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The Interaction Between Tau and Microglia-induced Neuroinflammation as a Cause of Alzheimer's Disease: A Computational Study

Sai Yashasvi Kasthala
saikasthala22@gmail.com

ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by gradual cognitive decline, memory loss, and neuronal death. Physically, AD is marked by amyloid-beta plaques, tau pathology, and neuroinflammation. While these processes, especially amyloid-beta, are usually studied independently, emerging evidence suggests they interact in a feedback loop that accelerates disease progression. This study aims to explore the impact of microglial activation on the rate of tau aggregation and propagation in Alzheimer's disease. A computational approach using Complex Pathway Simulator (COPASI) was implemented, using both a full brain model and a regional model with multiple, interconnected compartments representing Braak regions. Microglia activation levels were varied across three conditions (low, medium, high) and tau accumulation, propagation, and aggregation dynamics were examined. Results showed that increased microglial activation increased tau exposure, accelerated aggregation, and reduced the time to peak aggregation rate. However, final tau burden remained relatively stable, which could be attributed to system saturation. In the regional model, higher activation led to an increased impact in later Braak stages, and Braak staging was preserved throughout the simulation. These findings support the idea that neuroinflammation amplifies tau pathology through a positive feedback loop. It is also possible that microglial activation primarily impacts the rate of the processes rather than the magnitude of the processes themselves. This study highlights the importance of computational modeling in isolating variables, such that causal inferences may be drawn, and suggests that early, anti-inflammatory interventions may be critical for slowing disease progression.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is characterized by cognitive decline and widespread neuronal loss. It currently ranks as one of the leading causes of disability among the elderly, accounting for 60% to 70% of all dementia cases [1]. As of 2022, there were an estimated 7.2 million individuals living with AD in the United States alone. This number is predicted to increase to 13.8 million by 2060 [2].

Despite advances in the understanding of AD, its cause remains unknown. The pathophysiology of AD reveals two major markers: neuritic plaques (NPs) and neurofibrillary tangles (NFTs) [1]. Based on these markers, two main hypotheses for the cause of AD have been proposed. The first is the amyloid-beta cascade hypothesis (ACH), which suggests that AD is caused by the accumulation of toxic amyloid-beta in the form of plaques within the brain [3]. The second is the tau theory, which suggests that misfolding and aggregation of the tau protein, caused by hyperphosphorylation, leads to the formation of NFTs as misfolded tau builds up in the brain, disrupting axonal function and causing neuron death [4]. Additionally, neuroinflammation, caused by the activation of the microglial cells (immune cells of the brain), also seems to be a hallmark of Alzheimer's progression.

While early research on Alzheimer's, from 1999 to 2015, has emphasized the formation of amyloid-beta plaques as the primary causal factor of AD, emerging evidence, inconsistent results, and inconclusive therapeutic trials have led researchers to look elsewhere for the answers as to what causes AD. The paradigm shift that occurred in 2015 was best exemplified by the seminal critique of Karl Herrup, who argued that the existing Alzheimer's model was flawed due to its overreliance on amyloid-beta as the causal factor. Furthermore, Herrup produced evidence that showed individuals who were amyloid-positive maintained their cognitive health, or in other words, not all individuals with amyloid-beta plaques had or developed AD [5]. Therapeutic trials that targeted amyloid-beta in order to treat AD resulted in inconsistent findings, further undermining the credibility of the ACH [1].

Tau Protein and Neurodegeneration in Alzheimer's Disease

The growing disillusionment with the ACH has led researchers to study the tau protein as the cause of Alzheimer's disease. Tau pathology has emerged as a strong correlate of neuronal death and loss of cognitive function in AD. In a healthy individual, the tau protein serves to stabilize microtubules and support axonal transport. However, hyperphosphorylation leads to the misfolding of the tau protein, causing it to clump together in clusters that grow into neurofibrillary tangles. This disrupts axonal transport, having a direct impact on the health of the neurons in the brain [4]. This idea is further reinforced by data suggesting that the spatial distribution of aggregated tau is more closely associated with neurodegeneration than that of amyloid-beta [6]. However, tau aggregation does not occur in isolation. An ever-increasing body of evidence indicates that tau pathology interacts with other biological processes, particularly neuroinflammation, to accelerate neuronal damage.

Figure 1. Representative PET Scans of Spatial Tau Distribution in Healthy vs. Alzheimer's Brains

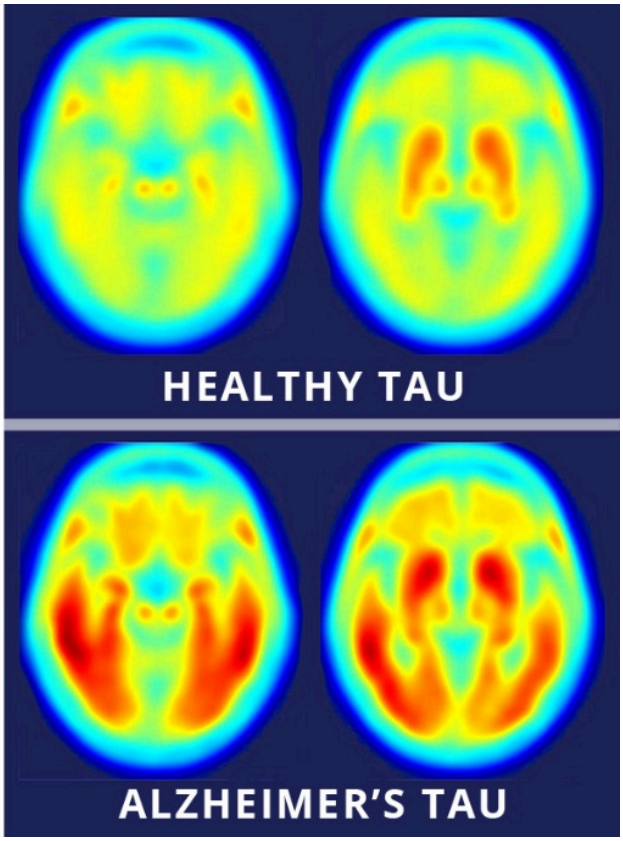

Figure 1. Representative PET scans of spatial tau distribution in Healthy vs. Alzheimer's Brains. The top panel represents baseline tau presence in a cognitively-normal individual. The bottom panel represents elevated and extensive tau accumulation characteristic of AD pathology. Image adapted courtesy of Washington University School of Medicine [7].

Neuroinflammation and Microglial Activation in Alzheimer's Disease

Neuroinflammation has been strongly implicated with respect to Alzheimer's progression across all disease stages. Microglial cells, the primary immune cells of the brain, respond to pathological threats by activating, thereby inducing neuroinflammation [8]. Microglial cells tend to aid in the fight against Alzheimer's in the early stages of disease progression by clearing up tau aggregates and amyloid-beta plaques [1,8]. On the other hand, during the middle and late stages of disease progression, microglial activation tends to exacerbate tau aggregation by releasing pro-inflammatory cytokines, kinases, and inflammasomes that exacerbate neuronal injury [1,8-10]. While this is the most accepted understanding of the role of microglia in Alzheimer's, some studies point to increased microglial dystrophy as the cause of

neurodegeneration in AD [11]. This disparity in the role of microglial cells in AD reinforces a gap that must be addressed in Alzheimer's research in order to gain a better understanding of disease pathogenesis; gaining more information on how microglial activation truly exacerbates tau aggregation may result in therapeutic implications that could accelerate the effectiveness of interventions in AD patients.

Molecular Interplay Between Tau Pathology and Neuroinflammation

Tau pathology and neuroinflammation are increasingly understood as interacting components of a pathological cycle rather than independent contributors to AD progression.

Neuroinflammation as an Exacerbator of Tau Aggregation

At the molecular level, neuroinflammation actively accelerates tau aggregation through microglia-mediated signaling pathways. The activation of microglial cells induces the release of kinases such as p38 MAPK, which promote tau hyperphosphorylation [9]. In a study examining the effect of inflammatory stimuli in mice with FTD, another tauopathy similar to AD, it was shown that these stimuli significantly accelerated tau aggregation and propagation across neurons [10]. These findings indicate that neuroinflammation is a driving force in the spread of tau pathology in Alzheimer's.

Tau-Induced Microglial Activation

Similarly, tau pathology itself contributes to neuroinflammation. Misfolded tau applied to microglial cultures induced proinflammatory cytokines, characteristic of microglial activation [12]. Reviews focusing on the mechanistic processes behind AD emphasize the role of aggregated tau in contributing to microglial activation, leading to inflammatory signaling and neuronal dysfunction [4]. These studies indicate that tau pathology and neuroinflammation are deeply intertwined in a feedback loop, as tau pathology induces a microglial response, which in turn exacerbates tau aggregation. However, the methodologies used in the mentioned studies seem unvaried (primarily systematic reviews), which suggests that a computational approach may provide new insights into the topic of inquiry.

In Vivo and Neuroimaging Evidence of Tau-Neuroinflammation Co-Localization

In vivo studies and neuroimaging provide further evidence of the close association between tau and neuroinflammation. Positron emission tomography (PET) imaging and magnetic resonance imaging (MRI) reveal a strong correlation between the spatial distribution of aggregated tau and the markers of neuroinflammation [6]. The relationship between tau and neuroinflammation is also supported temporally. Longitudinal imaging and in vivo studies in primates have shown that early tau deposition in certain brain regions elicits a heightened neuroinflammatory response, suggesting a close temporal relationship between the two pathological processes [13].

Methodological Limitations in Existing Literature

Despite an emerging consensus regarding the interaction between tau pathology and neuroinflammation, limited methodological practices constrain the field. Many studies rely on animal models, which may not fully replicate the relationship between these pathological processes within a human context. While neuroimaging studies are useful, they are mainly correlational and lack predictive capacity. Additionally, many researchers isolate tau pathology and neuroinflammation as separate, unrelated processes that independently contribute to AD progression, failing to consider their interactions within a dynamic system. This methodological homogeneity prevents meaningful translational potential and causal capabilities.

Conclusion of Literature Review

Contributions of Existing Literature

Taken together, the literature in this field significantly advances AD research by reconsidering the role of aggregated tau and neuroinflammation as interacting pathological features that work together in a feedback loop to contribute to neurodegeneration. By using animal models, neuroimaging, and systematic reviews, researchers have developed a strong mechanistic understanding of how tau pathology and neuroinflammation spread during disease progression.

Identified Gap

In the existing literature relating to tau and neuroinflammation, there are few studies that rely on computational modeling software to simulate the effect of microglial activation on the spatiotemporal spread of tau pathology in AD progression. The homogeneous methodologies of the field undermine the credibility of the findings, implying that the consistency may be due to the similarity in how the study is carried out. Furthermore, the ability of computational models to isolate a single variable and simulate changes in the system allow for greater causal inferences that may provide insight into the true role of microglia in AD progression. By pursuing a computational approach to explore the relationship between tau pathology and neuroinflammation in AD, the findings of the studies previously mentioned could be reinforced.

Hypothesis and Assumptions

The existing body of literature indicates that tau pathology and neuroinflammatory processes interact on the molecular level as opposed to acting as independent drivers of AD. This study is guided by the research question: How does microglial activation influence the rate of tau aggregation and propagation across neurons in Alzheimer’s Disease?

It is hypothesized that increased microglial activation exacerbates tau aggregation and propagation by accelerating kinase-mediated tau hyperphosphorylation. In other words, increased neuroinflammatory signaling mediated by microglial cells results in increased tau hyperphosphorylation, leading to greater accumulation and spread of aggregated tau across neurons.

This study assumes that the complex biological interactions between tau pathology and neuroinflammation can be reasonably approximated using a systems-level computational model. In other words, microglial activation and its effects can be sufficiently represented through parameterized biochemical pathways modeled in a Complex Pathway Simulator (COPASI) [14]. It is also assumed that the relationships observed between neuroinflammation and tau pathology in a COPASI model reflect biological processes closely enough so as to be able to model said processes correctly. Additionally, this study assumes that the spread of tau pathology occurs through Braak staging—the scientifically accepted path of tau progression across the brain in Alzheimer's disease—such that tau pathology spreads in a linear chain through each of the Braak regions. Though this is a simplification, it is assumed that it is sufficient to accurately model the interregional propagation. By using computational modeling to simulate Alzheimer's progression, this study may help validate an already held belief in an emerging field regarding the relationship between tau and neuroinflammation. It may reinforce the credibility of the tau theory using computational modeling, leading to increased support for research on therapeutic intervention possibilities in AD that relate to tau and neuroinflammation.

Conclusion

In sum, following the decline of the ACH, researchers have started to explore tau pathology as a cause of AD. An increasing body of evidence suggests that tau pathology and neuroinflammation (marked by microglial activation) interact in a positive feedback loop in order to increase the spatiotemporal spread of tau pathology and increase the rate of tau aggregation. Methodological homogeneity in this field, marked by a lack of computational studies, stands out as a major shortcoming of existing research. This study aims to address this shortcoming by implementing a COPASI model to examine the impact of microglial activation on tau pathology, to ultimately answer the question: How does microglial activation influence the rate of tau aggregation and propagation across neurons in Alzheimer's Disease?

METHODS

The objective of this research is to investigate the influence of microglial activation on the rate of tau aggregation and propagation, and the overall relationship to Alzheimer's progression. To achieve this, a two-model, computational design was implemented using the biochemical pathway modeling software COPASI. Computational modeling, particularly user-friendly simulators like COPASI, is accepted in systems biology research as a practical way to simulate intricate biochemical processes. COPASI is a widely used platform for simulating biochemical systems in the form of ordinary differential equations (ODEs) [14, 15]. The reaction-based foundation of the COPASI model allows for increased accuracy when evaluating the impact of certain variables, like microglial activation, on tau pathology. All

differential equations were implemented as custom reaction rate laws within COPASI, which utilized an ODE solver (LSODA) to integrate the system over the defined time period.

Variables

In order to create the model, certain variables were established within the study's structure. The primary independent variable was the level of microglial activation, which directly relates to the severity of the neuroinflammation that induces tau pathology in the positive feedback loop. It is represented through three distinct biological states for low activation, moderate activation, and high activation. The variables being measured were the rate of tau aggregation and the pattern of tau propagation. Further parameters were defined to ensure validity across all test cases.

Table 1. Parameter Values Used in Model

Parameter	Value	Meaning
α	0.08	Baseline tau aggregation rate
β	0.04	Tau propagation strength
$\gamma_{baseline}$	0.06	Baseline tau hyperphosphorylation
$\gamma_{amplification}$	0.15	Neuroinflammation-driven acceleration of tau aggregation
δ	0.008	Tau clearance
T_{max}	1	Maximum tau burden (normalized)
κ	1.5	Maximum microglial activation rate
η	0.02	Microglial decay

Table 1. Parameter values used in the COPASI model. Parameter values were selected to represent biologically plausible rates with regard to Alzheimer's pathogenesis as reported in pre-existing literature. Parameters values were drawn from other computational representations of Alzheimer's disease as well. All parameters were normalized to a scale of 0 to 1. Each parameter reflects relative strengths rather than absolute quantities. The rate of tau accumulation ($\alpha = 0.08$) was chosen in order to accurately represent the gradual buildup of tau, ensuring that it stayed consistent with the observed progression of tau pathology. The tau propagation strength ($\beta = 0.04$), or the fractional contribution of neighboring tau over time, was scaled accordingly [16]. The baseline rate of tau hyperphosphorylation ($\gamma_{baseline} = 0.06$) and the neuroinflammation-driven acceleration of tau aggregation ($\gamma_{amplification} = 0.15$) were set such that both would moderately accelerate the rate of tau aggregation, with $\gamma_{amplification}$ being greater than $\gamma_{baseline}$ so that microglial activation would have a pronounced effect on the rate of tau aggregation. The rate of tau clearance ($\delta = 0.008$) was set so that tau clearance would be much slower than tau aggregation, accurately reflecting disease dynamics in Alzheimer's. The same was done with the rate of microglial clearance ($\eta = 0.02$). The maximum tau burden and the maximum microglial activation rate were both set to represent saturated, logistic growth [17].

Model Structure

Two complementary COPASI models were constructed to examine the effect of microglial activation on tau pathology at different levels of biological specificity.

Conceptual Structure

To best understand the models' structure, one must first gain a sophisticated understanding of the positive feedback loop that governs the model's architecture and AD progression. In the healthy brain, the tau protein stabilizes microtubules, allowing for axonal transport, while the microglial cells clear cellular debris and toxic aggregates. However, in AD, tau proteins undergo hyperphosphorylation, causing them to misfold and clump together into tau aggregates, which later develop into NFTs. This aggregation activates the microglial cells, which release proinflammatory signals [4, 12]. While meant to clear up the toxic products, sustained exposure to tau pathology causes the microglial cells to overcompensate, leading to further neuronal damage and tau aggregation [9, 10].

Figure 2. Flowchart of Feedback Loop Governing COPASI Models

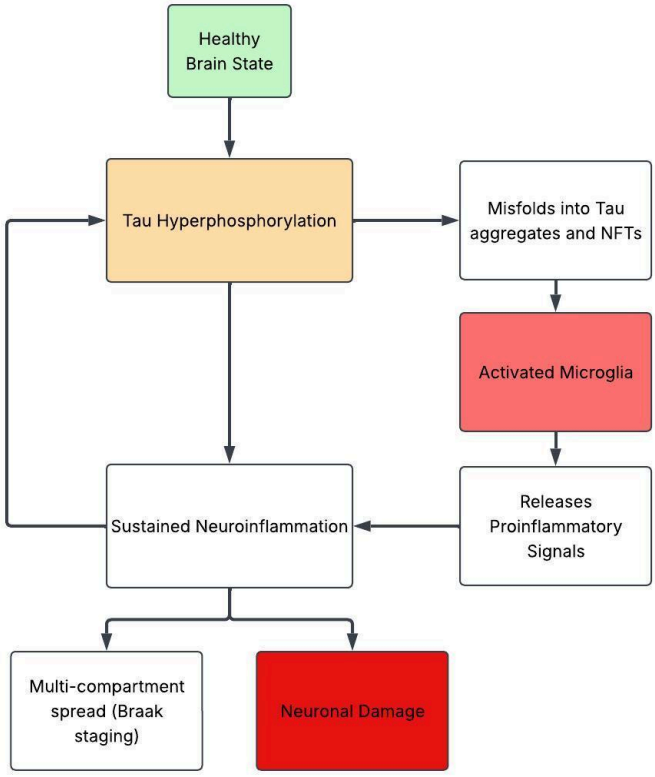

Figure 2. Flowchart of the feedback loop that governs the COPASI models.

The differential equations that govern the models' processes are designed to simulate this positive feedback loop. Instead of separating tau aggregation and neuroinflammation as two distinct events, each event influences the rate of the other. This way, the models treat them as the feedback loop described earlier.

Full-Brain Model

The first model treats the brain as a single compartment containing two interacting species, defined as tau (τ) and microglia (M). Tau was given an initial value of 0.08, representing the seeded tau within the entorhinal cortex. The initial value of microglia varied according to the defined level of activation (M = 0.2, 0.5, 0.8 for low, medium, and high, respectively). The differential equations governing tau growth and microglial activation were implemented as 4 separate rate laws derived from other computational representations of Alzheimer's disease [16]:

$$Tau\ Growth = \alpha\tau\left(1 - \frac{\tau}{T_{max}}\right) + \left(\gamma_{baseline} + \gamma_{amplification} * M\right)\tau\left(1 - \frac{\tau}{T_{max}}\right)$$

$$Tau\ Clearance = \delta * \tau$$

$$Microglial\ Activation = \kappa * \frac{\tau^2}{1+\tau^2}\left(1 - \frac{M}{M_{max}}\right)$$

$$Microglial\ Decay = \eta * M$$

This mathematical architecture defines the tau burden as a logistic equation, rather than modeling it linearly. Additionally, the tau burden is dependent on microglial activation. The microglial equation allows for tau to activate microglial cells, representing the positive feedback loop discussed earlier in the literature review. A parameter scan task was run for the microglial activation condition, producing a time-course simulation for 20 time units. It should be noted that T_{max} was set to 50 for the full brain model, so as to prevent the suppression of growth and to compensate for the lumping of all the brain regions into one compartment.

Multi-Compartment Regional Model

The second model extended the single-compartment framework to a six-compartment architecture, such that each compartment represented a brain region associated with each of the Braak stages. The six compartments were as follows: the entorhinal cortex (Stage I), the hippocampus (Stage II), the posterior cingulate (Stage III), the temporal cortex (Stage IV), the frontal cortex (Stage V), and the occipital cortex (Stage VI). Each compartment contained its own tau species and its own microglia species.

Within each compartment, four reaction processes impacted tau pathology. The first was the baseline tau aggregation, followed by the inflammation-driven tau aggregation, then tau clearance, and finally,

propagation reactions. The aggregation reactions and clearance reaction were adapted from the equations defined previously. The propagation reactions supported a linear chain propagation mechanism, and utilized the following mass-action formula:

$$Tau\ Propagation = \beta * \tau_n$$

It should be noted that n represents the Braak stage that the tau species corresponds to. This propagation structure reinforces Braak staging. Microglial activation and decay within each compartment followed the same mechanisms as defined in the full-brain model, with each compartment's microglial activation driven by the tau burden. Tau was seeded in the entorhinal cortex (Tau_I = 0.08) at t = 0, consistent with Braak staging. All three activation conditions were simulated for 24 time units.

Procedure

The research followed a structured four-step procedure to generate and analyze the primary data using the model. The first step consisted of system initialization for both models in COPASI, in which the global quantities (parameters), species, compartments, and reactions were defined. Next, time-course simulations were run using COPASI's LSODA solver for all three activation conditions. It should be noted that at this stage, the single-compartment, full brain model utilized a parameter scan to run a time-course analysis for all activation conditions simultaneously, while the initial values for microglial activation were manually changed in the six-compartment, regional model. Then, simulation outputs were exported as plotted sigmoidal functions and time-series files containing the concentration of each species at a given time point. Finally, the exported data was analyzed to extract key measurements, including the final total tau burden, the cumulative tau exposure given by the area under the curve, the time to 50% maximum tau burden, and the time and magnitude of peak aggregation rate, as well as the final regional tau burden per Braak stage.

Ethical Considerations

This study utilized COPASI biochemical modeling software to simulate tau spread across brain regions. Since the research only involves computational simulations and does not utilize human data or animal testing, it is exempt from ethical review.

RESULTS

Global Tau Dynamics Across Activation States

To examine the impact of microglial activation on the accumulation of tau pathology, the full brain model was run under three activation states (low: M = 0.2, medium: M = 0.5, high: M = 0.8) for 20 time units. Total tau burden consistently increased across all activation conditions. Yet, the final total tau values were relatively consistent across all activation states, suggesting the ultimate saturation of the system given sufficient time. Total tau concentration reached 49.21 for low activation, 49.77 for medium activation, and 49.81 for high activation (Table 2). Cumulative tau exposure, measured by the area under the curve (AUC), indicated a greater exposure with increasing activation state. The low activation yielded a tau exposure of 164.97, the medium a tau exposure of 257.21, and the high a tau exposure of 328.22. The increase in the AUC clearly supports the hypothesis as, despite system saturation limiting maximum accumulation, higher levels of microglial activation resulted in increased tau exposure at an earlier timeline. In other words, with increasing neuroinflammation, the brain saw more exposure to toxic tau species at an earlier time.

Table 2. Summary of Global Tau Dynamics Across Microglial Activation Conditions

Metric	Low	Medium	High
Final Total Tau	49.21	49.77	49.81
AUC (Cumulative)	164.97	257.21	328.22
Time to 50% Neurons Affected	t = 16.91	t = 15.06	t = 13.62
Time to Peak Aggregation Rate	t = 17.1	t = 15.24	t = 13.78
Peak Aggregation Rate	15.31	15.36	15.42

Table 2. Summary of global tau dynamics across microglial activation conditions. Values adapted from COPASI model output

Propagation Speed and the Rate of Aggregation

Microglial activation also significantly impacted the speed of tau propagation. In all conditions, tau propagation followed a sigmoidal curve, with a slow early stage, a rapid middle stage, and a plateauing late stage as the system becomes saturated (Figure 3). The time at which 50% of the neurons were affected varied across the activation states, with a higher state corresponding to a faster time. For the low

activation state, the time at which 50% of neurons were affected was t = 16.91; for the medium activation state, t = 15.06; and for the high activation state, t = 13.62 (Table 2). Furthermore, the peak aggregation rate shifted earlier with increasing microglial activation, with low activation peaking at t = 17.1, medium activation peaking at t = 15.24, and high activation peaking at t = 13.78. The leftward shift in both time to 50% neurons affected and time to peak aggregation rate explicitly validates the hypothesis that microglial activation is a kinetic mediator of tau spread, with increased levels of neuroinflammation leading to increased compression of temporal pathways of tau pathology.

Figure 3. Tau Accumulation and Aggregation Dynamics Across Activation States

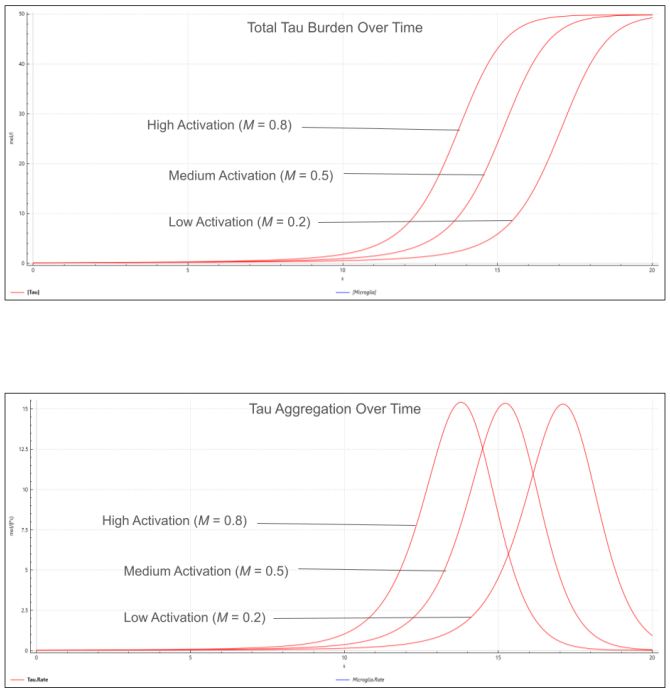

Figure 3. Tau accumulation and aggregation dynamics across activation states.

Regional and Braak Stage Progression

The six-compartment regional model was simulated for 24 units across the three microglial activation states. The sequence of the spread of tau pathology followed Braak Stage Progression in all three conditions. The entorhinal cortex (Stage I), seeded at τ=0.08, exhibited the highest tau burden at every timepoint across all conditions. Tau then spread to the hippocampus (Stage II), followed by the posterior cingulate region (Stage III), the temporal cortex (Stage IV), the frontal cortex (Stage V), and finally the occipital cortex (Stage VI), as consistent with standard Braak staging [18]. Though the sequence of regional progression remained consistent, the microglial activation state influenced the rate at which each

region reached high tau burden, as demonstrated by the final states of tau burden in each activation state. Differences between conditions became increasingly significant in later Braak stages, where tau spread has not yet saturated (Table 3). This demonstrates that anatomical connectivity determines the sequence of tau spread, and that microglial activation increases the speed of propagation, further validating the hypothesis.

Table 3. Regional Tau Burden at t = 24 Across Microglial Activation States

Brain Region (Braak Stage)	**Low (M = 0.2)**	**Medium (M = 0.5)**	**High (M = 0.8)**
Entorhinal Cortex (I)	0.937	0.938	0.939
Hippocampus (II)	0.912	0.931	0.942
Posterior Cingulate (III)	0.661	0.769	0.840
Temporal Cortex (IV)	0.263	0.392	0.534
Frontal Cortex (V)	0.070	0.122	0.202
Occipital Cortex (VI)	0.017	0.032	0.061

Table 3. Regional tau burden at t = 24 across microglial activation states.

DISCUSSION

Alzheimer's Disease has increasingly been thought of as a network-driven disorder in which tau pathology spreads across interconnected brain regions. In this study, two COPASI computational models were used to examine the way microglial activation influences tau aggregation and propagation in AD. The results of this study demonstrate that higher levels of microglial activation accelerate tau accumulation, aggregation, and increase tau exposure while the spread of tau pathology adheres to Braak staging.

Neuroinflammation's Acceleration of Tau Pathology

The finding that higher microglial activation amplifies the rate of tau aggregation and increases tau accumulation is consistent with existing literature on this subject [9, 10]. The findings of this study suggest that higher levels of microglial activation increase tau aggregation, resulting in earlier peak aggregation timing, extending existing ideas by quantifying the increases in the rate of aggregation and propagation. It should be noted that the computational approach is especially valuable in this scenario, as it is able to neatly isolate microglial activation as a single variable while keeping other parameters

constant, something that is difficult to do within a live biological system such as an animal model or a neuroimaging study [6, 13]. This ability to isolate a single variable may contribute to a clearer understanding of the mechanistic effects of neuroinflammation on the spread and accumulation of tau pathology. Additionally, tau burden in all conditions followed a sigmoidal trajectory, confirming previously observed patterns [17].

It should also be noted that final tau burden remained nearly identical across all activation conditions despite significant differences in tau exposure represented by the area under the curve. This finding indicates that microglial activation does not increase the maximum tau burden; rather, it compresses the disease timeline such that there is an earlier, and by extension, more prolonged exposure, to tau pathology. These findings lend credibility to the activation-based understanding of the role of microglia in AD, as increased activation accelerated tau pathology despite microglial clearance (given by $\eta*M$). If microglial dystrophy were the driver of AD progression, as suggested by Paasila et al. [11], higher M values would have not contributed to accelerated tau pathology. Instead, the findings of this study suggest that increased microglial activation exacerbates tau pathology, reinforcing the feedback loop supported by Chen & Yu [1].

Regional Pattern of Spread

Despite differences in the rate of aggregation and propagation of tau across microglial activation levels, the sequence of spread remained identical, following Braak staging. This finding confirms the computational Nexis framework proposed by Anand et al., showing that the structure of the model influences the pattern of tau spread rather than inflammatory factors within the system [16]. The most significant regional differences emerged in later Braak stages. While the tau burden in the entorhinal cortex was nearly identical across all conditions at $t = 24$, indicating the saturation of the region, the differences in tau burden in stages III to VI were particularly noteworthy, suggesting that the amplifying effect of microglial activation is more noticeable in later Braak stages. The preservation of Braak staging implies that the order of regional spread is not disrupted; rather, it is the speed at which each stage is reached that changes with increasing microglial activation. This finding extends the Nexis framework used by other researchers and tau-neuroinflammation co-localization findings by quantifying the degree to which microglial activation modifies the spatial pattern and rate of spread [6, 13, 15]. System saturation represents both a biological reality and a computational limitation in the case of this model. This saturation was a result of the logarithmic differential equations that were used to form the mathematical architecture of this model, producing a maximum tau ceiling that caused the burden to flatten out when it reached a certain level (which was nearly reached by all activation states). However, this is based on biological reality, as it reinforces the sigmoidal trajectory validated by Crespo et al. [17]. This feature of the model could be further validated using longitudinal data from datasets like ADNI or OASIS, which may provide insight into system saturation of tau burden using neuroimaging.

CONCLUSION

Implications

The results of this study have several implications for therapeutic interventions in Alzheimer's disease. The reduction of time to tau spread and burden between the different activation states shows that higher levels of neuroinflammation exacerbate tau pathology and spread during AD. This finding, coupled with the extensive cumulative tau exposure that results from the compressed timeline due to neuroinflammation, indicates that delayed intervention may pose significant risks. Thus, these findings give way to two suggestions: that anti-inflammatory treatments may prove effective in combatting the spread of tau pathology to slow disease progression, and that these treatments must be administered early, prior to increased tau spread and, by extension, levels of neuroinflammation. Additionally, these findings also suggest that targeting microglial activation may prove more effective than targeting tau pathology/aggregation alone, as it disrupts the positive feedback loop, and since the differences in microglial activation levels accounted for the severity of tau spread and accumulation in this model. Targeting neuroinflammation in this way could be achieved by inhibiting the function of key molecular mediators, such as the NLRP3 inflammasome, which, when rendered non-functional, resulted in reduced tau hyperphosphorylation and aggregation [10]. Targeting such mediators early may result in benefits for slowing AD progression.

Limitations

Because this study uses two COPASI models, it does not directly account for the molecular mediators of the neuroinflammation-tau feedback loop, such as kinases and inflammasomes. Additionally, the model focuses solely on microglial cells, rather than all related immune cells, like astrocytes, oligodendrocytes, and other glial cells. Furthermore, these models simplify tau propagation, simulating its diffusion as a linear chain rather than a complex bidirectional network. Apart from biological completeness, the parameter values of the model were chosen without validation against empirical patient data. Incorporating these components would improve biological accuracy and allow for more detailed analysis of the neuroinflammation-tau feedback loop and its role in the progression of AD.

Future Research

Based on the limitations of this study, several directions for future research are proposed. Firstly, the most important extension of this work involves validating the models' outputs against longitudinal neuroimaging datasets, available through ADNI and OASIS, which would further ground the models in biological realism by providing the researcher with a direct reference to compare to. In other words, using existing longitudinal datasets would allow the researcher to determine whether the model's quantitative findings translate to real patient trajectories. Secondly, accounting for the molecular mediators of the interaction between tau pathology and neuroinflammation, by implementing processes like the activation of the NLRP3 inflammasome and p38 MAPK signaling, for example, would improve the models'

biological accuracy, allowing them to better represent mechanistic processes in greater detail by increasing the detail of the biological models. Finally, extending the models to include other immune cells that contribute to the neuroinflammatory response would further improve their biological accuracy, providing a bigger picture of the interplay between the brain's immune system as a whole and the spatiotemporal spread of tau pathology.

AUTHOR CONTRIBUTIONS

Sai Yashasvi Kasthala conceptualized the computational study, designed both models in COPASI, performed time-course analyses and parameter scans, analyzed the data, generated the tables and figures, and wrote the manuscript.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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