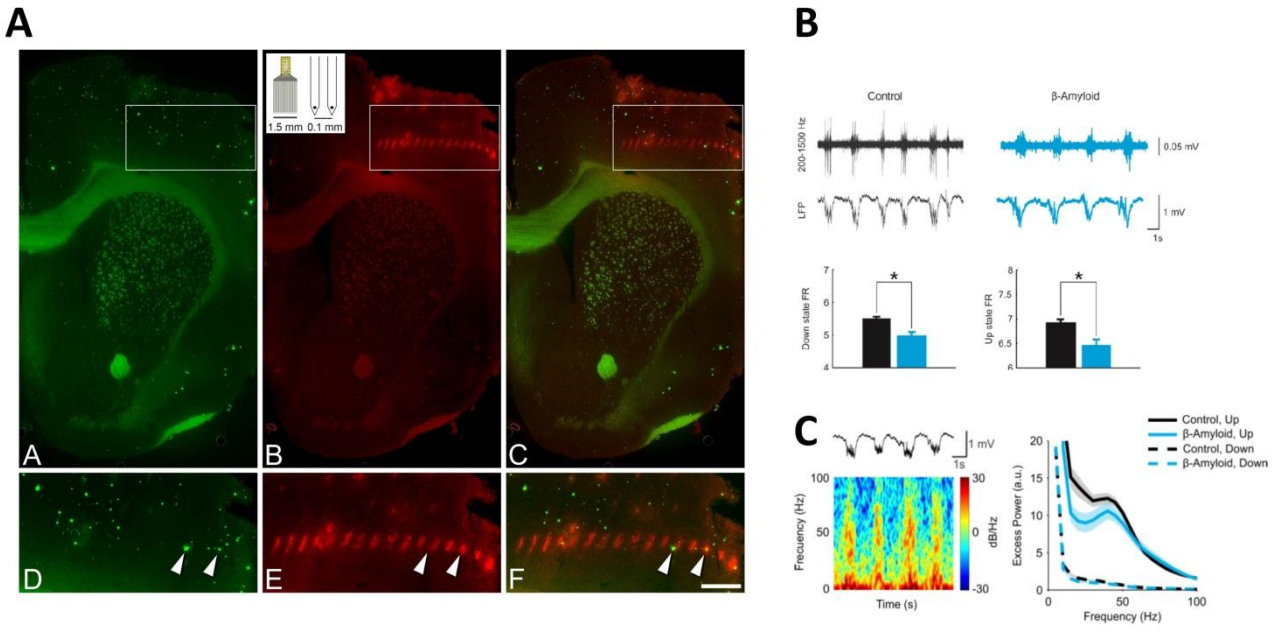


**Figure 3** Neuronal activity at different distances from amyloid plaques. (A) **A–C** Images taken from a section of an APP/PS1 mouse showing the relationship between Aβ plaques stained with thioflavin-S (**A, D**) and the electrode tracks (**B, E**). **C** and **F**, merged images. Inset in panel **B** shows a 16-channel array. Squared zones in panels **A-C** are, respectively shown at higher magnification in panels **D-F**. Arrow heads indicate contacts of certain electrodes with Aβ plaques. Scale bar in F: 505 µm in panels A–C; 270 µm in D-F. (B) Slow oscillation parameters in the vicinity of Aβ plaques in the APP/PS1 mouse model. Raw LFP recordings (*bottom*) and filtered between 200 and 1500 Hz (*top*) as an estimation of the

population firing rate. Below, firing rates in Down and Up states comparing the parameters obtained near an Aβ plaque and far away from them. Bars depict the mean, error bars are SE. **p*<0.0125. (C) High-frequency content of SO in the vicinity of Aβ plaques in the APP/PS1 mouse model. (*Top*) raw LFP recording in the prelimbic cortex of a control mouse under ketamine anesthesia. (*Bottom*): spectrogram showing the presence of high-frequency rhythms, mainly during the Up states. (*Right*) Excess power during the Up states and the Down states. The shaded area is the SE. Taken from Castano-Prat, P., Aparicio-Torres, G., Muñoz, A., & Sanchez-Vives, M. V. (2018). Influence of β-Amyloid Plaques on the Local Network Activity in the APP/PS1 Mouse Model of Alzheimer's Disease. In *Advances in Cognitive Neurodynamics (VI)* (pp. 245-253). Springer, Singapore. Used with permission.

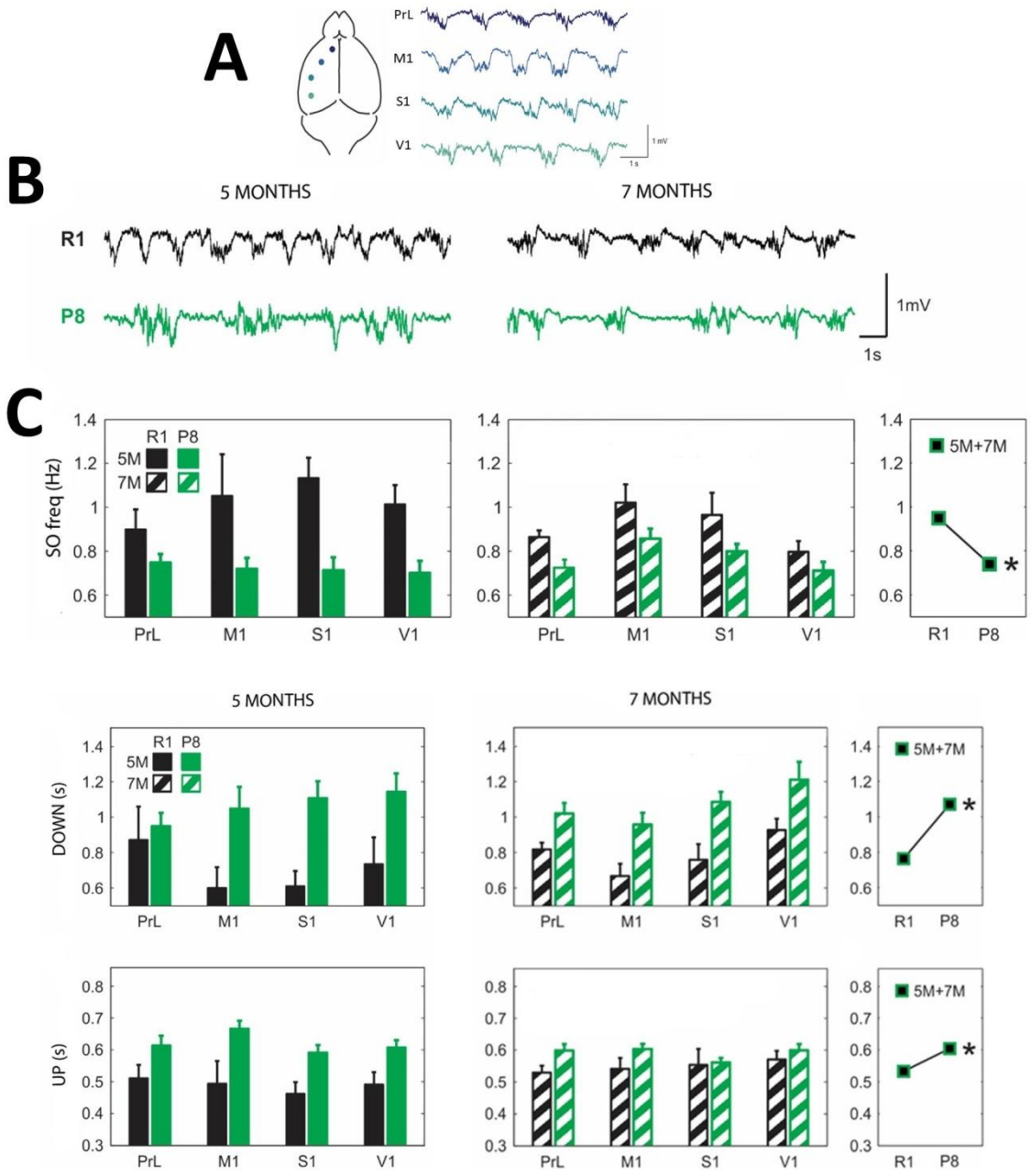

**Figure 4** Oscillatory activity in the PrL (prefrontal) cortex of senescence accelerated mouse resistance 1 (SAMR1; control) mouse under ketamine anesthesia. (A) Recordings of LFP in four cortical areas of the mouse. (B) Raw LFP recordings from right M1 cortex at five and seven months old, respectively, in SAMR1 (*black*) and SAMP8 mice (*green*). (C) Population data showing the evolution of SO frequency in the transition from five months to seven months old, in the four cortical areas in both groups for slow oscillatory frequency, Down and Up states duration. Bars and symbols depict the mean, error bars are SE. *$p$<0.05 SAMP8 vs. SAMR1 (control) in panels (C, D), and 5 vs. 7 months of age for each cortical area and group in (E). 5 M (5 months old), 7 M (7 months old). Prelimbic cortex (PrL), primary motor cortex (M1), primary somatosensory cortex (S1), primary visual cortex (V1). Taken from Castano-Prat, P., Perez-Zabalza, M., Perez-Mendez, L., Escorihuela, R. M., & Sanchez-Vives, M. V. (2017). Slow and fast neocortical oscillations in the senescence-accelerated mouse model SAMP8. *Frontiers in aging neuroscience*, *9*, 141. Used with permission.

## 3. Cortical Excitability in AD and Aging Models

Further to the study of alterations in the gamma rhythm, cortical hyperexcitability has been observed in different studies in AD models over the past two decades. This suggests that impairment in the excitation/inhibition balance of the cortical circuit could underlie altered emergent activity in AD. A major change in network function is the generation of epileptiform activity, with seizures having been observed in several APP-transgenic mouse strains [102-105], indicating a relative excess of excitatory neurotransmission. These findings were supported by electrophysiological recordings from the brains of several APP transgenic mouse strains [106, 107]. Along these lines, a set of studies reported hyperactivity in the mouse model APP23-PS45 [108, 109]. The authors found an increase in calcium transients after analyzing spontaneous calcium transients in combination with two-photon imaging in anesthetized animals. Interestingly, the hyperexcitability was observed near amyloid plaques in the frontal cortex [108] and was less prominent in the visual cortex [110]. Similarly, the authors observed an increase in calcium transients in other models of AD, such as PDAPP and Tg2576 [109]. It is noteworthy that these studies also show an increase in the proportion of hypoactive neurons in the transgenic mouse. Consistent with these findings of reduced activity, Stern et al. [111] observed in Tg2576 mice that evoked synaptic response of neurons to transcallosal stimuli were severely impaired in the cortex containing substantial plaque accumulation, with an average 2.5-fold greater rate of response failure and two-fold reduction in response precision compared with age-matched non-transgenic controls. Supporting an alteration in synaptic activity and excitability in aging, our characterizations of the 3xTg-AD mice and their controls showed increased network excitability in Up and Down states in 20-month-old mice, which seemed to be associated with age, as the increase did not significantly differ between the control and transgenic groups [93] (Figure 5). However, early aging SAMP8 mice showed stable firing rates in Up states and in Down states that even decreased with age. We found a slowing of the slow oscillation frequency with respect to their controls in both SAMP8 and 3xTg-AD mice while aging [93, 98] (Figures 4 and 5, respectively), suggesting a reduction of network excitability due to genotype. Interestingly, and in contrast with previous observations, we observed systematic reductions in neuronal firing rates during Up and Down states near amyloid plaques in APP/PS1 mice [94] (Figure 3). In that study, we identified

recordings obtained within 18 µm of an Aβ plaque and compared them with those obtained close to Aβ plaques and those obtained further away from them. Interestingly, the firing rate reduction in Up/Down states was recovered as recordings were further away from the plaques. Moreover, challenging the idea of increased excitability, evidence has shown that the overexpression of APP precursor hAPP in rat cortical neurons led to the inhibition of calcium oscillations in all cells of a neuronal network. Furthermore, this inhibition was independent of the production and secretion of Aβ and other APP metabolites [112]. This set of results supports a previous hypothesis of AD neurodegeneration understood as a synaptic failure [81].

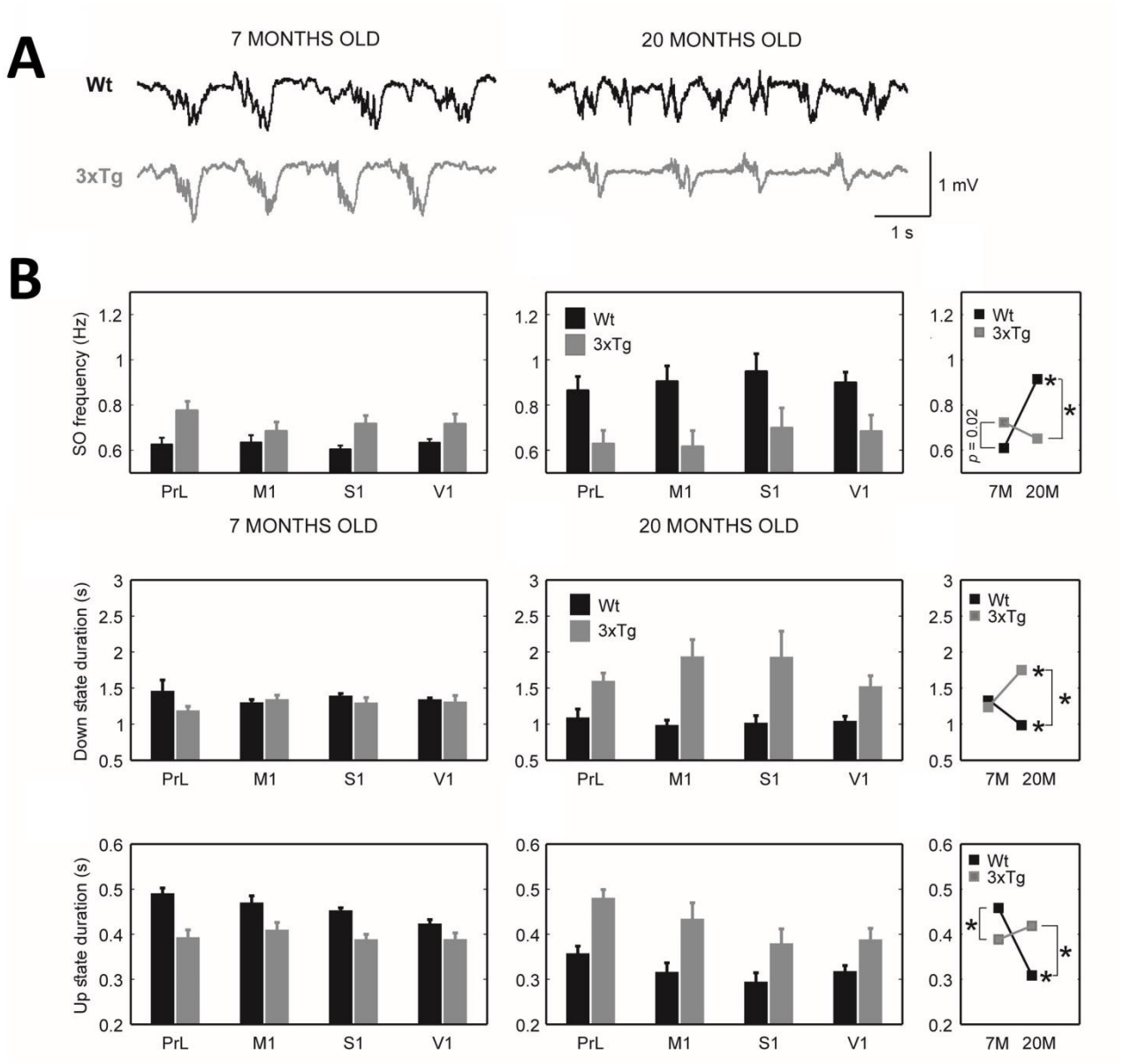


**Figure 5** Slow oscillations in 3xTg-AD mouse model. A. Raw LFP recordings from right M1 at 7 and 20 months, respectively, in Wt (black) and 3xTg-AD (gray) mice. B. Population data comparing the SO frequency between 3xTg-AD and Wt mice at 7 and 20 months of age, respectively, in the four cortical areas. B. Population data showing the evolution of SO frequency between 7 and 20 months in both groups, with the four

cortical areas pooled together. Bars and squares depict the mean, error bars are SE. * $p$<0.0125 3xTg versus Wt mice and 7 versus 20 months of age in (H). Abbreviations: AD, Alzheimer's disease; PrL, prelimbic cortex; M, months old; M1, primary motor cortex; S1, primary somatosensory cortex; V1, primary visual cortex. Taken from Castano-Prat, P., Perez-Mendez, L., Perez-Zabalza, M., Sanfeliu, C., Giménez-Llort, L., & Sanchez-Vives, M. V. (2019). Altered slow (< 1 Hz) and fast (beta and gamma) neocortical oscillations in the 3xTg-AD mouse model of Alzheimer's disease under anesthesia. *Neurobiology of Aging*, *79*, 142–151. Used with permission.

## 4. What is the Relationship between Network Firing Rate and Gamma Synchrony in AD?

In addition to being a complex topic, a hypothesis consisting of interictal cortical hyperactivity and reduced network synchrony in the gamma band in AD is indeed difficult to explain in local network terms. In non-pathological conditions, the excitatory input to the inhibitory system has to be guaranteed to maintain effective inhibitory synaptic input to excitatory neurons, and thus synchronize their activity with the gamma rhythm [30, 31, 88, 113]. However, we found that when NMDA input to the local network is decreased during *in vitro* Up and Down states, beta-gamma rhythm (15–90 Hz) is also increased, showing a hypersynchronization of fast rhythms. This suggests that NMDAR activation prevents hypersynchronization under physiological conditions [114]. Reduction of firing rates in the local network is most often associated with a decrease in the synchronization in the beta-gamma range in several cases; for example, cortical inhibitory alteration and overinhibition in a Down syndrome model [83], increased functional connectivity in a Williams–Beuren syndrome model [115], when comparing area-specific cortical activity [17], or even by the effect of temperature modulation [116]. Further to this, altered cholinergic input originating from the forebrain may play a role in network desynchronization [117], given that a lack of acetylcholine in the cortex directly leads to a loss of gamma rhythm synchronization (21–70 Hz) [118]. In addition, the cholinergic alteration of cortical and hippocampal network activity is at least in part caused by muscarinic modulation of inhibitory interneurons [100, 101]. Increased cholinergic input leads to stronger gamma synchronization (21–70 Hz) although not necessarily an increase in local firing rates [118]. However, further evidence is required to describe how the local neuronal population activity relates to the emergent rhythmic patterns in AD. Future work may also address the structural and functional synaptic connectivity contribution, or the role of neuromodulation involved in gamma band desynchronization, to understand the neurobiological basis of circuit impairment in neurodegeneration. Elucidation of the mechanisms underlying the desynchronization that is compatible with the occurrence of epileptic seizures in AD patients will contribute to the understanding of how a synaptic failure, observed hyperexcitability, inhibitory system impairment, and a cholinergic cortical deficit converge together [80].

## 5. Studying Sleep and Gamma Rhythms in Animal Models for Understanding Circuit Impairment and as Biomarkers for Detection and Treatment of AD

Studies using transgenic animals are valuable in elucidating the underlying mechanisms of AD network dysfunction, as they allow us to measure network properties in different features recapitulated in each model. However, a limitation is that they are only useful if they accurately

reflect the complete cellular and molecular processes involved in the human neurodegenerative process. Nevertheless, measuring rhythmic patterns could provide valuable information and clues that can guide the study of the circuit alterations behind altered oscillatory activity. In a variety of studies, electrophysiological measurements have been shown to precede cognitive impairment, suggesting they might be indicative of the preclinical stages of the disease. Therefore, it is critical to identify prodromal stages of the disease in order to initiate therapy before irreversible degeneration occurs. This, however, has so far been hampered by the lack of a reliable biomarker that would identify patients who are prone to develop future AD [80]. Recently, sleep has been postulated as a novel mechanistic pathway, biomarker, and treatment target in the pathology of AD [86]. As described in this work, this is attributed to the following: first, there is a bidirectional, causal interaction between NREM sleep and Aβ pathophysiology that may contribute to AD risk and progression; second, the disruption of NREM sleep may represent a novel pathway through which cortical Aβ impairs the hippocampus-dependent memory consolidation; third, the disruption of NREM sleep physiology offers potential diagnostic utility in the form of a non-invasive biomarker of Aβ pathology, AD risk, and/or AD pathophysiological progression; and finally, evidence implicates sleep disturbance as a consequence and cause of AD progression; one that is modifiable, thereby offering preventative and therapeutic treatment potential. Interestingly, inducing network synchrony via local GABA application or light stimulation with optogenetics over cortical excitatory cells restored the altered slow oscillation pattern in APP mice. Moreover, light stimulation halted plaque deposition and prevented calcium overload [119]. Furthermore, the modulation of gamma oscillations in the hippocampus attenuated amyloid load in the 5XFAD mouse model, showing that reduced gamma oscillations could serve as a potential biomarker and target for attenuating AD-associated pathology [120]. EEG patterns, such as sleep and gamma oscillations, have the advantage that they are relatively easy to measure and track. Framing the study and therapeutics of AD and neurodegeneration related to aging through the analysis and manipulation of emergent rhythmic patterns could bring forth a useful and novel perspective [80], contributing to the understanding of AD as an oscillopathy [121]. Furthermore, this framework could be applied to other diseases in which network dynamics become disrupted, such as schizophrenia [122], autism [123], and Down syndrome [124].

## 6. Conclusions

Neuronal network dysfunction is common to all major neurodegenerative disorders. The cortical oscillatory emergent activity can highlight circuit alterations underlying those processes. In AD, there is desynchronization of cortical circuits, combined with alterations in network excitability, whose nature remains unclear, along with the occurrence of hypersynchronized, seizure-like discharges. AD and early aging animal models, despite being diverse, have revealed alterations in cortical circuits through the study of rhythmic patterns. The alterations converge on the fact that there is an imbalance between excitation and inhibition. Sleep rhythmic patterns and gamma oscillations are postulated as biomarkers for the early detection of the neurodegenerative process present in AD and the mechanistic findings in animal models could guide future diagnostic and therapeutic approaches in humans.

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This is a review and all authors contributed to the written text.

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## Competing Interests

The authors have declared that no competing interests exist.

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