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Systematic Review

Hyperphosphorylated Tau Induces Cortical Hypoexcitability in Transgenic Mouse Models: A Meta-Analysis

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Abstract

Background: Neurofibrillary tangles, composed of hyperphosphorylated tau, have been implicated in the cognitive impairments observed in Alzheimer's disease. While the precise mechanism remains elusive, cognitive deficits in Alzheimer's disease have been associated with disrupted brain network activity. To investigate this mechanism, researchers have developed several tau transgenic models. However, the extent of variability in cortical network alterations across different genetic backgrounds and ages is still not clearly defined. **Objective**: To evaluate the oscillatory alterations in relation to animal developmental age and hyperphosphorylated tau protein accumulation, we reviewed and analyzed the published data on peak power and quantification of theta-gamma cross-frequency coupling (modulation index values). **Methods**: A systematic review was conducted to locate and extract all studies published from January, 2002 to March, 2024 involving *in vivo* cortical local field potential recording in tau transgenic mouse models, ensuring the most current search results. Our meta-analysis was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. **Results**: The presence of hyperphosphorylated tau was associated with oscillatory alterations primarily reflected in power decreases, while modulation index values did not exhibit significant alterations. **Conclusions**: In this analysis, we uncovered that neuronal oscillations in cortical networks are altered from the prodromal to late stages of pathology. Additionally, we found that hyperphosphorylated tau accumulation is strongly associated with cortical network hypoexcitability in tau transgenic models.

Keywords: Alzheimer's disease; cerebral cortex; tau protein; neural networks and phase synchrony

1. Introduction

Synchronous activity of neuronal networks produces oscillatory patterns [1]. Oscillations are essential for the temporal coding and decoding of neurons, making them necessary for proper brain function and cognition [2]. The theta rhythm is the largest synchronous signal generated in the hippocampus [3]. Notably, theta oscillations are believed to assist cognitive processes by coding with faster oscillatory rhythms (gamma oscillations), a mechanism called cross-frequency coupling (CFC) [4–8]. CFC has been described in several brain regions, like the hippocampus and cortex [4,9,10]. Strong CFC has been correlated with elevated cognitive performance, such as spatial resolution, memory, and learning [4,5,9,11]. Interestingly, altered oscillatory activity in lower rhythms like theta is a hallmark of dementia [12–14]. Furthermore, patients with dementia exhibit lower cortical CFC when performing memory tasks [15,16].

Alzheimer's disease (AD) is characterized by the gradual deterioration of cognitive functions, and is currently the most common form of dementia worldwide [17, 18]. Importantly, the hallmark of this neurological disorder is intracellular inclusions in the form of neurofibrillary tangles (NFTs), primarily composed of hyperphosphorylated tau (pTau), and amyloid-β (Aβ) plaques [19,20]. Under normal conditions, tau is a microtubule-associated protein that plays a role in regulating their dynamics and stability [21–23] not only in the soma and axons but also in dendrites [24–26]. Tau function is mainly regulated by post-translational modifications such as phosphorylation, acetylation, and ubiquitination [23]. However, pathological tau is associated with tau hyperphosphorylation at several sites such as Ser199, Thr205, Ser262, Thr212, Thr231, Ser396-404 and Ser422 [21,23,27–29], caused by an imbalance in kinase-phosphatase activity and Aβ load [20,21]. The main hypothesis states that the abnormal phosphorylation of tau inhibits its binding to microtubules, leading to its abnormal aggregation into NFTs, which disrupts neuronal structure and contributes to brain network alterations [28]. Recently, we reported that endogenous pTau is found in significant quantities at postsynaptic sites, where it interacts with the postsynaptic postsynaptic density protein

95-N-methyl-D-aspartate receptor (PSD95-NMDA) receptor complex, thereby affecting synaptic function that shapes brain activity and connectivity [21,30].

Several transgenic mouse models with pTau accumulation have been developed by researchers to investigate brain network activity and connectivity during pathological states [31,32]. However, the association between network changes and pTau accumulation is not yet fully understood. While certain review papers have examined the impact of protein accumulation on pTau transgenic (pTau-tg) mouse models and cognitive performance [31,33–35], they do not delve into network alterations or the methodological heterogeneity in the research.

In the last decade, our research group has focused on studying hippocampal network changes in pre-symptomatic stages of AD transgenic models [24,30,36,37]. Recently, we reported that Aβ accumulation was associated with electrophysiological alterations primarily reflected in hippocampal hyperexcitability, while pTau accumulation linked to hippocampal hypoexcitability [38]. This conclusion was based on the pathogenic interaction between Aβ and pTau disrupting the excitatory-inhibitory balance [38]. However, the hypothesis that pTau drives disease progression remains under debate [39]. Therefore, considering the prodromal stage and the functional connectivity between the hippocampus and cortex, this meta-analysis aims to evaluate the extent of cortical network activity changes in pTau-tg mouse models (Tables 1,2,3, Ref. [40–51]). To achieve this, we conducted a thorough review to collect and summarize data from all research on cortical local field potential (LFP) analysis in pTau-tg mouse models. Specifically, we focus on peak frequency, peak power, and modulation index analysis. This study is pertinent to the field of AD because, although symptoms can vary greatly, a more accurate diagnosis could be made using physiological parameters.

2. Materials and Methods

This report set out to pinpoint and outline literature demonstrating changes in neuronal oscillations from cortical networks in pTau-tg models (**Supplementary Fig. 1** and Table 1). Despite the absence of protocol registration, this meta-analysis was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (**Supplementary material_PRISMA_2020_checklist**) to ensure transparency and rigor. Inclusion criteria for this meta-analysis required the involvement of peer-reviewed studies, a PubMed search was conducted to locate all studies published in English from January 2002 to March 2024 using the terms [(tau OR tauopathy OR taupathy OR taupathies)] AND transgenic AND [(local field potential OR oscillatory activity OR EEG OR electroencephalography)]. A total of 152 articles were identified, 6 of which met the inclusion criteria for meta-analysis [46–51]. Initially, studies found through database searches were assessed based on their titles and abstracts. Each article included after the abstract screening was independently evaluated for full-text eligibility. Studies were included if they simultaneously fulfilled the following criteria: (a) the study reported original results from analysis of pTau-tg models; (b) Cortical LFP was recorded *in vivo* on anesthetized or asleep mice; (c) basal activity was reported; and (d) the report included peak power band, peak frequency, or modulation index for CFC. For this meta-analysis we gathered mean values of peak band power and modulation index from reported LFP analyses, along with standard deviations, sample size, age, and transgenic model. According to Cochran's Handbook for Systematic Reviews a meta-analysis can be conducted with as few as two studies [52]. Some papers did not provide enough information for a proper meta-analysis due to not being open-access, so they were only mentioned. After extracting all the data, it was normalized to a scale of 1 to facilitate comparison. Frequency bands were divided into 1.5–4 Hz delta, 4–10 Hz theta, 10–30 Hz beta, 30–80 Hz low-gamma, and 80–300 Hz high-gamma [1]. The analysis was based on published studies, meaning that ethical approval was not needed. Two authors performed data extraction independently, and any discrepancies were resolved through collective discussions.

Statistical methods. All data were analyzed using the software Review Manager (RevMan), Version 5.4 (The Cochrane Collaboration, London, England, 2020). Data were pooled using fixed-effect models to obtain the weighted standard mean difference (SDM) with 95% confidence intervals (CI) as the synthesized measure of effect size.

Weights were calculated with the inverse variance method (1 over the square of its standard error), which is appropriate for analyzing studies with different sample sizes and varying standard errors across multiple datasets. Heterogeneity of the studies was performed by visual inspection of the forest plot and the calculation of the I-squared (I^2) statistic to indicate heterogeneity as a percentage.

3. Results

Our search resulted in 152 potential articles through the electronic database (**Supplementary Fig. 1**). Articles were disregarded if they did not include reported mean values, standard error, and/or standard deviation or if this data was unattainable. Every study incorporated cortical oscillatory evaluations in a cohort of pTau-tg models alongside a control group of healthy individuals matched for age. Given that pTau accumulation in the brain has been linked to changes in neural networks [24,30,37], our objective was to gather information from research comparing the cortical oscillatory characteristics of pTau-tg models and age-matched controls across various developmental stages. Importantly, only anesthetized and head fixed experiments were included in the present study.

Table 1. Tau transgenic models included in this meta-analysis.

Transgenic model	Mutations	Genetic background	Promoter	Isoform	Neuropathology	Cognitive impairment	Synaptic loss	Neuronal loss	Regions affected	Primary publication
P301S	MAPT301S	(C57BL/6 × C3H)/F1	Mouse prion protein (Prnp)	4R/1N	Neurofibrillary tangles by 4 months.	2.5 months	3 months	9 months	Hippocampus, neocortex, EC, amygdala, brain stem, and spinal cord.	[40]
rTg4510	MAPT301L	129S6 × FVB	CaMKIIα-tTA	4R/0N	Pretangles by 2.5 months. Hippocampal tangles by 5.5 months.	2.5 months	8 months	5.5 months	Hippocampus, neocortex, olfactory bulb, and striatum.	[41,42]
rTgTauEC	MAPT301L	C57BL/6 × FVB	Neuropsin-tTA	4R	PHF by 18 months in neurons of the medial EC.	16 months	24 months	24 months	EC, hippomcapus, dentate gyrus, and cingulate cortex.	[43]

tTA, tetracycline-controlled transactivator; PHF, Paired helical filaments; EC, Entorhinal cortex; R = Microtubule binding domain; N = Amino terminal.

Table 2. Transgenic mice models with Aβ mutation included in discussion.

Transgenic model	Mutations	Genetic background	Promoter	Isoform	Neuropathology	Cognitive impairment	Synaptic loss	Neuronal loss	Regions affected	Primary publication
3xTg-AD	APP K670_M671(Swe), MAPT 301L, PSEN 1 M146V	C57BL/6; 129X1/SvJ; 129S1/Sv	thymus cell antigen protein (Thy1.2) Thy 1.2 monopolar spindle 1 kinase (mPS1)	695, 4R	Extracellular Aβ deposits by 6 months. Increased pTau by 12 months.	4 months	4 months	No extensive neuronal loss	Brain stem, neocortex, hippocampus, thalamus, and tectum.	[44]
J20	APPK670_M671 (Swe), APP V717F (Ind)	C57BL/6	platelet-derived growth factor (PDGF-β)	695<751, 770	Hippocampal Aβ aggregation by 1 month. Aβ plaques by 5–7 months in dentate gyrus (DG) and hippocamus.	4 months	3 months	12 weeks	Hippocampus, and neocortex.	[45]

Table 3. Characteristics of studies assessing the impact of pTau on oscillatory activity included in the meta-analysis.

Study author	Year	Transgenic mice model used in the study	Age	Objective	Main findings	Sex	Region recorded	Tau epitopes studied (antibody)	Primary publication
Parka	2023	rTg4510	3.8–4.2 months	To assess the impact of early pTau aggregation in visual cortex.	pTau aggregation in rTg4510 is associated with reduced inhibitory activity, abnormal theta oscillations and susceptibility to epileptogenesis in the preclinical stage of disease.	Male	Visual cortex	pS202, pT205 (AT8), pS396	[46]
Holton	2020	rTg4510	6–11 months	Authors measured potential sleep disturbances in a pTau model.	pTau models exhibit sleep disturbances reflected by changes in sleep architecture, EEG power, behavior and cognition.	Male	Frontal cortex	pS409	[47]
Rodriguez	2020	rTgTauEC, hAPP/J20, and rTgTauEC × hAPP/J20	16 months	Authors evaluated the impact of Aβ and pTau accumulation in a crossed model.	Aβ increases and accelerates pTau levels in the hippocampus. Aβ aggregation leads to hyperexcitability. Attenuation of hyperexcitability reduced Aβ levels.	Males and females	Entorrhinal cortex	amino acids 313-322 in the third repeat domain (MC-1)	[48]
Booth	2016	rTg4510	3 months	Authors evluated the impact of raly pTau aggregation in the medial enthorricanl cortex.	pTau reduces excitability in the dorsal medial enthorrinal cortex, leading to reduced theta-gamma coupling.	Male	Entorrhinal cortex	pS396	[49]
Holth	2017	P301S	3, 6, 9 and 11 months	To assess the effect of pTau aggregation with sleep disturbances.	pTau aggregation in P301S model is associated with decreased REM and non-REM sleep.	Male	Frontal cortex	pS202, pT205 (AT8)	[50]
Ahnaou	2020	P301S	3–9 months	Authors assessed the effect of pTau in functional brain connectivity.	Abnormal values of phase-amplitude coupling are driven by a reduction in gamma activity.	Male	Olfactory bulb	Not reported	[51]

pTau, hyperphosphorylated tau; EEG, electroencephalogram; MC-1, melanocortin-1; REM, rapid eye movement.

After carefully reviewing the title, abstracts, and full texts, 6 studies had been chosen in our analysis (Tables 1,3 and **Supplementary Fig. 1**). Regardless of the limited number of studies (n = 6), a substantial amount of mice data was obtained for delta (pTau-tg n = 203, no-Tg n = 205), theta (pTau-tg n = 215, no-Tg n = 216), and gamma (pTau-tg n = 36, no-Tg n = 32) power, and modulation index (pTau-tg n = 29, no-Tg n = 24) analysis. Transgenic models used in these studies [40–43] are summarized in Tables 1,3 and **Supplementary Fig. 1**. All results are explained in terms of heterogeneity.

Mice That Possess the pTau Mutation Exhibit Modifications in Cortical Activity

In the combined analysis, the presence of pTau was linked to a decrease in cortical delta power (–0.30 95% CI –0.32 to –0.29, Fig. 1a), cortical theta power (–0.28 95% CI –0.29 to –0.27, Fig. 1b) and cortical gamma power (–0.10 95% CI –0.15 to –0.04, Fig. 1c) compared to the aged-matched control group. No difference was found in the cortical modulation index for theta/gamma coupling in pTau-tg models compared to the aged-matched control goup (–0.12 95% CI –0.26 to 0.01).

Overall, heterogeneity was present when evaluating cortical oscillatory activity. Mutations that lead to pTau accumulation generate cortical changes that are mainly reflected in power decreases in low-frequency bands and no alterations in the modulation index for theta/gamma coupling (Figs. 1,2 present a summary of cortical oscillatory parameters for pTau-tg models).

4. Discussion

Molecular alterations, such as protein aggregation, interfere with proper neuronal function, leading to a breakdown of neuronal networks and cognitive decline [19,53]. The main focus of this study was on how pTau accumulation affects cortical networks in transgenic models. To our knowledge, this is the first meta-analysis to exclusively collect spontaneous cortical oscillatory activity in pTau-tg mouse models (Table 1). Regarding the impact of tau mutations on cortical oscillatory activity in different pTau-tg mouse models, the pooled analysis indicates that accumulation of pTau is associated with power decreases in low- and high-frequency bands (Fig. 1). Although our study has a small sample size and substantial heterogeneity, the data demonstrate a direct effect of pTau primarily on the amplitude of the delta, theta, and gamma bands (Fig. 1).

The substantial levels of heterogeneity in our meta-analysis may be attributed to several methodological factors present in the included studies, such as: (a) Age. The included studies evaluated oscillatory activity in transgenic models at different ages (3 to 16 months old, Table 3, Ref. [46–51]). Overall, delta, theta and gamma power demonstrated alterations as the disease progressed (Fig. 1), positioning pTau as a key player in spectral power alterations. (b) Genetic background. We found substantial heterogeneity between studies done in age-related transgenic mice with mutations in different genes, i.e., P301L and P301S. Differences were found particularly in delta and theta power, suggesting that genetic background influences spectral power effects. Accounting for differences, P301S Tg mice are characterized by pTau accumulation in the hippocampus, neocortex, entorhinal cortex (EC), amygdala, brain stem, and spinal cord, while P301L Tg mice are characterized by pTau accumulation in the hippocampus, neocortex, olfactory bulb, and striatum (Table 1). Finally, (c) Electrode location. Band power recordings were conducted in different cortical regions, including the primary visual cortex, frontal cortex, EC, and olfactory bulb (Table 3). A comparison of the same region in multiple mice could better inform the conclusion of the results. Despite these variations, spectral power alterations remained present (Fig. 1).

Supporting our findings, our previous study indicated that pTau accumulation is associated with oscillatory changes, mainly reflected in reduced power and frequency, while Aβ is linked to increased power [38]. In the same regard, by studying the 3x-Tg-AD model (Table 2) we have previously described that pTau accumulation in principal cells (PC) and interneurons expressing parvalbumin (PV) primarily leads to a hypoexcitable network state in the hippocampus [21,24,37]. The 3xTg-AD mice harbor mutated human amyloid precursor protein (APP K670), Tau (MAPT P301L), and Presenilin 1 (PSEN1) genes and exhibit cognitive impairments related to Aβ and pTau pathology as early as 4 months of age (Table 2) [44]. More recently, we found that cortical oscillatory alterations were correlated with pTau increases in neocortical PCs in PN30-35 triple-pTau-tg mice (unpublished data). However, previous conclusions were based on the pathogenic interaction between Aβ and pTau driving disease progression (Table 2) [21,37]. In contrast, the conclusions in this study are based solely on pTau as the driver of disease progression. Additionally, the pooled analysis further supports the hypothesis that pTau accumulation has a direct effect on spectral power and that these are modified as the disease progresses.

Aiming to unveil the mechanism behind the hypoexcitable network state, we have shown that this reduction can be explained as a direct effect of the interaction between tau protein and N-Methyl-D-Aspartate (NMDA)-sensitive glutamate receptors [19,21,37,54]. As we reported, the tau protein directly binds to the postsynaptic protein PSD-95 and the hyperphosphorylation of tau leads to the breakdown of the PSD-95-NMDA complex, which reduces NMDA receptor activity and post-synaptic excitability as a consequence [19,21,37,54]. Further supporting our hypothesis, Menkes-Caspi and colleagues demonstrated that non-fibrillar pTau reduces the activity of single neocortical PCs and the neocortical network in young pTau-tg mice [55]. Altogether, the data suggest that the accumulation of pTau, rather than NFTs is sufficient to cause hypoexcitability and impaired oscillatory activity [55].

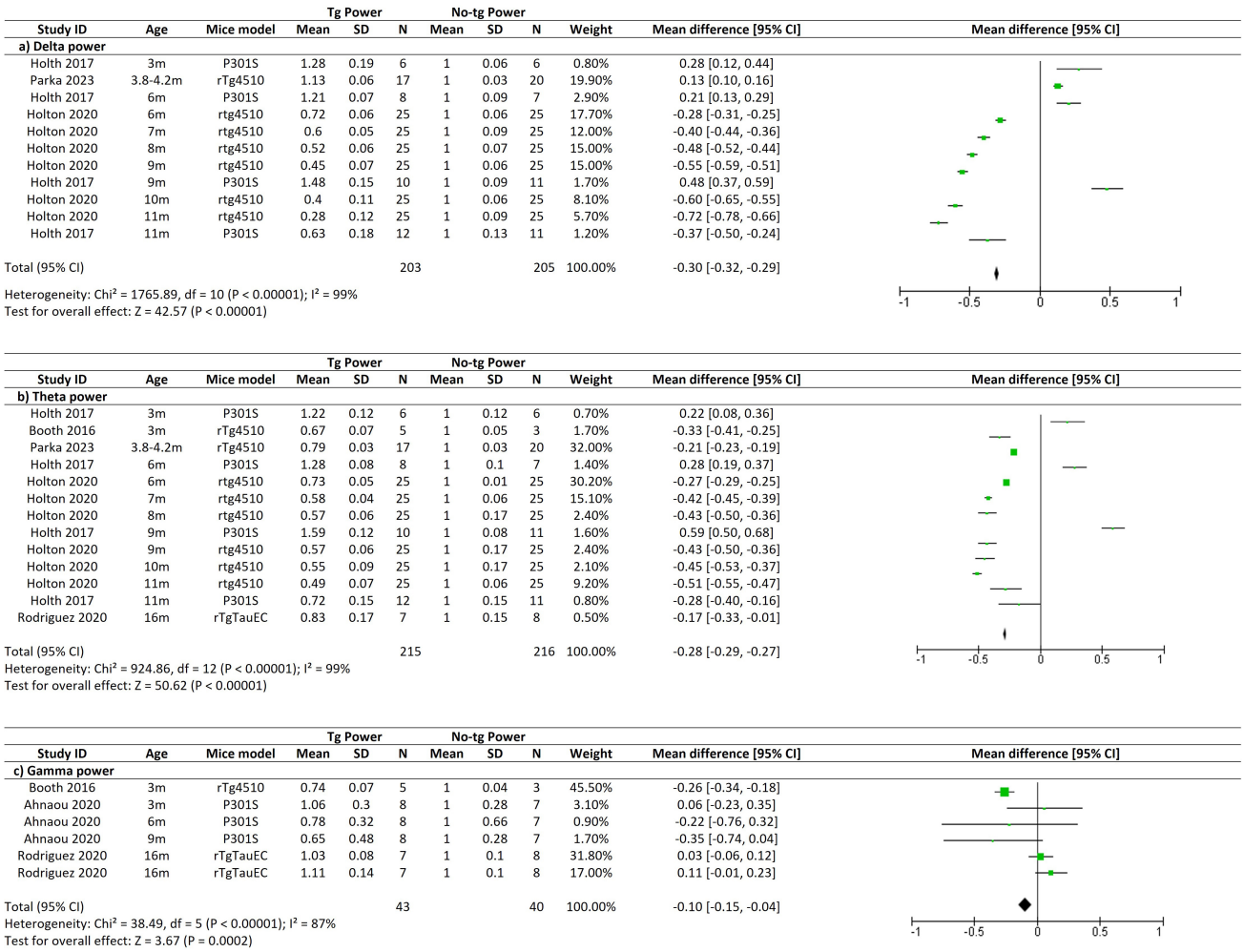

Fig. 1. Forest plot of cortical delta (a), theta (b), and gamma (c) power in pTau-tg mouse models compared with age-matched non-transgenic mice. The size of each green box reflects the weight assigned to the study relative to the combined effect estimate. The horizontal lines represent the 95% confidence interval for each mean difference. The black diamond symbolizes the overall effect estimate from the meta-analysis, with its center indicating the point estimate on the x-axis and its width representing the 95% confidence interval around the pooled effect. Weights are from fixed-effect analysis. Summary includes p = significance level; I^2 = percentage of heterogeneity.

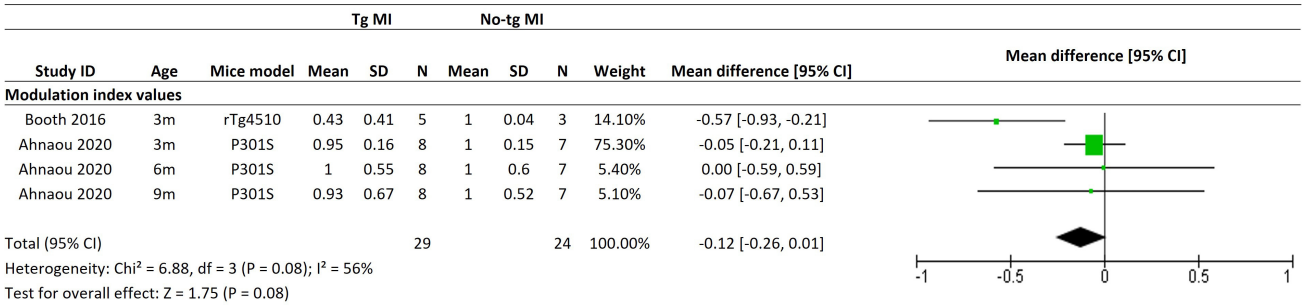

Fig. 2. Forest plot of cortical theta/gamma cross-frequency coupling (modulation index) in pTau-tg mouse models compared with age-matched non-transgenic mice. The size of each green box reflects the weight assigned to the study relative to the combined effect estimate. The horizontal lines represent the 95% confidence interval for each mean difference. The black diamond symbolizes the overall effect estimate from the meta-analysis, with its center indicating the point estimate on the x-axis and its width representing the 95% confidence interval around the pooled effect. Weights are from fixed-effect analysis. Summary includes p = significance level; I^2 = percentage of heterogeneity. MI, modulation index.

Overall, the mechanistic relationship suggests that pTau modulates brain networks through post-synaptic receptors such as NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA). Therefore, a precise understanding of pTau pathophysiology is critical for future therapeutic strategies. Notably, NMDA receptors are highly plastic, leading to a diverse range of subtypes. Since each subtype has distinct biophysical, pharmacological, and signaling properties, there is significant interest in determining whether specific subtypes perform unique functions in the CNS under both normal and pathological conditions.

In the prodromal stages of AD, soluble pTau appears in the EC and hippocampus [40,43]. Surprisingly, this study revealed a significant decrease in the excitability levels of the cortical circuits during the prodromal stages of the disease (Fig. 1). Power analysis of delta, theta, and gamma bands revealed alterations in the early stages of the pathology. Notably, delta amplitude was elevated at younger ages but declined as the mice aged (Fig. 1). In contrast, gamma amplitude progressively decreased with advancing age, while theta amplitude abnormalities remained relatively stable throughout the lifespan. These results suggest that not only the mutation but also the levels of pTau accumulation have a direct effect on spectral power and that these are modified as the disease progresses.

The properties of theta rhythms in the cortex are less studied than those in the hippocampus. However, it is known that hippocampal theta rhythm modulates the firing rate of PCs and PV interneurons [56]. As mentioned, we reported that pTau accumulation in PV cells leads to a reduction in theta power and frequency in the hippocampus [24]. More recently, we found that pTau accumulation in PV cells and neocortical PCs accounts for the reduction in theta power and frequency in the cortex (unpublished data). Because PV cells are responsible for the modulation of these rhythms [57] molecular alterations in this type of cell could be responsible for network disruption. Interestingly, the meta-analysis revealed that theta power is also reduced in the cortex (Fig. 1), suggesting a disrupted synchronous activity between PCs and PV interneurons. More research into the role of pTau in cortical PCs and PV cells is needed to understand brain network modulation in pathology.

Additionally, the pooled analysis showed that reductions in excitability levels are exacerbated in mouse models experiencing significant neuronal loss, particularly in the rTg4510 mouse line (Fig. 1). Specifically, delta power decreases were predominantly observed at ages corresponding to significant cell loss in these models (Fig. 1). Holth and colleagues [50] suggested that reduced power is linked to decreased cortical volume and neuronal loss in pTau-tg mice. However, the pooled analysis also demonstrated that decreases in theta and gamma power occur from early (3 months) and these remained until the late stage of disease (Fig. 1). Importantly, the rTg4510 mouse model does not exhibit cell loss at 3 months of age.

Furthermore, using the rTg4510 line, we previously demonstrated that power changes occur before neuronal loss becomes apparent [24]. Specifically, our results showed that neurons from PN30-35 rTg4510 mice accumulate pTau protein and power reductions in hippocampal oscillatory activity [24]. Collectively, these findings provide a foundation for the role of pTau in modulating brain network activity during pathology development, even before neuronal loss occurs [21,24,37].

Since cognitive functions rely on precise brain network activity patterns, early network dysfunction including neuronal hypoactivity, altered oscillatory activity, and disrupted neuronal synchrony, could play a crucial role in driving neurodegeneration. Therefore, restoring brain circuit activity represents a promising therapeutic strategy for preserving brain function. Optogenetics enables precise manipulation of specific cell types and brain circuits with minimal tissue damage and side effects [58,59]. As previously noted, PV interneurons play a key role in coordinating brain rhythms. To restore brain activity, we performed optogenetic activation of PV cells in the J20 transgenic model [30]. Using a linearly increasing sinusoidal frequency (0–12 Hz), transgenic mice responded reliably to light stimulation generating theta oscillations and gamma rhythms (both slow and fast) embedded within the theta cycles [30]. In summary, by modulating PV interneurons allows optogenetic control of theta amplitude and frequency [30]. Moving forward, we propose developing optogenetic protocols that target not only PV interneurons but also other brain cells essential for theta-gamma generation and modulation. Notably, optogenetic interventions have shown the most promising results during the prodromal stages of disease progression.

Detecting early-stage dementia remains a critical challenge in disease management. In AD, neurodegenerative processes begin decades before cortical atrophy becomes detectable through conventional neuroimaging techniques [45]. Our findings highlight electroencephalogram (EEG) as a valuable tool for detecting cortical alterations that precede macrostructural changes. Specifically, hippocampal alterations, primarily driven by pTau accumulation, extend to the cortex, further supporting the hypothesis that electrophysiological changes could serve as an early biomarker.

Alterations in EEG spectral power have already been used as a predictive marker of cognitive decline and as distinguishing features between AD and mild cognitive impairment (MCI) patients compared to healthy individuals [14,60,61]. For instance, EEG analyses have shown that patients with frontotemporal dementia, Parkinson's disease, and AD exhibit decreased delta power density alongside cognitive impairments and cortical dysfunction [62,63]. Early detection not only enhances diagnostic accuracy but

also opens the door for novel therapeutic strategies with potential clinical applications.

In summary, the pooled analysis showed that cortical oscillatory alterations are present from the prodromal stage to the advanced stage of disease progression (Fig. 1). The prodromal stage in pTau-tg mice is characterized by pretangle phosphorylated tau protein, a soluble precursor of NFTs, and not characterized by neuronal loss [24]. All pTau-tg mice included in the present study were characterized by soluble pTau at the prodromal stage and insoluble pTau as the mice aged. Adding to the substantial levels of heterogeneity in our meta-analysis, spatiotemporal dynamics of soluble and insoluble pTau were specific for each model.

Importantly, early soluble pTau directly downregulates NMDA receptor activation, acting as a neuroprotective mechanism that prevents NMDA receptor overexcitation [21]. However, the data suggests that chronic NMDA receptor downregulation leads to the alterations in cortical oscillatory activity and to the progressive deterioration of the brain circuits. Overall, additional studies on how the spatiotemporal progression of pTau affects glutamate receptors are much needed.

Despite this, the fact that cortical oscillatory changes were found since the prodromal stages of the disease further suggests that accumulation of pTau rather than NFTs, is sufficient to impair oscillatory activity and cognitive function [55].

As previously mentioned, low oscillatory rhythms (theta) are believed to assist cognitive processes by coding with faster oscillatory rhythms (gamma), a phenomenon called CFC [10]. Its strength relies on theta power as well as theta phase [10]. Not surprisingly, theta-gamma coupling has been reported as altered in dementia patients [16]. For instance, impaired CFC was correlated with MCI patients [16,64]. Parkinson's disease patients with MCI are characterized by a reduction in theta-gamma coupling and an increase in delta-theta coupling during cognitive tasks [65]. However, the combined analysis of our meta-analysis showed no alterations in theta/gamma modulation index in pTau-tg models (Fig. 2). The results are consistent with our previous study, which found that theta/gamma modulation index values remain unchanged in the hippocampus of pTau-tg models in the early stages [38]. Providing further support, we reported that the PN30-35 g rTg4510 mouse model (Table 2) has no detectable changes in hippocampal dependent tasks, such as spontaneous alternation and nesting, or locomotor activity [24].

In summary, the data suggests that non-fibrillar pTau is not sufficient to impair CFC during prodromal stages in pTau-tg models (Fig. 2). Concomitantly, hyperphosphorylation of tau could serve as a regulatory mechanism to prevent NMDA receptor overexcitation during early stages of disease progression [21].

Despite the compensatory mechanisms that prevent NMDA receptor overexcitation, the pooled analysis of the studies showed that power density variations were observed during the early stages of disease evolution, suggesting that they could be potential preclinical indicators. Thus, the finding of reduced delta, theta, and gamma power in the cortex of pTau-tg models showed that the brain network is affected across various levels. These results agree with analysis on patients with neurodegeneration.

5. Conclusions

This study has revealed that cortical network activity is altered in pTau-tg models. To our knowledge, this is the first meta-analysis that gathers the oscillatory impact of pTau accumulation in the cortex. The analysis allowed us to describe the effect of pTau accumulation in cortical networks. Overall, the findings in this meta-analysis revealed that pTau accumulation alters neuronal activity in the cortex from early stages of the disease and persists until advanced stages. Importantly, the detection of early stages of dementia constitutes one of the primary challenges in disease management. These results further support the hypothesis that cortical oscillatory changes could be used as a biomarker.

Disclosure

This manuscript is part of the requirements for obtaining a doctoral degree at the Posgrado en Ciencias Biológicas, UNAM, by CAGC.

Abbreviations

AD, Alzheimer's disease; CFC, cross frequency coupling; EEG, electroencephalogram; FTD, frontotemporal dementia; LFP, local field potential; MCI, mild cognitive impairment; NFT, neurofibrillary tangles; pTau, hyperphosphorylated tau.

Availability of Data and Materials

Data is available on request due to privacy/ethical restrictions.

Author Contributions

CAGC and SMR designed the research study. CAGC performed the research. CAGC and SMR analyzed the data. CAGC and SMR wrote the manuscript. GBI and CCR contributed to formal analysis, editing and funding. GP contributed to conception, editing and funding. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN39192.

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