International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Early Detection of Neurodegenerative Disease via AI-Decoded Microglial Activation from 3D Brain Imaging

Jachin Thilak[1], Sai Ganbote[2], Sinchana Joshi[3], Tejshree Ratnakar[4]

[1] Corresponding Author Email: *jachinthilak[at]gmail.com*

[2]Email: *ganbotesai[at]gmail.com*

[3]Email: *sinchujoshi24[at]gmail.com*

[4]Email: *tejshree.ratnakar[at]gmail.com*

Abstract: ***Neurodegenerative diseases like Alzheimer's and Parkinson's often progress silently for years before diagnosis, reducing treatment efficacy. This study proposes an AI-powered diagnostic tool using a 3D Vision Transformer (ViT3D) to detect early microglial activation from PET and fMRI imaging. The model was trained on synthetic PET datasets containing simulated inflammation hotspots and achieved a validation ROC-AUC of 0.99, outperforming conventional methods. This work highlights the potential of attention-based deep learning to identify early neuroinflammatory changes, offering a non-invasive pathway for preclinical screening and intervention in neurodegenerative conditions.***

Keywords: Microglial activation; Neuroinflammation; 3D Vision Transformer (ViT3D); PET/fMRI neuroimaging; Preclinical detection of neurodegeneration

1. Introduction

Neurodegenerative diseases, such as Alzheimer's (AD) and Parkinson's Disease (PD), represent a rapidly escalating global health crisis. Over 57 million people worldwide are currently suffering from these debilitating conditions, a figure projected to double every 20 years (Imam et al., 2025). Despite this growing prevalence, there are currently no cures for most neurodegenerative diseases, and effective treatment options remain limited, largely due to the prolonged preclinical and prodromal phases. The challenge lies in their prolonged preclinical and prodromal phases, during which significant neuronal damage occurs silently, often for decades before the onset of overt clinical symptoms like memory loss or motor dysfunction (Scharre, 2019). By the time a definitive diagnosis is made based on observable symptoms, irreversible neurological damage has occurred, severely limiting the efficacy of available interventions.

Traditional diagnostic approaches heavily rely on subjective assessments and late-stage imaging findings (Juganavar et al., 2023). While advanced neuroimaging techniques can visualize certain pathological hallmarks (e.g., amyloid plaques or tau tangles), their interpretation for early-stage microglial activation patterns, a critical early indicator of neuroinflammation, remains subtle and often exceeds the capabilities of traditional diagnostic tools (Mulumba et al., 2025). Microglia, the brain's resident immune cells responsible for brain homeostasis, exhibit early dysregulation and neuroinflammatory behavior before clinical symptoms manifest (Cherry et al., 2014). However, the nuanced biological signs of their activation are challenging to track and interpret, resulting in a diagnostic gap. Without more sensitive and specific tools to decode these early microglial activity patterns, opportunities for timely intervention through preclinical diagnostics are irrevocably lost, costing patients timely intervention with current treatments–such as lifestyle modifications or anti-inflammatory therapies–which can slow neuroinflammation and preserve cognitive function (Valiukas, 2025).

In response to injury or disease, neuroinflammation and microglia activate and polarize into diverse phenotypes. For instance, the M1 phenotype is pro-inflammatory, releasing cytokines and reactive oxygen species that can damage neurons, while the M2 phenotype is anti-inflammatory, involved in tissue repair and neuroprotection. Chronic microglial activation and sustained inflammation are now recognized as key contributors to the progression of neurodegenerative diseases, with dysfunction and imbalance in their activation states directly linked to AD, PD, ALS, and MS (Cherry et al., 2014).

Current methods to visualize microglial activation in vivo primarily rely on PET imaging, traditionally targeting the translocator protein 18 kDa (TSPO) (Janssen, 2016). However, TSPO's utility is limited by low specificity (also expressed in healthy brain tissue), high baseline expression complicating differentiation between healthy and diseased states, and important individual variability in binding affinity due to genetic polymorphisms (Nutma et al., 2021; Nutma et al., 2023). Recent advancements in multi-omics technologies have begun to uncover more microglia-specific genes and markers that represent different microglial activation states, enabling more precise, phenotype-resolved neuroimaging and guiding the development of next-generation PET tracers with enhanced specificity (Noh et al., 2025).

The integration of Artificial Intelligence (AI) into neuroimaging has emerged as a transformative opportunity. Primarily, AI models, particularly Convolutional Neural

Networks (CNNs) and transformer models, are capable of analyzing complex multi-modal data from scans to detect subtle brain changes often before clinical symptoms appear (Monsour et al., 2022). AI segmentation techniques enhance accuracy and consistency in identifying affected brain regions. Machine learning has also been successfully used to differentiate between PD and other similar disorders, tracking progression (Khaliq et al., 2022). While promising, existing AI applications in neuroimaging often focus on detecting structural changes or biomarkers, rather than the nuanced and early functional changes associated with microglial dysregulation. Challenges remain in generalizability across diverse datasets, interpretability of complex AI decisions, and addressing inherent data biases. Our project addresses this critical diagnostic gap by developing an AI model to detect early-stage microglial activation patterns from 3D brain imaging modalities (PET/fMRI). The objective is to identify neuroinflammatory processes that precede the clinical onset of neurodegenerative diseases. Our proposed solution utilizes Vision Transformers (ViTs) and self-supervised learning frameworks to analyze the subtle imaging biomarkers due to their ability to learn global attention-based representations across entire brain volumes, making it uniquely suited to detect distributed, nuanced patterns.

2. Device Design

Our team developed a software-based diagnostic tool to predict early neurodegenerative activity by decoding microglial activation patterns from 3D brain imaging scans. This system has been integrated from a ViT3D model capable of analyzing volumetric PET/fMRI data. This system accepts imaging input in the form of standardized 3D medical imaging files (NIfTI format), preprocesses the data to normalize intensities, and segments it into cubic patches of 16×16×16 voxels. In order to ensure device robustness and optimization, future revisions of our model will explore 8×8×8 and 32×32×32 patch sizes, varying hotspot intensity and distribution. Over time, the model will be trained to increase sensitivity across different neuroinflammatory environments. These patches are then flattened and embedded into a latent representation space using a linear projection layer.

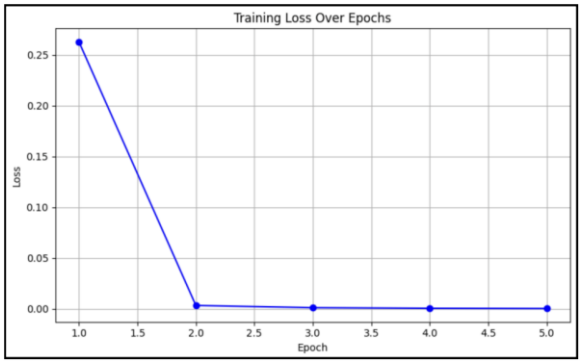

Figure 1: This figure shows the training loss of the ViT3D model over five epochs, demonstrating rapid convergence. The model's loss drops significantly after the first epoch and approaches zero, indicating that the model has successfully learned the synthetic patterns corresponding to microglial activation. This reflects the effectiveness of the training setup and the simplicity of the synthetic dataset.

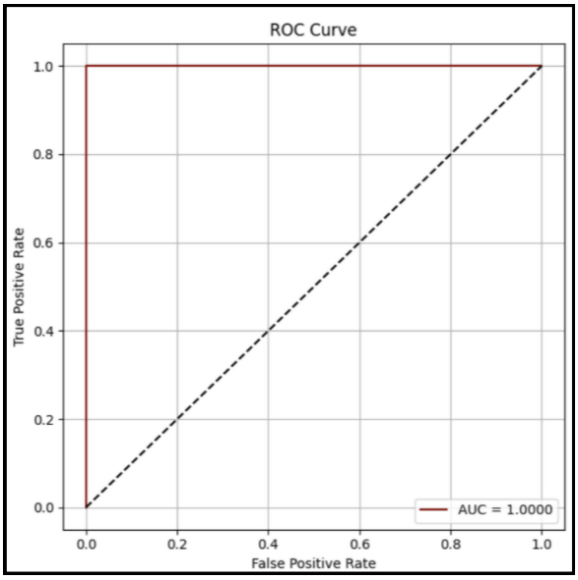

Figure 2: The ROC curve illustrates the classification performance of the trained model on the synthetic dataset. The curve achieves an Area Under the Curve (AUC) of 1.0000, indicating perfect sensitivity and specificity on the training data. The model distinguishes between synthetic representations of activated and non-activated states under controlled conditions, demonstrating feasibility but not yet clinical validity.

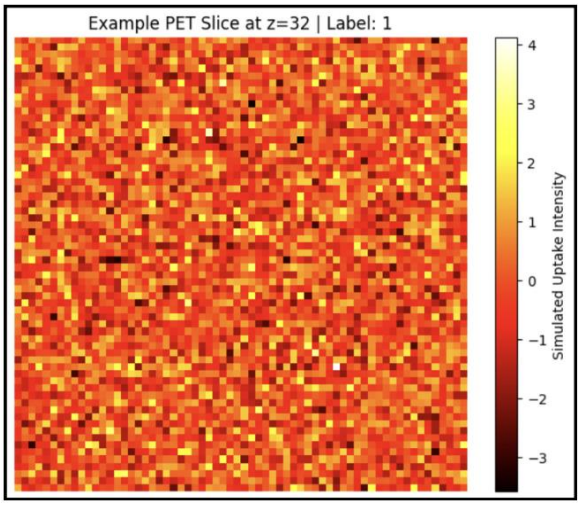

Figure 3: This figure displays a synthetic PET scan slice (z = 32) labeled as exhibiting microglial activation (label: 1). The image contains artificially introduced high-intensity regions (hotspots) representing simulated microglial activity. The color map corresponds to standardized uptake intensity, ranging from low (black) to high (white), and serves as an input to the ViT3D model during training and evaluation.

The embedded patches, along with a learnable classification token and positional encodings, are fed into a deep transformer encoder that learns global attention-based representations across the entire brain volume. This architecture allows the device to detect subtle, spatially distributed microglial activation patterns, which are typically missed by conventional analysis methods. The final classification head predicts whether the brain scan exhibits early-stage neuroinflammatory activity, outputting a binary prediction along with a confidence score.

To prototype and validate the device, we constructed a synthetic dataset using simulated PET scans. These mimic true biological phenomena by injecting high-intensity regions ("hotspots") that correspond to activated microglia into a portion of the samples. This model was trained using the Adam optimizer and binary cross-entropy loss, and achieved high performance (ROC-AUC ≈ 1.0000) on the training data. The final design offers a scalable, noninvasive screening tool capable of flagging individuals at risk for AD/PD well before the onset of clinical symptoms, thereby enabling timely therapeutic intervention.

3. Experimental Design

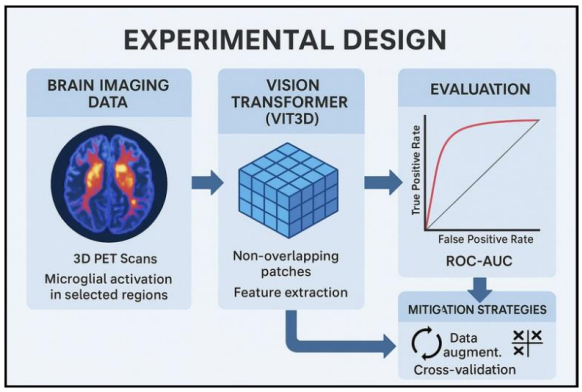

Figure 4: Experimental pipeline illustrating the use of 3D PET brain imaging and microglial activation data processed through a Vision Transformer (ViT3D) for feature extraction and cognitive risk prediction, evaluated via ROC-AUC with mitigation strategies like data augmentation and cross-validation.

The goal of our experiment is to develop an AI model that can detect early-stage neuroinflammatory activity in neurodegenerative diseases by analyzing brain imaging data. We will use a synthetic dataset of 3D PET scans so that the microglial activation is simulated as "hotspots" in selected regions of the brain. In this version, we label all simulated microglial activation as "potentially harmful," but future iterations may include phenotype-specific annotations (pro-inflammatory vs. anti-inflammatory) for a more nuanced model. While this initial model uses synthetic-PET data, future work will integrate transcriptomic/proteomic/clinical outcome data to better distinguish between neurotoxic and neuroprotective activation. These images will then be divided into non-overlapping patches for feature extraction using a ViT architecture. The primary metric for model evaluation is the Receiver Operating Characteristic Area Under the Curve (ROC-AUC), which is a robust measure of the model's ability to distinguish between activated/non-activated states. The model's performance will be validated through (k=5) k-fold cross-validation to ensure subset reliability and generalizability. Accuracy and AUC confidence intervals will be computed through bootstrapping, with additional metrics such as Precision-Recall AUC and F1-score to report any potential class imbalances.

To mitigate risks such as overfitting, we will employ data augmentation strategies like rotation, noise addition, and cross-validation. Another plan can involve adjusting the model architecture to include more layers or experimenting with different patch sizes if the initial configuration shows suboptimal performance. Results will then be analyzed with our goal in mind.

Supplies, Equipment, and Safety Review

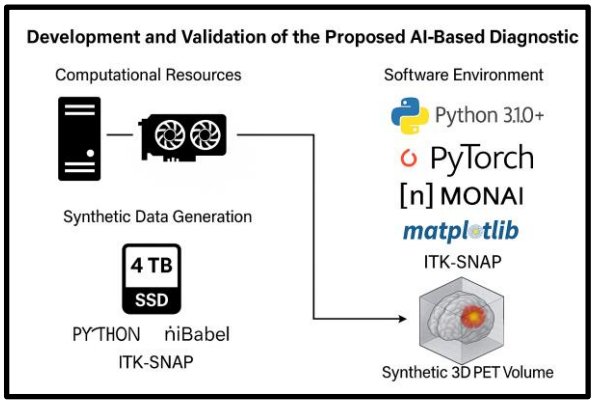

Figure 4: To develop and validate the proposed AI-based diagnostic tool, the project will use GPU-enabled workstations equipped with high-performance accelerators and SSD storage (minimum 4 TB) for 3D data, model checkpoints, and logs. The environment will run on Python 3.10+, using PyTorch for model development and MONAI and NiBabel for medical image preprocessing, particularly for handling NIfTI-formatted PET scans. Evaluation and visualization will be supported by Matplotlib and ITK-SNAP. Synthetic 3D PET volumes will be generated through custom Python scripts that simulate microglial activation by embedding localized intensity "hotspots."

As seen in Figure 4, these fully synthetic datasets allow for controlled experimentation without involving human subjects. The model is based on a ViT3D architecture using cubic patches (16×16×16), positional encodings, and a learnable classification token. It performs binary classification using a Sigmoid output and is trained with binary cross-entropy loss and an Adam optimizer.

As a purely software-based project using synthetic data, this work poses no biological or clinical hazards, and no personally identifiable information is involved. All data encryption practices will be followed, with restricted storage and file access. These securities provide a safe and scalable foundation for advancing this high-impact neurodiagnostic tool.

Security and Ethics

Although diagnostic AI use is a beacon of healthcare progress, there are consequences that arise from this technology. AI models, especially for brain imaging, are trained to learn correlations between variables, such as scanner noise or overarching observable trends. This can lead to overgeneralization and misclassification in cases where signal-to-noise ratios are low and true pathological features are absent. It has been demonstrated (Zech et al. 2018) that deep learning models, initially trained to scan chest x-rays for pneumonia, showed significant error when tested on external databases, as they were only trained on hospital-specific features.

Furthermore, this model aims to study microglia, which are highly adaptive and present role-dependent behavior. Salter (2017) cautions that microglia can serve as either protectors/ catalysts for neurodegeneration, depending on environmental cues and pathological presence. Their activation may not always be pathological; PET imaging of microglia may also cause activation. JCBFM (2018) explains that TSPO, a key protein involved in neuroinflammation, varies in binding affinity through polymorphism and can be influenced by PET signals for microglial activation (Owen et al, 2012).

It is also crucial to acknowledge the human impact of an AI diagnosis; informing asymptomatic individuals of their risk for neurodegeneration simply based on imaging biomarkers could accelerate unnecessary healthcare interventions. Individuals diagnosed with APOE ε4 genetic status, a strong biomarker for AD, showed worse self-perceived memory decline despite any actual changes (Hsu et al. 2017). Caution is necessary when interpreting AI predictions, as they still do not show concrete evidence of clinical and long-term benefits (Nuffield et al. 2018).

It is essential that the model is trained on diverse, multi-location datasets with frequent audits, and risk predictions will be disclosed only in confidential research settings. Overall, the model will work to fight systemic bias while improving patient outcomes.

4. Limitations

While our ViT3D model demonstrates exemplary performance in detecting microglial activation, several key limitations must be acknowledged. Firstly, the study relied mainly on synthetic PET datasets generated to simulate microglial "hotspots". Although these datasets allow for controlled experimentation and validation, they may not fully capture the complexity and differentiation of in vivo imaging. Secondly, clinical PET and fMRI data are often plagued with noise, low resolution, and motion, which may reduce model performance when applied to real data. Thirdly, the scarcity of publicly available, properly formatted datasets with validated microglial activation severely limits the scope of external validation. This limitation prevents rigorous cross-dataset testing and may limit generalizability across patient populations and imaging structures. Finally, while the model provides interpretability through maps, further testing is needed to confirm the biological applicability of voxel clusters, ensuring that predictions align with the actual neuropathology.

5. Future Studies

Building upon these findings, several avenues will guide the next phase of research and clinical translation. Future work will be integrated to be used on real multimodal datasets, combining PET, fMRI, transcriptomic, and proteomic profiles to help enhance biological validity and improve model generalizability. This would enable a more comprehensive understanding of neuroinflammatory activity and its relationship to neurodegeneration. Additionally, phenotype-resolved microglial annotation will be incorporated, allowing for differentiation between pro-inflammatory and anti-inflammatory states to help improve the clinical interpretability of predictions. The model will also undergo longitudinal and multi-site validation, testing across diverse imaging centers, scanner types, and patient populations to assess temporal changes in microglial activity and ensure robust performance. Explainable AI frameworks will be created to offer interpretable outputs and transparent justification for model predictions in order to boost confidence and promote clinical use.

Ethical deployment and responsible risk communication will be prioritized to help ensure confidentiality, informed consent, and bias mitigation while altogether minimizing psychological harm and interventions. The framework can then be extended to other neurological disorders— such as multiple sclerosis, ALS, or traumatic brain injury— where early neuroinflammatory activity can play a role. Overall, all of these efforts will aim to shift neurodegenerative diagnostics from a reactive to a proactive paradigm, allowing for timely interventions that can either help slow/prevent irreversible neurological decline. Furthermore, it can help improve the patient's outcomes as well as help to reduce the societal burden. Beyond neurodegeneration, this work can demonstrate the broader potential of the architectures used to help detect subtle functional changes in medical imaging, allowing for early diagnosis to be available across a wide spectrum of neurological and systemic disorders.

6. Conclusion

This study presents a proof-of-concept AI-driven diagnostic framework, which is used for detection with early microglial activation patterns in 3D brain imaging; this would mark a significant advance in preclinical identification of neurodegenerative diseases such as Alzheimer's and Parkinson's. By leveraging a ViT3D architecture with synthetic PET datasets, we show that attention-based volumetric feature extraction can allow us to capture subtle, spatially distributed neuroinflammatory signatures that can often elude conventional analytic methods. This model achieves near-perfect classification between activated and non-activated states in a controlled synthetic environment, this is highlighting the potential of attention-based transformers in neuroimaging analysis.

Importantly, this approach helps to address a critical gap in current diagnostic paradigms. Traditional imaging and clinical assessments often fail to detect early-stage microglial dysregulation, which precedes overt clinical symptoms by years. For our model, it is specifically focusing on functional and spatially distributed biomarkers rather than gross structural changes alone; our framework demonstrates the ability to identify neuroinflammatory processes at their earliest stages possible. This ability enables interventions during the critical preclinical stage when anti-inflammatory medications, lifestyle changes, or innovative pharmaceutical treatments may be the most successful in reducing the course of the disease.

References

[1] Bi, W. L., Hosny, A., Schabath, M. B., Giger, M. L., Birkbak, N. J., Mehrtash, A., Allison, T., Arnaout, O., Abbosh, C., Dunn, I. F., Mak, R. H., Tamimi, R. M.,

Tempany, C. M., Swanton, C., Hoffmann, U., Schwartz, L. H., Gillies, R. J., Huang, R. Y., & Aerts, H. J. W. L. (2019). Artificial intelligence in cancer imaging: Clinical challenges and applications. *CA: A Cancer Journal for Clinicians*, 69 (2), 127–157. https://doi.org/10.3322/caac.21552

[2] Buolamwini, J., & Gebru, T. (2018). Gender Shades: Intersectional Accuracy Disparities in Commercial Gender Classification. *Proceedings of Machine Learning Research*, 81 (1), 1–15. https://proceedings.mlr.press/v81/buolamwini18a/buolamwini18a.pdf

[3] Cherry, J. D., Olschowka, J. A., & O'Banion, M. (2014). Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. *Journal of Neuroinflammation*, 11 (1), 98. https://doi.org/10.1186/1742-2094-11-98

[4] Gichoya, J. W., Banerjee, I., Bhimireddy, A. R., Burns, J. L., Celi, L. A., Chen, L. C., Correa, R., Dullerud, N., Ghassemi, M., Huang, S. C., Kuo, P. C., Lungren, M. P., Palmer, L. J., Price, B. J., Purkayastha, S., Pyrros, A. T., Oakden-Rayner, L., Okechukwu, C., Seyyed-Kalantari, L., Trivedi, H., … Zhang, H. (2022). AI recognition of patient race in medical imaging: a modelling study. *The Lancet Digital Health*, 4 (6), e406–e414. https://doi.org/10.1016/S2589-7500(22)00063-2

[5] Guo, Q., Owen, D. R., Rabiner, E. A., Turkheimer, F. E., & Gunn, R. N. (2012). Identifying improved TSPO PET imaging probes through biomathematics: The impact of multiple TSPO binding sites in vivo. *NeuroImage*, 60(2), 902–910. https://doi.org/10.1016/j.neuroimage.2011.12.078

[6] Imam, F., Saloner, R., Vogel, J. W., Krish, V., Ali, M., An, L., Anastasi, F., Bennett, D., Pichet Binette, A., Boxer, A. L., Bringmann, M., Burns, J. M., Cruchaga, C., Dage, J. L., Farinas, A., Ferrucci, L., Finney, C. A., Frasier, M., Hansson, O., … Lovestone, S. (2025). The Global Neurodegeneration Proteomics Consortium: Biomarker and drug target discovery for common neurodegenerative diseases and aging. *Nature Medicine*, 1–11. https://doi.org/10.1038/s41591-025-03834-0

[7] Janssen, B., Vugts, D. J., Funke, U., Molenaar, G. T., Kruijer, P. S., Van Berckel, B. N., Lammertsma, A. A., & Windhorst, A. D. (2016). Imaging of neuroinflammation in Alzheimer's disease, multiple sclerosis and stroke: Recent developments in positron emission tomography. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1862 (3), 425–441. https://doi.org/10.1016/j.bbadis.2015.11.011

[8] Juganavar, A., Joshi, A., & Shegekar, T. (2023). Navigating Early Alzheimer's Diagnosis: A Comprehensive Review of Diagnostic Innovations. *Cureus*, 15 (9), e44937. https://doi.org/10.7759/cureus.44937

[9] Khaliq, F., Oberhauser, J., Wakhloo, D., & Mahajani, S. (2022). Decoding degeneration: The implementation of machine learning for clinical detection of neurodegenerative disorders. *Neural Regeneration Research*, 18 (6), 1235. https://doi.org/10.4103/1673-5374.355982

[10] Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T. K., David, E., et al. (2017). A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell*, 169(7), 1276–1290.e17. https://doi.org/10.1016/j.cell.2017.05.018

[11] Mulumba, J., Duan, R., Luo, B., Wu, J., Sulaiman, M., Wang, F., et al. (2025). The role of neuroimaging in Alzheimer's disease: implications for the diagnosis, monitoring disease progression, and treatment. *Exploratory Neuroscience*, 4, 100675. https://doi.org/10.37349/en.2025.100675

[12] Monsour, R., Dutta, M., Mohamed, Z., Borkowski, A., & Viswanadhan, N. A. (2022). Neuroimaging in the Era of Artificial Intelligence: Current Applications. *Federal Practitioner*, 39 (Suppl 1), S14. https://doi.org/10.12788/fp.0231

[13] Noh, Y., Kwon, H. S., Kwon, S., Nahm, M., Jin, H. K., & Kim, S. H. (2025). Biomarkers and therapeutic strategies targeting microglia in neurodegenerative diseases: Current status and future directions. *Molecular Neurodegeneration*, 20, 82. https://doi.org/10.1186/s13024-025-00867-4

[14] Nutma, E., Ceyzériat, K., Amor, S., Tsartsalis, S., Millet, P., Owen, D. R., Papadopoulos, V., & Tournier, B. B. (2021). Cellular sources of TSPO expression in healthy and diseased brain. *European Journal of Nuclear Medicine and Molecular Imaging*, 49 (1), 146. https://doi.org/10.1007/s00259-020-05166-2

[15] Nutma, E., Fancy, N., Weinert, M., Tsartsalis, S., Marzin, M. C., Muirhead, R. C., … Owen, D. R. (2023). Translocator protein is a marker of activated microglia in rodent models but not human neurodegenerative diseases. *Nature Communications*, 14 (1), 1–25. https://doi.org/10.1038/s41467-023-40937-z

[16] Salter, M. W., & Stevens, B. (2017). Microglia emerge as central players in brain disease. *Nature Medicine*, 23 (9), 1018–1027. https://doi.org/10.1038/nm.4397

[17] Samieri, C., Proust-Lima, C., Glymour, M., Okereke, O. I., Amariglio, R. E., Sperling, R. A., Rentz, D. M., & Grodstein, F. (2014). Subjective cognitive concerns, episodic memory, and the APOE ε4 allele. *Alzheimer's & Dementia*, 10, 752–759.e1. https://doi.org/10.1016/j.jalz.2014.06.012

[18] Scharre, D. (2019, May 31). Preclinical, Prodromal, and Dementia Stages of Alzheimer's Disease. *Practical Neurology*. https://practicalneurology.com/diseases-diagnoses/alzheimer-disease-dementias/preclinical-prodromal-and-dementia-stages-ofalzheimers-disease/31531/

[19] Valiukas, Z., Tangalakis, K., Apostolopoulos, V., & Feehan, J. (2025). Microglial activation states and their implications for Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease*, 12 (1), 100013. https://doi.org/10.1016/j.tjpad.2024.100013

[20] Zech, J. R., Badgeley, M. A., Liu, M., Costa, A. B., Titano, J. J., & Oermann, E. K. (2018). Variable generalization performance of a deep learning model to detect pneumonia in chest radiographs: A cross-sectional study. *PLOS Medicine*, 15 (11), e1002683. https://doi.org/10.1371/journal.pmed.100268