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# Sharp Wave Ripples in Alzheimer's Disease: In Search of Mechanisms

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Review of Caccavano et al.

## Introduction

Alzheimer's disease (AD) is the most common cause of dementia. The disease is associated with the presence of plaques and neurofibrillary tangles in the brain, which leads to synaptic and neuronal degeneration and progressive learning and memory impairment (Spires-Jones and Hyman, 2014). Work of the last decades has produced a variety of diagnostic tools and treatment alternatives, yet the mechanisms underlying the disease are poorly understood, and interventions are still minimally effective, possibly in part because they are started after irreversible damage has been done. Identifying early markers of AD might therefore advance therapeutic development and effectiveness.

A likely source of early AD biomarkers is hippocampal network activity. The hippocampus, an important region for acquisition and consolidation of memory, is particularly affected in AD (Braak and Braak, 1991). Normal hippocampal memory function relies on a variety of electrophysiological phenomena, perhaps the most notable of which are sharp wave ripples (SWRs) (Buzsáki, 2015). The spectrum of SWR oscillations spans from the $\gamma$ (30-80 Hz) to the ripple band (100-250 Hz). During SWRs, excitatory neurons and GABAergic interneurons engage in a delicate interaction that, if disrupted, can lead to pathologic forms of activity, including fast ripples (>250 Hz), very large amplitude ripples, and hyperexcitability (Aivar et al., 2014). SWRs emerge from the dynamical interaction between pyramidal cells and local circuit GABAergic interneurons. While the dynamics of SWRs are altered in various ways in AD models (Fig. 1) (Gillespie et al., 2016; Iaccarino et al., 2016; Witton et al., 2016; Jura et al., 2019), the role that each neuronal type plays in these changes is unclear. Therefore, a recent study by Caccavano et al. (2020) examined the mechanisms underlying disruption of the hippocampal network activity in a mouse model of AD.

The authors used the 5xFAD model of familial AD, which is characterized by heavy amyloid $\beta$ accumulation in hippocampus and associated cortical areas. After confirming the presence of amyloid $\beta$ plaques in the subiculum and hippocampal area CA1 of 3-month-old 5xFAD mice and demonstrating these animals' impaired performance on the Barnes maze, the authors turned to an *in vitro* preparation to study CA1 microcircuits using electrophysiological and calcium imaging techniques.

Caccavano et al. (2020) recorded the local field potential in CA1 in slices containing the medial hippocampus, where spontaneous SWRs emerge most consistently *in vitro*. They found that SWRs were more abundant, had larger amplitudes, slightly faster intraripple frequencies, and were of shorter duration in 5xFAD mice than in controls. More strikingly, the spectral organization of the events was altered in 5xFAD mice. While the power of the ripple band was relatively similar to control, the slow-$\gamma$ band was increased in recordings from these mice.

Multicellular imaging in 5xFAD mice crossed with Thy1-GCaMP6f mice, in which a calcium indicator is expressed in a subset of CA1 neurons, revealed differences in the ensembles of activated cells during SWR activity. In slices from 5xFAD/1;Thy1-GCaMP6f/1 mice, ensembles were larger and less similar compared with control Thy1-GCaMP6f/1 littermates, suggesting that aberrant cell participation may disrupt the neuronal orchestra in AD mice. This is consistent with a recent report by Poll et al. (2020), which showed that activation of additional ensembles interfered with memory recall in another model of AD. Interestingly, Caccavano et al. (2020) observed different alteration of firing dynamics of deep and superficial CA1 pyramidal cells. During SWRs, superficial cells fired more in 5xFAD mice than controls, whereas firing of deep neurons was similar in 5xFAD mice and controls. Voltage-clamp recordings confirmed cell-type-specific changes and provided additional hints on

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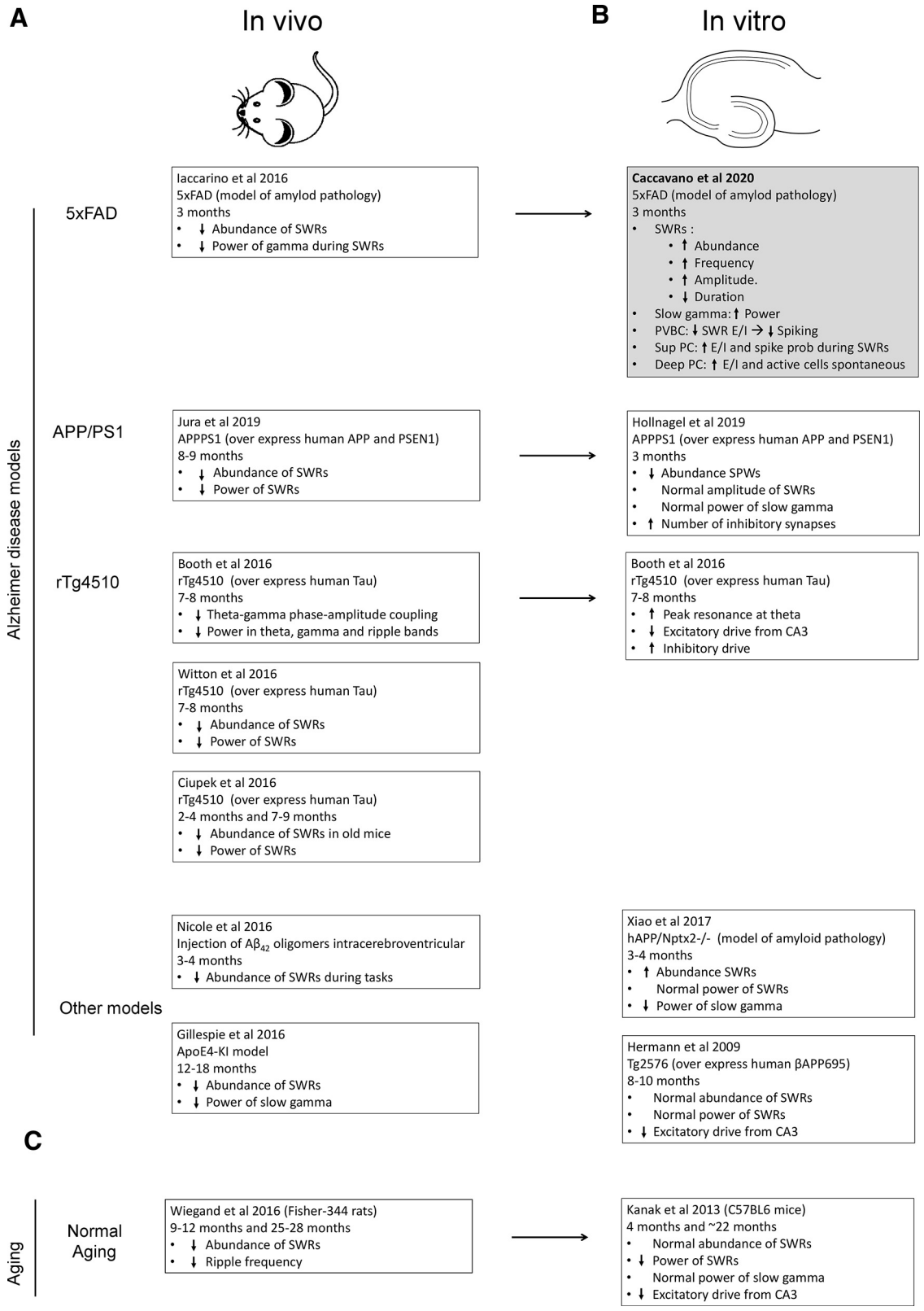


**Figure 1.** Summary of SWR alterations in AD models *in vivo* (***A***) and *in vitro* (***B***). Summary of Hermann et al. (2009); Ciupek et al. (2015); Booth et al. (2016); Gillespie et al. (2016); Iaccarino et al. (2016); Nicole et al. (2016); Witton et al. (2016); Xiao et al. (2017); Hollnagel et al. (2019); Jura et al. (2019); and Caccavano et al. (2020). ***C***, Findings for normal aging studies are also included. Summary of Kanak et al. (2013) and Wiegand et al. (2016).

the mechanisms: in superficial pyramidal cells from 5xFAD mice, although the frequency and charge of spontaneous IPSCs were reduced, the inhibitory charge during SWRs was not significantly different from controls. In contrast, the inhibitory charge increased during SWRs in deep neurons in 5xFAD mice. Consistent with these findings, only superficial CA1 pyramidal neurons from 5xFAD mice showed larger ratios of excitation to inhibition during SWRs.

To better understand the mechanisms underlying these changes, the authors performed loose cell-attached and patch-clamp recordings in CA1 parvalbumin-expressing ($PV^+$) neurons, which are the most active interneurons during SWRs *in vivo*. They classified $PV^+$ interneurons as basket cells (PVBCs), bistratified cells, or axo-axonic cells based on morphology and firing dynamics during SWRs. 5xFAD mice showed abnormal activity patterns in PVBCs during SWRs. The firing window of PVBCs was narrower and the firing rate was lower in 5xFAD than in controls. According to the authors, the firing of bistratified cells from 5xFAD remained relatively preserved, although there was a trend to widen their firing window. They also noted that axo-axonic interneurons from 5xFAD mice had a nonstatistically significant trend to reduce their firing and to shift their phase preference during SWRs. Together, these data by Caccavano et al. (2020) suggest a major role of PVBC activity underlying hyperexcitability and cell ensemble disruption in the hippocampus of 5xFAD mice, leading to distortion of SWR dynamics.

What are the mechanisms underlying SWR alterations in AD? Under physiological conditions, firing of pyramidal cells and PVBCs during SWRs is appropriately coordinated (Somogyi and Klausberger, 2005), and ripples rarely accelerate because most neurons are under strong inhibitory control, which is reflected by the rhythmic positive deflection of the local field potential (Aivar et al., 2014). Loss of this perisomatic inhibition by PVBCs in the hippocampus leads to massive bursting of pyramidal neurons and the generation of pathologic ripples (Gulyás and Freund, 2015). Perisomatic disinhibition may slightly accelerate cycles that are now dominated by excitation, triggering large-amplitude ripples that reflect synchronous in-phase firing, or fast ripples reflecting out-of-phase firing of pyramidal neurons (Aivar et al., 2014). In addition, enlarged-amplitude events that occur in 5xFAD mice may result from stronger excitatory transmission from CA3 pyramidal neurons during SWRs. Indeed, alterations in excitatory and inhibitory transmission in the CA3 and dentate gyrus have been described in other AD models (Palop et al., 2007; Booth et al., 2016; Hollnagel et al., 2019). Perisomatic disinhibition also has major effects on SWR duration, by favoring abnormal bursting with prominent after-hyperpolarization that may shorten the oscillation, as happens in 5xFAD mice. Similar effects have been shown in experiments with optogenetic silencing of $PV^+$ interneurons during SWRs, which shortened the oscillation (Schlingloff et al., 2014). Interestingly, tasks demanding strong memory load have been shown to require long SWRs, and prolongation of SWRs improves memory (Fernandez-Ruiz et al., 2019), whereas interruption of SWRs results in memory deficits (Roux et al., 2017). Thus, these mechanisms may contribute to AD-associated cognitive deficits.

While PVBCs seem to be the most affected interneuronal type in 5xFAD mice, Caccavano et al. (2020) did not discard the possibility that mild alterations in PV axo-axonic cells may also contribute to hyperexcitability, given the strategic location of their synapses in the axon initial segment for controlling pyramidal cell firing (Somogyi et al., 1983). Indeed, loss of axo-axonic cells and their synapses in cerebral cortex and hippocampus are known to contribute to epileptogenesis (DeFelipe, 1999; Alhourani et al., 2020), which is noteworthy because seizures are up to 6 times more prevalent in AD than in age-matched controls (Pandis and Scarmeas, 2012). Seizures and hyperexcitability emerge early during AD progression (Palop et al., 2007), and alterations of the normal SWR patterns may be informative about disease progression. Thus, it is possible that broad populations of $PV^+$ GABAergic cells are affected in AD.

Changes in the firing patterns of PV neurons might stem from several factors. For instance, intrinsic factors, such as downregulation of $Na_{v1.1}$ channels, may contribute, as shown in other AD models (Verret et al., 2012). Caccavano et al. (2020) also suggest that loss of perineuronal nets surrounding $PV^+$ interneurons could explain their reduced excitability, given that PV cells from genetic KO and knockdown of the perineuronal net protein brevican receive fewer excitatory synapses (Favuzzi et al., 2017). In this regard, it has recently been shown that microglia facilitate the extensive loss of perineuronal nets in 5xFAD mice and in human tissue (Crapser et al., 2020). Perineuronal nets surround preferentially PVBCs compared with the rest of PV interneurons (Yamada and Jinno, 2015), potentially explaining why PVBCs seem to be the most affected PV population in the experiments by Caccavano et al. (2020). Potential treatments might target voltage-dependent sodium channels or perineuronal net proteins to restore the inhibitory activity (Xu et al., 2020). Indeed, early restoration of $PV^+$ interneuron activity prevents network hyperexcitability and memory loss in a mouse model of AD (Hijazi et al., 2020). Importantly, although changes in $PV^+$ interneurons likely contribute to the hyperexcitability observed by Caccavano et al. (2020), other factors, including impairment of interneuronal types not examined by the authors, may play roles as well. For instance, lower dendritic inhibition mediated by oriens-lacunosum moleculare interneurons has been linked to the increased excitability (Cossart et al., 2001).

How comparable are these observations across AD models? Different rodent models have been used to elucidate changes and mechanisms underlying hippocampal dysfunction in AD, but *in vivo* and *in vitro* studies often yield contradictory results. For instance, *in vivo* recordings consistently report a decrease in the rate of SWR events in 5xFAD (Iaccarino et al., 2016), APPPS1 (Jura et al., 2019), APoE4 (Gillespie et al., 2016), and rTf4510 models of AD (Ciupek et al., 2015; Witton et al., 2016) (Fig. 1*A*), whereas *in vitro* recordings from the same models show variable results, including increases, decreases, and no change in SWR rate compared with controls (Hermann et al., 2009; Xiao et al., 2017; Hollnagel et al., 2019) (Fig. 1*B*). Furthermore, ripples recorded *in vivo* in most AD models show reduced power, especially at the slow $\gamma$ band (Fig. 1*C*), whereas *in vitro* recordings of these very same models reflect disparate trends (Fig. 1*B*,*C*). How can these disparate observations be explained?

The slice preparation is useful for dissecting microcircuit mechanisms that are currently elusive *in vivo*, but extrapolation is challenging. First, most *in vivo* recordings are obtained from the dorsal hippocampus, while slices are typically prepared from horizontal sections of the ventral hippocampus, and molecular and electrophysiological differences have been described along the dorsoventral axis (Lee et al., 2014; Kouvaros and Papatheodoropoulos, 2017). Second, the composition of the extracellular medium, as well as the level of oxygenation and recording conditions (i.e., interface vs submerged chambers) all affect the type of SWR events that spontaneously emerge from slices (Hájos and Mody, 2009; Aivar et al., 2014). Simply modifying the balance between calcium and magnesium has a major effect in the excitation to

inhibition ratio and the physiological or pathologic types of SWR recorded in slices prepared from normal rodents (Aivar et al., 2014). To facilitate comparison and enhance replicability, *in vitro* SWRs should match the properties of *in vivo* SWRs.

It is still unknown how different excitatory sources and the interaction of diverse neuronal subpopulations determine the spectral properties of SWRs *in vivo*. Caccavano et al. (2020) propose that spike rate reduction of PVBC firing explains distortion of SWR-associated activity in 5xFAD mice. Yet, spike rate alterations in PVBC as well as the consistent decrease of slow $\gamma$ power seen *in vivo*, among other changes, can only be fully understood after the many microcircuits underlying SWR events are identified (de la Prida, 2020). For instance, emerging data suggest that not only interneuronal subtypes, but also deep and superficial pyramidal cells, have critical impact on SWR dynamics (Valero et al., 2015; Wu et al., 2015), given specific connectivity between PVBC, superficial, and deep pyramidal cells (Lee et al., 2014). Since different proportions of CA1 deep and superficial pyramidal cells exist along the septotemporal axis of the hippocampus, comparisons between dorsal and ventral hippocampal slices of 5xFAD mice might help to further clarify the issue.

In conclusion, Caccavano et al. (2020) shed light on an early and important disturbance in the hippocampal CA1 microcircuit *in vitro* of AD-model mice. The critical role of interneurons and specific subcircuits innervating deep and superficial CA1 pyramidal cells suggests that early alterations operate at the microcircuit level. A major readout of local microcircuit function (Buzsáki, 2015), SWR dynamics, was significantly altered in the AD model. More work is required to gain additional insights into the *in vivo* mechanisms to put together the emerging advances (Fig. 1) and better understand the role of SWRs in AD's pathophysiology.

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