UNIVERSITY OF CALIFORNIA,
IRVINE

Quantifying Neuroinflammation-related Processes in Alzheimer's Disease Using Diffusion Imaging-Based Biophysical Modeling

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Biological Sciences

by

Dana McDonnell Parker

Dissertation Committee:
Professor Michael A. Yassa, Chair
Professor Thomas Lane
Professor Matthew Blurton-Jones

2026

DEDICATION

To Jinxx,

You raised me as much as I raised you. You were my best friend and partner in crime. This journey is and was because of you. Love you forever.

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ACKNOWLEDGMENTS

I have been fortunate to have been supported by a large group of strong, loving, brilliant people throughout my graduate career and my time in science, each of which I cannot begin to thank enough for making me into the scientist that I am today.

I would like to start off by thanking my advisor Dr. Michael A. Yassa for being willing to take a risk on me. While others didn't believe in my ideas, background or goals you have always been my biggest cheerleader. When others told me that a past music teacher could never succeed in neuroscience you never doubted. I am still in awe of how you can be such an incredible scientist while also leading with kindness and endless compassion for others. You have always made time to be there for me, even in some of my darkest moments. I have had the opportunities to chase my scientific dreams without hesitation or fear of failure and for that I am eternally grateful to you. Because of you I have developed into a scientist who is curious, brave and excitedly sees challenges as a way to further push myself. From the very first month in the lab there has never been a moment that I have hesitated to go after the hardest projects and ask the limit pushing questions. The right mentor doesn't just teach you the science; they show you who you can become. Thanks to your support, generosity and encouragement I have had opportunities to speak at, present at, and connect with so many areas of the science that I love. Thank you for letting diffusion be my whole personality.

To all my lab members, thank you so much for your seemingly endless love and support. Specifically, Leah, Bianca, Destiny, Abbey, Gimarie and Ray for being in the trenches together. I couldn't have asked for a better group of people to go through this with. To Liv, thank you endlessly for all the snacks, pep talks, money requests, and all other things I've put you through over the years. I know we all joke and say that you are the "real boss" of this lab, but I honestly don't think there is anyone else who is more fitting of that title. We are truly lucky to have you looking over us and protecting us from the insanity. To Jerod, thank you for starting my love of inflammation. The walk back from Fibre where you sent me the article that created the snowball effect that shaped my whole PhD has remained a pivotal moment in my career. Thank you for always being a sounding board and for helping me see the questions I was asking clearly. To Scotty, I didn't realize how lonely it was being obsessed with MRI physics until you joined. Having you to talk through things, design sequences, help make my diffusion scans the best they could possibly has been the greatest improvement to my research. You are a force of nature, and I am honored that I get to say I was there when Scotty joined the lab.

To Jenna, thank you for being here from day one. For sitting with me in the conference room and helping me realize that I can indeed do statistics and that writing scientific papers is not in fact the scariest thing in the world. You have always been the best travel buddy, mentor and friend. I am forever grateful for those first planning meetings before I had even started in the lab and for all the endless support and question answering. Oh, and also that one time you had to fill in for me to give a talk last minute! To Emily, I knew when you first came into the lab that you were going to be a force to be reckoned with. I had hopes of getting to work together to create science that would have impact larger than the two of us. It has been one of the greatest joys of my degree to have gotten to work with you. Not only the papers, posters, science parts but also to share a mentoring

experience and to raise our three summer institute students. I will forever cherish the times we have worked together, and I can't wait to watch you change the world.

To my UCI friends, thank you for making the move away from home feel so seamless. To the league, Natalie, Erin, Morgan, Joey, Scott and Rolland, thank you for making me feel loved and for all the incredible football knowledge. You all have made me feel so supported and loved. I can't imagine a life without all of you in it and I am so grateful to be loved and accepted by you.

I would also like to thank the members of my committee, Dr. Mathew Blurton-Jones and Dr. Thomas Lane. Thank you for not only your helpful words and mentorship on my studies but for also being willing to go above and beyond to help me incorporate animal research into my work. I wouldn't be able to fully answer my scientific questions without your knowledge and input for every aspect outside of my comfort zone.

Thank you to my family for their endless support. From taking me to rehearsals, competitions, then to symphony performances and my own groups performances you have always supported my dreams. We have come a long way from the band room, but I have never felt like you weren't behind me one hundred percent. To my father Patrick McDonnell, thank you for always encouraging me to be the best. It's easy to say that I have the best dad. From Metallica and Korn concerts to Ozzfest and for all the King's basketball games that you took me to for getting good grades has made me an incredible student. Thank you for everything you have given me and here's to more concerts! To my mother Carla McDonnell, you are the reason I am a scientist. From a young age you have encouraged me to do whatever I was passionate about. But beyond that you instilled a medical mind in me by always being curious yourself. I remember all our conversations over shared fascination of human psychology and behavior. You started my love of being curious and I am forever grateful. To my sister, Amy McDonnell, there are few words that I can say that would even begin to describe my first best friend. You have always been the person who sees the best in people, you love with your whole heart and those that are lucky enough to be loved by you are beyond special. Thank you for always loving me even though I am prickly. There has never been a moment in my life that I didn't know that I could talk to you, cry to you, or even just send a weird funny video to you. You have overcome so much, and you continue to be one of the best, most caring, most empathetic people I have ever meant. I am honored to be your sister.

To the people who were the first to take a chance on me from the Stanford Day lab there are not words to describe my deep gratitude. To Dr. John Day, you were my first PI, and I cannot thank you enough for giving me a chance to become the scientist I am today. You hired me with only months of experience and continued to provide me with the tools and resources to follow my passions. You supported me learning and experiencing things that few people outside of medical school get to experience. I am forever grateful for your kindness and support.

To Dr. Tina Duong, there is no other person that I have learned more about running research studies than you. Being on the ground floor of the development of Digby is still one of my greatest accomplishments. It is so rare to have a front row seat to such a powerful and incredible scientist as you Tina. Thank you for showing me that even though the world might not be ready for you, you are ready for the world.

To Dr. Jacinda Sampson, you took time out of your full clinic schedule to educate me in ways that, so few get to experience. I learned not only the technical aspects of the medicine and care for our participants but also the mechanisms and genetics behind it. You were the first mentor I had who had full and complete trust in my ability to learn and become a scientist. There seemed to never be a doubt in your mind that I would earn this degree, even though there were lots of doubts in mine. It is because of your curiosity and love of medicine and science that I decided to become a PhD, and I will forever be deeply honored that you made time and included me during my time in the lab. I look forward to a future where we can work together again.

Moving to start grad school was extra hard because it meant leaving behind some of my very best friends. Vik and Ero, you are two of the most incredible people that I have gotten the chance to know. Vik you are incredibly loving, talented and beautiful. It has been incredible to watch you evolve into the PA and wife that you are today. Ero, there is no doubt that you are hands down the person who loves and protects to a level that few deserve. I am so grateful that I have gotten to know you and to experience your beautiful culture and that unwavering loyalty. I know I could call on you two for anything at any time. To Corrina and Jared, thank you for always letting me crash your beautiful home. For all the amazing times and experiences that I wouldn't have had without you! To Jared, you have always treated me like we have known each other for years. The first time we met it was very clear that we would be friends. You have a warmth and hospitality that is unmatched! To Corrina, along the path to my PhD you were the start. You were the first person to tell me that it doesn't matter what my background was but that if I liked doing MRI that I should. You mentored me, showed me my first command line, shared with me all of your imaging processing and analyzing. You continue to be the first person that I go to with hard science questions. I am so excited that the universe decided to see what we have all know for decades. You walked into my first lab already at a level of a PI and you have only become more impressive as time has gone on. I am so lucky you decided I was worth your time way back running milkshake fMRI tasks. To Khang, thank you for consistently being one of the funniest people I know. Under that quiet exterior lives an observant mind that sees everything and then replays that in the absolute best ways. Thank you for all the endless projects, Josh has started because of you, I am definitely lucky that he always wants to make our home better after hanging out with you! To Monica, where to begin, from our first 209 encounter in my interview to way too much caffeine Caltrain rides, I consider myself so lucky that I got to work with you and become your friend. I still have dreams of us being neighbors someday, but until then the random look what he is doing now texts will have to suffice.

To the incredible Whitney Tang. You are the person that everyone wishes they had in their corner. You love fiercely and give every ounce of yourself to others. I will never understand why I have been so lucky as to call you my best friend. We have been working together since 2018 and during the times in-between (sadly there were a couple) it just never felt right. It is my personal goal to try and work on the same team with you until the day we retire. You are the keeper of my chaos, the mac to my cheese, the butter to my bread. Life has been endlessly better because I know you. Thank you for reading hundreds of pages of writing, editing endless versions of paragraphs and for providing the words that I so frequently can't communicate.

To Joshua Boone Parker, the day I met you my life changed forever. You were my first friend at a time in my life that was scary, new, exciting and lonely. I had only dreamed that you would take

interest in me because I saw instantly how incredible of a person you are. From the moment we started our relationship I knew we would be forever. There was never a question in my mind that you were and are the love of my life. You have been with me through all the careers, all the hard decisions, the worst day of my life, all of it. And in every moment, I knew that I was safe and that everything was going to be ok because you were there. There have been more moments than I can count where I've wondered why me? How did I become so lucky? What did I do to deserve you? From allowing me to chase dreams even if it meant me taking no pay and spending money and time working late in labs. Once you told me that you thought I was the kind of person who goes on to cure cancer. I remember sitting in silence realizing that you saw something in me that I didn't. You have so selflessly supported this whole degree. From moving your job and leaving your team to leaving your very best friend Emma, you have supported me unwaveringly. This degree is not a solo decision; YOU had to change your life to allow me to follow my dreams. I hope every day that I have lived up to what you see in me, that this decision is going to be worth it, that all of the continuous work and love and help you give me daily was the right move for us. There are so many times that I joke that husbands should also get the PhD with their partners but there is ZERO doubt that you did this degree with me. You have kept me fed, on time, healthy and even hydrated during my defense and not once have you complained or made me feel like I am too much. Everything in this dissertation, all of my work, all of my success is because of you. All that I am is because of you.

The text of portions of Chapter 2 and 3 of this dissertation is adapted from previously published and submitted works authored by Dana M. Parker and colleagues. Chapter 2 is adapted from material published in Imaging Neuroscience and distributed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license. Chapter 3 is adapted from material previously disseminated as a preprint and distributed under a Creative Commons Attribution 4.0 International (CC BY) license. The coauthors listed in these publications contributed to the research presented in this dissertation. Michael A. Yassa directed and supervised the research which forms the basis of this dissertation.

Permission to reproduce copyrighted figure 1 in Chapter 1 was granted by Springer Nature. Additionally figures 19, 20, and 21 in Chapter 5 are adapted from work published by Garcia-Hernandez et al. Financial support for this work was provided by the Howard Schneiderman Training Program in Learning and Memory at the University of California, Irvine, and by the National Institutes of Health under awards *T32MH119049 (to MAY), U19AG068054 (to ADC), and R01AG053555 (to MAY).*

VITA

Dana M. Parker

EDUCATION

Ph.D. in Neurobiology & Behavior
University of California, Irvine • Irvine, CA
Advisor: Michael Yassa
Expected: June 2026

M.S. in Biological Sciences
University of California, Irvine • Irvine, CA
2025

M.S. in Psychology
Palo Alto University • Palo Alto, CA
2018

B.M. in Music Education
University of the Pacific • Stockton, CA
2013

RESEARCH EXPERIENCE

Graduate Researcher
Yassa Lab, University of California, Irvine • Irvine, CA
2022 – 2026

- Investigate relationships between peripheral inflammatory biomarkers and medial temporal lobe white matter microstructure across aging, Alzheimer's disease, and Down syndrome cohorts.
- Develop reproducible neuroimaging pipelines using QSIPrep, FreeSurfer, MRtrix3, and ANTs on high-performance computing clusters with containerized workflows.
- Integrate multimodal datasets (MRI, PET, cytokines, cognition) across large longitudinal cohorts.
- Perform statistical modeling in R and Python (regression, interaction models, mediation analyses).

- Lead manuscript development on sex differences in inflammation, white matter microstructure, and diffusion biomarkers in Alzheimer's disease.

Imaging and Data Research Scientist
Day Lab, Stanford University • Palo Alto, CA
2021 – 2022

Imaging Studies of Patients with Myotonic Dystrophy (PI: John Day)
- Managed and processed a database of 200+ structural and functional MRI datasets using MATLAB, Python, and Flywheel.
- Contributed to and reviewed manuscripts for submission.
- Performed statistical analyses using R, Python, and MATLAB.

Whole Body Muscle MRI in Neuromuscular Diseases (PI: John Day)
- Independently acquired MRI scans on 3T GE scanners.
- Developed whole-body MRI protocols for neuromuscular disease populations.
- Established analysis pipelines including preprocessing, segmentation, and organization of whole-body muscle MRI data.

Observational Study of Nusinersen (Spinraza) in Adults with Spinal Muscular Atrophy (PI: John Day)
- Developed study protocols and participant visit workflows.
- Implemented whole-body MRI protocols to optimize biopsy site selection and support clinical decision-making.
- Created and maintained automated quarterly data reporting scripts in Python.

Exercise Testing in Neuromuscular Disease (PI: John Day)
- Maintained cardiopulmonary exercise testing (CPET) and EKG datasets for physician safety review.
- Contributed to manuscript preparation and analysis of CPET data.

Clinical Research Coordinator Associate
Day Lab, Stanford University • Palo Alto, CA
2019 – 2021

- Served as primary contact for research participants, sponsors, and regulatory agencies.
- Coordinated clinical studies from start-up through close-out.
- Screened participants for eligibility and obtained informed consent in accordance with study protocols.
- Assisted in developing and implementing recruitment strategies.
- Prepared study materials, coordinated procedures, tracked billing, and led monitoring visits with sponsors.

- Maintained regulatory documentation and ensured compliance with institutional and federal guidelines.

Research Assistant
Pediatric Emotion and Resilience Lab, Stanford University • Palo Alto, CA
2018 – 2019

- Performed data entry and management for 400+ participants across multiple studies, including cleaning and maintaining archival datasets.
- Assisted with setup and execution of MRI/fMRI protocols and oral glucose tolerance tests (OGTTs).
- Administered neurocognitive assessments (e.g., TRAILS, Epstein Task, WASI).
- Supported daily lab operations, including preparing participant materials, organizing study documentation, and maintaining experimental spaces.

TECHNICAL SKILLS

Neuroimaging:
MRtrix3, FSL, FreeSurfer, ANTs, FreeSurfer, FMRIprep, AFNI, QSIPrep, QSIRecon, DiPy, NiLearn, ITK-SNAP, MRIcroGL, ImageJ, Surfice

Programming & Analysis:
R, Python (Pandas, NumPy), Bash, C++, Git, Visual Studio, Jupyter Notebook, Jamovi

Computing:
HPC/SLURM environments, Singularity/Apptainer containers

PUBLICATIONS

Parker, D., Yi, E., Tang, W., Bamford, A., Taylor, L., Simmons, S., Meza, N., Tuteja, N., Avila, B., Chang, E., Bock, J., McMillan, L., Kim, S., Adams, J., Thomas, E., Jacobs, E., & Yassa, M. (2026). Sex-specific immune–brain coupling in hippocampal circuits and Alzheimer's disease vulnerability. Preprint in *Research Square*

Parker, D. M., Fischer, L., Maboudian, S., Fonseca, C., Tato-Fernandez, C., Annen, L., Arunachalam, P., Bacci, J. R., Barboure, M., Capelli, S., Karagianni, S., Collij, L. E., Edison, P., Fox, N. C., Franzmeier, N., Grothe, M. J., Jagust, W. J., Maass, A., Malpetti, M., Paterson, R. W., Sogorb-Esteve, A., & Schöll, M. (2025). Longitudinal biomarker studies in human neuroimaging: Capturing biological change of Alzheimer's pathology. *Alzheimer's Research & Therapy*. In press.

Parker, D. M., Adams, J. N., Kim, S., McMillan, L., & Yassa, M. A. (2025). NODDI-derived measures of microstructural integrity in medial temporal lobe white matter pathways are associated with Alzheimer's disease pathology and cognition. *Imaging Neuroscience*. In press.

Tucker, H. L., Karat, B., de Ruiter, A. T., **Parker, D.,** Lim, S. A., Denning, A. E., Ittyerah, R., Levorse, L. M., Trotman, W., Bahena, A., Chung, E., Prabhakaran, K., Bedard, M. L., Ohm, D. T., Xie, L., Das, S. R., Pluta, J. B., Schuk, T., Liu, W., Pickup, S., Artacho-Perula, E., Iniguez de Onzono Martin, M. M., Munoz, M., Romero, F. J. M., Delgado Gonzalez, J. C., Srroyo Jimenez, M. M., Marcos Rabal, M., Insausti Serrano, A. M., Vilaseca Gonzalez, N., Cebada Sanchez, S., de la Rosa Prieto, C., Lee, E. B., Detre, J. A., Tisdall, M. D., Irwin, D. J., Wolk, D. A., Adler, D. H., de Flores, R., Berron, D., Ding, S. L., Yushkevich, P. A., Hodgetts, C. J., & Wisse, L. E. M. (2025). Characterization of hippocampal subfields using histology-based annotated postmortem MRI: Lessons for in vivo segmentation II. *bioRxiv* (preprint; under review at *Hippocampus*).

Christle, J. W., Duong, T., **Parker, D.,** Stevens, V., Dunaway Young, S., Kaufman, B. D., Tang, W., Sampson, J., Myers, J., Ashley, E. A., Day, J., & Wheeler, M. T. (2023). Cardiopulmonary exercise testing for patients with neuromuscular disease and limited mobility. *Journal of Clinical Exercise Physiology*. In press.

Tang, W. J., Gu, B., Montalvo, S., Dunaway Young, S., **Parker, D. M.**, de Monts, C., Ataide, P., Ni Ghiollagain, N., Wheeler, M. T., Rocha, C. T., Christle, J. W., He, Z., Day, J. W., & Duong, T. (2023). Assessing the assisted six-minute cycling test as a measure of endurance in non-ambulatory patients with spinal muscular atrophy (SMA). *Journal of Clinical Medicine*. In press.

Beaudin, M., Kamali, T., Tang, W., Hagerman, K. A., Dunaway Young, S., Ghiglieri, L., **Parker, D. M.**, Lehallier, B., Rocha, C. T., Sampson, J. B., Duong, T., & Day, J. W. (2023). Cerebrospinal fluid proteomic changes after nusinersen in patients with spinal muscular atrophy. *Journal of Clinical Medicine*. In press.

Kamali, T., Day, J. W., Deutsch, G. K., Sampson, J. B., Murad, A., Chaufty, J., **Parker, D.,** & Wozniak, J. R. (2023). Learning spectral fractional anisotropy and mean diffusivity features as neuroimaging biomarkers for tracking white matter integrity changes in myotonic dystrophy type 1. In *Proceedings of the IEEE Engineering in Medicine and Biology Society (EMBC)*.

Dunaway Young, S., Pasternak, A., Duong, T., McGrattan, K. E., Stranberg, S., Maczek, E., Dias, C., Tang, W., **Parker, D**., Levine, A., Rohan, A., Wolford, C., Martens, W., McDermott, M. P., Darras, B. T., & Day, J. W. (2023). Assessing bulbar function in spinal muscular atrophy using patient-reported outcomes. *Journal of Neuromuscular Diseases*. In press.

Deutsch, G. K., Hagerman, K. A., Sampson, J., Dekdebrun, J., **Parker, D. M.**, Thornton, C. A., Heatwole, C. R., Subramony, S. H., Mankodi, A. K., Ashizawa, T., Statland, J. M., Arnold, W. D., Moxley, R. T., & Day, J. W. (2022). Brief assessment of cognitive function in myotonic dystrophy: Multicenter longitudinal study using computer-assisted evaluation. *Muscle & Nerve*. In press.

Kamali, T., Deutsch, G. K., Hagerman, K. A., **Parker, D.,** Day, J. W., & Sampson, J. B. (2022). Cognitive impairment analysis of myotonic dystrophy via weakly supervised classification of neuropsychological features. In *Proceedings of the IEEE Engineering in Medicine and Biology Society (EMBC)*.

Duong, T., Tang, W., Nelson, L., **Parker, D.,** Pasternak, A., Dunaway Young, S., Muni-Lofra, R., Marzek, E., Mitchell-Sodi, J., Moat, D., Chatfield, S., Appleton, P., Day, J., Glanzman, A., & Mayhew, A. (2022). Adaptive test for neuromuscular disorders: Design of a wheelchair-based assessment. *Neuromuscular Disorders*. In press.

Kamali, T., **Parker, D.**, Day, J. W., Sampson, J. B., Deutsch, G. K., & Wozniak, J. R. (2021). Toward developing robust myotonic dystrophy brain biomarkers using white matter tract profiles, sub-band energy, and ensemble predictive learning. In *Proceedings of the IEEE Engineering in Medicine and Biology Society (EMBC)*.

MANUSCRIPTS IN PREPARATION / UNDER REVIEW

Parker D.M, et al. Systemic inflammation Is Associated with Limbic White Matter Microstructural Alterations in Adults with Down Syndrome. (In prep)

Parker D. M., Fischer L., et al. Changes in MRI-derived measures in the medial temporal lobe in aging and disease using neuroimaging. (In prep)

Parker, D. M., Rasmussen, J., Yassa, M. A., & Adams, J. N. (2025). Mapping spatial white matter integrity linked to tau accumulation: Insights from tractometry with multishell diffusion imaging. (In Prep)

ORAL PRESENTATIONS

Parker, D. M., Yi, E., Tang, W., Bamford, A., Kim, S., Simmons, S., Meza, N., Tuteja, N., Avila, B., Chang, E., McMillan, L., Kim, S., Thomas, E. A., Adams, J. N., & Yassa, M. A. (2026). Estradiol moderates the association between neuroinflammation and medial temporal lobe white matter microstructure in aging. Abstract submitted to Alzheimer's Association International Conference (AAIC), London, UK. *(selected for neuroblitz)*

Astrogliosis, Inflammation, and Lifestyle/Endocrine Impacts Alzheimer's Association International Conference (AAIC) July 12-15, 2026, London, UK. (*invited session chair)*

Parker, D. M., Tang, W. J., Rasmussen, J., Yassa, M. A., & Adams, J. N. (2025). Mapping spatial white matter integrity linked to tau accumulation: Insights from tractometry with multishell diffusion imaging. Presented at the Human Amyloid Imaging (HAI) Conference, January 15-17, 2025, San Juan, Puerto Rico. *(selected for podium presentation)*

Parker, D., Dunaway Young, S., Tang, W., Wolford, C., He, Z., Day, J., & Duong, T. (2021). Quantitative muscle strength changes in adults with SMA receiving nusinersen. Presented at

CureSMA Annual Conference June 16-19, 2021, Anaheim, CA. (*selected for clinical podium presentation*).

POSTER PRESENTATIONS

Parker, D. M., Yi, E., Tang, W., Bamford, A., Kim, S., Simmons, S., Meza, N., Tuteja, N., Avila, B., Chang, E., McMillan, L., Kim, S., Thomas, E. A., Adams, J. N., & Yassa, M. A. (2026). Estradiol moderates the association between neuroinflammation and medial temporal lobe white matter microstructure in aging. Abstract submitted to Alzheimer's Association International Conference (AAIC), London, UK.

Adams, J. N., Fischer, L., Bock, J., Taylor, D., **Parker, D. M.,** Taylor, L. M., Tang, W., Simmons, S., Chang, E., Avila, B., Meza, N., Tuteja, N., McMillan, L., & Yassa, M. A. (2026). Statistical learning reflects tau-related hippocampal CA1 dysfunction in preclinical Alzheimer's disease. Abstract submitted to Alzheimer's Association International Conference (AAIC), London, UK.

Varghese, L., Tang, W., Taylor, L. M., **Parker, D. M.,** Yi, E., Kim, S., Meza, N., Avila, B., Chang, E., Tuteja, N., Simmons, S., McMillan, L., Yassa, M. A., & Adams, J. N. (2026). Staging medial temporal lobe tau progression distinguishes age-related from Alzheimer's disease-related pathology. Abstract submitted to Alzheimer's Association International Conference (AAIC), London, UK.

Yi, E., Tang, W., Taylor, L. M., **Parker, D. M.,** Varghese, L., Bamford, A., Meza, N., Tuteja, N., Avila, B., Chang, E., Simmons, S., McMillan, L., Kim, S., Thomas, E. A., Adams, J. N., & Yassa, M. A. (2026). APOE ε4 moderation of inflammation–tau associations is sex-specific in cognitively unimpaired older adults. Abstract submitted to Alzheimer's Association International Conference (AAIC), London, UK.

Tang, W. J., **Parker, D. M.,** Bock, J., Taylor, L. M., Yi, E., Varghese, L., Meza, N., Tuteja, N., Avila, B., Chang, E., Simmons, S., McMillan, L., Kim, S., Adams, J. N., & Yassa, M. A. (2026). Differential associations between limbic NODDI metrics and memory-related cognitive variability in healthy older adults. Abstract submitted to Alzheimer's Association International Conference (AAIC), London, UK.

AT de Ruiter, HL Tucker, B Karat, **D Parker,** SA Lim, AE Denning, R Ittyerah, LM Levorse, W Trotman, A Bahena, E Chung, K Prabhakaran, ML Bedard, DT Ohm, L Xie, SR Das, JB Pluta, T Schuck, W Liu, S Pickup, E Artacho-Pérula, MM Iñiguez de Onzoño Martin, M Muñoz, FJM Romero, JC Delgado González, MM Arroyo Jiménez, M Marcos Rabal, AM Insausti Serrano, N Vilaseca González, S Cebada Sánchez, C de la Rosa Prieto, EB Lee, JA Detre, MD Tisdall, DJ Irwin, DA Wolk, DH Adler, R de Flores, D Berron, SL Ding, PA Yushkevich, N Villain, CJ Hodgetts, LEM Wisse (2026) Characterization of hippocampal subfields using histology-based annotated postmortem MRI: Lessons for in vivo segmentation in dementia research. Abstract submitted to Alzheimer's Association International Conference (AAIC), London, UK.

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GRANTS, FELLOWSHIPS, & AWARDS

Alergan Foundation Graduate Student Award
School of Biological Sciences • Irvine, CA
2026

Howard Schneiderman T32 Fellowship in Learning and Memory
2024 – 2026

Renée Harwick Award
Center for the Neurobiology of Learning and Memory • Irvine, CA
2025

Neurodegenerative Disease Biomarker Course: Novel Biomarker Pitch – 3rd Place
University of Gothenburg • Gothenburg, Sweden
2024

TEACHING & MENTORSHIP

Program Mentor
UC Irvine Summer Institute of Neuroscience University of California, Irvine • Irvine, CA
2024-2025

10-week research program, supported by the University of California UC-HBCU Initiative, where graduate student mentors and undergraduate student mentees are paired, mentors had bi-weekly mentorship training sessions, undergraduates were expected to learn a research study and present a poster by the end of summer under mentor's guidance

Teaching Assistant
University of California, Irvine • Irvine, CA
Fall 2024 – Winter 2024

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Director of Instrumental Music
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- Taught courses in marching band, concert band, wind ensemble, string orchestra, symphony orchestra, jazz band, auxiliary percussion, and color guard.
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Substitute Teacher
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- Taught courses including concert band, wind ensemble, beginning string orchestra, and intermediate/combined string orchestra.

PROFESSIONAL SERVICE

Founding Member, Neurobiology and Behavior Culture Club
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Graduate Student Representative, Neurobiology and Behavior Department
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Member, International Society for Magnetic Resonance in Medicine (ISMRM)
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Member, Society for Neuroscience (SfN)
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ABSTRACT OF THE DISSERTATION

Quantifying Neuroinflammation-related Processes in Alzheimer's Disease Using Diffusion Imaging-Based Biophysical Modeling

by
Dana McDonnell Parker
Doctor of Philosophy in Biological Sciences
University of California, Irvine, 2026
Professor Michael A. Yassa, Chair

Neuroinflammation is increasingly recognized as a key contributor to Alzheimer's disease (AD), yet the mechanisms linking systemic immune processes to brain structure and cognition remain poorly understood. This dissertation proposes that white matter (WM) microstructure represents a critical intermediate phenotype through which neuroinflammation influences neural circuit integrity and cognitive decline.

To test this framework, this work utilized advanced diffusion MRI, specifically Neurite Orientation Dispersion and Density Imaging (NODDI), to characterize biologically meaningful features of WM microstructure within medial temporal lobe pathways. This dissertation first evaluated whether NODDI, a multi-shell, multi-compartment model, provided greater sensitivity to AD-related changes compared to traditional diffusion tensor imaging (DTI). The findings established that advanced diffusion-derived metrics offer enhanced sensitivity to AD pathology and cognitive function while capturing distinct features of tissue organization inaccessible with conventional methods.

Building on this foundation, the subsequent analyses reveal that the relationship between peripheral cytokine neuroinflammation and brain structure is not uniform but instead reflects differences in circuit level vulnerability. Neuroinflammatory effects on WM microstructure and cognition vary as a function of biological sex, suggesting that disease risk is shaped not only by systemic burden, but by the brain's sensitivity to those signals. Extending this work to a genetically

high-risk population, individuals with Down syndrome, this dissertation further demonstrates that chronic systemic neuroinflammation is associated with selective alterations in limbic white matter pathways, supporting a model in which neuroinflammation contributes to structural brain vulnerability.

Together, these findings identify white matter microstructure as a key link between systemic biology and cognitive decline. By integrating diffusion imaging with neuroinflammatory and cognitive measures, this work provides a framework for understanding how neuroinflammation related processes shape brain structure during the earliest stages of disease. These results have important implications for the development of non-invasive biomarkers aimed at improving early detection and informing therapeutic strategies in Alzheimer's disease.

Chapter 1: Introduction

1.1 Alzheimer's Disease in the Context of Brain Aging

Alzheimer's disease (AD) represents a significant and escalating public health crisis that often emerges against the background of age-related decline. Currently, an estimated 6.7 million Americans are living with clinical AD, a number projected to reach 14 million by 2060 (Rajan et al., 2021). Crucially, the neurobiological alterations in brain circuits and the development of pathology manifest well before the first clinical symptoms appear (Barthélemy et al., 2020; Heiko Braak et al., 2011; Jack et al., 2010). In this context, the baseline inflammaging of the brain in normal aging is pathologically amplified, characterized by the chronic activation of microglia and astrocytes (Glass et al., 2010; Janus et al., 2000). Because these changes occur during a prolonged prodromal stage, it is vital to identify non-invasive biomarkers that allow for earlier detection and support the development of new treatments moving through clinical trial pipelines.

As the global population shifts toward an older demographic, understanding the biological trajectory of the aging brain has become a central focus of neuroscience. The standard aging process is associated with widespread biological changes that impact brain structure and systemic physiology. These include gradual declines in white matter (WM) integrity, an increase in extracellular water, and subtle alterations in immune regulation. Importantly, these changes are not uniform across the brain. Instead, they follow regionally specific patterns of vulnerability, particularly within the medial temporal lobe (MTL) regions essential for memory. Beyond these structural shifts, aging is accompanied by a chronic low-grade inflammatory state, often referred to as 'inflammaging', which sets a complex neurobiological baseline for the later emergence of disease. The specific nature of these age-related declines and their intersection with pathological neurodegeneration are explored in detail in Section 1.2.

Chronic neuroinflammation is increasingly recognized as a potential driver of neurodegeneration, potentially influencing disease onset and progression rather than simply reflecting downstream pathology (Glass et al., 2010; Jack et al., 2018). Neuroinflammation represents a complex, multi-cellular and systemic phenomenon that remains difficult to characterize in human populations. Despite the abundance of evidence from preclinical models, neuroinflammation remains largely understudied in humans, primarily due to a lack of available biomarkers. Despite the recognition of neuroinflammation as a key contributor to AD, it remains difficult to characterize *in vivo* without the use of invasive cerebrospinal fluid (CSF) sampling or expensive Positron Emission Tomography (PET) (Blennow & Zetterberg, 2018). The biological mechanisms by which this inflammatory state drives microstructural decay and the modulating roles of sex and genetic risk are further examined in the sections on neuroinflammatory drivers (1.4) and biological risk factors (1.5). Furthermore, these inflammatory pathways are likely modulated by biological sex and genetic predispositions, such as those seen in Down Syndrome, which provide a window into accelerated neurodegeneration (see Section 1.6).

There is, therefore, a critical need for accessible, non-invasive approaches that can capture downstream effects of neuroinflammation on brain structure. One promising avenue is the investigation of WM microstructure within the MTL (Heneka et al., 2015; H. Zhang et al., 2012), which is uniquely vulnerable to both aging and AD pathology. Importantly, these pathways serve as the structural substrate through which inflammatory processes may influence cognitive decline. While traditional diffusion tensor imaging (DTI) metrics such as fractional anisotropy (FA) and mean diffusivity (MD) have been widely used, they lack biological specificity and are limited to their ability to disentangle distinct microstructural components (Basser et al., 1994). Advanced diffusion models, such as Neurite Orientation Dispersion and Density Imaging (NODDI),

overcome these limitations by providing more interpretable metrics (H. Zhang et al., 2012). A comprehensive review of these advanced diffusion techniques and their utility in resolving the biological biomarker gap is provided in Section 1.3.

1.2 White Matter Microstructural Degeneration in Aging and Alzheimer's Disease

WM integrity declines as a function of normal aging, with widespread alterations in structural connectivity observed even in cognitively unimpaired individuals (Bennett & Madden, 2014; Lebel et al., 2012). These related changes include reductions in myelination, axonal degeneration, and increased extracellular water, all of which can disrupt efficient neural communication across distributed brain networks (Peters, 2002). Importantly, such alterations are not uniform across the brain but instead show regionally specific patterns of vulnerability (Salat et al., 2005).

In the context of AD, WM degeneration is not merely a downstream consequence of gray matter atrophy but is increasingly recognized as an early and potentially independent feature of disease progression (Bennett & Madden, 2014; Nasrabady et al., 2018). Evidence from both cross-sectional and longitudinal studies suggests WM changes can be detected during preclinical stages of AD, prior to the onset of overt cognitive symptoms (Bartzokis et al., 2012; Nasrabady et al., 2018; Zhuang et al., 2012). This evidence raises the possibility that WM integrity may serve as a sensitive marker of early disease related processes.

Within the WM, limbic pathways are of particular relevance to AD due to their central role in supporting memory function and their early signs of degeneration (Lacalle-Aurioles & Iturria-Medina, 2023; Metzler-Baddeley et al., 2012). Regions such as the hippocampal and cingulate components of the cingulum bundle, the uncinate fasciculus, and the fornix form critical

connections between MTL structures and distributed cortical regions (Benear et al., 2020; Bubb et al., 2018). These pathways are consistently implicated in episodic memory processes and are among the earliest to exhibit microstructural alterations in both aging and AD. Their selective vulnerability positions them as key candidates for understanding how pathological processes translate into cognitive decline.

Taken together, these findings suggest that WM integrity is not simply a marker of neural degradation but may instead represent a critical pathway through which AD pathology impacts cognitive function. However, conventional neuroimaging approaches lack the biological specificity needed to disentangle the microstructural processes underlying these changes, limiting our ability to understand how factors such as neuroinflammation contribute to WM alterations *in vivo*. Ultimately, age-related vulnerability in WM may provide a structural substrate upon which AD pathology and inflammatory processes act.

1.3 Diffusion MRI as a Window into White Matter Microstructure

In the context of aging and AD, where multiple interacting biological processes shape WM integrity, diffusion magnetic resonance imaging (dMRI) provides a non-invasive method for probing the microstructural organization of WM *in vivo* by measuring the diffusion of water molecules within tissue (Basser et al., 1994; Le Bihan et al., 1986). Because water diffusion is constrained by cellular structures such as axonal membranes and myelin, dMRI offers indirect sensitivity to the underlying architecture of WM pathways.

Traditional diffusion approaches, particularly diffusion tensor imaging (DTI), have been widely used to characterize WM integrity through metrics such as fractional anisotropy (FA) and mean diffusivity (MD) (Basser et al., 1994). While these measures have provided valuable insights

into age and disease related changes, they are inherently limited in their biological specificity. DTI models diffusion as a single tensor within each voxel, which cannot adequately capture complex fiber configurations such as crossing or branching fibers, nor can it disentangle distinct microstructural components such as neurite density, extracellular free water, or fiber dispersion. As a result, changes in FA or MD are difficult to interpret biologically, as they may reflect multiple underlying processes.

To address the limitations, advanced diffusion models, such as NODDI, have been developed to provide more specific and interpretable measures of tissue microstructure. NODDI enables the decomposition of the diffusion signal into multiple compartments that more closely reflect underlying biological features. The key metrics of NODDI include intracellular volume fraction (ICVF), which serves as a proxy for neurite density; isotropic volume fraction (ISOVF), which reflects extra cellular free water and has been associated with neuroinflammatory processes; and orientation dispersion (OD), which captures the degree of variability in fiber orientation within a voxel (H. Zhang et al., 2012).

By separating these components, NODDI allows for a more nuanced characterization of WM microstructure, moving beyond nonspecific markers of damage toward metrics that can be more directly linked to underlying biological processes. This increased specificity is particularly important in the context of aging and AD, where multiple interacting mechanisms, including neurodegeneration, demyelination, and neuroinflammation, are likely to contribute to observed changes in WM integrity. This is particularly critical for studying processes such as neuroinflammation, which are hypothesized to impact brain microstructure at a cellular level and may manifest as changes in extracellular water and neurite integrity detectable with advanced diffusion models. Applying these metrics to limbic WM pathways provides a powerful framework

for investigating how microstructural alterations within memory relevant circuits relate to neuroinflammation and cognitive decline.

1.4 Neuroinflammatory White Matter Alterations

Aging is accompanied by a chronic, low-grade inflammatory state, often referred to as 'inflammaging,' which represents a central biological process linking systemic aging to neurodegeneration. With advancing age, there is a progressive increase in circulating pro-inflammatory markers, reflecting sustained immune activation that may have widespread effects on brain structure and function (Franceschi et al., 2000).

In the context of AD, neuroinflammation is further amplified, with evidence of increased microglial activation and dysregulation of cytokine signaling (Cunningham, 2013). Microglia, the brain's resident immune cells, play a critical role in maintaining neural homeostasis (Ransohoff & Perry, 2009), however chronic activation can contribute to synaptic dysfunction, neuronal injury, and the propagation of neurodegenerative processes (Salter & Stevens, 2017) **(Figure 1)**. While much of the evidence for these mechanisms comes from preclinical and postmortem studies, their characterization in living human populations remains an area of active investigation. This is reflected in the fact that gold-standard frameworks of AD, such as the Jack biomarker curves (Jack et al., 2013) and the Amyloid, Tau, and Neurodegeneration (ATN) model (Jack et al., 2018) have historically lacked inflammation components as primary drivers. While the new NIA framework now includes "I" (inflammation) as an optional category (Jack et al., 2018), more work is needed to transition this biomarker from an experimental option to a clinical standard. Establishing non-invasive *in vivo* measures of neuroinflammation is a prerequisite for integrating this "I" component into a more comprehensive, personalized model of AD progression.

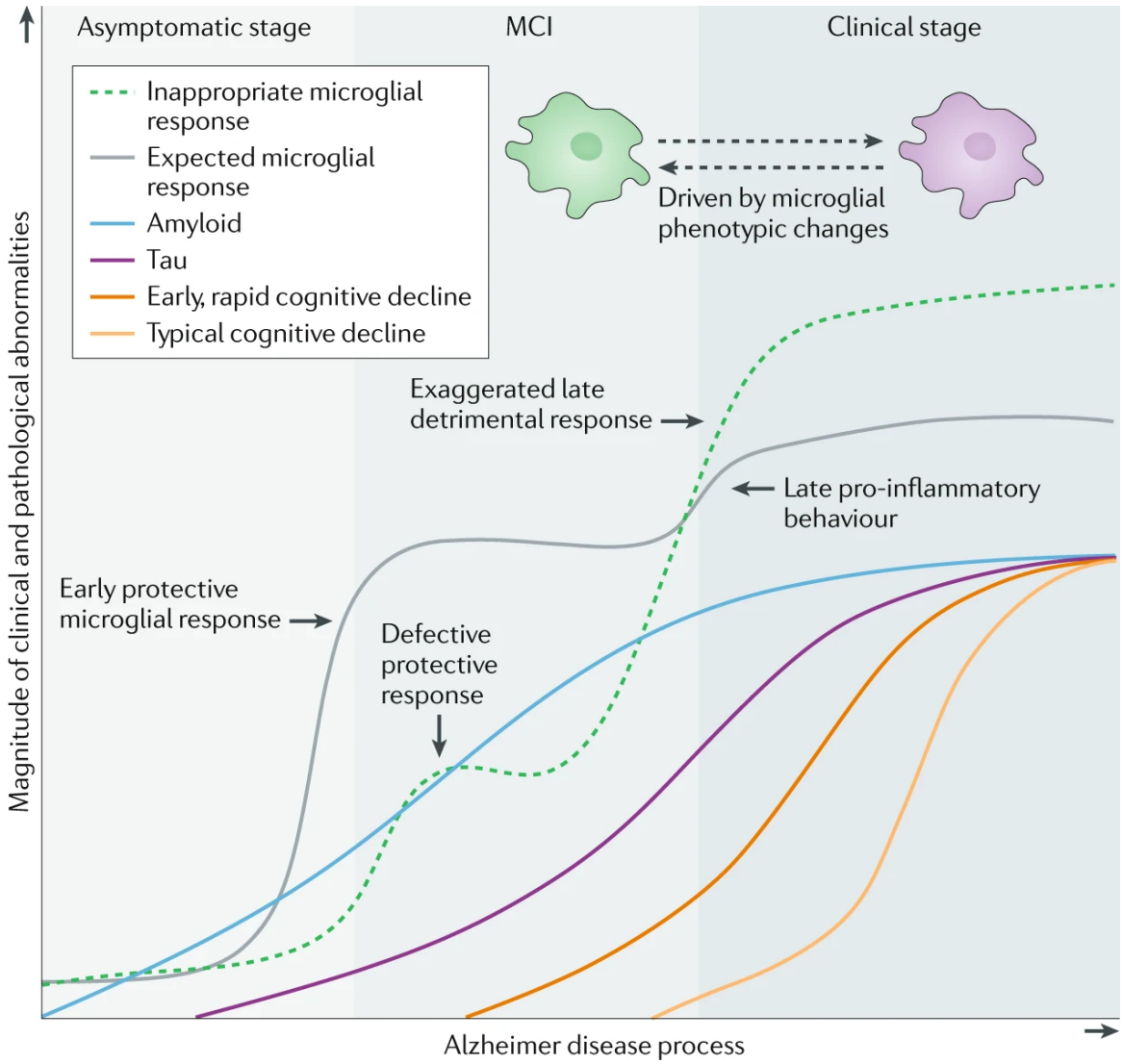


Figure 1 Dynamic changes in microglial activation that affect Alzheimer disease progression.

This figure is an adaptation from the Jack curves showing microglial response trajectories in both expected response state as well as an inappropriate response state. Current evidence suggests that during the prodromal stage of AD, the initial microglial response is protective overall but as AD progresses, chronic activation causes a shift in the microglia behavior causing damage to neuronal networks. Reproduced with permissions from the publisher Springer Nature (Leng & Edison, 2021).

To this end, peripheral neuroinflammation is increasingly recognized as a key contributor to central nervous system changes. Circulating inflammatory markers can influence brain structure through multiple pathways, including blood brain barrier permeability, signaling cascades, and

immune cell trafficking; pro inflammatory cytokines such as IL-6 and TNFα can cross a compromised blood brain barrier to engage endothelial and microglial signaling to propagate neuroinflammatory responses (Dantzer et al., 2008). Once in the central nervous system, these signals can activate microglia and astrocytes, amplifying local inflammatory responses and disrupting axonal and myelin integrity. This bidirectional communication between the peripheral immune system and the brain suggests that systemic neuroinflammation may have measurable effects on neural integrity, particularly within vulnerable WM pathways.

WM microstructure may be especially sensitive to inflammatory processes. Chronic neuroinflammation has been associated with alterations in myelination, axonal integrity, and extracellular fluid balance, all of which can disrupt efficient neural communication (Franklin & Ffrench-Constant, 2008; Pasternak et al., 2012; Trapp & Nave, 2008). These effects are particularly relevant in limbic pathways, which are both structurally vulnerable and critical for memory function.

Advanced diffusion imaging provides a framework for linking these biological processes to *in vivo* measures of brain microstructure. Within the NODDI model, ISOVF is thought to reflect extracellular free water and may be sensitive to neuroinflammation related changes in the tissue's environment, including edema, vascular leakage, and expansion of the extracellular space. ICVF provides an index of neurite density and may capture degradation or loss of axonal structure, while OD reflects the organization of fiber reorganization. Together, these metrics offer a biologically informed approach to investigating how inflammatory processes may shape WM integrity. Consequently, neuroinflammation emerges as a potential mechanistic driver of WM microstructural alterations, particularly within vulnerable limbic pathways. However, these

relationships are also unlikely to be uniform across individuals and may depend on biological context, including factors such as sex and genetic risk.

1.5 Sex Differences in Neuroinflammation and White Matter Integrity in Alzheimer's Disease

Biological factors may modulate the relationship between neuroinflammation and WM integrity, contributing to variability in AD risk across individuals. Among these factors, sex has emerged as a critical, yet often underexplored, determinant of disease susceptibility and progression.

Women account for a disproportionate number of AD cases exhibit a higher lifetime risk of developing the disease compared to men (Hebert et al., 2013). While increased longevity has historically been proposed as an explanation, accumulating evidence suggests that biological differences between sexes, particularly in immune function, may also play a significant role (Hebert et al., 2013; Klein & Flanagan, 2016; Mielke et al., 2014). Women generally exhibit more robust immune responses than men, including heightened production of pro-inflammatory cytokines and greater immune reactivity (Ferretti et al., 2018; Klein & Flanagan, 2016).

These differences extend to neuroimmune signaling, where sex hormones such as estrogen are known to influence both central and peripheral immune processes. Across the lifespan, fluctuations and eventual declines in estrogen levels may alter inflammatory regulation, potentially increasing vulnerability to sustained immune activation in aging (Klein & Flanagan, 2016; Straub, 2007). This heightened inflammatory responsiveness may, in turn, have downstream effects on brain structure.

Given the established sensitivity of WM microstructure to inflammatory processes, these findings raise the possibility that the coupling between neuroinflammation and WM integrity may differ by sex. Such differences may contribute to variability in the extent to which inflammatory processes impact limbic pathways and, ultimately, cognitive outcomes. Additionally, these sex differences may become particularly pronounced with aging, as hormonal changes and age-related immune shifts after inflammatory regulation, potentially transitioning women from a relatively immuno-protective to a more pro-inflammatory state and increasing susceptibility of limbic white matter to inflammatory injury. This raises the possibility that neuroinflammation and WM coupling may be sex specific, contributing to differential vulnerability to AD.

1.6 Down Syndrome as a Model of Accelerated Neurodegeneration and Immune Dysregulation

Down syndrome provides a unique and powerful model for studying the biological mechanisms underlying aging and AD. Rather than representing a separate clinical condition, DS can be conceptualized as a model of accelerated aging, in which key processes implicated in AD emerge earlier and with greater consistency across individuals (Head et al., 2016).

Trisomy of chromosome 21 results in the overexpression of genes that are directly relevant to both amyloid production and immune function, creating a unique genetic effect that primes the brain for neurodegeneration (Fortea et al., 2020; Snyder et al., 2020). Individuals with DS exhibit early and progressive accumulation of amyloid beta pathology, often beginning decades prior to the onset of clinical symptoms (Fortea et al., 2020; Head et al., 2012). In parallel, trisomy 21 is associated with lifelong immune dysregulation, characterized by chronic elevation of inflammatory markers and altered cytokine signaling (Sullivan et al., 2016). These persistent

inflammatory states may interact with developing neuropathology to influence brain structure and function across the lifespan.

By mid-adulthood, nearly all individuals with DS exhibit AD neuropathology, making this population uniquely suited for investigating early and preclinical disease processes (Fortea et al., 2020; Head et al., 2012). Importantly, the convergence of chronic neuroinflammation and early amyloid accumulation in DS provides a rare opportunity to examine how these factors jointly contribute to neurodegeneration *in vivo*. This synergy suggests that the neuroinflammatory environment in DS is not merely a secondary response to amyloid, but a primary driver that lowers the threshold for microstructural decay.

Within this framework, WM pathways, particularly those within the MTL, may represent a critical site of vulnerability. Limbic regions that support memory function are not only affected early in AD but may also be especially sensitive to the combined effects of neuroinflammation and pathology in DS. As such, examining WM microstructure in this population offers valuable insight into how neuroinflammation related processes may disrupt neural circuits underlying cognition. Down Syndrome therefore provides a unique model to investigate how chronic neuroinflammation interacts with brain microstructure across the lifespan, particularly within limbic pathways that support memory function.

1.7 Overview and Conceptual Framework of the Dissertation

Building on the framework outlined above, this dissertation investigates the role of neuroinflammation in shaping WM microstructure and its implications for cognitive function across aging and AD risk. Specifically, this work adopts an integrative approach to examine how

inflammatory processes relate to microstructural properties of MTL WM pathways and how these relationships vary across biological contexts.

To address these questions, this dissertation leverages advanced dMRI techniques, including NODDI, to provide biologically interpretable measures of WM microstructure. By focusing on limbic pathways that are critical for memory function and vulnerable to early degeneration, this work aims to identify structural signatures that may link neuroinflammation to cognitive decline.

The first chapter (D. M. Parker et al., 2025) addresses the biomarker gap identified in Section 1.1 by evaluating whether NODDI-derived measures of WM microstructure are associated with AD pathology and cognitive performance By establishing the sensitivity of these advanced diffusion metrics to disease related changes and evaluating their relevance to memory function, this chapter validates the use of microstructural imaging as a foundation for investigating the more complex pathways discussed in subsequent chapters.

The second chapter (D. Parker et al., 2026) investigates the relationship between peripheral neuroinflammation and WM microstructure, specifically addressing the critical oversight of biological sex in neuroinflammatory research. Given known differences in immune function and AD risk between women and men, this chapter tests whether the coupling between inflammatory markers and WM integrity differs by sex and whether these relationships are associated with AD-related cognitive outcomes.

The third chapter addresses the problem of pathological heterogeneity by extending this framework to individuals with Down Syndrome, a population characterized by chronic immune dysregulation and elevated risk for early onset AD. This chapter examines whether neuroinflammation is associated with alterations in limbic WM microstructure in this high-risk

group, providing insight into disease mechanisms that are often obscured by the variability of standard aging.

Together, these studies aim to advance our understanding of how neuroinflammatory processes contribute to limbic WM microstructural alterations and cognitive decline across the AD spectrum. By integrating measures of neuroinflammation, advanced diffusion imaging, and cognition, this work seeks to establish a biologically informed framework for investigating the mechanisms underlying neurodegeneration and identifying potential targets for early intervention. Collectively, this dissertation positions limbic WM microstructure as a critical pathway through which neuroinflammation may influence cognitive decline and highlights the utility of advanced diffusion imaging in capturing these processes *in vivo*.

Chapter 2: NODDI-derived measures of microstructure integrity in medial temporal lobe white matter pathways are associated with Alzheimer's disease pathology and cognition

All findings in this study have been published in a paper by Parker et al. (2025)

2.1 Introduction

Alzheimer's disease (AD) poses a significant public health challenge, which is exacerbated by the aging population. Currently it is estimated that roughly 6.7 million Americans are suffering from AD dementia with the potential of that number growing to 14 million in 2060 (Rajan et al., 2021). Emerging evidence indicates that development of pathology and neurobiological alterations in brain circuits occur long before the manifestation of symptoms, possibly even decades in advance (Barthélemy et al., 2020; Heiko Braak et al., 2011; Jack et al., 2010). Consequently, there is a pressing need to establish neuroimaging biomarkers with the ability to detect early neurobiological changes that contribute to the onset of cognitive deficits in AD.

White matter (WM) tracts – large bundles of axons – enable communication between gray matter regions. The integrity of these tracts are intriguing biomarkers in AD due to their vulnerability to Alzheimer's pathology and subsequent impact on cognitive decline. The integrity of WM within the medial temporal lobe (MTL) may have particular relevance to detecting the earliest stages of AD. The MTL, encompassing the hippocampus, amygdala, and parahippocampal gyrus, plays a vital role in spatial and episodic memory (Cutsuridis & Yoshida, 2017; Eichenbaum et al., 2007). Notably, the MTL is recognized as one of the earliest sites of atrophy (de Flores et al., 2022) and tau tangle pathology (H. Braak & Braak, 1995). Previous research has demonstrated strong relationships between gray matter integrity of the MTL, such as hippocampal volume

(Anderson et al., 2012; Xiao et al., 2023), and disease progression. Further, MTL regions have been shown to have declining WM microstructure associated with normal aging (Teipel et al., 2014). Biomarkers of MTL WM integrity in the earliest stages of AD have been less studied (Alm & Bakker, 2019; Magalhães et al., 2023), though they may provide more sensitive information on structural decline.

Diffusion magnetic resonance imaging (dMRI), a noninvasive neuroimaging method, holds great promise in assessing the integrity of WM pathways. By employing dMRI, subtle and early changes in the brain's WM can be detected (Márquez & Yassa, 2019; Teipel et al., 2014). Diffusion Tensor Imaging (DTI) can be used to calculate scalar indices derived from eigenvalues which are employed to describe anisotropy (Teipel et al., 2014). The most frequently utilized DTI indices include mean diffusivity (MD), which reflects the overall mean squared displacement of water molecules, and fractional anisotropy (FA), a measure of the magnitude of molecule diffusion that can be equated to anisotropic (i.e. directional) diffusion (**Figure 2A**) (Le Bihan, 1995; Teipel et al., 2014). Both FA and MD are widely used as proxies for observing microstructural tissue changes during brain aging (Ciccarelli et al., 2008). However, this tensor model poses major limitations as it fails to capture the complex architecture of WM characterized by crossing, bending, twisting, and kissing fibers (Jensen et al., 2005).

An alternative approach in dMRI involves tensor-free modeling, which encompasses various methods such as Q-shell imaging, Diffusion Kurtosis Imaging, and freewater elimination modeling (Jensen et al., 2005; Pasternak et al., 2009). Neurite Orientation Dispersion and Density Imaging (NODDI), another emerging tensor-free method, has the distinct advantage of allowing the examination of multiple compartments through multi-shell imaging, thereby offering a closer representation of the brain's actual architecture (Motovylyak et al., 2022; Timmers et al., 2016; H.

Zhang et al., 2012). Specifically, NODDI incorporates three microstructural compartments: intra-cellular, extracellular, and cerebrospinal fluid (CSF) (H. Zhang et al., 2012). NODDI generates metrics such as Neurite Density Index (NDI), which represents the portion of the tissue that is composed of axons and dendrites, and Orientation Dispersion Index (ODI), which reflects the angle variation and configuration of the neurite structure (**Figure 2A**) (Billiet et al., 2015). Previous research has validated NODDI measures against histological markers, revealing robust associations with compartment-specific indicators of neurite integrity. For example, Colgan et al. (2016) reported that NODDI, in a mouse model of human tauopathy (rTg4510), demonstrated the capacity to establish correlations within brain regions affected by tau. Remarkably, NDI outperformed the conventional FA metric by being the sole metric capable of detecting a correlation with tau burden in the hippocampus (Colgan et al., 2016).

Prior studies have begun to demonstrate associations between NODDI metrics and tau deposition or cognition in Alzheimer's disease, including voxelwise associations in both gray and white matter regions (Sone et al., 2020; Tian et al., 2023; Wen et al., 2019; Weston et al., 2023)Tian et al., 2023; Weston et al., 2023; Sone et al., 2020; Wen et al., 2019). However, few studies have directly compared tensor-based and NODDI models within the same sample, across multiple medial temporal white matter pathways, and within a multisite harmonized dataset. The present study extends this literature by evaluating both tensor and NODDI metrics in parallel, applying mediation models to test mechanistic pathways linking pathology and cognition, and using machine learning approaches to compare estimation performance across models.

A growing number of studies have applied NODDI to examine microstructural alterations in Alzheimer's disease and have reported that NODDI metrics may outperform conventional DTI measures in detecting early pathological changes (Gallagher et al., 2023; Moody et al., 2022; Vogt

et al., 2020, 2022; Yu et al., 2024). Building upon this prior work, the present study leverages harmonized multishell diffusion data from the ADNI3 cohort, applies NODDI and tensor models across multiple medial temporal white matter pathways, incorporates mediation analyses linking pathology and cognition, and evaluates classification performance using machine learning approaches.

While NODDI represents a promising improvement to dMRI analyses of WM integrity, it has not yet been thoroughly investigated in the context of AD specifically within the ADNI cohort since prior to ADNI3 there was no multishell diffusion weighted imaging (DWI) sequence. The objective of this study is to investigate whether NDI and ODI metrics, obtained through NODDI models of dMRI, exhibit improved performance of detecting AD pathology in MTL WM. Given that memory loss is a hallmark of early Alzheimer's disease, we focused on memory outcomes and pathology in relation to early alterations in major white matter pathways within the medial temporal lobe that are particularly vulnerable in the initial stages of the disease, specifically the cingulum, fornix, and uncinate fasciculus. We hypothesize that NODDI metrics will enhance sensitivity in detecting microstructural changes in WM across our population of cognitively unimpaired, mild cognitively impaired, and individuals with AD dementia.

2.2 Methods

Data Source

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other

biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see www.adni-info.org. Ethical approval was obtained by the ADNI investigators at each participating ADNI site. All participants provided written informed consent.

Study Participants

All participants from the ADNI3 protocol were evaluated for inclusion of the multi-shell DWI sequence giving us a total of 230 initial participants for this study. After initial quality control to assess scan completeness, protocol alignment, and scanner harmonization (ensuring all scans were acquired on Siemens MRI machines), visual inspection was performed to identify issues such as motion and susceptibility artifacts (n = 5), registration failures (n = 8), and missing b-shells (n = 2). Following this process, 199 participants were retained for analysis. Due to a low number of participants with a dementia diagnosis (N=12), individuals diagnosed with MCI were combined with participants diagnosed with dementia for a Cognitively Impaired (CI) group (N=77), which were compared against a Cognitively Normal (CN) group (N=121). **Table 1** provides a breakdown of participant demographics. The cognitively impaired group included individuals classified as either mild cognitive impairment (n = 65) or mild Alzheimer's disease dementia (n = 12) per ADNI3 clinical criteria. The dementia cases were all diagnosed as probable AD. Inclusion of both MCI and mild dementia cases allowed us to capture a broader continuum of AD-related cognitive and biomarker variability for dimensional analyses. Molecular biomarker data were available for a subset of participants. Amyloid PET (Florbetapir or Florbetaben, converted to Centiloids) was available for 146 participants, with 25 cognitively normal (20%) and 32 cognitively impaired participants (41%) classified as amyloid positive (Centiloid > 18). Tau PET (Flortaucipir) data

were available for 135 participants; mean entorhinal tau SUVRs were 1.8 (CN) and 1.9 (CI) and mean meta-temporal tau SUVRs were 1.6 (CN) and 1.7 (CI). These molecular biomarkers were used in correlational and mediation models throughout the analyses.

	CN (N=121)	CI (N=77)		p-value
		MCI(N=65)	AD(N=12)	
Age (range)	71(51-90)	72.3(49-90)	76.6(59-89)	0.09
Aβ+ (%)	25(20)	25(39)	7(59)	0.00002†
APOE4 (%)	28(23)	19(29)	6(50)	0.02†
Entorhinal Tau (std)	1.8(0.45)	2.1(0.7)	3.1(0.8)	0.001
Meta Temporal Tau (std)	1.6(0.25)	1.8(0.6)	2.6(0.9)	0.0001
Sex: Female (%)	79(65)	29(45)	7(59)	0.01†
Years of Education (std)	17(2.36)	16(2.6)	15(2.7)	0.04
Race				0.4†
White (%)	94(78)	56(86)	8(67)	–
Black (%)	19(16)	5(8)	3(25)	–
Asian (%)	6(5)	2(3)	0	–
More than one (%)	2(2)	2(3)	1(8)	–
Ethnicity				0.6†
Hispanic/Latino (%)	2(2)	3(4)	0	–
Unknown (%)	1(0.8)	1(1)	0	–
Not Hispanic/Latino (%)	118(98)	61(94)	12(100)	–
CDR-SB (std)	.03(2.36)	1.6(1.3)	5.4(3.2)	0.00001
ADNI-MEM (std)	1.12(0.69)	0.3(0.7)	-0.6(0.5)	0.00001

Table 1 Demographics 2.2

CN, Cognitively Normal; CI, Cognitively Impaired; CDR-SB, Clinical Dementia Rating Sum of Boxes; ADNI-MEM, ADNI memory composite score; std, standard deviation. P-values are statistical comparisons between CN and CI groups. † denotes comparison via chi-squares test; otherwise all comparisons were independent samples t-tests.

Structural and Diffusion MRI Processing

To ensure the homogeneity of the scan data across different sites, only scans obtained using Siemens MRI machines were selected for analysis. This decision aimed to minimize potential variations that could arise from using different machine manufacturers and ensure a more consistent and standardized dataset for the study. To further assess potential site-specific effects, we conducted our regression models including scanner site as a control as well as age, sex, and education. These analyses did not reveal significant site differences for any of the NODDI metrics across the regions of interest (all $p > 0.1$), suggesting that site variance was minimal after limiting to Siemens Prisma scanners. All participants were scanned using the ADNI 3.0 Advanced MRI scanning protocol, the first ADNI protocol to include multi-shell scan sequences. Each participant underwent a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: echo time (TE)=2.98 ms, repetition time (TR)=2300 ms, inversion time=900ms, flip angle=10◦, field of view (FOV)=208×240×256 mm3, acquired resolution =1×1×1mm. MRI parameter specifics can be found at http://adni.loni.usc.edu/methods/documents/mri-protocols/. T1-weighted images were corrected using Freesurfer 7 pipeline, which corrected for head motion and intensity inhomogeneity then the removal of non-brain tissue. After structural scans were quality checked, corrected hippocampal volume was calculated using intracranial volume and raw hippocampal volume Freesurfer output.

Diffusion scans were acquired via the following parameters: 232x232x160 mm @ 2x2x2 mm; TE=71 TR=3300. Three separate shells were collected at the following b-values: 500, 1,000, and 2,000 s/mm² for a total of 112 directions. For the tensor metrics (FA and MD) the 1,000 s/mm² shell was chosen as it was the b-value that was used in the single shell diffusion scan in the non-advanced ADNI3 protocol. Scans were preprocessed using MRtrix3 (Tournier et al., 2012)

(www.mrtrix.org). Diffusion data preprocessing included denoising using MRtrix3's dwidenoise function, correction for Gibbs ringing artifacts (Kellner et al., 2016), susceptibility-induced distortions using fieldmap-based EPI distortion correction, eddy current and motion correction using FSL's eddy tool, and bias field correction. These steps were all completed prior to manual quality control. Tensor metrics were extracted via MRtrix3 and maps were created for FA and MD (**Figure 2A**). The Microstructure Diffusion Toolbox (MDT) (Harms et al., 2017) was used to calculate NDI and ODI maps (**Figure 2A**). Although FISO may provide useful insights into extracellular free water, it is particularly susceptible to partial volume effects from CSF, especially in small MTL tracts such as the fornix. Given our focus on robust tract-level estimates of tissue microstructure, we prioritized NDI and ODI as the most biologically interpretable and reliable NODDI metrics for this dataset.

The following MTL ROIs from the JHU DTI based WM atlas (https://identifiers.org/neurovault.collection:264) were used in this analysis **(Figure 2B)**: cingulum cortex, hippocampal cingulum, fornix column body, fornix ST (stria terminalis) and uncinate. Following preprocessing of the dMRI, images metrics for both NODDI and DTI were transformed to MNI space, and then the mean values of FA, MD, NDI, and ODI were extracted from each tract. Given the small size and partial volume susceptibility of certain medial temporal tracts, particularly the fornix ST, we implemented multiple safeguards. All diffusion images were visually inspected after preprocessing and spatial normalization to verify accurate registration and anatomical localization of the fornix ST across participants. ROI extraction was performed using standardized atlas-based masks in MNI space to ensure consistency. Importantly, the NODDI model itself provides partial mitigation of partial volume effects by explicitly estimating

intracellular, extracellular, and CSF compartments, thereby reducing contamination from surrounding tissues.

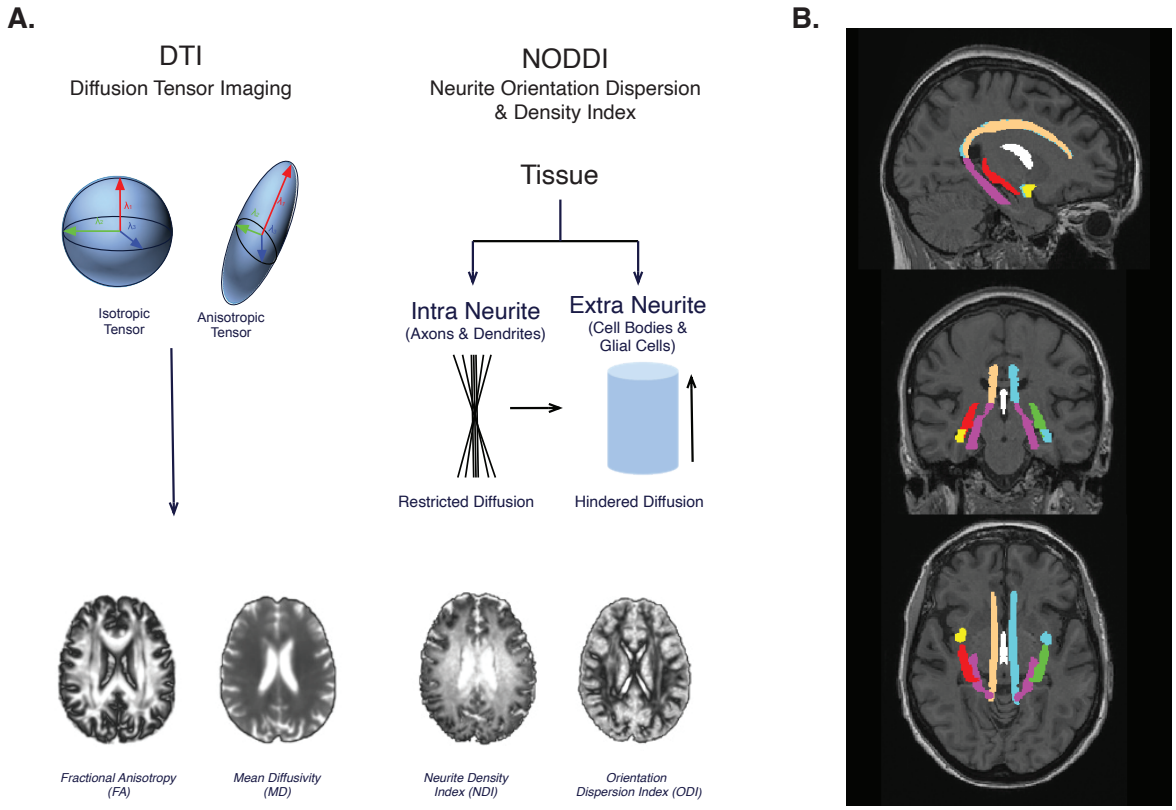


Figure 2 Overview of diffusion modeling

A. Overview of Diffusion Tensor imaging and overview of NODDI. B. Example of JHU WM Atlas ROIs

Clinical and Cognitive Measures

We analyzed the Clinical Dementia Rating Scale - Sum of Boxes score (CDR-SB), the Clinical Dementia Rating Scale - Memory (CDR-MEM) and ADNI-MEM as primary measures. The CDR-SB is a widely used clinical measure that assesses the severity of dementia in patients at a given time point. The "sum of boxes" component of the CDR provides enhanced precision for tracking changes over time and minimizes potential computational errors. The memory component

of the CDR scale provides additional insights into the population based on their overall memory performance. Out of 199 included participants, 195 successfully completed the CDR and thus were included in the analyses of this measure (Morris, 1993).

To assess memory performance, we used the ADNI-MEM, a composite memory score derived from the cognitive battery as described by Crane et al. (2012) (Crane et al., 2012). We opted to utilize this measurement as it provides a combined single memory score that serves as a robust and comprehensive representation of memory performance (Crane et al., 2012). Out of the 199 participants, 186 had data available for ADNI-MEM.

Positron Emission Tomography

PET imaging protocols included 18F-Flortaucipir (FTP) to measure tau pathology and either 18F-Florbetapir (FBP) or 18F-Florbetaben (FBB) to measure Aβ pathology (depending on availability at time of collection). All preprocessing was completed by the ADNI PET core at UC Berkeley. Full details on PET processing and acquisition are available at the ADNI website https://adni.loni.usc.edu/wp-content/uploads/2012/10/ADNI3_PET-Tech-Manual_V2.0_20161206.pdf.

FTP data was analyzed between 80-100 minutes post-injection across four 5-minute frames, normalized using an inferior cerebellum gray reference region, and a Rousset approach for partial volume correction (Baker et al., 2017; Rousset et al., 1998). The mean standardized uptake value ratio (SUVR) values of FreeSurfer regions (version 7.1.1) were used. We focused on the mean SUVR of the entorhinal cortex and a meta-temporal ROI, which is a composite of the following regions: entorhinal, parahippocampal cortex, amygdala, fusiform, medial temporal, and inferior temporal (Jack et al., 2010).

FBP data was analyzed between 50-70 min post-injection, while FBB data were analyzed 90-110 min post-injection. both across four 5-minute frames. Both FBP and FBB were normalized using a whole cerebellum reference region. Global amyloid-beta was calculated using a cortical summary region consisting of Freesurfer-defined (version 7.1.1 processing) frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal regions (Landau et al., 2013, 2012). To enable combination of the two tracers, regional and global FBP and FBB values were converted to the Centiloid scale, and a threshold of 18 Centiloids was used on the cortical summary region to determine amyloid-beta positivity (Royse et al., 2021).

Statistical Analysis

All statistical analyses were performed in Jamovi 2.3 (The Jamovi Project 2022) or Python (version 3.8). Mediation analyses were performed in Jamovi using the medmethod module. Correlation analyses performed were partial correlations controlling for age, sex, and education (Seongho Kim, 2015). All p-values were corrected using the Bonferroni–Holm method in R (version 3.6.2) https://rdocumentation.org/packages/stats/versions/3.6.2 (correcting for 5 comparisons) using the p.adjust function from the "stats" package in R. We also conducted exploratory subgroup analyses, repeating partial correlations separately within CN and CI groups to evaluate whether findings were driven by diagnostic group.

Random forest classification models were used to estimate CDR-SB classification (CDR > 0 vs CDR = 0) and ADNI-MEM (mean split). Models were constructed as (1) tensor only, (2) NODDI only, and (3) combined models (best tensor, NODDI, and demographics). Random forest (Breiman, 2001) is a type of ensemble machine learning algorithm that is widely used for classification or regression models including multi-dimensional variables (Delgado et al., 2014).

We developed and implemented RF algorithms in Python using the Scikit-Learn library (Pedregosa et al., 2012). 100 decision trees consisting of different combinations of estimation variables were built for each model. Model performance was evaluated using area under the curve (AUC) of the receiver operating characteristic (ROC) curves, which was plotted from all the estimated values of the test data set using leave-one-out cross validation (LOOCV). The LOOCV design was specifically chosen given the small sample size (Falahati et al., 2014) and built n classification models using n-1 subject each time which then utilized the classifier to determine the class of the left-out subject. Sensitivity and specificity were computed for each classification. We also performed bootstrapping (1000 simulations) to estimate 95% confidence intervals for the AUCs. Feature importance was also obtained using the Gini impurity index (Breiman, 2001).

2.3 Results

NODDI measures show stronger associations with AD-related outcomes

We aimed to determine if using NODDI metrics could more sensitively account for complexities in WM tract microstructure, thus revealing stronger associations with outcome measures. Our two primary NODDI outcome measures were NDI, reflecting the density of how the neurites are packed, and ODI, reflecting orientation and directionality of the neurites (**Figure 2A**).

We first tested relationships between NODDI metrics of the MTL with clinical and cognitive performance, specifically the CDR-SB, CDR-MEM, and ADNI-MEM. Partial correlation analysis of NODDI results revealed that NDI consistently exhibited a larger frequency of significant correlations with outcome measures when compared to ODI across all outcome measures, as shown in **Figure 3A** and **Supplementary Table 2.** Specifically, NDI in the cingulum

cortex and hippocampal cingulum regions demonstrated consistent and significant correlations with cognitive outcomes ($p_{FDR} < 0.05$). In contrast, ODI only showed significant associations predominantly in the fornix and uncinate regions. Interestingly, ODI displayed consistent correlations across all three outcome measures (CDR-SB, ADNI-MEM, and hippocampal volume) in the fornix ST ($p_{FDR} < 0.001$). In most tracts, NODDI metrics showed significantly stronger associations with cognitive performance compared to FA; however, in the cingulum cortex, the difference between ODI and FA was not statistically significant. To determine if NDI indeed had a stronger association than ODI, we formally tested the strength of the associations using a Steiger's z test. We found that the correlation between NDI of the hippocampal cingulum regions was stronger than ODI hippocampal cingulum regions ($z = 2.0251$, p-value = 0.0214). This was also the case for NDI cingulum cortex and ODI cingulum cortex ($z = 2.0560$, p-value = 0.0199). Additional Steiger Z-tests indicated that ODI outperformed NDI in estimating memory performance in the fornix ST ($z = 2.5486$, $p = 0.0054$) but not the uncinate fasciculus ($z = -0.35$, $p = 0.64$). Across the full set of medial temporal tracts, NDI and ODI demonstrated region-specific strengths, suggesting complementary sensitivity across white matter pathways relevant to memory. These results demonstrate that among the NODDI metrics, a significant decrease in neurite density is correlated with a decline in cognitive performance. While ODI showed fewer relationships, it was still able to show that reduced neurite orientation was associated with worse cognitive performance. We next tested associations between NODDI with Alzheimer's pathology, specifically global Aβ, and both entorhinal and meta-temporal tau. Both NDI and ODI of various WM tracts exhibited significant correlations with pathology, with entorhinal tau demonstrating the greatest number of associations across both NODDI metrics. Entorhinal tau was significantly associated with NDI in the hippocampal cingulum ($r = -0.375$; $p < 0.001$) and in the uncinate ($r =$

-0.373; $p < 0.001$), and with ODI in the fornix ST ($r = -0.288$; $p = 0.004$). Notably, ODI of the fornix ST showed significant associations with both tau ROIs (entorhinal $r = -0.288$; $p < 0.001$; meta-temporal $r = -0.319$; $p < 0.001$). Z tests showed that neither the NDI hippocampus nor the uncinate was more significant than ODI fornix ST. Our analyses showed that with greater tau pathology there was reduced neurite density as well as a reduction in the orientation of the neurites, demonstrating a reduction in diffusion properties in regions impacted by AD-related tau pathology.

Finally, we investigated associations between NODDI measures and hippocampal volume as a proxy of neurodegenerative processes. Notably, hippocampal volume exhibited relatively fewer significant associations with the NODDI metrics. Hippocampal volume was only significantly associated with ODI of the fornix ST ($r = -0.301$; $p < 0.001$) and NDI of the hippocampal cingulum ($r = -0.226$; $p = 0.0125$) and fornix ST ($r = -0.215$; $p = 0.01$). Exploratory subgroup analyses stratifying by cognitive status demonstrated largely consistent patterns of association across both groups, with attenuated effect sizes observed in the CN group due to reduced range of pathology and cognitive impairment. Full subgroup correlation results are provided in Supplementary Tables 5 and 6.

FA shows fewer relationships between cognitive and pathological outcome measures

We then examined the relationship between standard tensor-based diffusion metrics, namely FA and MD, with these same cognitive and pathology outcome measures (**Figure 3B**). Among the three cognitive outcome measures, there were no significant correlations with FA of any WM tracts assessed. On the other hand, MD of the hippocampal cingulum ($r = -0.185$; $p = 0.02$), fornix ST ($r = -0.273$; $p < 0.01$), and uncinate ($r = 0.244$; $p = 0.01$) demonstrated strong associations with ADNI-MEM. CDR-SB and CDR-MEM also showed similar results to ADNI-

MEM (**Figure 3B**; **Supplementary Table 3A).** No other regions demonstrated significant findings in relation to MD.

We next assessed relationships between tensor metrics with AD pathology and hippocampal volume. There were no significant correlations between FA in any tract with either global Aβ or tau pathology in entorhinal cortex or meta-temporal ROI ($p_{FDR} > 0.075$). However, FA of the fornix ST and fornix column body had significant relationships with hippocampal volume. MD across multiple tracts such as the fornix ST and fornix column body did show relationships with pathology and hippocampal volume, as indicated in **Figure 3B** and **Supplementary Table 3**.

Using the Steiger Z test, we found that NDI was significantly more strongly correlated with cognitive outcomes when compared to FA ($z > 2.7$; $p < 0.012$). We also found that ODI was significantly more strongly correlated with cognitive outcomes when compared to FA, except in the cingulum cortex. Correlations between outcome measures and NDI were significantly stronger than with MD, further confirming our hypothesis that NDI can be considered a more sensitive metric for AD-related white matter changes.

Together, our results show that worse cognitive and pathological outcomes are associated with significant decreases in NDI and ODI which reflects a loss of neurite density as well as an increase in neurite dispersion. This demonstrates the high sensitivity of NODDI metrics to detect these processes. In contrast, for the tensor metrics, increases in MD, but not FA, were associated with these measures, which highlights the reduced sensitivity of traditional DTI models, especially the commonly used metric of FA.

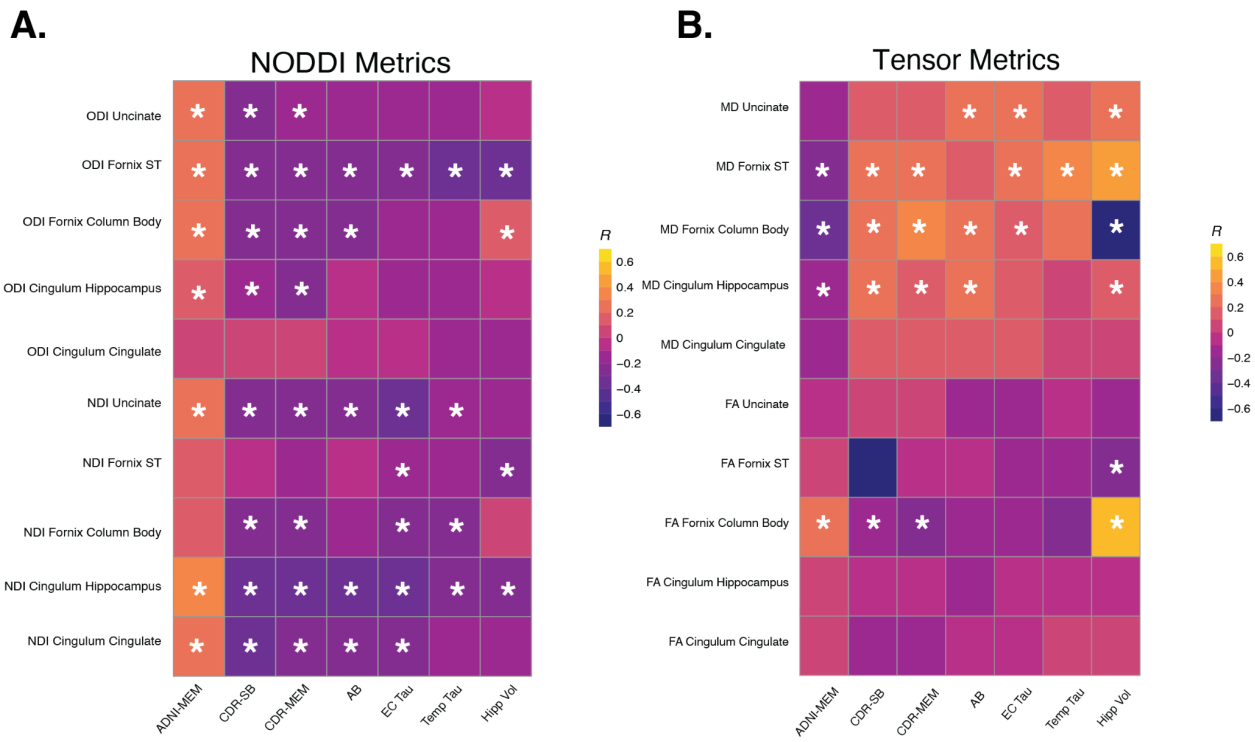


Figure 3 Correlation matrices of NODDI metrics

(A) *Associations for NODDI-derived metrics, including orientation dispersion index (ODI) and neurite density index (NDI).* ***(B)*** *Associations for conventional diffusion tensor imaging (DTI) metrics, including mean diffusivity (MD) and fractional anisotropy (FA). Rows represent tract-specific diffusion measures across the uncinate fasciculus, fornix, cingulum hippocampus, and cingulum cingulate, while columns represent Alzheimer's disease pathology and cognitive outcomes. Colors reflect the magnitude and direction of the partial correlation coefficient (R), controlling for age, sex, and education. Asterisks indicate statistically significant associations after correction for multiple comparisons. Abbreviations: Fornix ST = Fornix Stria Terminalis, CDR-SB = Clinical Dementia Rating Scale Sum of Boxes, β-amyloid = Amyloid Beta, EC Tau = Entorhinal Tau, Temp Tau = Meta Temporal Tau, Hipp Vol = Hippocampal Volume.*

Mediation Models show strength of NODDI in showing mechanistic underpinnings of neurodegeneration

We next tested potential mechanistic links between pathology, NODDI metrics of WM integrity, and cognitive performance. We chose the hippocampal cingulum due to its strong associations found in our correlation models and known role in memory processing. We chose to examine NDI rather than ODI from NODDI also due to its more sensitive performance in our statistical models. Additionally, we did not find relationships with MD or FA and either entorhinal

or meta temporal tau, so we were unable to use these metrics as part of our mediation modeling. ADNI-MEM was selected as the cognitive outcome measure due to previous work demonstrating its increased sensitivity to memory decline in MCI and AD populations (Crane et al., 2012). We performed mediation models to test whether NDI of the hippocampal cingulum mediated the relationship between AD pathology and the ADNI-MEM cognitive outcome measure. Our results showed that NDI of the hippocampal cingulum partially mediated the relationship between entorhinal tau and ADNI-MEM (indirect effect: $\beta = -0.09$, $p = 0.036$; direct effect: $\beta = -0.64$, $p < 0.00001$; total effect: $\beta = -0.725$, $p < 0.00001$; **Figure 4A**). We also found that NDI of the hippocampal cingulum partially mediated relationships with ADNI-MEM in models of both meta temporal tau (indirect effect: $\beta = -0.09$, $p = 0.024$; direct effect: $\beta = -0.59$, $p < .00001$; total: $\beta = -0.69$, $p < 0.00001$; **Figure 4B**) as well as Aβ (indirect effect: $\beta = -0.002$, $p = 0.005$; direct effect: $\beta = -0.006$, $p = 0.0005$; total effect: $\beta = -0.008$, $p < .00001$; **Figure 4C**). These mediation results further support the sensitivity of NDI to detect mechanistic relationships in AD. Additionally, we did not find significant associations between FA and either the predictor variables (tau or amyloid) or the outcome measures (cognition), which initially precluded construction of mediation models for FA. However, to fully address the possibility of indirect-only effects, we conducted exploratory mediation analyses using FA as a mediator. These models yielded nonsignificant indirect effects across all mediation pathways (entorhinal tau: $p = 0.35$; meta-temporal tau: $p = 0.57$; amyloid: $p = 0.42$), further supporting the absence of meaningful mediation for FA.

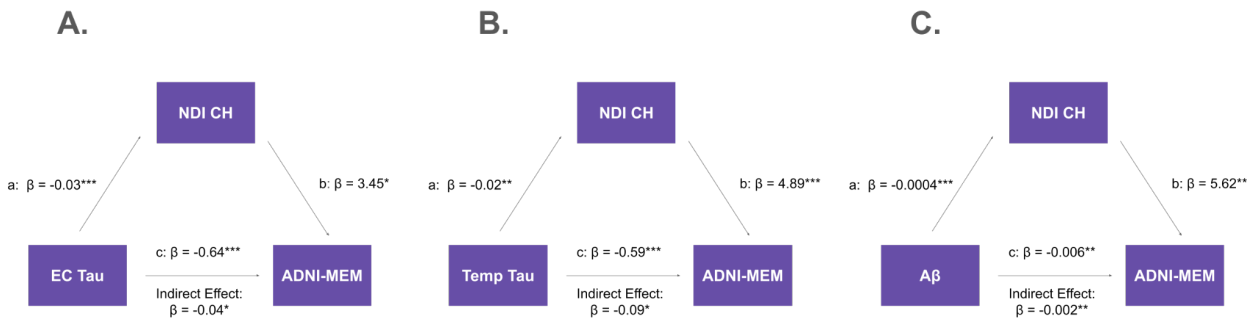


Figure 4 Mediation Models demonstrating the relationship of NODDI's NDI metric on AD pathology.

*All correlations shown here are partial. (**A**) NDI mediates the relationship of entorhinal tau and ADNI-MEM (**B**) NDI mediates the relationship of meta temporal tau and ADNI-MEM **(C)** NDI mediates the relationship between β-amyloid and ADNI-MEM. NDI, neurite orientation index; ODI, * indicates p-value ≤ 0.05, ** indicates p-value ≤ 0.001, *** indicates p-value ≤ 0.0001 Abbreviations: NDI = Neurite Density Index, CH = Hippocampal Cingulum, EC Tau = Entorhinal Tau, Temp Tau = Meta Temporal Tau, β-amyloid = Amyloid Beta.*

Combination of NODDI and Tensor Metrics Best Estimate Clinical/Cognitive Outcomes

Our final goal was to test which combination of diffusion metrics best estimated cognitive outcome measures associated with AD, and to determine the strength of estimation of these models, using ROC analyses. First, we constructed separate models to compare NODDI and tensor metrics directly. Second, we took the top metric from each model to create a combined diffusion model to maximize estimations. Due to the significant association between outcomes such as memory and demographic variables, final combined models included participants' age, sex, and education. Additionally, the separate metrics models were performed both with and without demographics included. On the models with demographics there was only a slight change in the ROC (~0.03 difference) showing that inclusion of demographics in the independent metric model runs was not impacting the model in a positive nor negative way. Relative feature importance was also checked and demographics consistently scored at the middle to bottom of the table further showing the lack of impact of demographics on the individual models' metrics selection.

We first tested the estimation of memory performance using ADNI-MEM **(Figure 5A)**. Participants were divided into two subgroups using a median split method. Initial models were conducted separately for the NODDI metrics and tensor metrics, revealing distinct outcomes. The NODDI model (AUC = 0.65; CI 95% bootstrap: [0.649,0.651]) displayed a more even distribution of Gini importance values across all included tracts and metrics (**Figure 5D**), whereas the tensor model (AUC = 0.67 [0.669,0.671]) had a clear top performer, with a 29% performance gap between MD cingulum cortex (71%) and MD fornix column body (100), the two highest-ranking metrics on the importance table (**Figure 5C**)**.** For the combined model, NDI hippocampal cingulum and MD fornix column body were selected along with the demographic variables. This combined model resulted in the strongest estimation, with an AUC of 0.76 [0.759,0.761].

We next tested estimation of the CDR-SB score (**Figure 5E**). We first classified participants as having a score indicating impairment (CDR-SB > 0; n = 77) or no impairment (CDR-SB = 0; n = 115). The NODDI model had an AUC of 0.69 [0.689,0.691]. Within this model, ODI of the fornix ST had the highest Gini value and was therefore the best metric for estimating the outcome, compared to the other NODDI tract metrics. (**Figure 5H**). The tensor model had an AUC of 0.70 [0.699,0.701]. MD of the fornix column body had the highest Gini importance index (**Figure 5G**). The combined model, incorporating these top two performers, demonstrated an even higher estimation value for CDR-SB classification, yielding an AUC of 0.74 [0.739,0.741]. Specificity and sensitivity for each model can be found in **Supplementary Table 4.** CDR-MEM was not used as a model due to a lack of response diversity making it an insufficient outcome measure to be used with a machine learning model.

Formal pairwise comparisons of the AUC curves were conducted using the roc.test function in R. For ADNI-Mem, the combined DTI + NODDI model demonstrated significantly

higher AUC compared to NODDI alone (p = 0.01) and showed a trend toward outperforming DTI alone (p = 0.06). No significant AUC differences were observed between NODDI and DTI directly. For CDR-SB, no significant AUC differences were detected between any of the models.

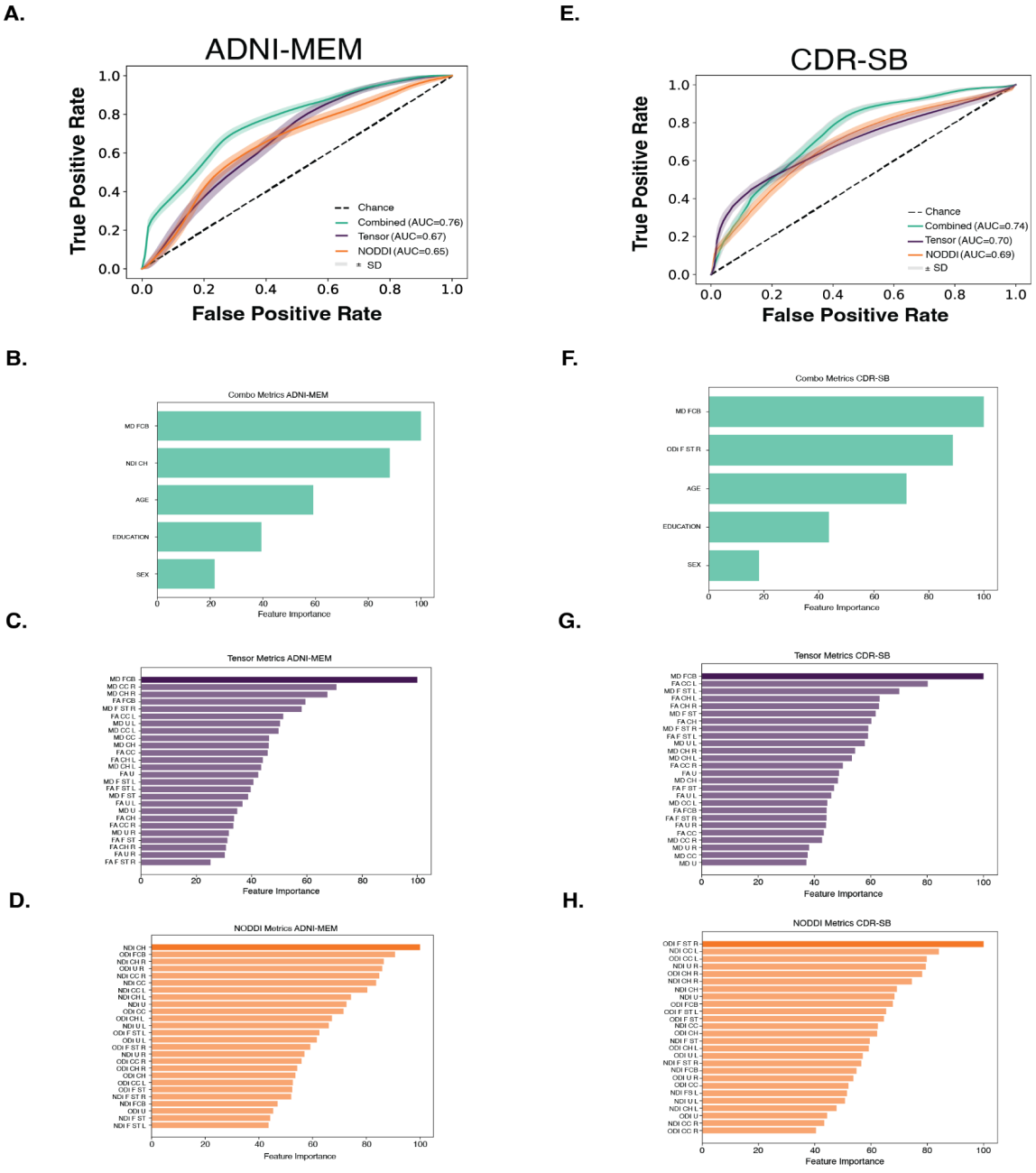


Figure 5 Characteristic curves for random forest classification models

(A) *ADNI-MEM model showing combined metrics (green), tensor metrics (purple) and NODDI metrics (orange).* ***(B)*** *Gini Importance Table showing combined model results for ADNI-MEM.* ***(C)*** *Gini Importance Table showing just tensor metric results for ADNI-MEM. D. Gini Importance Table showing only NODDI metrics results for ADNI-*

MEM. ***(E)*** *CDR-SB model showing combined metrics (green), tensor metrics (purple) and NODDI metrics (orange).* ***(F)*** *Gini Importance Table showing combined model results for CDR-SB.* ***(G)*** *Gini importance table showing only tensor metric results for CDR-SB.* ***(H)*** *Gini Importance table showing only NODDI metrics results for CDR-SB. Dotted line = chance. Combination models included age, gender and education. Tensor and NODDI Gini Tables have top importance features bolded to show it was used in the combination modeling. Abbreviations: CC = cingulum cortex, CH = hippocampal cingulum, FCB = Fornix Column Body, F ST = Fornix Stria Terminalis, U = Uncinate, R = Right hemisphere, L=left hemisphere.*

2.4 Discussion

The utilization of multishell diffusion imaging has opened new doors to understanding AD in ways that were previously unattainable through standard diffusion tensor modeling techniques. Previous studies using standard single shell tensor models have left significant gaps in our understanding of the complexities of how WM microstructure is impacted by AD. Our research clearly highlights the advantages of employing the NODDI multishell compartmental model for gaining deeper insights into the pathology and cognitive outcomes of aging and AD. Our study demonstrates significant associations between NODDI and overall cognitive/clinical status, memory-related processes, as well as Alzheimer's pathology. Overall, our study suggests that while single shell DTI is a useful tool for studying aging, NODDI is able to give us additional information when it comes to cognition and pathology where tensor metrics such as FA fail to show significance. Exploratory subgroup analyses suggest that the observed associations are not solely driven by cognitively impaired individuals; however, smaller sample sizes within these subgroups may limit statistical power.

Our study delved into the association between NODDI and tensor metrics with outcomes specific to aging and AD. The NODDI measure NDI, specifically when measured in the hippocampal cingulum, demonstrated more significant associations with cognition and pathology than tensor measures. In contrast, FA did not exhibit many associations with cognition and pathology. NDI had strong associations specifically in the cingulum cortex and hippocampal

cingulum regions for tau and Aβ burden. Mediation models demonstrated that NDI was a significant mediator of the relationship between ADNI-MEM and entorhinal tau, meta temporal tau and β-amyloid, further supporting our hypothesis that the utilization of NODDI can show more specific results than those of just DTI alone as FA was unable to be used for mediation models due to lack of significant associations. Our results highlight significant associations between these NODDI metrics and tau pathology, with the NDI showing heightened sensitivity of entorhinal tau. Additionally, our results showed that Aβ had associations with the integrity of the cingulum, uncinate and fornix across both NDI and ODI metrics.

Although DTI has been widely employed to describe WM properties in previous research, it is not without limitations, such as issues related to crossing fibers (Chen et al., 2023). It is widely recognized that as humans age, irrespective of the presence of neurodegenerative diseases, there is typically a reduction in fractional anisotropy (FA). However, FA can be a somewhat ambiguous metric, with the decline potentially attributable to various structural factors, including demyelination or a decrease in axon density (Sampaio-Baptista & Johansen-Berg, 2017). While the development of alternative diffusion analysis pipelines has helped mitigate some of these limitations associated with DTI, the application of NODDI has emerged as a valuable method for assessing microstructural changes (Chen et al., 2023). Our study demonstrates that FA alone exhibited weak, non-significant strength of association with nearly all the study's outcome measurements. Recently, a study conducted on the ADNI3 cohort by Chen et al. (2023) (Chen et al., 2023) demonstrated that FA within specific MTL regions, particularly the hippocampal cingulum, exhibited correlations with tau burden. Our findings provide a more comprehensive examination of the compartmental complexity of WM, revealing that a stronger and more detailed association can be derived with NODDI than from the FA metric measurement alone. Based on

this observation, we posit that NODDI metrics, with their capacity to discern alterations in microstructure, play a pivotal role in understanding the underlying changes occurring in WM during both the aging process and the progression of AD. While prior studies have demonstrated the utility of NODDI for detecting microstructural changes in Alzheimer's disease and have compared NODDI to DTI in several contexts (Radhakrishnan et al., 2022), our findings add to this growing literature by systematically evaluating both tensor and NODDI models within a harmonized multisite cohort and testing mechanistic mediation models linking white matter changes with both pathology and cognition.

NDI may have increased sensitivity to detect early pathological changes compared to other metrics due to its ability to provide information at the cellular level. This information, which is achieved through NODDI's use of multi-compartment analysis via the acquisition of multishell imaging, gives information at an anatomical level. This in turn is more nuanced and in depth when compared to the DTI methods which use a single diffusion shell to make more generalized statements about the status of water molecule movement within a region of tissue. Our study expands on previously published studies that investigated aging using NODDI and provides a more comprehensive assessment of how tensor metrics compare to multiple compartment approaches such as NODDI. One recent study found that both NODDI and tensor metrics are sensitive to age related changes in WM regions that are associated with aging (Motovylyak et al., 2022). While our work is similarly focused on the differences between these two diffusion analyses methods, our goal was to identify which measures were more associated with Alzheimer's pathology (measured by PET) and related cognitive outcomes, and not the aging process per se. Another recent study investigated the relationship between flortaucipir PET and WM health focusing on NDI as their primary metric (Tian et al., 2023). The authors showed that as Braak stages

progressed, implying worsening levels of tau depositing, NDI in WM tracts decreased. Our findings build upon this previous work by demonstrating that utilizing a large multisite cohort study such as ADNI3 can allow for the extension of the previous work by comparing both cognitive and PET measurements within one study, with implications for follow-up studies to show longitudinality. Additionally while our study focused primarily on the white matter changes other studies such as Vogt et al., 2020 found a drop in NDI within the MCI group further showing NODDIs utility for identifying cortical microstructural degeneration (Vogt et al., 2020). Future studies could potentially use the ADNI3 cohort to further investigate those findings. We also recognize that the use of mediation models specifically with NODDI metrics is complicated and not to be easily reduced to a confirmatory metric. There are clearly multiple processes that may impact the physiological properties of the AD-related pathways we investigated, including axonal degeneration, demyelination, Wallerian degeneration secondary to gray matter neuronal loss, neuroinflammatory activity, vascular dysfunction, and extracellular matrix alterations. While our diffusion metrics are sensitive to microstructural change, they cannot fully disentangle the relative contributions of these mechanisms. Our work demonstrating the significance of NODDI in these models confirms this diffusion metric's ability to detect alterations but cannot inform as to the specific cell types or structures involved. The present findings indicate that neither NDI nor ODI uniformly outperformed the other across all medial temporal tracts. Rather, the two metrics demonstrated region-specific associations, supporting the utility of examining both parameters when characterizing white matter microstructural changes in Alzheimer's disease.

Although previous studies have examined associations between NODDI metrics and Alzheimer's pathology, our work extends these findings by simultaneously evaluating both tensor and NODDI-derived diffusion metrics across multiple medial temporal white matter pathways

using a harmonized, multisite ADNI3 sample. In addition to characterizing region-specific associations, we employed mediation analyses to explore mechanistic relationships linking white matter microstructure with amyloid and tau pathology as well as cognitive outcomes. Furthermore, our integration of machine learning approaches provides an initial assessment of the predictive utility of these diffusion metrics, offering new insights for potential future clinical applications.

Finally, we tested the utility of NODDI and tensor metrics in estimating cognitive outcomes. We used the general rule that an AUC of 0.5 suggests no ability to estimate, and 0.7 to 0.8 is acceptable estimation (Sampaio-Baptista & Johansen-Berg, 2017). NODDI metrics, notably the NDI of the hippocampal cingulum, proved to be superior estimations of clinical outcomes when compared to demographic variables such as age, gender, and education. Similarly, tensor metrics, specifically the MD of the right fornix, exhibited acceptable estimative performance. The fusion of these metrics with demographic information yielded increased estimation models characterized with higher AUC values, suggesting models combining both NODDI and tensor metrics have increased sensitivity in the estimation of cognitive performance. These results suggest that while NODDI and DTI individually perform comparably for classifying cognitive performance, the combination of both diffusion models provides modest but significant incremental improvement.

Currently, within the clinical trial and diagnostic realms, structural MRI serves as a crucial step in the process of confirming AD staging (Jack et al., 2010). However, while volumetric measurements are employed to identify gray matter atrophy, the characterization of WM integrity can add more information about how neural communication and networks may be impacted. Our study underscores the value of integration of multishell diffusion acquisitions into the ADNI3 protocol, which has enabled a more complete understanding of the neurodegenerative processes

occurring in both the aging population and individuals with AD. These metrics also open new avenues for future clinical trials, offering the potential to quantify early disease markers that were previously beyond reach using standard dMRI sequences. This advance holds promise for enhancing our ability to detect and address neurodegenerative conditions at earlier stages, potentially improving therapeutic interventions (Jack et al., 2010).

The study had several limitations that are important to note. First, the ADNI3 sample is not particularly diverse with respect to race and ethnicity. While our cohort includes individuals across a range of cognitive status, including mild dementia, this design was intentional to permit modeling of continuous relationships across the full AD spectrum, rather than restricting to isolated preclinical or prodromal stages. Our machine learning models would greatly benefit from a broader and more diverse dataset, as machine learning is not expected to generalize well to other samples if the training dataset is not sufficiently diverse (Gong et al., 2018). Second, due to the sensitivity of neuroimaging to movement and imaging artifacts, our sample size was limited due to the need to censor participant data that did not pass quality control. Additionally, while we limited data to Siemens Prisma scanners to minimize inter-scanner variability, we formally tested for residual site differences in NODDI measures. These analyses did not identify significant site effects, supporting the comparability of diffusion metrics across sites. The decision to use only a single shell during the DTI analysis was because prior ADNI cohorts only collected a single b=1,000 shell. One goal of this paper is to stress the importance of continuing to include multishell sequences such as the newly added ADNI3 advanced protocol. We would like to recognize that utilizing multishell or even a higher b-shell for the DTI analysis would more than likely improve the strength of the DTI results. While the fornix ST remains susceptible to partial volume effects due to its small size, we applied visual quality control and used NODDI modeling to mitigate these concerns by accounting

for tissue compartmentalization within each voxel; however, some residual contamination cannot be fully excluded. Further, while our study focused on WM within the MTL, future work should extend these analyses to whole brain tractography to assess whether the observed sensitivity of NODDI metrics in MTL tracts generalizes across other white matter pathways. For this study we chose to only focus on four DWI analysis metrics (FA, MD, NDI, and ODI) future studies should branch out to include additional metrics for both NODDI and DTI analyses (such as free-water isotropic volume fraction, radial diffusivity, axial diffusivity) as well as potentially investigating other analyses such as Diffusion Kurtosis Imaging (DKI). Finally, neuroimaging studies investigating early stages of neurocognitive change with aging are limited by the relatively low sensitivity of neuropsychological and clinical measures of impairment. The use of more sensitive cognitive tasks is warranted in future studies.

In conclusion, our study offers new insights into the estimation potential of NODDI metrics in studies of AD. While tensor metrics have traditionally served as the standard for leveraging dMRI in assessing alterations in pathology and memory related to AD, our research suggests that conventional FA and MD measurements may miss more subtle microstructural changes. Notably, NDI emerges as an exceptionally sensitive metric, particularly in the context of entorhinal tau pathology and memory-related outcome measures. This underscores the potential of NODDI metrics to uncover subtle yet crucial insights into the complex dynamics of neurodegenerative processes. Taken together, these findings suggest that multimodal diffusion models enhance classification performance, whereas NODDI measures in particular provide more sensitive and mechanistically interpretable markers of MTL white matter integrity in AD. Thus, these approaches should be considered complementary, with combined models maximizing predictive accuracy and NODDI contributing additional biological specificity.

Supplemental

	ADNI-MEM	CDRSB	CDR-MEM	Aβ	Entorhinal	Meta Temporal	Hippocampal Volume
NDI CC	0.233 (0.0017)	-0.308 (3.05E-05)	-0.291 (3.69E-05)	-0.239 (0.0067)	-0.266 (0.0033)	-0.168 (0.065)	-0.137 (0.0975)
NDI CH	0.343 (8.52E-06)	-0.367 (6.66E-07)	-0.325 (3.62E-06)	-0.332 (0.00023)	-0.375 (2.32E-05)	-0.254 (0.015)	-0.226 (0.0125)
NDI Fornix Col Body	0.126 (0.1075)	-0.263 (0.000342)	-0.240 (0.00072)	-0.153 (0.08375)	-0.207 (0.02)	-0.228 (0.02)	0.092 (0.197)
NDI Fornix ST	0.106 (.15)	-0.093 (0.195)	-0.101 (0.162)	-0.068 (0.417)	-0.192 (0.026)	-0.152 (0.080)	-0.215 (0.0125)
NDI Uncinate	0.250 (0.00145)	0.250 (0.000523)	-0.234 (0.001)	-0.277 (0.00190)	-0.373 (2.32E-05)	-0.199 (0.035)	-0.142 (0.0975)
ODI CC	0.075 (0.308)	0.031 (0.663)	0.015 (0.836)	-0.041 (0.625)	-0.063 (0.47)	-0.160 (0.1067)	-0.112 (0.24833)
ODI CH	0.164 (0.03125)	-0.179 (0.015)	-0.256 (0.028468)	-0.073 (0.48)	-0.147 (0.11375)	-0.132 (0.128)	-0.073 (0.44)
ODI Fornix Col Body	0.228 (0.005)	-0.216 (0.0033)	-0.207 (0.004)	-0.223 (0.0175)	-0.190 (0.0633)	-0.133 (0.128)	0.190 (0.0175)
ODI Fornix ST	0.253 (0.00247)	-0.253 (0.00091)	-0.256 (0.00031)	-0.252 (0.01118)	-0.288 (0.004)	-0.319 (0.00085)	-0.301 (2.00E-06)
ODI Uncinate	0.218 (0.005)	-0.255 (0.0009)	-0.195 (0.006)	-0.151 (0.070)	-0.179 (0.06333)	-0.162 (0.10667)	-0.027 (0.734)

Table 2 NODDI Metrics Partial Correlations with raw p-values

R-value (P value); hippocampal volume was corrected with individual participants' intracranial volume. All p-values corrected with FDR.

	ADNI-MEM	CDRSB	CDR-MEM	Aβ	Entorhinal	Meta	Hippocampal Volume
FA CC	0.057 (0.62875)	-0.160 (0.0625)	-0.136 (0.058)	-0.076 (0.455)	-0.069 (0.429)	0.047 (0.7388)	0.009 (0.911)
FA CH	0.049 (0.62875)	-0.061 (0.396)	-0.042 (0.563)	-0.171 (0.1)	-0.082 (0.429)	-0.024 (0.784)	-0.086 (0.3375)
FA Fornix Col Body	0.232 (0.005)	-0.198 (0.025)	-0.240 (0.000729)	-0.190 (0.1)	-0.181 (0.18)	-0.211 (0.075)	0.552 (1.43E-16)
FA Fornix ST	0.084 (0.62875)	-0.61 (0.396)	-0.077 (0.285)	-0.002 (0.98)	-0.126 (0.2733)	-0.129 (0.345)	-0.249 (0.0025)
FA Uncinate	-0.032 (0.662)	0.062 (0.396)	0.020 (0.776)	-0.111 (0.305)	-0.121 (0.2733)	-0.052 (0.739)	-0.169 (0.04833)
MD CC	-0.138 (0.075)	0.137 (0.07)	0.117 (0.103)	0.114 (0.173)	0.153 (0.077)	0.096 (0.325)	0.064 (0.412)
MD CH	-0.185 (0.02)	0.211 (0.005)	0.159 (0.026)	0.288 (0.0011622)	0.167 (0.06625)	0.086 (0.325)	0.143 (0.0825)
MD Fornix Col Body	-0.311 (7.61E-05)	0.255 (0.0015797)	0.306 (1.35E-05)	0.287 (0.0011622)	0.197 (0.0367)	0.202 (0.0475)	-0.629 (1.34E-22)
MD Fornix ST	-0.273 (0.00041)	0.234 (0.0025)	0.247 (0.000505)	0.174 (0.04625)	0.290 (0.0033)	0.349 (0.00018)	0.452 (9.44E-17)
MD Uncinate	-0.108 (0.142)	0.109 (0.131)	0.112 (0.120)	0.244 (0.005)	0.248 (0.01)	0.169 (0.085)	0.248 (0.0017)

Table 3 Tensor metrics partial correlations

R-value (P value); hippocampal volume was corrected with individual participants' intracranial volume. All p-values corrected with FDR.

Classification	Features	AUC [CI]	Sensitivity (%) [CI]	Specificity (%) [CI]
ADNI-MEM	NODDI	0.65 [0.649 to 0.651]	62 [0.619 to 0.621]	65 [0.619 to 0.621]
	Tensor	0.67 [0.669 to 0.671]	59 [0.589 to 0.591]	65 [0.649 to 0.651]
	Combination	0.76 [0.759 to 0.761]	69 [0.689 to 0.691]	71 [0.709 to 0.711]
CDR-SB	NODDI	0.69 [0.689 to 0.691]	60 [0.599 to 0.601]	69 [0.689 to 0.691]
	Tensor	0.70 [0.699 to 0.701]	68 [0.678 to 0.682	70 [0.699 to 0.701]
	Combination	0.74 [0.739 to 0.741]	63 [0.629 to 0.631]	70 [0.699 to 0.701]

Table 4 Model performance evaluation metrics

AUC = Area under the curve, CI = 95% Confidence Intervals, ADNI-MEM = Alzheimer's Disease Neuroimaging Initiative Memory composite score, CDR-SB = Clinical Dementia Rating Scale Sum of Boxes

	ADNI-MEM	CDRSB	CDR-MEM	Aβ	Entorhinal	Meta Temporal	Hippocampal Volume
NDI CC	-0.111 (0.24)	0.183 (0.04)	0.073 (0.43)	-0.26 (0.01)	-0.188 (0.09)	-0.188 (0.09)	-0.045 (0.6)
NDI CH	-0.009 (0.93)	0.127 (0.17)	0.04 (0.67)	-0.24 (0.02)	-0.127 (0.2)	-0.13 (0.26)	0.003 (0.9)
NDI Fornix Col Body	-0.04 (0.69)	0.018 (0.85)	-0.09 (0.33)	-0.19 (0.06)	0.22 (0.05)	-0.22 (0.05)	0.076 (0.4)
NDI Fornix ST	0.034 (0.72)	0.03 (0.75)	-0.06(0.51)	0.01 (0.9)	0.008 (0.9)	0.008 (0.94)	0.07 (0.5)
NDI Uncinate	-0.000007 (0.99)	0.01 (0.91)	-0.026 (0.77)	-0.156 (0.14)	-0.09 (0.4)	-0.09 (0.4)	-0.06 (0.5)
ODI CC	0.191 (0.04)	-0.05 (0.61)	-0.028 (0.76)	-0.05 (0.63)	0.05 (0.67)	0.05 (0.7)	0.117 (0.2)
ODI CH	-0.02 (0.81)	0.03 (0.69)	0.09 (0.33)	0.06 (0.55)	-0.04 (0.7)	-0.04 (0.7)	0.157 (0.09)
ODI Fornix Col Body	0.04 (0.70)	0.04 (0.61)	0.06 (0.52)	-0.09 (0.42)	-0.07 (0.5)	-0.07 (0.5)	0.102 (0.3)
ODI Fornix ST	-0.03 (0.76)	0.03 (0.75)	0.02 (0.79)	-0.12 (0.24)	-0.02 (0.9)	-0.02 (0.86)	0.235 (0.01)
ODI Uncinate	-0.01 (0.88)	0.175 (0.06)	0.20 (0.03)	-0.02 (0.82)	-0.02 (0.9)	-0.02 (0.9)	0.012 (0.9)

Table 5 NODDI exploratory subgroup analyses of cognitively unimpaired

R-value (P value); hippocampal volume was corrected with individual participants' intracranial volume.

	ADNI-MEM	CDRSB	CDR-MEM	Aβ	Entorhinal	Meta Temporal	Hippocampal Volume
NDI CC	0.23 (0.06)	-0.261 (0.03)	-0.1678 (0.2)	0.06 (0.66)	-0.136 (0.3)	-0.066 (0.6)	-0.024 (0.8)
NDI CH	0.48 (.0003)	-0.388 (0.0007)	-0.256 (0.03)	-0.13 (0.37)	-0.38 (0.006)	-0.272 (0.05)	0.318 (0.005)
NDI Fornix Col Body	0.133 (0.3)	-0.315 (0.007)	-0.249 (0.03)	0.019 (0.9)	-0.182 (0.2)	-0.26 (0.06)	0.003 (0.9)
NDI Fornix ST	0.006 (0.9)	-0.06 (0.6)	-0.038 (0.8)	0.104 (0.5)	-0.203 (0.1)	-0.175 (0.21)	0.05 (0.7)
NDI Uncinate	0.34 (0.004)	-0.278 (0.01)	-0.189 (0.1)	-0.059 (0.7)	-0.411 (0.002)	-0.214 (0.1)	0.207 (0.07)
ODI CC	-0.005 (0.97)	0.04 (0.7)	-0.015 (0.9)	-0.026 (0.9)	-0.144 (0.3)	-0.252 (0.07)	0.074 (0.5)
ODI CH	0.28 (0.02)	-0.186 (0.1)	-0.092 (0.4)	-0.115 (0.43)	-0.153 (0.3)	-0.11 (0.4)	-0.049 (0.7)
ODI Fornix Col Body	0.25 (0.04)	-0.182 (0.1)	-0.1207 (0.3)	-0.17 (0.2)	-0.195 (0.2)	-0.111 (0.4)	0.033 (0.8)
ODI Fornix ST	0.37 (0.002)	-0.202 (0.09)	-0.143 (0.2)	-0.10 (0.5)	-0.421 (0.002)	-0.469 (0.0005)	0.254 (0.02)
ODI Uncinate	0.363 (0.002)	-0.343 (0.003)	-0.229 (0.05)	-0.117 (0.4)	-0.245 (0.08)	-0.229 (0.102)	0.223 (0.05)

Table 6 NODDI exploratory subgroup analyses of cognitively impaired

R-value (P value); hippocampal volume was corrected with individual participants' intracranial volume.

Chapter 3: Sex-specific immune–brain coupling in hippocampal circuits and Alzheimer's disease vulnerability

All findings in this study have been published as a preprint by Parker and Yi et al. (2026)

3.1 Introduction

Alzheimer's disease (AD) disproportionately affects women. Even after accounting for differences in longevity, women face approximately twice the lifetime risk of developing AD compared with men (Rajan et al., 2021) and follow a more aggressive disease course, characterized by accelerated accumulation of pathology, steeper cognitive decline, and greater functional loss (Buckley et al., 2018; Coughlan et al., 2025). Critically, these disparities are not fully explained by survival bias or known demographic risk factors, suggesting that sex-specific *biological mechanisms* contribute to differential vulnerability. Yet, despite decades of research, the upstream processes that render women more susceptible to neurodegeneration remain poorly defined.

Inflammation represents a plausible candidate mechanism for this disparity. Chronic inflammation has been implicated as both a marker and driver of AD risk, with inflammatory-related conditions such as obesity, stroke, and sepsis associated with increased incidence of AD (Novoa et al., 2022). Importantly, immune processes are robustly sex-dimorphic across the lifespan, with females generally exhibiting heightened immune responsiveness from early adulthood onward (Dunn et al., 2024; Klein & Flanagan, 2016; Müller et al., 2025). Aging in women is marked by a pronounced shift towards low-grade chronic inflammation that is amplified by the menopausal transition (Karpuzoglu et al., 2025; Yasui et al., 2007). This transition involves profound endocrine and immune remodeling, with sustained elevations in pro-inflammatory cytokines, including IL-6, IL-1β, and TNFα, alongside shifts in regulatory mediators such as IL-

10 (Müller et al., 2025; Olivieri et al., 2023). These circulating cytokines are not peripherally confined. They can promote blood-brain barrier dysfunction and glial reactivity, providing a mechanistic bridge between peripheral immune aging and central neuroinflammatory activation (Müller et al., 2025).

A central assumption in this literature is that elevated inflammatory burden confers risk. However, this framework does not account for whether equivalent levels of circulating cytokines exert similar effects on neural circuits across individuals or sexes. An alternative possibility is that vulnerability is determined by the degree to which peripheral immune signals couple to the integrity of AD-relevant brain circuits. Consistent with this account, microglia (which both produce and respond to TNFα) exhibit sex-specific activation profiles, with female hippocampal microglia showing heightened TNFα-related signaling in the context of aging. This suggests that vulnerability in women may reflect *greater neural sensitivity* to inflammatory signals rather than greater inflammatory exposure (Ocañas et al., 2023). Despite this evidence, whether sex differences in peripheral inflammatory signaling translate into differential vulnerability of AD-relevant neural circuits, and whether this coupling is detectable before the onset of clinical symptoms, remains unknown.

Medial temporal lobe (MTL) white matter pathways, including the hippocampal cingulum, fornix, and uncinate fasciculus, are among the earliest structures disrupted in AD, which may lead to early deficits in hippocampal-dependent memory. Microstructural changes to white matter in these tracts assessed by diffusion tensor imaging (DTI) have been shown in the context of cognitive decline(Archer et al., 2023). However, more advanced multishell diffusion imaging methods, such as neurite orientation dispersion and density imaging (NODDI), can now resolve tissue compartments into biologically interpretable metrics that are capable of detecting more subtle

changes that precede overt cognitive decline (Daducci et al., 2015; Nazeri et al., 2015; H. Zhang et al., 2012). Prior work has shown that NODDI outperforms traditional DTI in sensitivity to detecting sex differences (Lawrence et al., 2021) and AD-related microstructural decline (D. M. Parker et al., 2025). Further, converging evidence demonstrates that NODDI measures are sensitive to inflammation-related changes both in humans (Dowell et al., 2019; Szaflarski et al., 2025) and rodents (E. Kim et al., 2023), positioning NODDI as particularly well-suited to characterize sex differences in inflammation-related white matter vulnerability and relationships to subtle memory deficits in the preclinical phase of AD.

Characterizing the functional impact of this microstructural decline requires cognitive assessments specifically tuned to medial temporal integrity. Changes in hippocampal-dependent memory emerge prior to clinical symptom onset and can be quantified with sensitive tools, such as the Mnemonic Discrimination Task (MDT) (Soyun Kim et al., 2023; Trelle et al., 2021). As a paradigm sensitive to hippocampal pattern separation, the MDT detects subtle decline in hippocampal integrity as early as the fourth decade of life and captures variance in hippocampal circuit function that standard neuropsychological batteries miss entirely (Leal & Yassa, 2018). By pairing the MDT with advanced microstructural imaging and peripheral inflammatory profiling, we can effectively test how pathways linking immune signaling to circuit-level dysfunction may confer cognitive deficits in a sex-specific manner.

Here, we tested the hypothesis that AD vulnerability is better captured by *inflammatory sensitivity*, defined as the coupling between peripheral cytokine signaling and MTL circuit integrity, rather than by cytokine levels alone, and that this sensitivity differs by sex. We addressed this question using the Biomarker Exploration in Aging, Cognition, and Neurodegeneration (BEACoN) study sample, a deeply phenotyped cohort of cognitively unimpaired older adults

combining advanced multimodal neuroimaging, peripheral cytokine profiling, and cognitive assessment with the hippocampus-dependent MDT. We identify a sex-specific pattern of immune-brain coupling that may serve as a candidate pathway for differential AD vulnerability.

3.2 Methods

Participants and Study Design

Participants were recruited from the Biomarker Exploration in Aging, Cognition, and Neurodegeneration (BEACoN) Study at the University of California, Irvine (NIA R01AG053555; PI: Yassa). This ongoing study is designed to characterize early biological signatures of neurodegeneration risk through deep multimodal phenotyping, including high-resolution structural, functional and diffusion MRI, validated digital cognitive assessments including the MDT, and collection of peripheral biospecimens, enabling comprehensive examination of brain-behavior-immune relationships in aging. Prior work in this cohort has established that plasma and salivary biomarkers reflect AD-relevant pathological burden (Bamford et al., 2024, 2025), that performance on the mnemonic discrimination task indexes preclinical amyloid accumulation with diagnostic sensitivity (Soyun Kim et al., 2023; Vanderlip et al., 2025) , and that white matter integrity in MTL pathways predicts memory performance (Rizvi et al., 2023), collectively validating the core measures and analytic approach of the present study.

Participants were enrolled if they were 60-85 years old, possessed visual and auditory acuity adequate to complete cognitive assessments, and were cognitively unimpaired as defined by a score of zero on the Clinical Dementia Rating (CDR) scale (Morris, 1993). Exclusion criteria included a history of significant neurological or psychiatric comorbidity, alcohol or substance use disorder within the preceding two years, major medical conditions with known effects on

cognition, or a diagnosis of mild cognitive impairment, dementia, or other cognitive disorder. While all women included were postmenopausal, specific data regarding the initiation, type, and duration of MHT was not available. All experimental protocols were approved by the Institutional Review Board of the University of California, Irvine, and all participants provided written informed consent prior to enrollment.

The final analytic sample for the present study comprised 121 participants (78 female, 43 male; mean age 69.3 years) with complete multi-shell diffusion MRI and salivary cytokine data. Comprehensive demographic and clinical characteristics are detailed above in **Table 2**.

The ratio of women to men reflects the higher epidemiological burden of AD risk in women and is consistent with the sex distribution of cognitively unimpaired aging cohorts more broadly. To account for this imbalance, all sex-interaction models were evaluated using robust standard errors. Sensitivity analyses and bootstrapping were employed to ensure that the observed sex-specific effects were driven by biological divergence rather than differences in group-level statistical power or variance heteroscedasticity.

Temporal Mnemonic Discrimination Task

We used the Temporal Mnemonic Discrimination Task as the primary cognitive outcome based on its sensitivity to preclinical amyloid accumulation in frontotemporal circuits (Vanderlip et al., 2025), its known dependence on hippocampal-prefrontal cortical processing (Devito & Eichenbaum, 2011), and its hypothesized sensitivity to the MTL-prefrontal white matter pathways examined here (i.e., fornix, cingulum, and uncinate fasciculus). During the study phase participants made an incidental judgment in response to pictures of everyday items (“indoor” vs. “outdoor”) presented for 2000 msec each (500 msec inter-stimulus interval). During the test phase they were

shown pairs of items that were previously presented during study and made a temporal order judgment (which came first?). We varied similarity/interference by varying the temporal lag between the items that were tested. We focused on the high similarity lure trials (items presented close together in time), which were the more challenging judgments and a more sensitive probe of hippocampal-prefrontal memory. A schematic of the task is shown in **Figure 9C**.

Saliva Cytokine Collection and Quantification

Unstimulated whole saliva (~2 ml) was obtained via passive drool between 7am and 5pm according to previously established protocols (Mortazavi et al., 2024; Xu et al., 2025). Participants were asked to refrain from smoking, eating, drinking, or oral hygiene procedures for 30-60 minutes prior to collection. Samples were frozen at -80C within one hour, and subsequently thawed and centrifuged (5000 g; 15 min; 4ºC) to remove mucins and cellular debris prior to analysis.

Ten cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα, and IFN-γ) were measured using the V-PLEX Proinflammatory Cytokine Panel 1 (Meso Scale Discovery, Gaithersburg, MD). This electrochemiluminescence (ECL)-based multiplex immunoassay was selected for its superior dynamic range and sensitivity of detection compared with conventional ELISA. Assays followed manufacturer protocol with minor modifications validated for salivary matrices (Parkin et al., 2023). To maximize statistical power, salivary samples collected and analyzed in two separate waves (2023 and 2025) were combined. Cross-wave compatibility was verified by log10-transforming concentrations and modeling as a function of collection wave. Notably, IL-13 was excluded from all final analyses due to higher inter-assay variability and poor technical reproducibility across runs.

Concentrations (pg/ml) were determined using MSD Discovery Workbench Software using curve fit models. Lower limits of detection (LLoD) were calculated as the concentration corresponding to the signal 2.5 times standard deviation above background. Across both analytical waves, the mean intra-assay coefficients of variation (CV) were <15% for most analytes. The most conservative, or highest, LLODs were as follows: IL-1β (0.036 pg/ml, 10.5%), IL-2 (0.041 pg/ml, 9.23%), IL-4 (0.03 pg/ml, 7.78%), IL-6 (0.079 pg/ml, 12.81%), IL-8 (0.039 pg/ml, 9.17%), IL-10 (0.052 pg/ml, 9.0%), IL-12p70 (0.011 pg/ml, 16.3%), TNFα (0.05 pg/ml, 10.01%), and IFN-γ (0.028 pg/ml, 4.4%). Concentrations were log10-transformed to address positive skew.

While plasma is traditionally used for systemic inflammatory profiling, salivary cytokine measurement provides a non-invasive, scalable alternative validated within the BEACoN cohort. Our prior work in this cohort (Parkin et al., 2023) demonstrated significant positive associations between plasma and salivary concentrations for IFNy, IL-6, and TNFα, though absolute concentrations were consistently higher in saliva, likely reflecting the unique immunological environment of the oral mucosa. The broader 10-plex panel was included to allow for discovery-based characterization of the brain-immune relationship (Riis et al., 2015). Although direct oral health indicators were unavailable, we implemented a rigorous statistical quality control pipeline to exclude analytes below the LLOD and identify participants with profiles indicative of acute inflammation (i.e. extreme outliers), ensuring the stability of the inflammatory signal.

MRI Acquisition

All participants were scanned at the University of California, Irvine on a 3T Prisma scanner (Siemens Medical Systems) equipped with a 32-channel head coil. A whole-brain T1-weighted volumetric image was acquired using a magnetization-prepared rapid acquisition gradient echo

(MPRAGE) sequence (voxel size: 0.8 mm isotropic; TR: 2300 ms; TE: 2.38 ms; TI: 902 ms; flip angle: 8°). Multi-shell diffusion-weighted images were acquired using a Pulsed Gradient Spin Echo with single shot echo planar imaging (EPI) read out with 72 interleaved axial slices (voxel size: 1.7 mm isotropic; FOV: 218 mm; matrix: 128 × 128; TR: 3500 ms; TE: 102 ms). Three diffusion shells were acquired at b = 0, 1500, and 3000 s/mm², with 64 diffusion directions per shell.

Structural and Diffusion MRI Processing

T1-weighted images were preprocessed using Freesurfer v7.4 (Fischl, 2012), including correction for head motion and intensity inhomogeneity and removal of non-brain tissue. Diffusion scans were preprocessed using QSIPrep v0.24.0 (Cieslak et al., 2021), a standardized preprocessing pipeline that integrates tools from FSL, MRtrix3, and ANTs. Raw diffusion images were denoised using MP-PCA (Veraart et al., 2016) via MRTrix3's dwidenoise (Tournier et al., 2019), followed by correction of head motion and eddy current distortions using FSL's eddy (Andersson & Sotiropoulos, 2016) with model-based motion correction. Preprocessed images were then resampled to 1mm isotropic resolution prior to microstructural modeling.

NODDI microstructural modeling was performed using QSIRecon (v0.24.0 (Cieslak et al., 2021)) via the Accelerated Microstructure Imaging via Convex Optimization (AMICO) framework (Daducci et al., 2015; H. Zhang et al., 2012), incorporating participant-specific anatomical information from FreeSurfer segmentations. Outputs included three NODDI metrics: intracellular volume fraction (ICVF; indexing neurite density and white matter integrity), isotropic volume fraction (ISOVF; indexing extracellular free water fraction, a marker sensitive to neuroinflammatory processes, perivascular edema, and tissue loss), and orientation dispersion

index (ODI; capturing the angular complexity of fiber architecture). Microstructural maps were used for subsequent region-of-interest (ROI) based analyses defined using the Johns Hopkins University ICBM-DTI-81 white matter atlas (Mori et al., 2008). ROIs were selected a priori based on their relevance to the MTL connectivity and AD vulnerability.

Statistical Analyses

All analyses were performed in R (4.1.2), including structural equation modeling conducted using the *lavaan* package (Rosseel, 2012). Statistical significance was evaluated using two-tailed tests with $\alpha = 0.05$ throughout, except where noted. Initial correlational analyses were conducted as a screening step to identify candidate cytokine-region associations (**Supplemental Figure 10-11).** The identified cytokine-region correlations were then corrected for multiple comparisons using within-family false discovery rate (FDR), with family defined as a given NODDI metric and cytokine pair, across all regions.

Regression and mediation models were then restricted to a limited set of predefined cytokine-regions. Primary analyses adjusted for age to account for biological differences known to influence white matter microstructure. Sex differences in MTL WM microstructure and cytokine concentrations were evaluated using Wilcoxon rank-sum tests with FDR correction, and effect sizes were estimated using Cohen's d with 95% confidence intervals.

To assess the landscape of inflammation-microstructure associations (discovery), Spearman rank correlations were computed between inflammatory markers and NODDI-derived ICVF and ISOVF within sex-stratified samples. These analyses were used to evaluate the strength, direction, and anatomical specificity of cytokine-tract relationships and to confirm the selection of TNFα and IL-10 as the primary inflammatory markers for subsequent modeling, a selection

informed *a priori* by their established relevance to AD pathophysiology and sex-dimorphic immune aging (Müller et al., 2025; Ocañas et al., 2023). ODI was examined in sex difference analyses but excluded from inflammation-focused modeling given its more complex interpretation in the context of crossing fibers.

Moderation by sex was tested using age-adjusted models with cytokine × sex interaction terms. Significant interactions were followed by sex-stratified simple slope estimation to characterize within-sex associations. Model fit was summarized using adjusted R^2.

To examine the joint associations among peripheral inflammation, MTL white matter microstructure, and mnemonic discrimination, we conducted *moderated mediation analyses*. Behavioral performance on the more difficult high-similarity trials in the MDT-T was selected as the primary cognitive outcome due to its heightened sensitivity to subtle brain changes. TNFα was the primary inflammatory predictor and hippocampal cingulum ICVF the mediating variable, selected based on their *a priori* relevance to hippocampal-prefrontal connectivity in AD (Archer et al., 2023) and confirmed by the strongest and most anatomically consistent associations in correlation and regression analyses. Sex was included as a moderator on all paths in the mediation model (total, direct, and indirect).

In accordance with contemporary statistical frameworks, the significance of the indirect pathway was prioritized as the primary metric of immune-brain-behavior coupling. This approach remains reliable even when individual path components exhibit marginal magnitudes, as the model evaluates the conditional dependence of mnemonic performance on the inflammation-white matter interface rather than isolated indirect effects. The indirect effect of TNFα on MDT-T performance through hippocampal cingulum ICVF was estimated separately within each sex, and the sex difference in indirect effects was formally tested. Sensitivity analyses excluding influential

observations identified via Cook's distance were conducted for all primary regression and mediation models.

3.3 Results

Characterization of the Cohort

To investigate the relationships between peripheral inflammation, white matter integrity, and memory, we utilized a well-characterized cohort of N=121 cognitively unimpaired older adults (mean age 69.3 years; 64% female) from the BEACoN study (**Table 2**). This cohort was specifically selected for its deep phenotyping, including high-resolution multimodal MRI and validated digital cognitive assessments, which have previously been shown to index preclinical AD pathology (Bamford et al., 2024, 2025; Soyun Kim et al., 2023; Vanderlip et al., 2025). All participants were confirmed to be free of dementia (Clinical Dementia Rating - CDR=0) as well as other major neurological or psychiatric comorbidities. All female participants were postmenopausal. Detailed recruitment criteria are provided in the Methods.

Variable	Female (n=78)	Male (n=43)	Total (n=121)	p-value
Age, years (Mean [SD])	68.9 [6.7]	70 [6.4]	69.3 [6.6]	0.353
Education, years (Mean [SD])	16.2 [2.4]	17 [2.4]	16.5 [2.4]	0.072
Hispanic ethnicity (n,%)	12,15.4%	6, 14%	18, 15%	1.000†
MMSE (Mean [SD])	28.3 [1.6]	28.4 [1.7]	28.4 [1.7]	0.832
ApoE ε4 carrier (n,%)	25, 32.1%	16, 37.2%	41, 34%	0.664†
TNFα (Median [IQR])	0.78 [0.55,1.13]	0.83 [0.52,1.13]	0.78 [0.53,1.13]	0.968‡
IL-10 (Median [IQR])	0.30 [0.16, 0.58]	0.33 [0.19,0.62]	0.31 [0.16, 0.60]	0.627‡

Table 7 Demographics 3.3

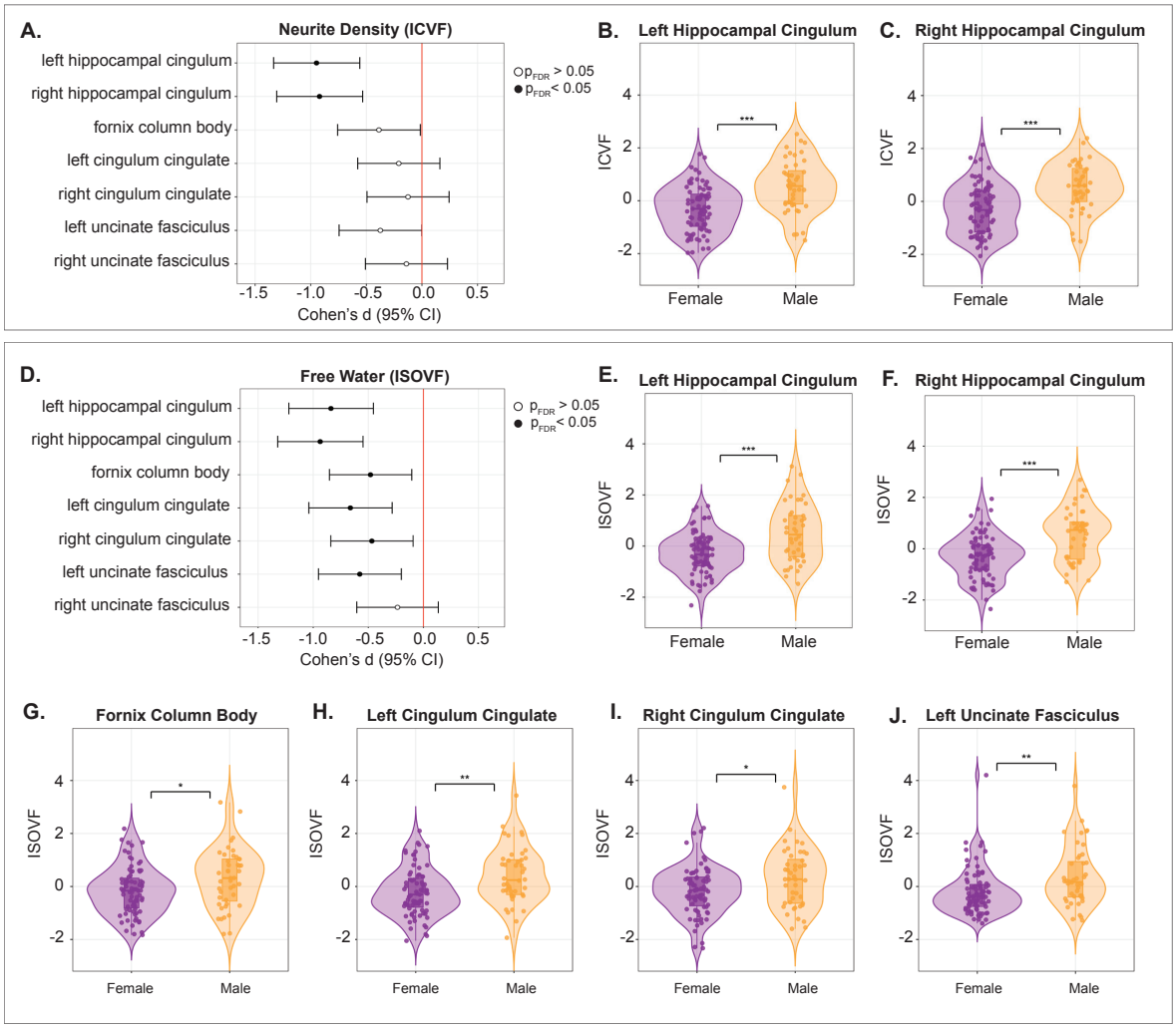
†Chi-square tests for categorical variables; ‡Wilcoxon rank-sum tests for non-normally distributed variables; all other comparisons used independent samples t-tests. MMSE, Mini-Mental State Examination; ApoE ε4, apolipoprotein E ε4; TNFα, tumor necrosis factor-α; IL-10, interleukin-10.

Sex Differences in MTL White Matter Microstructure

To test our hypothesis that MTL white matter microstructure is differentially vulnerable in women compared with men, we performed FDR-corrected Wilcoxon rank-sum tests on NODDI diffusion metrics of the hippocampal cingulum, cingulum cingulate, fornix column body, and uncinate fasciculus. Specifically, we examined intracellular volume fraction (ICVF), which serves as a proxy for neurite density, isotropic volume fraction (ISOVF), which reflects extracellular free water and has been associated with neuroinflammatory processes, and orientation dispersion index (ODI), which captures the degree of variability in fiber orientation within a voxel (H. Zhang et al., 2012). Our analyses revealed pronounced sex differences in MTL white matter microstructure across multiple NODDI derived metrics (**Figure 6A).** Women exhibited significantly lower ICVF than men across the hippocampal cingulum (left: Cohen's d = -0.948, $p_{FDR} < 0.001$; right: Cohen's

d = -0.921, $p_{FDR} < 0.001$) **(Figure 6B-C)**, indicating reduced neurite density in these tracts compared with men. In contrast, no significant sex differences in ICVF were observed within other MTL areas, suggesting regional specificity to hippocampal-associated tracts, rather than a global white matter effect **(Figure 6A)**.

ISOVF was significantly lower in women across multiple MTL tracts (**Figure 6D**), including the hippocampal cingulum (left: Cohen's d = -0.839, $p_{FDR} < 0.001$; right: Cohen's d = -0.936, $p_{FDR} < 0.001$) **(Figure 6E-F)**, fornix column body (Cohen's d = -0.480, $p_{FDR} = 0.02$) **(Figure 6G)**, cingulum cingulate (left: Cohen's d =-0.663, $p_{FDR} = 0.002$; right: Cohen's d = -0.468, $p_{FDR} = 0.02$) **(Figure 6H-I)** and uncinate fasciculus (left: Cohen's d = -0.578; $p_{FDR} = 0.008$) **(Figure 6J)**, indicating lower extracellular free water signal. ODI was also lower in women across multiple pathways (**Figure 6K)**, including the hippocampal cingulum (left: Cohen's d = -1.029, $p_{FDR} < 0.001$; right: Cohen's d = -1.065; $p_{FDR} < 0.001$) (**Figure 6L-M**), fornix column body (Cohen's d = -0.602, $p_{FDR} = 0.004$) **(Figure 6N)**, and cingulum cingulate (left: Cohen's d = -0.608, $p_{FDR} = 0.004$; right: Cohen's d = -0.746, $p_{FDR} < 0.001$) (**Figure 6O-P**). MTL pathways are schematically represented in **Figure 6Q** for reference. Together, these findings demonstrate pronounced and regionally specific sex differences in MTL white matter microstructure. These structural differences raised the question of whether peripheral inflammatory signaling might differentially couple to white matter integrity in women and men, and whether such coupling could explain the pattern of microstructural vulnerability observed here.


A.
Neurite Density (ICVF)
left hippocampal cingulum
right hippocampal cingulum
fornix column body
left cingulum cingulate
right cingulum cingulate
left uncinate fasciculus
right uncinate fasciculus
-1.5 -1.0 -0.5 0.0 0.5
Cohen's d (95% CI)
○ pFDR > 0.05
● pFDR < 0.05
B.
Left Hippocampal Cingulum
C.
Right Hippocampal Cingulum
ICVF
Female
Male
***
D.
Free Water (ISOVF)
E.
Left Hippocampal Cingulum
F.
Right Hippocampal Cingulum
ISOVF
G.
Fornix Column Body
H.
Left Cingulum Cingulate
I.
Right Cingulum Cingulate
J.
Left Uncinate Fasciculus
*
**

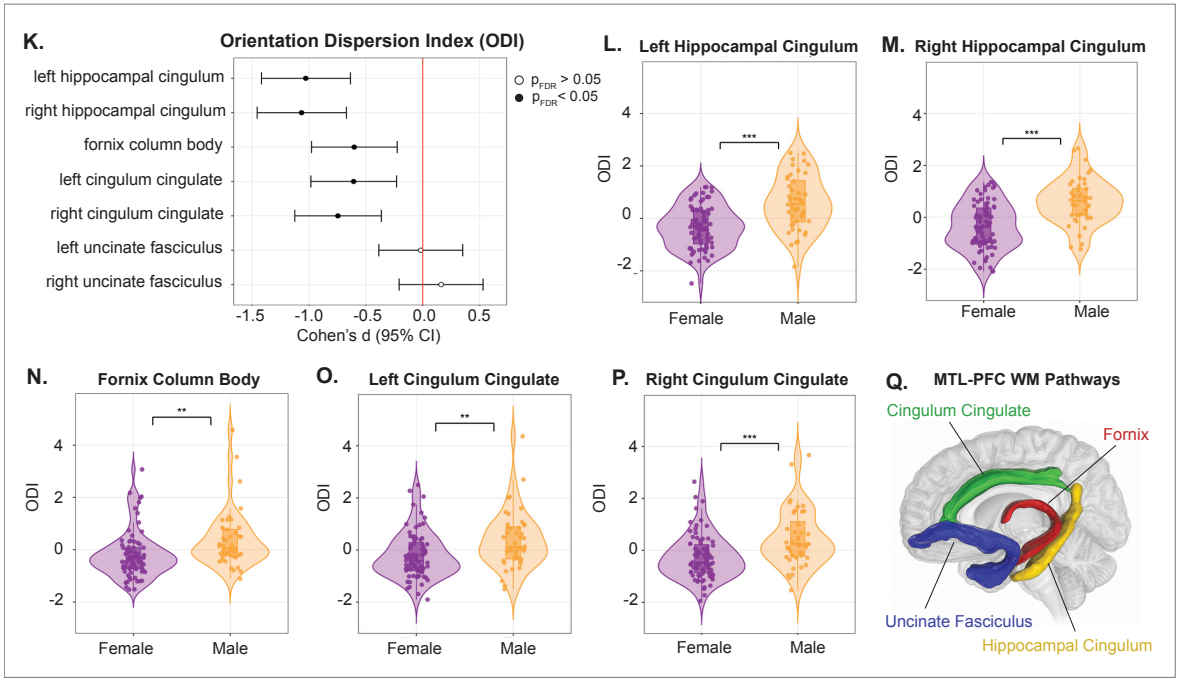

K.
Orientation Dispersion Index (ODI)
left hippocampal cingulum
right hippocampal cingulum
fornix column body
left cingulum cingulate
right cingulum cingulate
left uncinate fasciculus
right uncinate fasciculus
-1.5 -1.0 -0.5 0.0 0.5
Cohen's d (95% CI)
○ pFDR > 0.05
● pFDR < 0.05
L.
Left Hippocampal Cingulum
M.
Right Hippocampal Cingulum
ODI
Female
Male
***
N.
Fornix Column Body
O.
Left Cingulum Cingulate
P.
Right Cingulum Cingulate
**
Q.
MTL-PFC WM Pathways
Cingulum Cingulate
Fornix
Uncinate Fasciculus
Hippocampal Cingulum

Figure 6 Sex differences in MTL white matter microstructure.

*Forest plots (**A,D,K**) show effect sizes (Cohen's d) for sex differences in NODDI-derived diffusion metrics across MTL white matter pathways, with 95% confidence intervals. Results are shown separately for ICVF (**A**), ISOVF (**D**) and OD (**K**). Filled circles indicate regions surviving within-family FDR correction (q < 0.05). The vertical red line denotes no sex difference (d = 0); negative values reflect lower metric values in females relative to males. Violin plots (**B–C,E–J,L–P**) show the distribution of diffusion metrics by sex for selected regions; points represent individual observations and distributions indicate group density. **Q.** Conceptual schematic of MTL-frontal white matter pathways investigated. Significance annotations (*P < 0.05, **P < 0.01, ***P < 0.001) correspond to group comparisons. ICVF, intracellular volume fraction; ISOVF, isotropic volume fraction; ODI, orientation dispersion index.*

Coupling between Peripheral Inflammation and MTL White Matter Microstructure is Sex-Dependent

We next tested our hypothesis that peripheral inflammatory markers associate differentially with white matter integrity in women and men. We approached this in two steps: first characterizing the landscape of inflammation-microstructure associations using sex-stratified correlations, then formally testing sex moderation using multiple linear regression models with interaction between sexes and microstructure prediction of measures of inflammation.

Correlation analyses reveal selective inflammation-microstructure coupling in women

Spearman rank correlations computed within sex-stratified samples revealed anatomically specific associations between inflammatory markers and MTL white matter microstructure in women (**Figure 7**). We note that these correlation analyses were used as discovery/screening analyses; confirmatory moderation models are shown in **Figure 8**.

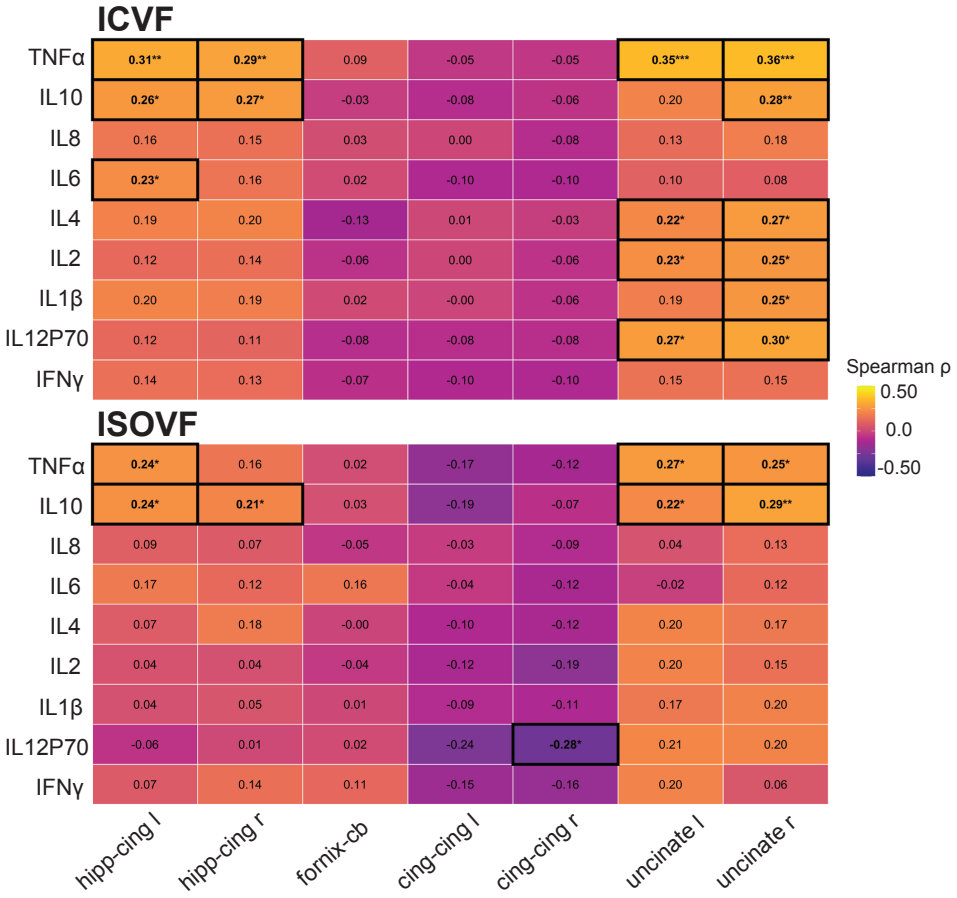
In women, TNFα showed the strongest and most consistent associations with MTL NODDI metrics, with higher TNFα positively correlated with ICVF in the bilateral hippocampal cingulum and uncinate fasciculus (Spearman $\rho \approx 0.29 – 0.36$, $p < 0.01$) **(Figure 7A, 7B)**. Parallel associations were observed for ISOVF, with significant positive correlations between TNFα and ISOVF in the uncinate fasciculus ($\rho \approx 0.25$ - 0.27, $p < 0.05$) **(Figure 7A, 7C)**. IL-10 showed a convergent pattern

with TNFα, with higher concentrations of IL-10 positively correlated with ICVF in the bilateral hippocampal cingulum and uncinate fasciculus ($\rho \approx 0.26 – 0.28$, $p < 0.05$) **(Figure 7A, 2B)** and with ISOVF in the right uncinate fasciculus ($\rho \approx 0.29$, $p < 0.01$) **(Figure 7A, 7C)**. The observation of both a pro-inflammatory marker (TNFα) and an anti-inflammatory marker (IL-10) positively associated with white matter integrity in women, but not men, suggests heightened inflammatory sensitivity of MTL white matter in women.

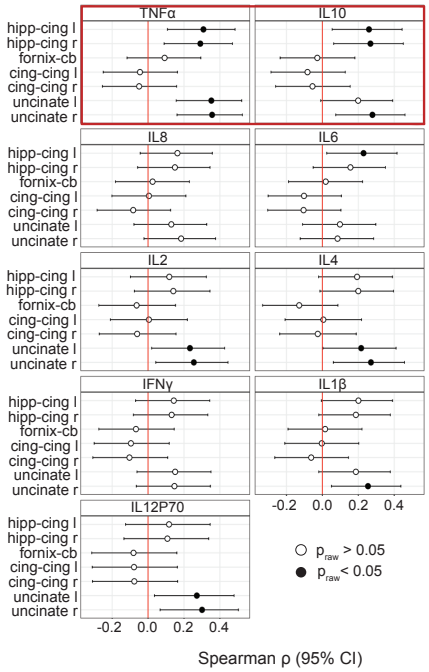
Moderate associations were additionally observed for IL-6 and IL-4 in hippocampal cingulum and fornix segments ($\rho \approx 0.20 – 0.23$) **(Figure 7A)**, though these were smaller in magnitude and less spatially consistent. In contrast, corresponding analyses in men revealed weak and spatially inconsistent relationships, with no cytokine showing reproducible associations with MTL white matter metrics (**Extended Data Figure 10, 11**).

As a sensitivity analysis to demonstrate regional specificity, inflammatory associations with white matter integrity in women were *absent* in the cingulum cingulate, an extension of the cingulum bundle outside the MTL proper, suggesting that inflammatory coupling is preferentially concentrated in hippocampal circuits rather than reflecting a global effect of peripheral inflammation on white matter integrity.

A. Cytokine associations with white matter microstructure



B. ICVF vs. cytokines



C. ISOVF vs. cytokines

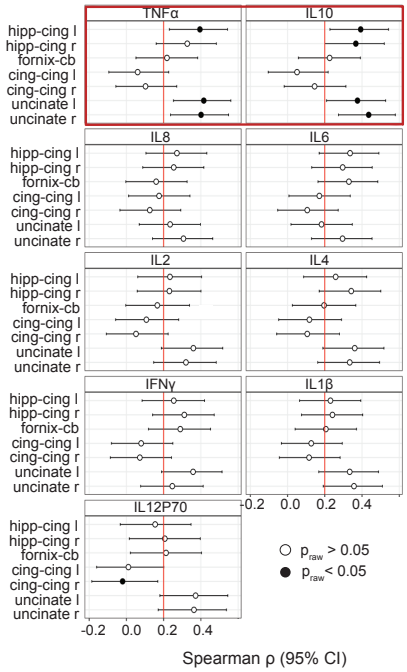


Figure 7 Associations between inflammatory markers and MTL white matter microstructure in females.

*(**A**) Heatmaps show Spearman correlations (ρ) between log-transformed cytokine concentrations and NODDI-derived diffusion metrics across MTL white matter pathways in females. Top and bottom panels show correlations with ICVF and ISOVF, respectively. Cell color represents the magnitude and direction of associations, with warmer colors indicating stronger positive correlations; numeric values indicate Spearman ρ. Asterisks denote uncorrected significance (*P < 0.05, **P < 0.01, ***P < 0.001), and black outlines highlight significant correlations. (**B, C**) Forest plots show cytokine–diffusion correlations for ICVF (**B**) and ISOVF (**C**), with points representing Spearman ρ and whiskers indicating 95% confidence intervals. Filled circles indicate significant associations (*P < 0.05), and open circles indicate non-significant associations. The vertical red line denotes no association (ρ = 0). Hipp-cing L, hippocampal cingulum left; Hipp-cing R, hippocampal cingulum right; fornix-CB, fornix column/body; cing-cing L, cingulum cingulate left; cing-cing R, cingulum cingulate right; uncinate L, uncinate left; uncinate R, uncinate right; IL, interleukin; TNFα, tumor necrosis factor-α; IFNγ, interferon-γ.*

Sex differences in circulating cytokine levels do not account for microstructural differences

To determine whether the observed sex differences in associations between white matter integrity and peripheral inflammation could be attributed to elevated systemic inflammation in women, we examined sex differences in salivary cytokine concentrations. Wilcoxon rank-sum tests revealed no significant sex differences in any of the measured cytokines, including TNFα and IL-10, following FDR correction for multiple comparisons (**Extended Data Fig. 12**). Effect sizes for sex differences across the cytokine panel were small, with 95% confidence intervals for Cohen's *d* inclusive of zero in all cases. Notably, TNFα and IL-10, the markers most strongly implicated in the previous analyses, showed no group-level sex differences. These findings indicate that women and men in this sample were exposed to comparable levels of circulating inflammatory cytokines, suggesting that the sex-dependent associations between inflammation and white matter microstructure cannot be attributed to differences in mean inflammatory burden between sexes.

Regression analyses formally confirm sex moderation of inflammation-microstructure associations

To test whether the sex differences observed in correlational analyses reflected statistically reliable moderation of inflammation-microstructure associations by sex, beyond mean-level differences in cytokines or white matter metrics, we fit age-adjusted linear regression models incorporating cytokine × sex interaction terms.

TNFα demonstrated strong sex-dependent associations with MTL white matter. In women, higher ICVF was strongly and positively associated with TNFα in the bilateral hippocampal cingulum (left: $\beta = 2.20$, SE = 0.68, $p = 0.0017$; right: $\beta = 2.33$, SE = 0.66, $p = 0.001$) and bilateral uncinate fasciculus (left: $\beta = 2.69$, SE = 0.66, $p < 0.001$; right: $\beta = 2.72$, SE = 0.71, $p < 0.001$). Corresponding associations in men were small and non-significant (all $p > 0.35$). Formal tests of sex moderation confirmed significantly steeper TNFα-NODDI slopes in women than men across these tracts (e.g., uncinate left: $\Delta\beta = 3.31$, $p = 0.0015$; uncinate right: $\Delta\beta = 3.66$, $p = 0.0030$) (**Figure 8A**). A parallel pattern was observed for ISOVF, with TNFα significantly associated with uncinate ISOVF in women (left: $\beta = 4.44$, SE = 1.08, $p < 0.001$; right: $\beta = 3.70$, SE = 1.25, $p = 0.0037$) but not men, yielding large sex differences in slope (left uncinate: $\Delta\beta = 6.03$, $p < 0.001$) (**Figure 8A**).

IL-10 showed a similar but attenuated pattern to TNFα. In women, IL-10 was positively associated with ICVF in the hippocampal cingulum (left: $\beta = 1.82$, SE = 0.62, $p = 0.0039$; right: $\beta = 2.19$, SE = 0.58, $p < 0.001$) and uncinate fasciculus (left: $\beta = 1.74$, SE = 0.61, $p = 0.0049$; right: $\beta = 2.60$, SE = 0.62, $p < 0.001$), while associations in men were largely absent **(Figure 8B)**. Sex differences in slope reached significance for right uncinate ICVF ($\Delta\beta = 2.13$, $p = 0.048$) and left uncinate ISOVF ($\Delta\beta = 3.21$, $p = 0.029$) (**Figure 8B**). All primary regression results were robust to

the exclusion of influential observations identified via Cook's distance, confirming that findings were not driven by a small number of extreme values.

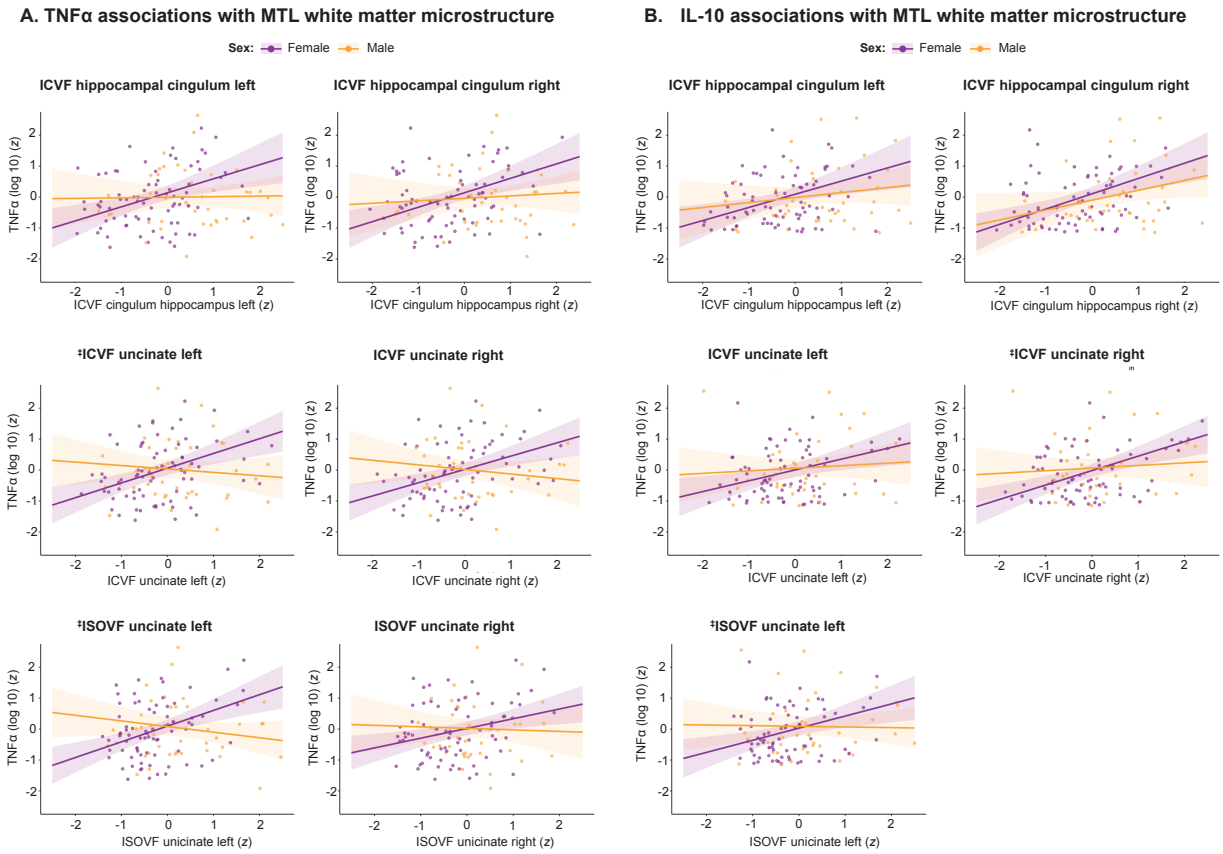


Figure 8 Sex moderation of cytokine-MTL microstructure associations in MTL pathways.

*(**A,B**) Age-adjusted scatterplots show associations between peripheral cytokine concentrations and NODDI-derived diffusion metrics. Panel **A** shows associations with TNFα and panel **B** shows associations with IL-10. Points represent individual participants. Solid lines indicate sex-specific regression slopes for females (purple) and males (orange), with shaded bands representing 95% confidence intervals. Panels show associations within the hippocampal cingulum and uncinate fasciculus bilaterally for ICVF and ISOVF. Asterisks denote significant cytokine × sex interaction effects (*P < 0.05, **P < 0.01, ***P < 0.001). ‡ indicates regions showing a significant main effect of sex. TNFα, tumor necrosis factor-α; IL-10, interleukin-10; ICVF, intracellular volume fraction; ISOVF, isotropic volume fraction; MTL, medial temporal lobe.*

Coupling Between MTL White Matter Integrity and Hippocampal-Dependent Memory is Sex-Dependent

Having established that peripheral inflammatory markers couple more strongly to MTL white matter microstructure in women than men, we next examined whether this sex-specific

microstructural variation carries functional consequences for hippocampal-dependent memory. We focused on temporal mnemonic discrimination performance (MDT-T) as our primary cognitive outcome given its established sensitivity to hippocampal-prefrontal circuit integrity (Barker et al., 2017) and preclinical AD-related change (Vanderlip et al., 2024).

Sex moderates the relationship between MTL white matter integrity and memory

Regression models revealed a significant interaction between left hippocampal cingulum ICVF and sex in predicting MDT-T performance ($\beta = -0.72$, $p = 0.04$) (**Figure 9A)**, indicating that the microstructure-memory relationship differed by sex. Consistent with this interaction, sex-stratified models showed a marginal positive association between hippocampal cingulum ICVF and performance in women ($\beta = 0.46$, $p = 0.06$) (**Figure 9A)** that was absent in men. This pattern is interpretable within the context of the moderated mediation framework described below. A trend-level interaction between TNFα and sex predicting performance was also observed ($\beta = -0.10$, $p = 0.09$) **(Figure 9B)**, consistent with the broader pattern of sex-specific inflammatory coupling and motivating formal examination of the mediated pathway. The design of the MDT-T task is shown in **Figure 9C** and described in the Methods section.

Hippocampal white matter mediates the association between TNFα and memory selectively in women

To formally test whether hippocampal cingulum ICVF mediates the relationship between TNFα and memory in a sex-dependent manner, we conducted a moderated mediation analysis **(Figure 9D)**. This framework is appropriate for evaluating conditional indirect effects when the

pathway from predictor to outcome is hypothesized to operate through a mediator whose relevance differs by group, which is precisely the architecture our prior findings suggest.

Higher TNFα significantly predicted higher hippocampal cingulum ICVF in women (path a: $\beta = 0.30$, $p = 0.007$), and this relationship was not significant in men ($\beta = -0.29$, $p = 0.15$). Higher hippocampal cingulum ICVF predicted better memory in women (path b: $\beta = 0.35$, $p = 0.0004$), and worse memory in men ($\beta = -1.86$, $p = 0.002$), indicating that the functional relevance of white matter microstructure for memory differed by sex. The indirect effect of TNFα on memory through hippocampal cingulum ICVF was significant in women ($\beta = 0.10$, $p = 0.031$) and absent in men ($\beta = -0.01$, $p = 0.76$), and the sex difference in indirect effects was statistically reliable ($\beta = -0.11$, $p = 0.024$). The direct effect of TNFα on memory was not significant in women ($\beta = 0.07$, $p = 0.56$), nor men ($\beta = -0.28$, $p = 0.19$), indicating that the association between TNFα and memory in women was statistically consistent with an indirect pathway through white matter microstructure (**Figure 9D**).

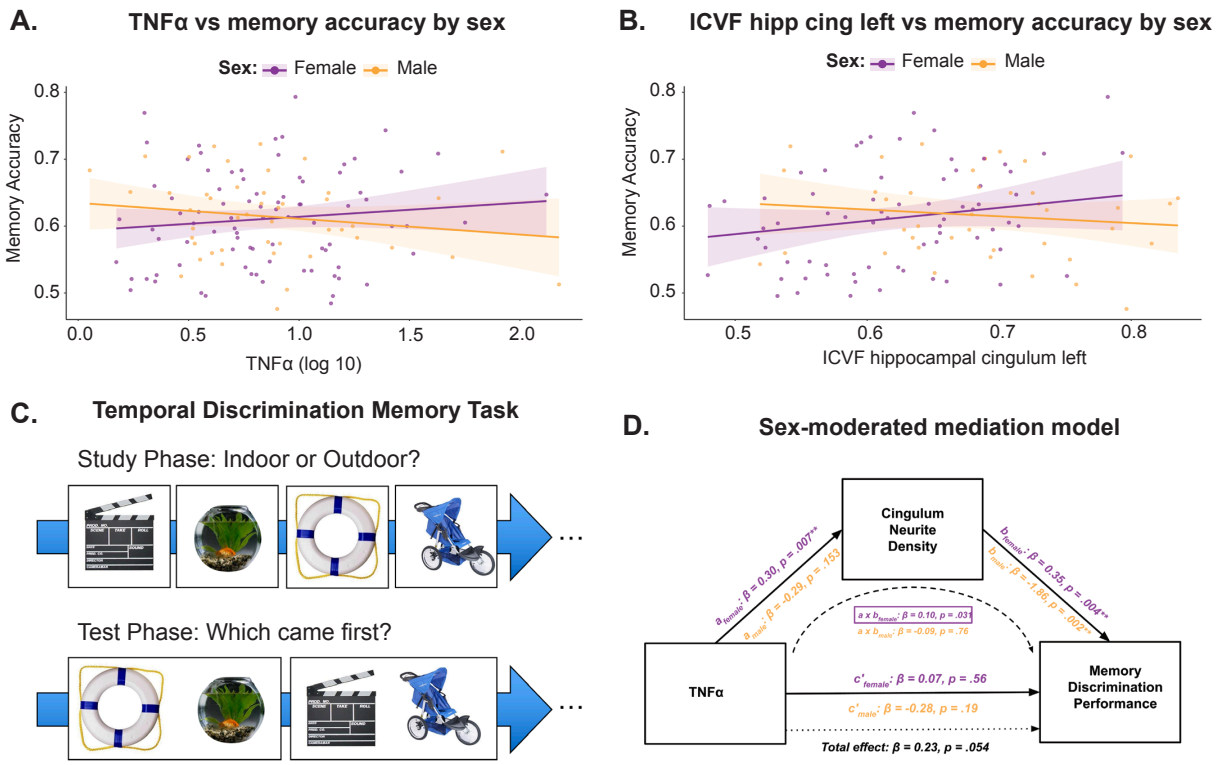


Figure 9 Sex-stratified and sex-moderated associations between inflammation, white matter microstructure, and temporal discrimination memory.

*(**A, B**) Age-adjusted scatterplots show sex-specific associations between hippocampal cingulum ICVF and temporal discrimination memory accuracy (**A**), and between and peripheral TNFα levels and temporal discrimination memory accuracy (**B**). Points represent individual participants. Solid lines indicate age-adjusted linear fits within each sex (female, purple; male, orange), with shaded bands representing 95% confidence intervals. (**C**) Temporal discrimination memory task schematic showing the two phases of the procedure. (**D**) Sex-moderated mediation model testing whether hippocampal cingulum ICVF mediates the relationship between TNFα and mnemonic discrimination performance, with sex moderating model pathways. Values shown are standardized regression coefficients. TNFα, tumor necrosis factor-α; ICVF, intracellular volume fraction.*

3.4 Discussion

Here, we report a pattern of immune-brain coupling that reframes sex-specific inflammatory risk for AD as a property of circuit-level sensitivity rather than inflammatory burden. MTL white matter microstructural features were differentiated by sex, wherein women had lower mean ICVF and ISOVF than men. Peripheral inflammatory markers were differentially associated with MTL white matter microstructure by sex, with women exhibiting stronger and more anatomically consistent associations across cytokines and tracts. This indicates that sex differences

in mean microstructure and within-sex immune–brain coupling reflect distinct effects. Rather than explaining the lower group-level microstructural values in women, peripheral cytokines appeared to track individual differences in MTL tissue state among women. The parallel positive associations with ICVF and ISOVF suggest a regulated immune–tissue coupling process involving both neurite density and extracellular water compartments, rather than a simple model in which higher inflammatory burden uniformly predicts microstructural injury.

These effects were not explained by differences in circulating cytokine concentrations, indicative of a sex-specific sensitivity to inflammatory signaling. Notably, these associations were concentrated in hippocampal-prefrontal pathways, including the hippocampal cingulum and uncinate fasciculus, and were absent in non-hippocampal white matter tracts (i.e., cingulum cingulate bilaterally). This regional selectivity argues against a global effect of systemic inflammation on white matter, pointing instead to the preferential vulnerability of circuits among the earliest and most consistently disrupted in AD.

Moderated mediation analyses confirmed the functional relevance of this immune-brain coupling, identifying MTL WM microstructure as a sex-specific pathway linking peripheral TNFα to hippocampal-dependent memory. A key feature of this scheme is that while TNFα was associated with hippocampal cingulum integrity comparably across sexes, the cognitive relevance of that microstructural variation was unique to women. Specifically, white matter integrity in hippocampal-prefrontal pathways predicted mnemonic discrimination performance in women but not in men. Consequently, the indirect pathway from peripheral inflammation to memory was significant only in women, suggesting that women's brains are not merely exposed to a more inflammatory environment, but are *differentially sensitized* to its neural and cognitive consequences.

These findings align with evidence of more pronounced associations between white matter integrity and cognitive performance in women (Hsu et al., 2021), and identify a specific inflammatory driver of this variability. We have previously shown in the same cohort that the cognitive outcome most sensitive to this pathway, temporal discrimination accuracy, is selectively vulnerable to preclinical amyloid deposition in frontotemporal memory circuits (Vanderlip et al., 2025). Thus, the inflammation-white matter-memory chain identified here may represent a functional signature of circuit vulnerability that precedes clinical symptoms of AD.

NODDI-derived metrics revealed regionally specific sex differences in MTL white matter integrity, with women showing lower neurite density, lower extracellular free water signal, and lower fiber dispersion across hippocampal-associated pathways. While traditional DTI has yielded inconsistent findings regarding sex differences in white matter microstructure during aging (Eikenes et al., 2023; Kitamura et al., 2011; Phillips et al., 2013; Rathee et al., 2016) , the multi-compartment specificity of NODDI provides a more sensitive framework for detecting sex-dimorphic microstructural shifts (Lawrence et al., 2021; D. M. Parker et al., 2025). Our findings suggest that such biophysical modeling reveals a female-specific vulnerability in these critical memory circuits.

These microstructural profiles may presage an accelerated accumulation of AD-related pathological burden in women, consistent with evidence of sex-dimorphic tau propagation and white matter involvement in early disease stages (Buckley et al., 2019). Alternatively, these differences may inherently amplify circuit vulnerability, compromising the structural integrity of circuits through which pathology propagates. While the cross-sectional nature of these data precludes directionality, our findings suggest that stronger immune-white matter coupling in women may contribute to these differences. We hypothesize that age-related shifts in inflammatory

signaling, particularly during the menopausal transition, contribute to the emergence and widening of these microstructural sex differences across the lifespan.

The strong, consistent association between salivary cytokines (TNFα, IL-10) and MTL white matter integrity in women, contrasted with the weak, inconsistent patterns in men, reveals a dimension of sex-specific sensitivity that has been largely overlooked in aging research. While elevated systemic inflammation is traditionally associated with poorer cognitive performance (Fard et al., 2022; Leonardo & Fregni, 2023) and white matter integrity in aging (Arfanakis et al., 2013; Gu et al., 2017; Satizabal et al., 2012), higher cytokine levels are often linked to tissue compromise in pathological states (Benedetti et al., 2016; Boots et al., 2020; Breit et al., 2023; Gertje et al., 2023). Yet our findings in cognitively unimpaired adults suggest that elevated TNFα and IL-10 may index adaptive immune surveillance and tissue maintenance. The parallel positive associations of both pro- and anti-inflammatory markers (TNFα and IL-10, respectively) (Chang et al., 2017; Chaplin, 2010) suggest a coordinated immune response that is inconsistent with a simple model of inflammatory toxicity. It is more likely a form of regulated coupling between immune signaling and tissue state, consistent with context-dependent immune-brain interactions described in prior work.

This sex-dependent coupling likely reflects fundamental differences in central immune regulation. At the cellular level, microglia, which both produce and respond to TNFα, exhibit sex-specific activation profiles (Yazar et al., 2025), with female hippocampal microglia showing heightened TNFα-related signaling in the brain during aging (Ocañas et al., 2023). In healthy aging, this pronounced immune signaling appears to support homeostatic immune-tissue interactions, yet this state represents a double-edged sword. While it maintains circuit integrity under stable conditions, it may paradoxically amplify vulnerability to chronic dysregulation as

AD-related pathological burden accumulates. This adaptive-to-maladaptive transition may be further catalyzed by endocrine remodeling during the menopausal transition. Estrogen exerts broad neuroprotective effects by modulating microglial activation and maintaining blood-brain barrier integrity (Zárate et al., 2017); its withdrawal removes a key buffer against inflammatory dysregulation, potentially "unmasking" latent vulnerabilities in the hippocampal cingulum.

Whether menopausal hormone therapy (MHT) can preserve this buffer remains an essential, untested question. While our sample consisted entirely of postmenopausal women, specific data regarding the initiation, type, and duration of MHT was not available in the current cohort. Given the known heterogeneity in MHT timing and formulation, larger longitudinal studies are required to determine if exogenous estrogen can maintain the adaptive inflammatory sensitivity or delay its pathological transition.

Several considerations bear on the interpretation of these findings. First, the cross-sectional design precludes strong conclusions about the directionality of the observed associations. Mediation models are used here to test conditional statistical architecture rather than temporal causality. Longitudinal studies tracking inflammatory profiles across the menopausal transition are required to establish temporal precedence and evaluate whether the immune-brain coupling identified here predicts subsequent neurodegeneration. Second, while salivary assays have been validated against plasma in this cohort (Parkin et al., 2023), additional validation against CSF or PET-based assays is a natural future direction. That said, the associations between salivary-based inflammatory markers and circuit-specific outcomes support biological relevance as a scalable peripheral assay. Third, women were more represented in the cohort, consistent with enrollment patterns in aging studies and the epidemiology of AD risk. Robust standard errors and sensitivity analyses were used to account for unequal group sizes. Fourth, salivary cytokines may reflect local

oral inflammatory processes. To address this concern, we implemented rigorous quality control to exclude analytes below the LLOD and remove participants with profiles indicative of acute inflammation as extreme outliers. Nevertheless, future replication with plasma and CSF assays will be important. Finally, future work integrating genetic risk factors (e.g., ApoE ε4 status) and co-pathologies (e.g., vascular and metabolic conditions) will be essential to partition the relative contributions of these factors to the sex-specific microstructural profiles observed here.

These results have important implications for how sex differences in neurodegeneration risk are conceptualized (Arenaza-Urquijo et al., 2024). Our data suggest that risk models based solely on circulating cytokine concentrations may overlook a critical dimension of vulnerability. Individuals with comparable peripheral inflammatory profiles can differ markedly in how those signals map onto vulnerable neural circuits. Inflammatory sensitivity may therefore represent a more informative axis of risk than inflammatory burden alone. In parallel, our results support peripheral cytokine profiling as a scalable and minimally invasive approach for indexing the immune-brain interface during the preclinical phase of AD.

More broadly, these findings position the peripheral immune-brain interface as a candidate pathway for sex-specific AD vulnerability that is measurable before the onset of clinical symptoms. Longitudinal studies are now needed to determine whether this coupling predicts subsequent white matter decline, tau accumulation, or cognitive deterioration, and whether it can be modified through immune, hormonal, or lifestyle interventions. By identifying specific circuits through which peripheral biology relates to early neural vulnerability, this work motivates future precision prevention strategies and helps identify women most likely to benefit from early intervention.

Supplemental

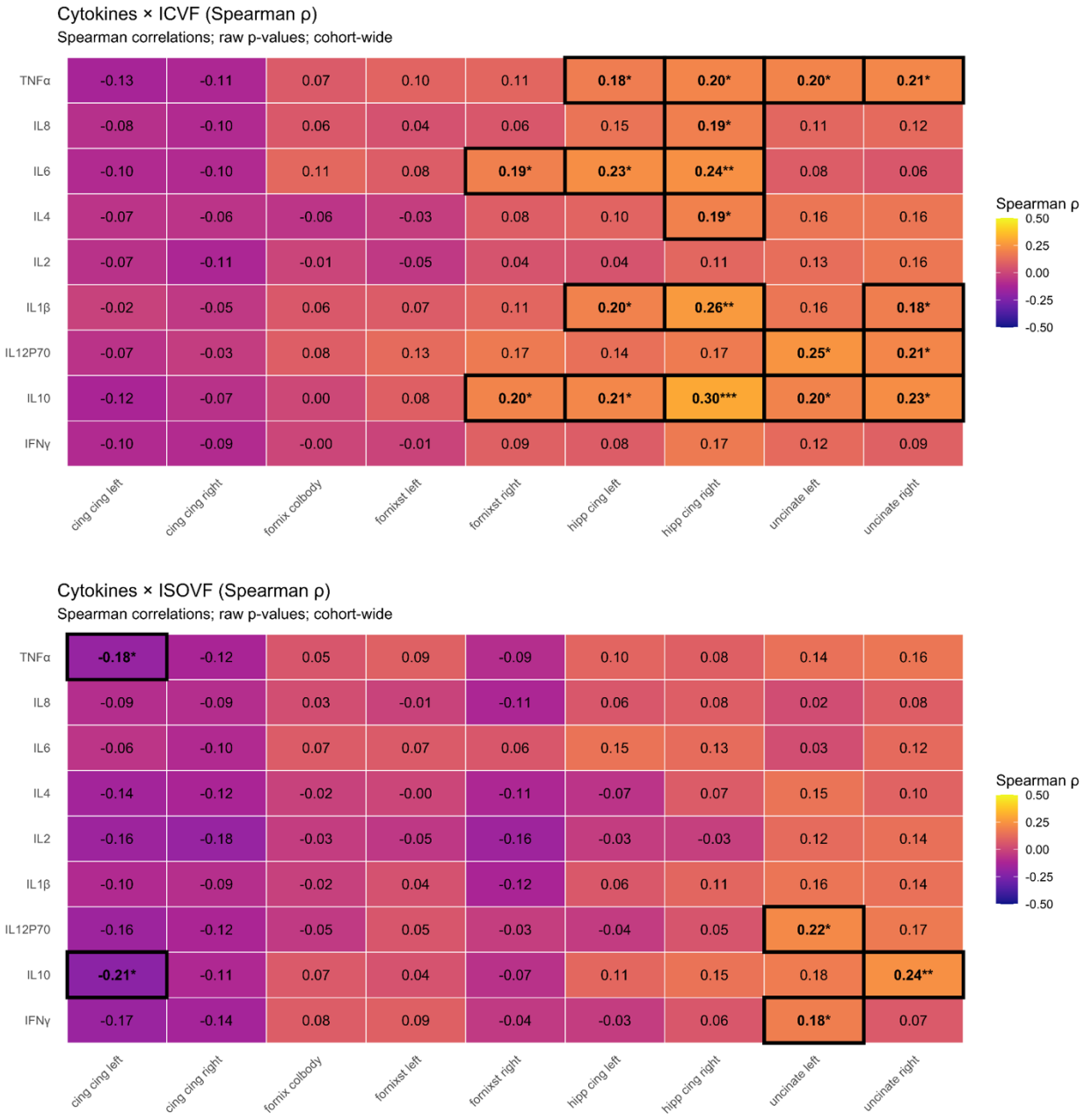


Figure 10 Cohort wide correlogram of inflammatory markers and MTL white matter microstructure.

*Spearman correlation matrices showing associations between cytokines and NODDI diffusion metrics across MTL white matter pathways in the full cohort. The top panel displays correlations with ICVF, and the bottom panel displays correlations with ISOVF. Cell values represent Spearman ρ, with asterisks indicating raw p-values (*p < 0.05, **p < 0.01, ***p < 0.001; significant associations are additionally outlined. Compared with the female-specific analyses presented in the main text, cohort wide relationships were weaker and less spatially consistent across regions.*

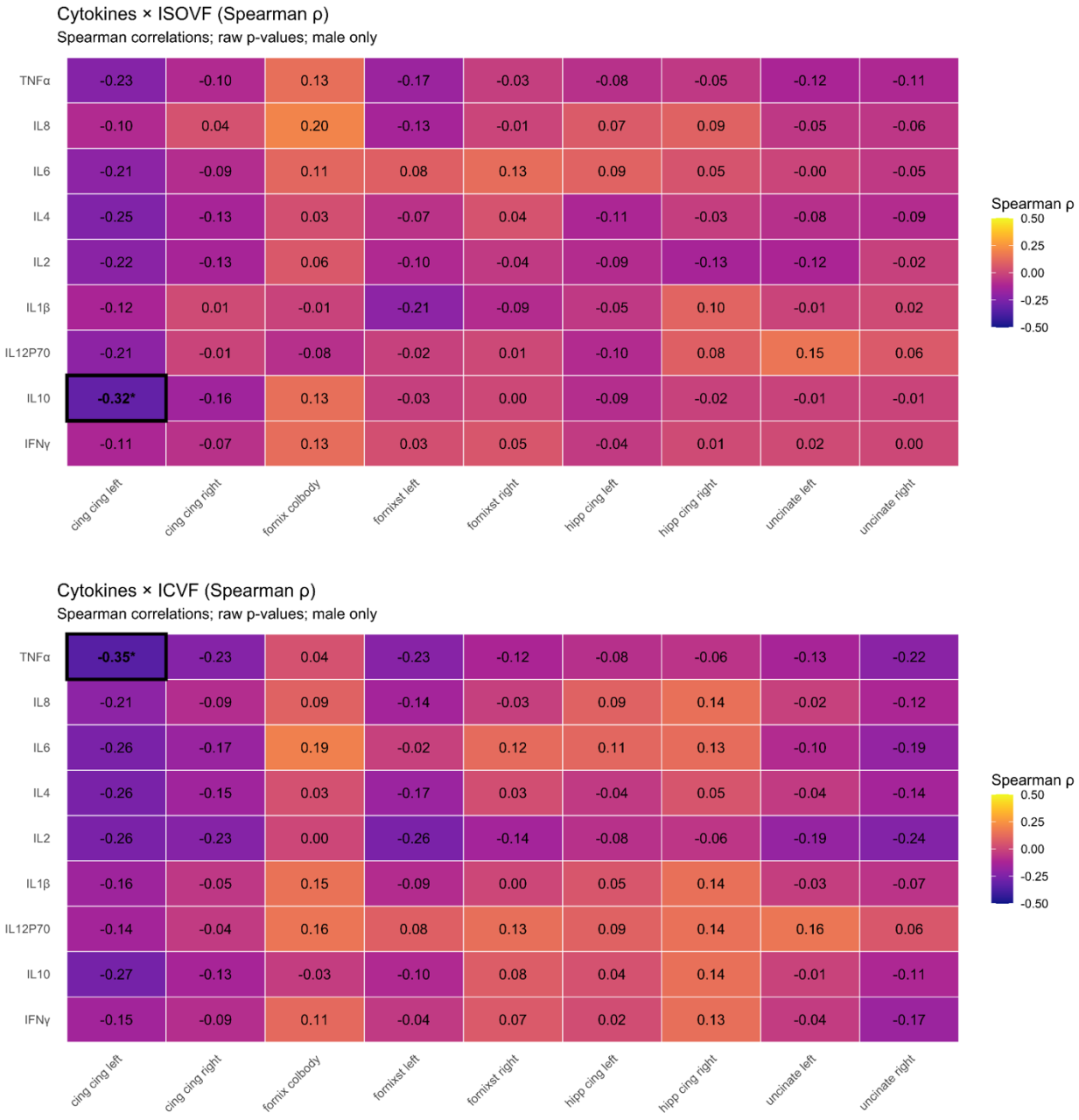


Figure 11 Men only correlogram of inflammatory markers and MTL white matter microstructure.

*Spearman correlations matrices showing associations between cytokines and NODDI diffusion metrics across the MTL white matter pathways in men only. The top panel displaces correlation with ICVF and the bottom displays correlations with ISOVF. Cell values represent Spearman ρ, with asterisks indicating raw p-values (*p < 0.05) and significant associations outlined. Overall, men exhibited few significant relationships between inflammatory markers and diffusion metrics, with only isolated negative associations observed in the cingulum, indicating weaker and less spatially consistent inflammation microstructure coupling compared with females.*

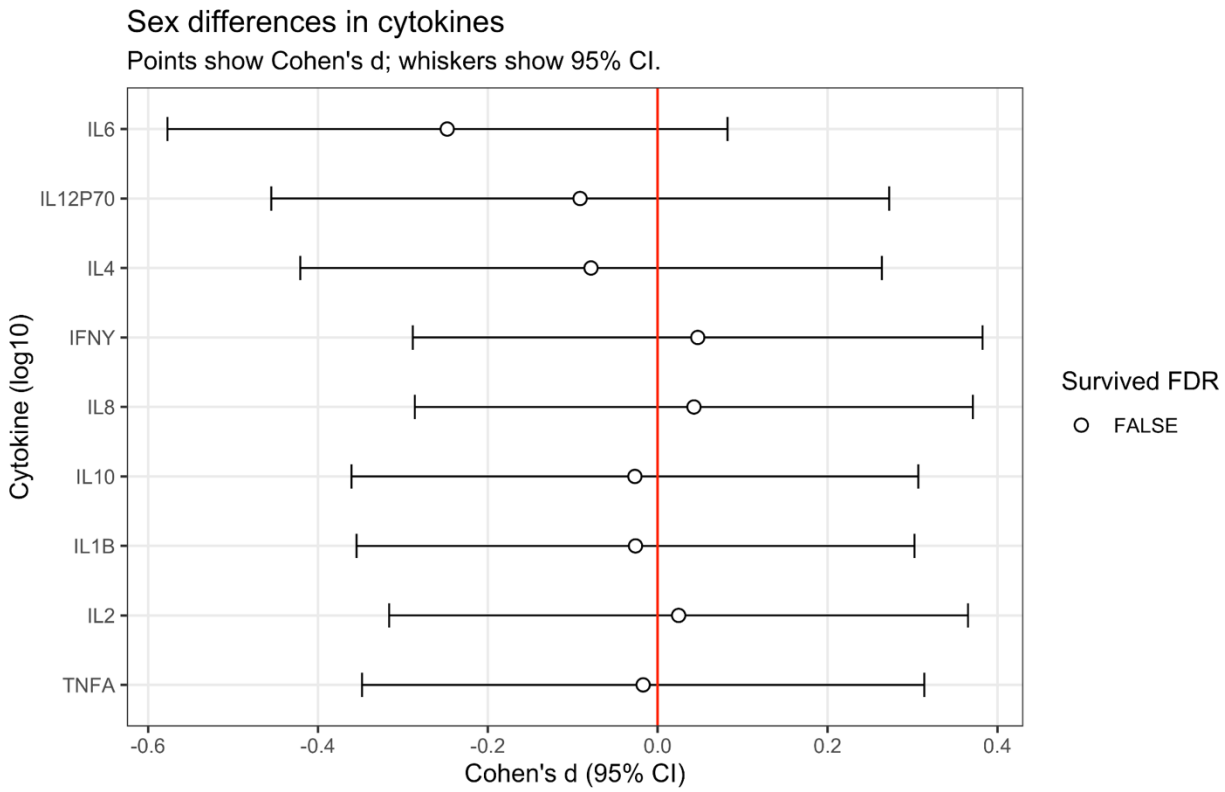


Figure 12 Sex differences in circulating cytokine concentrations.

Forest plot displaying effect sizes for sex differences in log-transformed cytokine concentrations. Points represent Cohen's d for the difference between females and males, and whiskers indicate 95% confidence intervals. The vertical red line denotes no sex difference (d=0). None of the cytokines survived within family FDR correction.

Chapter 4: Systemic inflammation is associated with limbic white matter microstructural alterations in adults with Down Syndrome

4.1 Introduction

Individuals with Down syndrome (DS) represent one of the largest genetic high-risk populations for Alzheimer's disease (AD) (Potter et al., 2020). By age 40, nearly all individuals exhibit significant amyloid-B deposition, followed by predictable tauopathy (Fortea et al., 2020; Hithersay et al., 2017; Lott & Head, 2019). While the triplication of the amyloid precursor protein (APP) gene on chromosome 21 renders proteopathy inevitable, the clinical trajectory of cognitive decline remains strikingly heterogeneous. This variance suggests that secondary "biological hits", such as chronic systemic inflammation, may erode structural brain reserve, thereby accelerating the conversion from preclinical proteopathy to clinical dementia (Silva et al., 2025; Wilcock, 2012). Recent work has suggested that systemic inflammation may be a key player in the pathophysiology of Down Syndrome-associated AD (DS-AD) (Huggard et al., 2020; Qu et al., 2026). yet the mechanisms through which it influences brain structure and function remain poorly understood.

Converging evidence further indicates that individuals with DS exhibit a chronic pro-inflammatory phenotype, driven in part by the triplication of interferon receptor genes on chromosome 21 (Sullivan et al., 2016). This genetic interferonopathy creates a state of systemic immune hyper-responsiveness, resulting in chronically elevated levels of interleukin-6 (IL-6) and C-reactive protein (CRP), both of which have been linked to cognitive decline and AD pathology (Hithersay et al., 2017; Iulita et al., 2016) and to variation in frontolimbic WM development and cognition (Rasmussen et al., 2019).

While this systemic inflammation is hypothesized to explain the link between genetic predisposition and clinical symptoms (Sankowski et al., 2015), the precise nature of this immune-brain coupling remains poorly defined. Specifically, it is unclear whether systemic cytokines primarily drive transient inflammatory processes, such as extracellular fluid shifts and edema, or contribute to more permanent structural erosion, including neurite loss and microstructural disorganization. Distinguishing among these possibilities is essential for understanding the biological mechanisms underlying WM degeneration in DS-AD.

A growing body of diffusion tensor imaging (DTI) studies has demonstrated widespread white matter (WM) alterations in DS even prior to measurable cognitive decline (Rosas et al., 2020). These changes are most pronounced in the limbic circuitry, specifically the uncinate fasciculus and cingulum bundle, which are tracts that are essential for memory and represent the earliest sites of WM degeneration within the AD continuum (Romano et al., 2018). These late-myelinating association fibers (uncinate and cingulum) are characterized by lower structural reserve and higher metabolic demand, rendering them vulnerable to systemic inflammation (B. Reisberg et al., 1999). However, the biological interpretation of traditional DTI remains challenging. Scalar measures like fractional anisotropy cannot inform on the underlying microstructural processes, failing to distinguish between axonal loss, demyelination, and extracellular fluid accumulation (Jeurissen et al., 2013).

To better understand the neurobiological processes impacted in DS-AD, we utilize Neurite Orientation Dispersion and Density Imaging (NODDI) (H. Zhang et al., 2012), a multi-compartment diffusion framework that decomposes the diffusion signal into three biologically interpretable variables: (1) intracellular volume fraction (ICVF) reflecting neurite density, (2) orientation dispersion (OD) reflecting fiber organization, and (3) isotropic volume fraction

(ISOVF), reflecting extracellular free water. Unlike traditional DTI scalars such as fractional anisotropy, which conflate these processes into a single measure, NODDI can distinguish neurite loss and fiber disorganization from transient extracellular fluid accumulation. This distinction is critical for determining whether systemic inflammation drives permanent structural erosion of WM architecture (reduced ICVF, increased OD) or transient vascular permeability changes (elevated ISOVF), and whether these effects selectively target limbic pathways that are both developmentally vulnerable and among the earliest sites of AD-related degeneration in DS (Heneka et al., 2015; Pasternak et al., 2009; H. Zhang et al., 2012).

In this study, we employed the hypothesis-driven, mutli-compartment NODDI approach to characterize the relationship between systemic inflammation and WM microstructure in adults with DS. Our primary aim was to determine whether blood-based cytokines relate to brain structure beyond the effects of chronological age. While we evaluated a comprehensive panel of systemic inflammatory markers, we specifically focused our secondary analyses on those demonstrating robust, age-independent associations with WM microstructure (notably CRP and IL-6). To achieve this, we utilized NODDI to disentangle competing microstructural signatures, specifically evaluating whether inflammation-related changes manifest as neurite depletion (ICVF), fiber disorganization (OD), or extracellular free water expansion (ISOVF). By focusing our functional analysis on the limbic pathways (uncinate and cingulum), we sought to define the pathological triad linking peripheral immunity to the structural and cognitive markers of accelerated aging in DS.

4.2 Methods

Participants

Participants enrolled in the Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS) study underwent neuroimaging and neuropsychological assessments. All research procedures were reviewed and approved by the institutional review boards of collaborating institutions (University of Pittsburgh, University of Wisconsin–Madison, Washington University in St. Louis, University of Cambridge, Columbia University Irving Medical Center, Massachusetts General Hospital, University of California, Irvine, University of Kentucky, and University of Kansas) and were performed in accordance with the Declaration of Helsinki. Informed consent, as well as assent, was obtained from all participants and/or their legally authorized representatives.

MRI acquisition

Data were acquired on 3T MRI scanners following standard protocols based on the Alzheimer's Disease Neuroimaging Initiative (ADNI 3.0). Siemens Prisma scanners were used at University of Pittsburgh, Washington University in St. Louis, Columbia University, Massachusetts General Hospital, University of California, Irvine, and University of Kentucky, a Siemens Skyra scanner was used at University of Kansas, and a GE Discovery scanner was used at University of Wisconsin–Madison. For T1-weighted structural images, all scans were collected using 1.0 mm isotropic voxels. For Siemens scanners, MPRAGE scans were collected with TR/TE/TI of approximately 2300/3/900 ms and a 9° flip angle. For GE scanners, IR-IFSPGR scans were collected with TR/TE/TI of approximately 7.5/3/400 ms with a 11° flip angle.

Diffusion-weighted images were acquired using a multiband echo-planar imaging (EPI) sequence. On Siemens prisma scanners, diffusion data were collected with the following parameters: TR = 3400 ms, TE = 71 ms, voxel size = 2.0 x 2.0 x 2.0 mm^3, field of view (FOV) =

232 mm, 81 axial slices. Diffusion weighting was applied along 126 directions with a monopolar diffusion scheme at values of 0, 500, 1000, 2000 s/mm^2. Phase encoding was performed in the posterior to anterior direction.

Structural and Diffusion MRI Processing and Analysis

T1-weighted images were preprocessed using Freesurfer (v7.4) (Fischl, 2012), which corrected for head motion and intensity inhomogeneity prior to the removal of non-brain tissue. Diffusion scans were preprocessed using QSIPrep (0.24.0), a standard and reproducible preprocessing pipeline that integrates tools from FSL, MRtrix3, and ANTs (Cieslak et al., 2021). Raw diffusion images were first denoised using MP-PCA (Veraart et al., 2016) denoising implemented in MRTrix3's dwidenoise (Tournier et al., 2019). Head motion and eddy current induced distortions were corrected using FSL's eddy (Andersson & Sotiropoulos, 2016), with a model-based head motion correction strategy. Preprocessed images were then resampled to 1 mm isotropic resolution to harmonize across participants and facilitate downstream analyses. These resampled images were subsequently used as inputs for microstructural modeling and reconstruction using QSIRecon.

Preprocessed diffusion data were reconstructed using QSIRecon (v0.24.0) (Cieslak et al., 2021). Reconstruction was performed using the Accelerated Microstructure Imaging via Convex Optimization (AMICO) framework (Daducci et al., 2015) with the NODDI model (H. Zhang et al., 2012). This was performed at the participant level using subject specific anatomical information derived from FreeSurfer segmentations, supplied from earlier T1-weighted image

preprocessing. All reconstructed scans were resampled to 1 mm isotropic resolution to ensure consistency across participants and compatibility within group level analyses. Outputs included NODDI microstructural metrics: ICVF, ISOFV, OD. Reconstructed microstructural maps were used for subsequent region of interest (ROI) based analyses and were defined using the Johns Hopkins University ICBM-DTI-81 WM atlas (Mori et al., 2008). Atlas based ROIs were selected a priori based on their relevance to medial temporal lobe (MTL) connectivity and AD vulnerability.

Diffusion MRI Quality Control

Quality control (QC) procedures were applied to all diffusion MRI scans to ensure the reliability of downstream microstructural estimates. Scans that were identified as outliers (>3 standard deviations) on noise-related QC metrics, and on which subsequent visual inspection confirmed the presence of substantial artifacts were excluded from further analyses.

QC metrics were derived to capture subject motion, signal quality and registration performance. Quality control flags were defined using cohort-relative percentile thresholds across these domains, identifying scans with elevated motion, reduced signal quality, or increased registration uncertainty. In addition to relative QC thresholds, absolute plausibility checks were performed on NODDI derived parameters. Specifically, scans were evaluated for biologically implausible values in ICVF, OD, and ISOVF. No scans demonstrated implausible NODDI parameter estimates.

Plasma Collection and Processing

Venous blood was collected into EDTA-coated tubes following cognitive assessment. To minimize ex vivo cytokine production, samples were processed within three hours of collection by centrifugation at 2200g for 10 minutes at room temperature. Plasma supernatant was immediately aliquoted into 250 uL polypropylene cryovials and stored at -80 C until analysis. Samples underwent a single freeze-thaw prior to assay.

Determination of Cytokine Levels

Systemic inflammatory markers were quantified using the Meso Scale Discovery (MSD) electrochemiluminescence platform (Rockville, MD). The V-PLEX Proinflammatory Panel 1 (Human) was used to measure a multiplexed suite of cytokines, including IL-1B, IL-6, IL-8, IL-10, and TNF-a. Assays were performed in duplicate according to the manufacturer's protocols. To ensure longitudinal consistency, all samples were randomized across plates, and clinicians were blinded to the cytokine data during consensus diagnosis. The lower limit of detection (LLOD) was calculated as 2.5 standard deviations above the background signal. Samples falling below the LLOD were removed from the dataset. Inter-assay and intra-assay coefficients of variation were maintained below 10% and 5%, respectively.

Neuropsychological Assessments

The Down Syndrome Mental Status Exam (DSMSE) is an adapted version of the Mini Mental Status Exam that assesses orientation, personal information, short-term memory, language, visuospatial construction, and praxis (Haxby, 1989). An expanded version of the DSMSE that included memory for nine common objects was used (Hom et al., 2021; Rosas et al., 2020). Lower

total score indicates worse global cognition. In this study we used the DSMSE Memory subtest + Shoe Box Memory Test for our total memory score (TMS).

Episodic memory was assessed using a modified version of the Cued Recall Test (mCRT) validated for use in people with intellectual disability which is also sensitive to preclinical and clinical AD in people with DS (Benejam et al., 2020; Hartley et al., 2020) Administration of the mCRT has been described previously (DiProspero et al., 2024). The total recall score (TRS) represents the sum of the free recall score (FRS) and cued recall score (CRS) across three 12-item trials, resulting in a maximum score of 36. Due to the dependence of CRS on FRS, CRS was converted to a percentage by dividing by the number of items missed on the free recall portion (i.e., 36 minus FRS).

Determination of Clinical Status

To determine cognitive status, participants underwent clinical characterization by a multidisciplinary expert panel blinded to neuroimaging, mCRT, and biomarker data (Krinsky-McHale & Silverman, 2013). Diagnosis was based on neuropsychological performance, informant interviews, and functional history, adhering to ICD-10 and DSM-IV-TR criteria (Sheehan et al., 2015). Participants were categorized into five initial groups: cognitively stable (CS), mild cognitive impairment (MCI-DS), possible dementia, definite dementia, or unable to determine.

Statistical Analysis

All statistical analyses were conducted in R (version 4.1.2). Continuous variables were inspected for normality and log-10 transformed where appropriate to reduce skew. Associations between systemic inflammation and WM microstructure were assessed using linear mixed effects models implemented with the lme4 package in R. NODDI derived metrics were modeled as dependent variables and inflammatory markers were modeled as fixed effects. To account for site-related variability, a random intercept for site was included in all models. Given the strong influence of age on both inflammatory markers and WM microstructure, models were evaluated both with and without age at visit included as a covariate. This approach allowed for characterization of inflammation microstructure associations independent of age, as well as identification of age-dependent effects. Separate models were fit for each combination of inflammatory marker, diffusion metric, and region of interest. To account for multiple comparisons, false discovery rate (FDR) correction was applied using the Benjamini-Hochberg procedure within families of related tests such as across tracts for a given inflammatory marker and diffusion metric (Benjamini & Hochberg, 1995). Statistical significance was defined as FDR-corrected $p < 0.05$ unless otherwise noted.

4.3 Results

Participant Demographics

A total of 110 baseline visits from the ABC-DS repository met our inclusion criteria, which required both a multi-shell diffusion scan (necessary for NODDI modeling) and concurrent inflammatory marker data. After excluding cases that failed neuroimaging quality control (n= 14), the final cross-sectional sample comprised 96 participants **(Table 8)**.

Variable	Summary (N = 96)
Age (mean [SD])	41.83 [9.54]
Sex, N (%)	
Female	36 (37.5%)
Male	60 (62.5%)
APOE ε4 carrier status, N (%)	
No	76 (80.9%)
Yes	18 (19.1%)
Missing	2 (2.1%)
Premorbid function level, N (%)	
Mild	45 (46.9%)
Moderate	50 (52.1%)
Severe	1 (1.0%)
Consensus diagnosis, n (%)	
Cognitively stable	90 (93.8%)
Mild cognitive impairment (MCI-DS)	6 (6.2%)
Dementia	0 (0%)

Table 8 Demographic 4.3

Systemic Inflammaging and Loss of Immune Regulation

Significant positive associations with age were observed for FABP3 ($\rho = 0.48$, $p_{FDR} < 0.001$), sVCAM-1 ($\rho = 0.31$, $p_{FDR} = 0.020$), and PPY ($\rho = 0.29$, $p_{FDR} = 0.021$) (**Figure 13)**. In contrast, IL-7, a key immune-regulatory cytokine, showed a significant negative association with

age ($\rho = -0.29$, $p_{FDR} = 0.021$). Thus, age was associated with increases in markers of vascular and metabolic injury and a concomitant decrease in immune regulatory signaling.

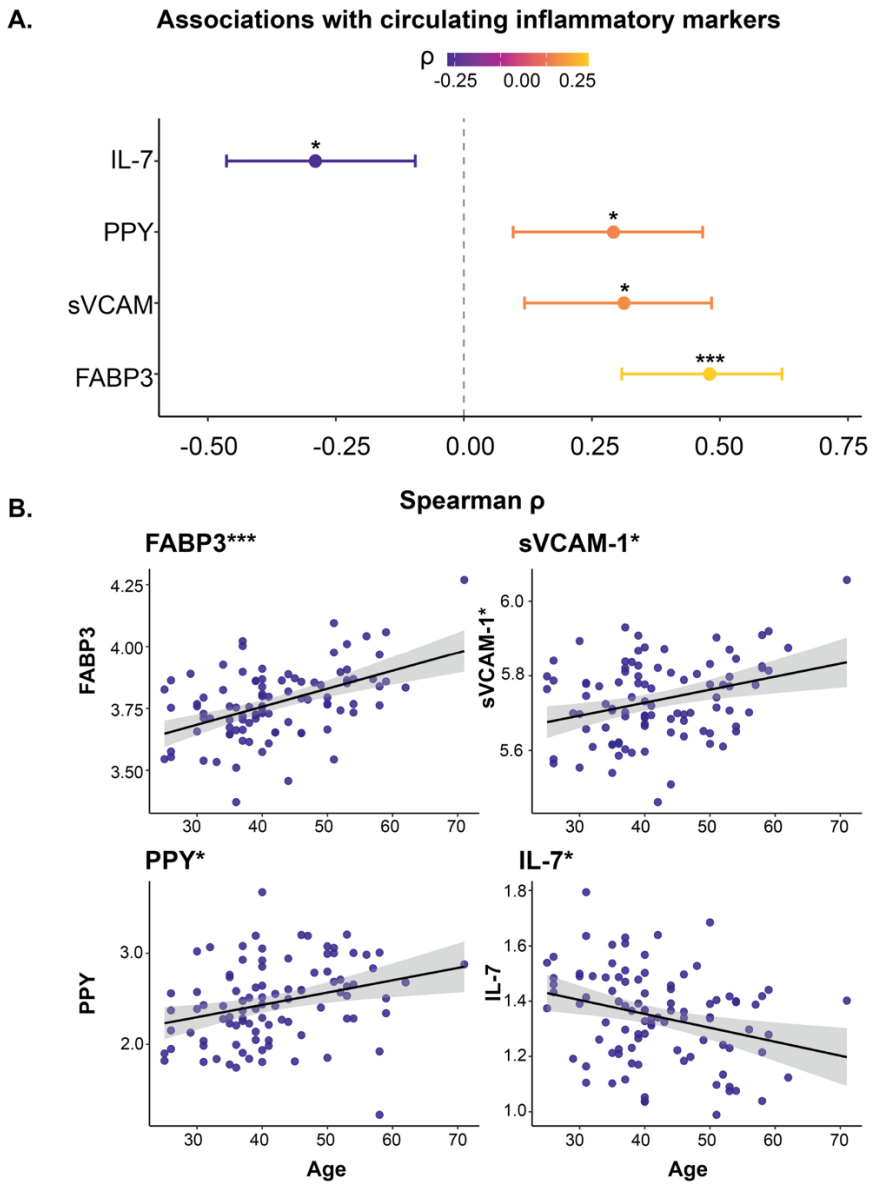


Figure 13 Age associations with circulating inflammatory markers.

(A) *Forest plot illustrating associations between age and circulating inflammatory markers. Points represent Spearman correlation coefficients (ρ), and horizontal bars denote 95% confidence intervals estimated using Fisher z-transformation. Colors reflect the magnitude and direction of the correlation, and a dashed line indicates no association (ρ = 0).* ***(B)*** *Scatter plots illustrating associations between age and circulating inflammatory markers.*

*Points represent individual participants, and solid lines indicate linear fits with 95% confidence intervals. Reported statistics correspond to Pearson correlation coefficients. Statistical significance is denoted by FDR-corrected p-values (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).*

Selective Anatomical Vulnerability of Limbic Pathways

Lower neurite density (ICVF) was observed in the cingulum cingulate (left: $\rho = -0.25$, $p_{FDR} = 0.041$; right: $\rho = -0.28$, $p_{FDR} = 0.022$). Meanwhile, greater OD was localized to the left hippocampal cingulum ($\rho = 0.26$, $p_{FDR} = 0.037$), with no significant associations observed in the cingulate cingulum or uncinate regions. Elevated free water (ISOVF) was most prominent in the right uncinate fasciculus ($\rho = 0.36$, $p_{FDR} < 0.001$) (**Figure 14)**, while other regions did not survive FDR correction. Therefore, age was associated with widespread differences in WM microstructure, with effects primarily localized to tracts essential for memory and AD.

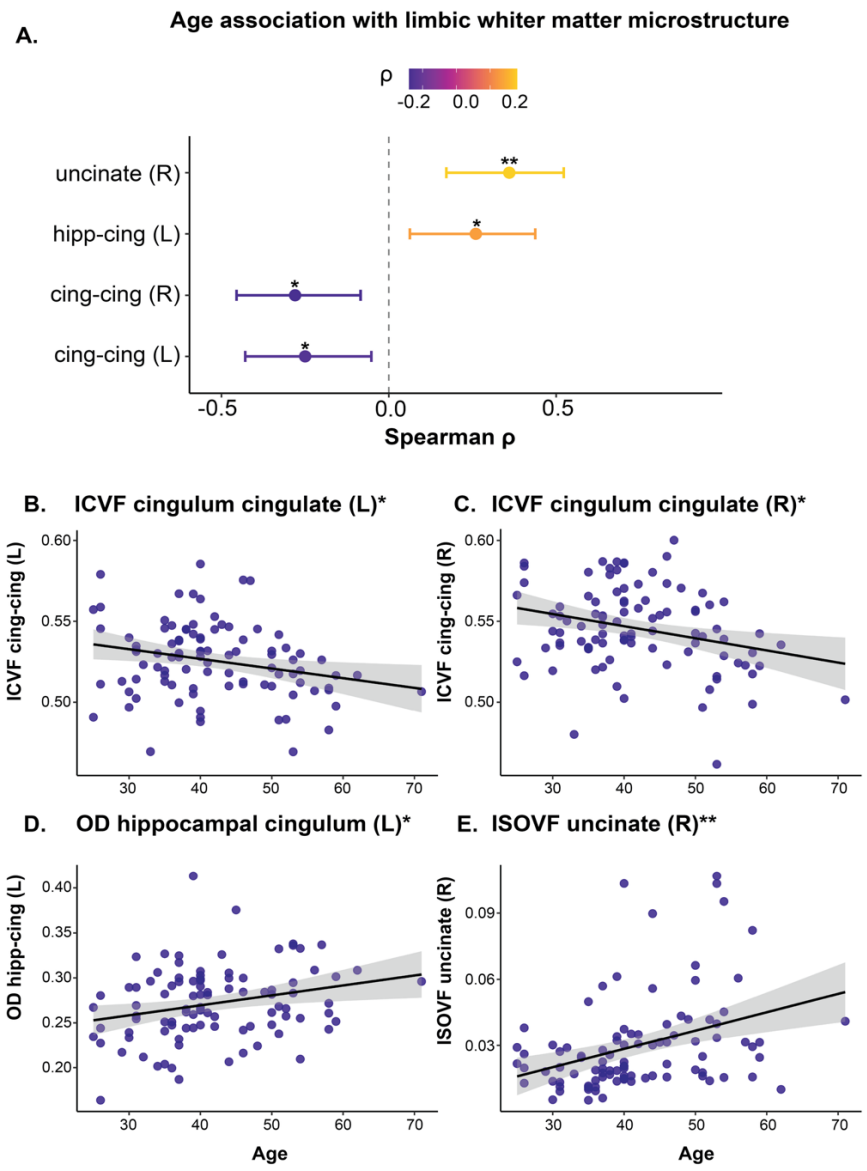


Figure 14 Age associations with limbic white matter microstructure

(A)*Forest plot illustrating associations between age and NODDI derived measures of white matter microstructure. Points represent Spearman correlation coefficients (ρ), and horizontal bars denote 95% confidence intervals estimated using Fischer z-transformation. Colors reflect the magnitude and direction of the correlation, and a dashed vertical line indicates no association (ρ = 0).* ***(B)*** *Scatter plots depicting relationships between age and NODDI derived measures of WM microstructure for significant associations. Points represent individual participants, and solid lines indicate linear fits with 95% confidence intervals. Color gradients reflect diffusion metric values. Statistical significance is denoted by FDR-corrected p-values (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).*

CRP, IL-6, and IL-18 are Associated with Age-Independent Neurite Loss and Disorganization in Limbic WM

While several inflammatory markers initially correlated with WM microstructure **(Supplementary 17A-C)**, only a specific subset emerged as robust predictors of structural damage independent of chronological age. CRP and IL-6 demonstrated the most consistent and spatially widespread associations with microstructural erosion. Higher levels of these markers were independently associated with lower neurite density (ICVF) in the uncinate fasciculus (CRP right: $\beta = -0.014$, $p_{FDR} = 0.023$; IL-6 right: $\beta = -0.052$, $p_{FDR} = 0.023$; IL-6 left: $\beta = -0.042$, $p_{FDR} = 0.023$) and greater fiber dispersion (OD) in both the uncinate (IL-6 right: $\beta = 0.156$, $p_{FDR} = 0.00048$; CRP right: $\beta = 0.042$, $p_{FDR} = 0.00048$) and hippocampal cingulum (IL-6 left: $\beta = 0.086$, $p_{FDR} = 0.0013$; CRP left: $\beta = 0.021$, $p_{FDR} = 0.0030$) **(Figure 15)**.

In addition to these effects, IL-18 showed robust, age-independent associations with increased OD in the hippocampal cingulum (right: $\beta = 0.076$, $p_{FDR} = 0.0042$; left: $\beta = 0.060$, $p_{FDR} = 0.0080$) **(Figure 15)**, indicating a more spatially specific contribution to microstructural disorganization within limbic pathways.

In contrast to these detrimental associations, Eotaxin-3 emerged as a unique independent predictor of ICVF. Higher levels of Eotaxin-3 were associated with greater ICVF across cingulum regions ($\beta \approx 0.017–0.019$, $p_{FDR} = 0.023$) **(Figure 15)**, suggesting marker specific differences in how inflammatory processes relate to microstructural integrity. Notably, these relationships persisted after adjustment for age and site.

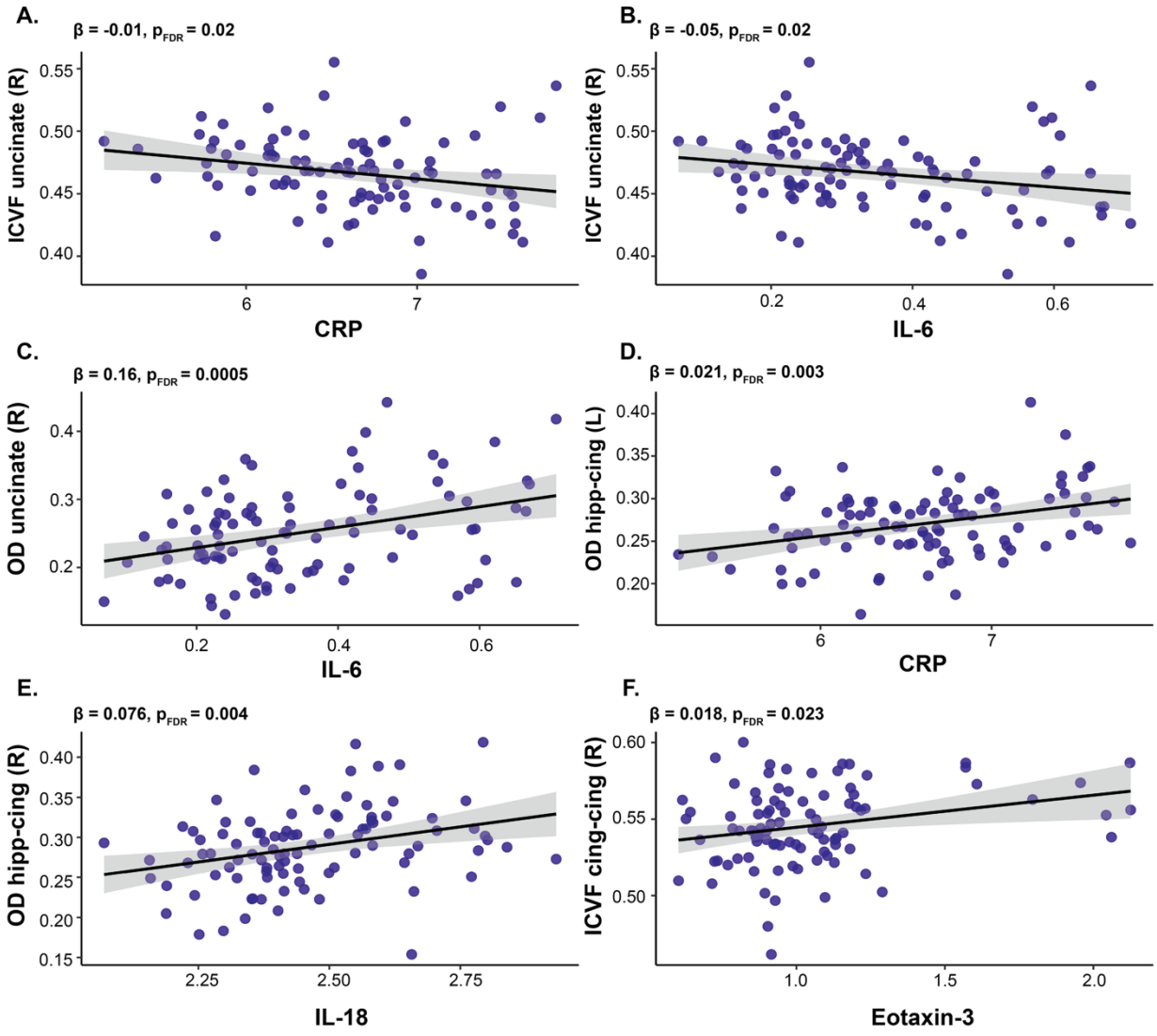


Figure 15 Associations between inflammatory markers and limbic white matter microstructure.

(A-F) *Scatter plots depicting relationships between inflammatory markers (CRP, IL-6, IL-18, and Eotaxin-3) and NODDI metrics across selected limbic tracts. Points represent individual participants, and solid lines indicate model predicted linear fits with 95% confidence intervals. β coefficients and FDR corrected p values are displayed for each panel.*

Dissociation of Inflammation from Extracellular Free Water

Associations between inflammatory markers and ISOVF were dependent on age. In models excluding age (with site as a random effect), higher levels of FABP3 were associated with greater ISOVF in the right hippocampal cingulum ($\beta = 0.092$, $p_{FDR} = 0.0057$). Additional nominal

associations were observed for IL-6, IL-18, and CRP across the uncinate fasciculus and hippocampal cingulum (β range ≈ 0.015–0.059, all $p < 0.05$), although these effects did not survive FDR correction.

Following formal adjustment for age, these relationships were substantially attenuated. Although modest associations persisted for FABP3 in the hippocampal cingulum and IL-18 in the uncinate fasciculus at the uncorrected level ($p < 0.05$), no inflammatory or vascular markers remained significant predictors of ISOVF after FDR correction ($p_{FDR} \geq 0.15$).

Cognition Is Associated with White Matter Microstructure

To evaluate the functional relevance of these structural changes, we examined the relationship between inflammation, WM, and cognition. Systemic inflammation was not directly associated with cognitive performance, with no significant associations observed for TRS, FRS, or CRS, and only trend-level effects for TMS ($p \approx 0.07–0.09$).

In contrast, WM microstructure emerged as a selective and significant predictor of cognition, particularly for TMS. Higher OD in the hippocampal cingulum (right: $\beta = -69.50$, p-FDR = 0.0091) and uncinate fasciculus (right: $\beta = -52.03$, $p_{FDR} = 0.0091$), along with higher ISOVF in the uncinate (right: $\beta = -169.27$, $p_{FDR} = 0.0161$; left: $\beta = -88.45$, $p_{FDR} = 0.0213$), were associated with worse TMS performance. In contrast, higher ICVF in the left uncinate fasciculus was associated with better performance ($\beta = 116.27$, $p_{FDR} = 0.0166$) **(Figure 16)**. In combined models, WM measures remained significant predictors of cognition, while inflammatory markers were attenuated to non-significance (IL-7 and ISOVF model: ISOVF $\beta = -163.28$, $p = 0.0098$; IL-7 $p = 0.085$).

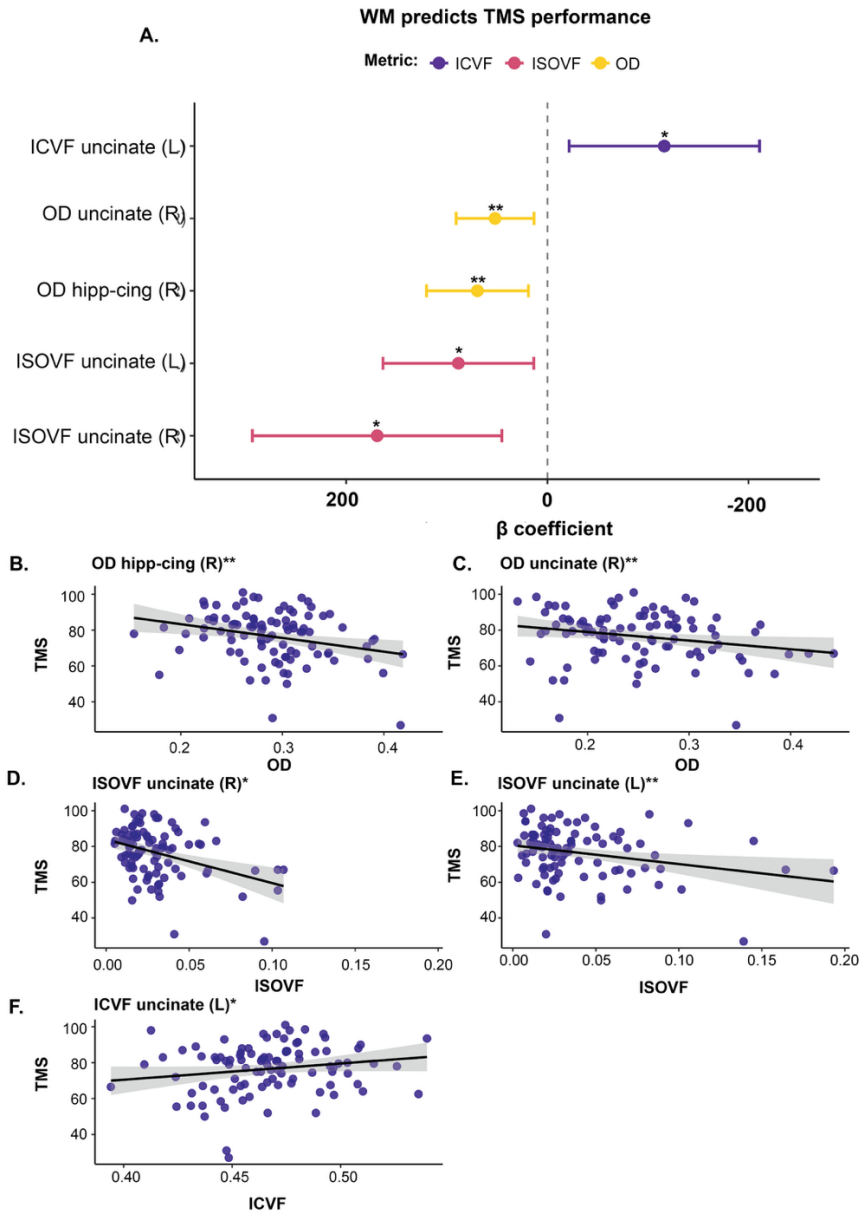


Figure 16 White matter microstructure predicts TMS performance

(A)*Forest plot illustrating associations between NODDI derived measures of WM microstructure and TMS performance. Points represent standardized regression coefficients (β) and horizontal bars denote 95% confidence intervals from linear models adjusted for age and site. All displayed associations survived FDR correction within diffusion metric families. Colors correspond to NODDI metrics: ICVF, ISOVF, OD, and a dashed vertical line indicates no effect (β=0).* ***(B)*** *Scatter plots depicting relationships between NODDI derived measures of WM microstructure and TMS performance for each significant association are shown. Points represent individual participants, and solid lines indicate linear fits with 95% confidence intervals. Color gradients reflect the values of each diffusion metric. Statistical models were adjusted for age and site. Plots display raw data with fitted regression lines for visualization.*

4.4 Discussion

Summary and Interpretation of Key Findings

The present study investigated the relationship between systemic inflammation, WM microstructure, and cognition in DS, with a focus on identifying biologically specific pathways linking peripheral immune processes to brain integrity. Aging in DS was associated with both widespread changes in WM microstructure and a shift in circulating inflammatory markers towards a profile characterized by increased endothelial activation and cellular injury. As evidenced by increases in markers FABP3 and sVCAM-1 alongside reduced immune regulatory signaling via IL-7. Together, these findings indicate that aging in DS is defined by an inflammaging phenotype, marked by endothelial activation and cellular injury alongside a decline in protective immune signaling, providing the biological context for subsequent microstructural erosion.

Inflammatory markers, most notably CRP and IL-6, were robustly associated with reduced ICVF and increased OD within limbic pathways. Importantly, these associations persisted after accounting for age, indicating that inflammation explains unique variance in WM microstructure beyond shared aging effects. In contrast, association with ISOVF were substantially attenuated following age adjustment. These findings are consistent with a growing body of literature linking systemic inflammation, including CRP and IL-6, to WM damage and structural brain alterations. A Meta-analysis demonstrated that inflammatory markers are associated with increased WM hyperintensity burden, a well-established marker of WM injury and small vessel disease (Sini et al., 2026). Additional work has linked inflammation to both WM integrity and cognitive performance in older adults, with IL-6 associated with poorer executive function and CRP associated with reduced WM integrity (Boots et al., 2020). Together, this work suggests that

systemic inflammation contributes to WM vulnerability at a macrostructural level. Extending these findings, the present results indicate that inflammatory processes are also associated with more specific microstructural alterations, including reduced neurite density and increased fiber disorganization. In a study of older adults (39-68 years) with DS, an increased presence of dystrophic microglia, as well as rod-like microglia aligned along neurons harboring tau pathology, was observed (Flores-Aguilar et al., 2020). These microglial phenotypes are thought to reflect chronic neurodegenerative processes rather than acute inflammatory responses and may contribute to axonal injury and synaptic remodeling. Such mechanisms are more consistent with reduction in neurite density and increased fiber disorganization rather than isolated increases in extracellular free water. This further supports the theory that inflammation in this context is linked to structural degeneration within vulnerable limbic pathways potentially acting as a selective accelerant of neurodegeneration in circuits for critical memory and cognitive function.

Finally, while inflammation was not directly associated with cognitive performance, WM microstructure showed significant relationships with cognition, particularly within the TMS. These findings suggest that alterations in limbic WM pathways are functionally relevant to memory performance in this cohort. Although systemic inflammation did not directly predict cognitive scores in this sample, its association with WM degeneration suggests that inflammatory processes may still play an indirect role in the neurocognitive profile of DS.

The present findings provide evidence that systemic inflammation in DS is associated with microstructural changes indicative of structural degeneration rather than transient extracellular processes. The persistence of inflammation-related associations with ICVF and OD, alongside the attenuation of ISOVF effects after age adjustment, suggests that inflammatory processes are linked to axonal loss and disruption of fiber organization rather than generalized increases in extracellular

diffusion. This distinction is critical, as it indicates that inflammation may contribute to lasting alterations in WM architecture rather than reversible inflammatory swelling.

Importantly, these effects were not uniformly distributed across the brain but were consistently localized to limbic WM pathways, particularly the uncinate fasciculus and cingulum bundles. These results establish that aging in DS naturally targets the limbic system, particularly the cingulum and uncinate, providing an anatomical foundation for interpreting the selective impact of systemic inflammation. While these tracts are known to decline in aging, they are also among the earliest to exhibit pathological changes in the AD continuum (Gozdas et al., 2020; Wen et al., 2019; Zhuang et al., 2013). The specific involvement of these limbic circuits suggests that WM vulnerability in DS follows a spatial pattern that mirrors AD-related neurodegeneration, potentially representing an accelerated or early-onset pathological process beyond what is expected in generalized brain aging. This regional specificity implies that systemic inflammation does not act as a diffuse stressor, but rather as a targeted hit to the circuits most critical for memory and executive function, the same pathways that bridge the gap between preclinical pathology and clinical dementia.

One potential mechanism contributing to this pattern is age-related vascular dysfunction, which is increasingly recognized as a feature of aging in DS. Neuropathological evidence demonstrates widespread blood brain barrier disruption, including increased vascular permeability, often described as “leaky” cerebral vessels and endothelial dysfunction, in individuals with DS and AD (Aguilar et al., 2023; Edwards et al., 2025; Sweeney et al., 2018). Consistent with this, circulating markers of vascular injury and endothelial activation, including FABP3 and sVCAM-1, showed strong positive association with age in the present sample. This widespread attenuation of ISOVF, contrasting sharply with the robust, age-independent effects

observed for neurite density and dispersion, reinforces the conclusion that extracellular free water in the DS brain is a signature of chronological aging, whereas systemic inflammation specifically targets the structural integrity of the neurite architecture. Our data suggest a dual-pathway model of brain aging in DS: while age-related vascular dysfunction drives a global increase in extracellular noise (ISOVF), systemic inflammation acts as a selective accelerant that erodes the actual neurite architecture (ICVF/OD) of the limbic system.

In contrast, association between inflammatory markers and both ICVF and OD remained robust after accounting for age, suggesting that inflammation contributes to microstructural degeneration beyond vascular-related fluid shifts. These findings support a model in which vascular dysfunction may underlie global, age-related increases in extracellular water, while inflammation acts more selectively to drive neurite loss and fiber disorganization within limbic pathways.

This selective vulnerability of the uncinate and cingulum may further reflect their unique development and structural properties. As late-myelinating association fibers, these tracts are characterized by a high surface-to-volume ratio and a lower density of protective oligodendrocytes, a profile that confers reduced structural reserve (Bartzokis, 2004). This inherent fragility aligns with a model suggesting that the latest maturing pathways are the first to undergo degeneration (Barry Reisberg et al., 2002). While traditional DTI studies have noted progressive microstructural decline within these limbic pathways prior to the onset of overt dementia (Mayo et al., 2017), our findings extend this work by demonstrating that this decline is specifically driven by reductions in neurite density and increased fiber disorganization as captured by ICVF and OD, respectively. By decoupling these metrics from free water, we provide evidence that the early degeneration of late-

maturing pathways is not merely a byproduct of age-related fluid shifts but a targeted erosion of the underlying axonal architecture.

These findings suggest a converging model in which age-related vascular dysfunction contributes to global extracellular changes, while inflammation selectively accelerates degeneration within structurally and developmentally vulnerable limbic circuits. This interaction may help explain why WM alterations in DS are both spatially specific and closely aligned with networks for critical memory and cognitive function.

The dissociation between inflammation and cognitive performance, alongside the robust associations between WM microstructure and cognition, further suggests a hierarchical relationship among these processes. In this framework, systemic inflammation may act as a distal contributor to neurodegeneration, influencing cognitive outcomes indirectly through its impact on WM integrity, which represents a more proximal substrate of cognitive performance (Brickman et al., 2012; Charlton et al., 2006). This interpretation is supported by evidence that WM alterations in AD reflect underlying biological processes, including demyelination, axonal injury, and glial activation (Rosas et al., 2020), and are closely linked to clinical decline. The absence of statistically significant mediation effects indicates that these relationships may be complex and potentially moderated by additional pathological processes, such as amyloid or tau accumulation, which are highly prevalent in DS.

Notably, markers associated with immune regulation, such as IL-7 (Mazzucchelli & Durum, 2007), and chemokines, including eotaxin-3, showed positive associations with WM integrity. These effects were most pronounced for neurite density, suggesting that regulatory and chemokine signaling pathways may be linked to preservation of microstructural reorganization. In contrast, pro-inflammatory markers were associated with increased fiber disorganization.

Together, these findings support a broader pattern in which immune signaling in DS reflects both pro-inflammatory and regulatory processes with distinct microstructural associations. Extending this pattern to cognitive outcomes, WM microstructure, but not systemic inflammation, was associated with cognitive performance. This dissociation suggests that microstructural alterations may represent a more proximal correlate of cognition, while inflammatory processes may relate more strongly to upstream structural changes. Although these relationships do not establish a causal pathway, they are consistent with the possibility that inflammatory and microstructural alterations emerge prior to measurable cognitive impairment. Together these findings indicate that while chronic systemic inflammation (CRP, IL-6, IL-18) is linked to the active degradation of limbic architecture, other immune signaling pathways may reflect processes of microstructural resilience in the aging DS brain.

Together, these findings may reflect a broader pathological triad in which systemic inflammation, WM disruption, and cognitive decline are interconnected but not linearly coupled. In this model, inflammation and WM degeneration may precede measurable cognitive impairment with additional pathological processes required for clinical expression.

Several distinct strengths enhance the validity and impact of the current findings. Methodologically, the application of multi-compartment diffusion imaging (NODDI) represents a significant advancement over traditional DTI. By decoupling the signal into neurite density (ICVF), fiber orientation (OD), and extracellular free water (ISOVF), we were able to move beyond the non-specific fractional anisotropy to identify the exact biological substrates of white matter decline. This granularity is critical for distinguishing between permanent structural erosion (neurite loss) and transient vascular shifts (free water), providing a level of mechanistic insight previously unavailable in DS research.

Furthermore, the integration of high-sensitivity inflammatory profiling, advanced neuroimaging, and cognitive metrics within a well-characterized DS cohort offers a powerful framework for mapping the preclinical window of AD. Given that the DS population represents a unique genetic model of AD, these findings provide a rare opportunity to examine how peripheral immune dysregulation may act as a modifiable driver of neurodegeneration. By identifying specific limbic pathways targeted by systemic inflammation, this work establishes a biological foundation for future longitudinal studies and potential early-intervention targets aimed at preserving cognitive reserve.

Despite these strengths, several methodological considerations should be noted when interpreting the present findings. The cross-sectional design of this study limits the ability to infer temporal or causal relationships between systemic inflammation, WM microstructure, and cognition. While the observed pattern is consistent with a model in which inflammation contributes to microstructural degeneration, longitudinal data are required to determine the directionality and progression of these associations over time. In particular, it remains unclear whether inflammatory processes precede WM changes or whether both reflect parallel downstream effects of underlying disease mechanisms.

Inflammatory markers were measured peripherally, which may not directly reflect central nervous system inflammatory processes. Although peripheral inflammation has been shown to influence brain structure and function through multiple pathways, including blood brain barrier signaling and neurovascular interactions (Beltran-Velasco & Clemente-Suárez, 2025) the extent to which circulating markers such as CRP and IL-6 capture neuroinflammatory activity remains an important consideration. Future studies integrating peripheral and central measures of inflammation such as cerebrospinal fluid or PET, would help clarify these relationships.

Although the use of NODDI provides increased specifically compared to conventional diffusion metrics, these measures remain indirect proxies of underlying microstructure. Metrics such as ICVF and OD are interpreted as reflecting neurite density and fiber organization, respectively, but may also be influenced by factors such as partial voluming effects and modeling assumptions. As such, while the observed patterns are consistent with neurite loss and microstructural disorganization, these interpretations should be made with appropriate caution.

While the inclusion of site as a covariate helps account for potential multi-site variability, residual differences in acquisition parameters or scanner characteristics may still influence diffusion measures. Similarly, although age was systematically examined and included in adjusted models, other unmeasured factors, such as vascular health, medication use, or comorbid conditions, may contribute to both inflammatory and WM variation.

Cognitive associations were modest and primarily limited to a single outcome (TMS), with no direct relationships observed between inflammation and cognition. While this pattern supports a model in which WM microstructure represents a more proximal determinant of cognitive performance, it also suggests that the current cognitive measures may not fully capture the domains most sensitive to inflammation-related brain changes. Additionally, the lack of significant mediation effects may reflect limited statistical power or the need to consider additional pathological processes, such as amyloid and tau accumulation, which were not assessed in the present study. However, the lack of formal mediation likely reflects the temporal lag between early microstructural erosion and the later emergence of overt cognitive impairment, suggesting that our cohort captures a critical preclinical window where inflammatory damage is occurring but has not yet reached the threshold for functional collapse.

In conclusion, this study demonstrates that systemic inflammation in DS is a biologically specific driver of neurite degeneration within AD-vulnerable limbic pathways, distinct from generalized brain aging. While inflammatory markers do not directly map onto cognitive scores, their robust association with white matter microstructure suggest inflammatory processes may still play an indirect role in the neurocognitive profile of DS. These findings identify the uncinate and cingulum as critical intersections between systemic immunity and structural decline, offering specific neurobiological targets for early intervention in the DS-AD continuum.

Supplemental

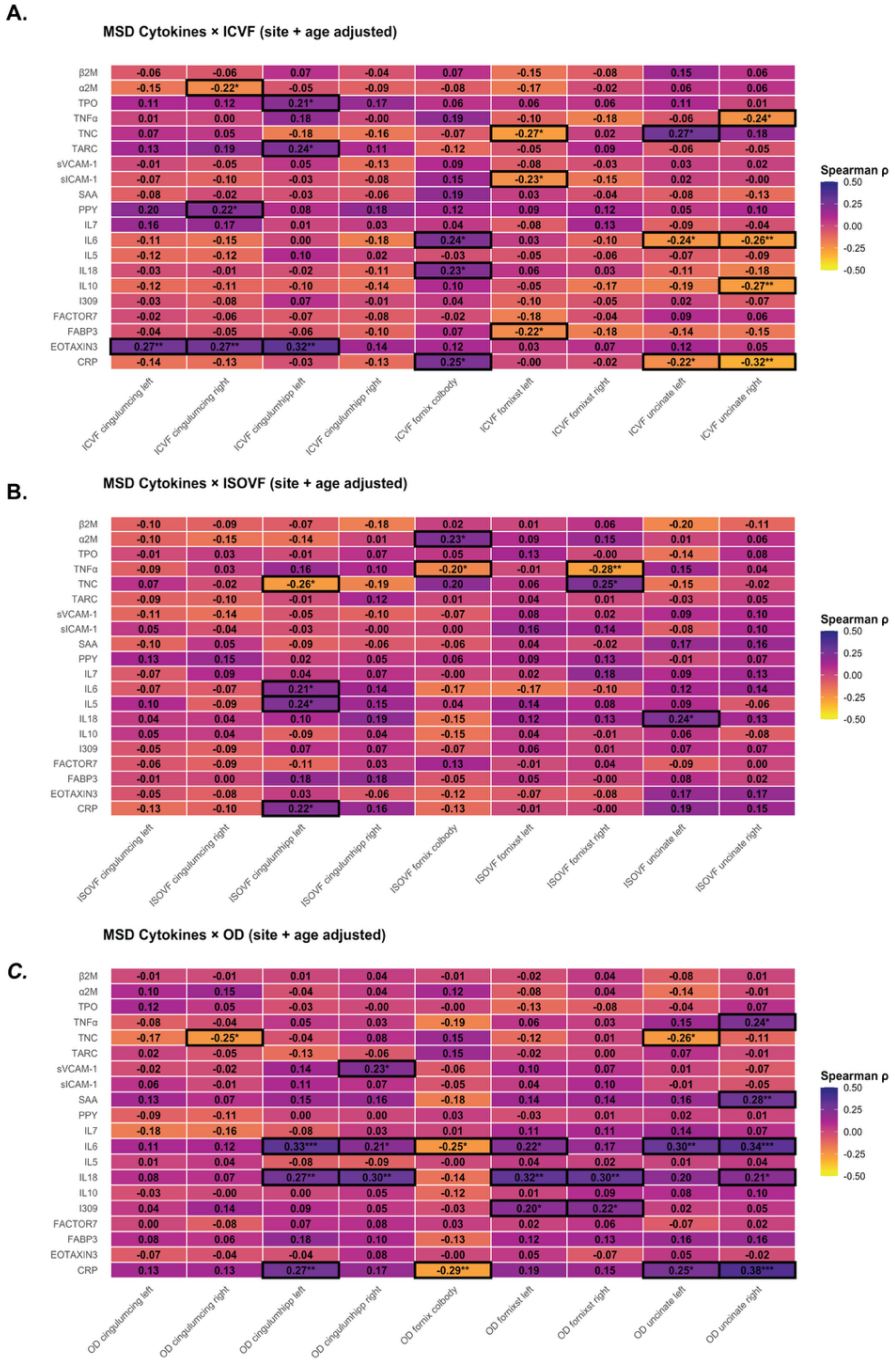


Figure 17 Age independent full cohort results

(A-C) *Heatmaps illustrating Spearman correlation coefficients (ρ) between circulating MSD cytokines and NODDI metrics of WM microstructure, including ICVF* ***(A),*** *ISOVF* ***(B),*** *OD* ***(C).*** *All associations are adjusted for site and age. Rows represent cytokines and columns represent white matter regions. Color scale reflects the magnitude and direction of correlations. Numerical values within each cell indicate Spearman ρ. Black outlines denote statistically significant associations following FDR correction ($p < 0.05$).*

Chapter 5: Synthesis and Conclusions

5.1 A systems level framework of White Matter Vulnerability

Alzheimer's disease (AD) is increasingly understood as a systems level disorder in which molecular pathology, large scale brain networks, and cognitive function are tightly interconnected. While traditional models have emphasized gray matter degeneration as the primary substrate of disease progression, emerging evidence suggests that white matter (WM) microstructure represents a critical and potentially earlier site of vulnerability. This dissertation aimed to investigate whether WM integrity, particularly within medial temporal lobe (MTL) pathways, serves as a sensitive and mechanistically informative link between systemic biological processes and cognitive decline.

Across three complementary studies, this work examined the role of advanced diffusion MRI, specifically Neurite Orientation Dispersion and Density Imaging (NODDI), in characterizing limbic WM microstructure associated with aging and AD-related contexts. In Chapter 2, we demonstrated that NODDI derived metrics provide enhanced sensitivity to AD pathology and cognitive performance compared to traditional diffusion tensor imaging (DTI). In particular, neurite density and fiber organization within MTL pathways, including the hippocampal cingulum and uncinate fasciculus, showed robust associations with tau pathology and memory performance, while conventional tensor metrics such as fractional anisotropy (FA) showed limited sensitivity. Importantly, mediation analyses revealed that WM microstructure, as indexed by neurite density, partially mediated the relationship between AD pathology and cognition, positioning WM as a mechanistic bridge between molecular and behavioral domains.

Building upon this foundation, Chapter 3 extended this framework by examining biological moderation of neuroinflammation, limbic WM, and cognition relationships. These findings

demonstrated that the coupling between systemic neuroinflammation and limbic WM microstructure is not uniform across individuals, but instead changes as a function of sex, with stronger associations observed in women. This suggests that biological context plays a critical role in shaping vulnerability to neuroinflammation related neurodegeneration.

Finally, Chapter 4 investigated these relationships in Down Syndrome (DS), a population characterized by lifelong immune dysregulation and elevated risk for early onset AD. In this context, systemic neuroinflammation was associated with spatially specific alterations in WM microstructure, particularly within limbic pathways such as the hippocampal cingulum and uncinate fasciculus. Notably, these associations were driven by reduction in neurite density and increases in orientation dispersion, rather than generalized increases in extracellular free water, suggesting that neuroinflammation related processes preferentially impact structural integrity rather than transient fluid shifts.

Taken together, this dissertation advances a unified framework in which WM microstructure serves as a sensitive and biologically meaningful substrate linking systemic processes, including neuroinflammation, to AD related pathology and cognitive decline. Rather than reflecting diffuse brain aging, these findings support a model of selective vulnerability within limbic WM networks that are central to memory function and early disease progression.

5.2 Integrating New Insights: A model of Selective Limbic White Matter Vulnerability

The findings across this dissertation converge on a central conceptual shift: systemic biological processes, particularly inflammation, do not exert uniform effects on the brain but instead act selectively on specific neural circuits that are inherently vulnerable to AD. This work supports a model of selective limbic white matter vulnerability, in which medial temporal

pathways serve as key sites where molecular pathology, systemic biology, and cognitive function intersect.

5.2.1 From Global Degeneration to Spatial Specificity

Historically, neuroinflammation and aging have often been conceptualized as diffuse processes leading to widespread brain degeneration (Adamu et al., 2024; W. Zhang et al., 2023). However, the present findings challenge this assumption by demonstrating that WM alterations are not uniformly distributed. Across the present series of studies, the strongest and most consistent effects were observed within limbic pathways, particularly the hippocampal cingulum, cingulum cingulate, and uncinate fasciculus. This spatial specificity was especially pronounced in the DS cohort, where systemic inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) were selectively associated with microstructural alterations in these pathways. Importantly, the inclusion of age as a covariate attenuated more diffusion associations, further reinforcing the interpretation that inflammation is not simply accelerating global aging but is instead targeting specific networks central to memory function.

5.2.2 Microstructural Mechanisms: Evidence for Neurite Degeneration and Disorganization

A key contribution of this work lies in the use of NODDI to disentangle distinct microstructural processes underlying WM alterations. While traditional interpretation of inflammation related brain changes often emphasize increases in extracellular water or edema, these present findings suggest a different primary mechanism (Pasternak et al., 2009). Across analyses, association with isotropic free water were largely attenuated after accounting for age, whereas effects on neurite density and fiber organization remained robust.

These patterns indicate that systemic neuroinflammation is more strongly associated with permanent neurite loss and microstructural disorganization than with transient increases in free water. Reductions in neurite density likely reflect axonal degeneration or reduced packing of fibers, while increased orientation dispersion suggests disruption in fiber coherence and organization. This distinction is critical, as it fundamentally shifts the interpretation of inflammation-related WM changes from transient or nonspecific processes to structural alterations indicative of neurite loss and network disruption, providing a plausible mechanistic link between systemic inflammation and cognitive decline.

5.2.3 Biological Context and Moderators of Vulnerability

The degree and pattern of WM vulnerability are shaped by biological context. In Chapter 3, sex differences emerged as an important moderator, with women showing stronger coupling between inflammation, WM microstructure, and memory performance. This finding suggests that sex-specific biological factors, potentially including hormonal influences or immune responses or immune response differences, may modulate susceptibility to inflammation related neurodegeneration. Similarly, the DS model demonstrates how lifelong immune dysregulation may amplify or unmask relationships between systemic inflammation and WM integrity that are more subtle in the general aging population. Whether driven by the sex-specific immune profiles in aging women or the genetic priming inherent to Trisomy 21, these findings indicate that neuroinflammation is not a uniform driver of white matter change, but a context dependent process shaped by an individual's biological milieu.

5.2.4 White Matter as a Mechanistic Bridge in Alzheimer's Disease

Finally, this work positions WM microstructure as a critical intermediate phenotype linking upstream biological processes to downstream cognitive outcomes. The mediation findings in Chapter 2 demonstrated that neurite density within the hippocampal cingulum partially mediated the relationships between AD pathology and memory performance, providing direct evidence that WM integrity is not merely a byproduct of disease but plays an active role in the pathway from pathology to cognitive impairment.

When considered alongside the inflammation findings from later chapters, this framework suggests a broader mechanistic model: systemic inflammation contributes to microstructural degeneration within limbic WM pathways, which in turn disrupts network connectivity and leads to cognitive decline. The convergence of findings across these contexts suggests that both lifetime exposure to inflammatory processes and intrinsic biological factors shape the degree and pattern of WM vulnerability.

5.3 Implications for Alzheimer's Disease and Biomarker Development

Building on this biological framework, the evidence of selective microstructural decay has important implications for the development of the next generation of neuroimaging biomarkers and how AD is classified and tracked in clinical settings. Traditionally, AD biomarker frameworks have focused on molecular pathology, including amyloid and tau, alongside measures of gray matter atrophy. However, the present work highlights white matter microstructure as a critical and previously underappreciated bridge linking systemic biology to cognitive decline. Within this context, the present findings provide structural evidence supporting the elevation of neurodegeneration (N) beyond gray matter atrophy alone, and more broadly suggest that

microstructural imaging markers could strengthen the role of neuroinflammation (I) component within the ATN framework.

Across the present series of studies, NODDI derived metrics provided enhanced sensitivity to disease relevant processes compared to conventional diffusion measures, enabling the differentiation of distinct microstructural features such as neurite density and orientation dispersion. These measures not only detached association with pathology and cognition but also revealed mechanistic pathways through which these relationships may operate. In particular, the identification of WM microstructure as a mediator between pathology and cognition supports its role as an intermediate phenotype that captures biologically meaningful aspects of disease progression.

Critically, these effects were not spatially uniform. WM alterations preferentially affected limbic pathways that are central to memory function and early AD vulnerability. This spatial specificity suggests that WM biomarkers may provide enhanced sensitivity for detecting early disease related changes, particularly in preclinical or at risk populations.

These findings have direct implications for existing biomarker frameworks, such as the ATN framework (Jack et al., 2018) which primarily captures molecular pathology and downstream structural atrophy. While recent efforts have proposed expanding this framework to incorporate vascular ("V") and inflammatory ("I") components **(figure 18)**, the role of microstructural white matter changes has not been fully integrated (Kobayashi et al., 2026). The present findings suggest that diffusion derived measures may capture an earlier stage of neurobiological alteration, reflecting subtle neurite loss and disorganization that precede overt neurodegeneration detectable with conventional structural imaging.

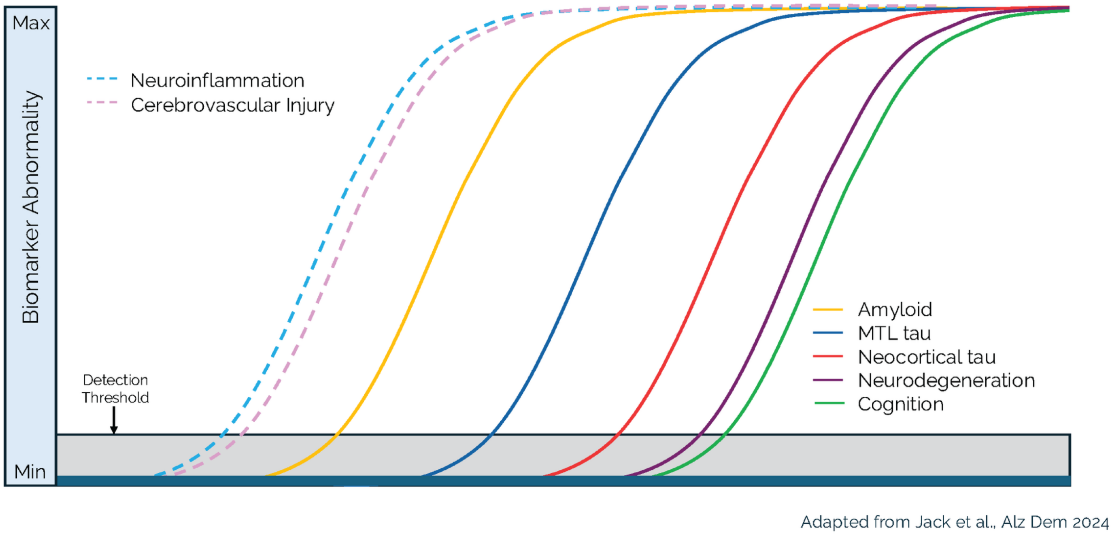


Figure 18 Temporal progression of AD related biomarkers across the disease continuum.

Schematic representation of the relative trajectories of AD related biomarkers as a function of disease progression. The y-axis reflects biomarker abnormality (from minimal to maximum), and the x-axis represents disease stage. Dashed lines indicate early changes in neuroinflammation and cerebrovascular injury. Solid curves depict the sequential emergence of amyloid (yellow), MTL tau (blue), neocortical tau (red), neurodegeneration (purple), and cognitive decline (green). The horizontal line denotes a theoretical detection threshold for biomarker abnormality. Adapted from (Jack et al., 2024).

Because these metrics provide sensitivity to disease-relevant processes compared to conventional measures (DTI), they offer a powerful complement to molecular imaging techniques. Moreover, the ability to capture distinct microstructural processes, such as neurite loss and disorganization, positions diffusion MRI as a promising tool for early detection (identifying early disease-related changes in preclinical or at-risk populations where global measures may fail), monitoring disease progression (capturing biologically meaningful structural remodeling over time), and therapeutic evaluation (serving as a sensitive outcome measure for clinical trials evaluating novel interventions targeting neuroinflammation and neurodegeneration).

5.4 Methodological Contributions and Considerations

This dissertation also makes several methodological contributions that are relevant to the broader fields of neuroimaging. First, the use of advanced diffusion modeling approaches, including NODDI, allowed for the decomposition of complex diffusion signals into biologically meaningful components. This represents a significant advancement over traditional diffusion tensor imaging, which provides limited specificity regarding underlying tissue architecture.

Second, the integration of multimodal data, including diffusion MRI, peripheral inflammatory markers, and cognitive measures, enabled a more comprehensive characterization of the relationships between systemic biology, brain structure, and behavior. The use of linear mixed effects models, with careful consideration of site and age effects, further strengthened the robustness and interpretability of the findings. Notably, the comparison of models with and without age adjustment provided important insights into the extent to which observed associations reflect inflammation specific processes versus generalized aging effects.

Third, this work emphasizes the importance of spatially resolved analyses. By focusing on region specific measures within anatomically defined medial temporal lobe pathways, rather than global summary metrics, this dissertation avoided the washout effects that often arise in whole brain analyses, where spatially localized signals are diluted by averaging across heterogeneous regions, enabling the identification of anatomically specific patterns of vulnerability.

Despite these strengths, several limitations should be acknowledged. The majority of analyses were cross-sectional, which limits the ability to make definitive causal inferences or characterize temporal dynamics. However, the use of mediation and moderation frameworks allowed for the testing of statistically directional relationships grounded in biological hypotheses, providing insight into potential mechanistic pathways linking inflammation, WM microstructure,

and cognition. While these approaches do not establish causality, they offer an important step toward identifying plausible intermediate processes that can be tested in future longitudinal studies and experimental designs.

Additionally, while peripheral inflammatory markers may not fully capture central nervous system immune processes, they nevertheless provide practical and scalable approaches to assessing systemic inflammatory states, which are increasingly recognized as key drivers of brain health. In the present work, these markers were interpreted in light of this broader systemic framework. Future studies integrating central measures of inflammation, such as cerebrospinal fluid or neuroimaging-based markers, will be important for further refining these relationships. Ongoing and future work aims to incorporate such approaches to enable a more direct characterization of neuroimmune processes and their relationship to WM integrity.

Finally, while advanced diffusion models improve biological specificity relative to conventional approaches, they remain indirect measures of tissue microstructure and rely on underlying model assumptions. Continued refinement and validation of these models will be critical, specifically in the context of neuroinflammation. This may include integration with complementary imaging modalities such as Arterial Spin Labeling (ASL) and FLAIR MRI to assess WM hyperintensities, as well as validation against histological measures in animal or postmortem models where causal manipulation and direct tissue characterization are possible.

Taken together, these challenges define a path forward for integrating microstructural imaging with emerging models of neuroinflammation and disease progression, while providing a clear roadmap for extending the present work and refining our understanding of these processes.

5.5 Future Directions: Toward a New Generation of Inflammation Sensitive Diffusion MRI

Building directly upon the methodological roadmaps outlined above, the findings of this dissertation point toward several promising directions for future research, particularly in the development of diffusion MRI approaches that are more directly sensitive to neuroinflammation processes.

5.5.1 Imaging Neuroinflammation Beyond Free Water

A key insight from this work is that inflammation related WM alterations are not primarily driven by increases in extracellular free water but instead reflect changes in neurite density and microstructural organization. While this dissertation used NODDI to identify the downstream effects on neurites, the next logical step is to utilize advanced models to bridge the gap between systemic markers and the primary cellular actors, microglia and astrocytes. Recent advances in diffusion modeling have demonstrated that the diffusion weighted MRI signal contains a signature of microglia and astrocyte morphology (Garcia-Hernandez et al., 2022). By using a multicompartment framework informed by glial biology **(figure 18)**, specific diffusion parameters can distinguish between microglial activation, astrocytic responses, and neuronal degeneration (Garcia-Hernandez et al., 2022). Notably, this new model is able to detect glial activation independently of neurodegeneration and to differentiate inflammation from demyelination, addressing a major limitation of conventional MRI approaches. As described in the model schematic **(figure 19A-B)** and validation experiments (**figure 20A-F**), distinct compartments representing cellular processes ("sticks") and cell bodies ("spheres") captured changes in glial morphology that were tightly correlated with histological measures (**figure 19B)**. These findings suggest that diffusion MRI can move beyond indirect proxies of inflammation toward more

specific, cell informed biomarkers. Integrating such models with NODDI derived measures may provide a more complete picture of how inflammation influences both cellular and network level brain organization.

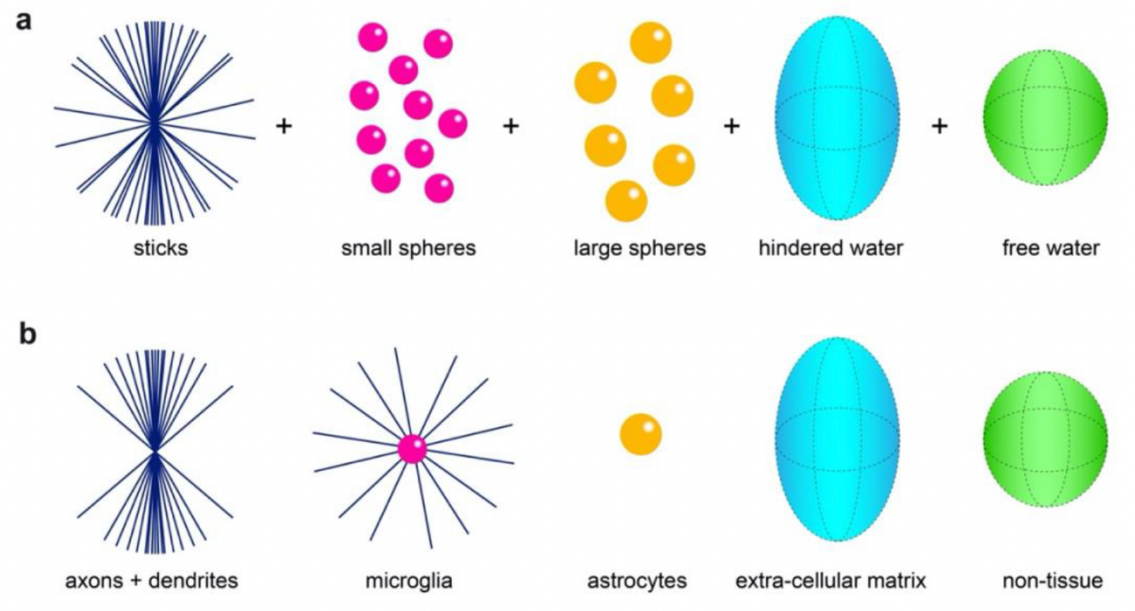


Figure 19 Schematic representation of the MCM tissue model

(A) *Schematic representation of the MCM tissue model comprising one compartment of water undergoing restricted diffusion in cylindric geometry (representing water trapped into cell ramifications) with a main orientation and a Watson dispersion term, two spherically restricted compartments, one extracellular space matrix, aligned with the main cylinder orientation and modelled as a tensor, and one compartment of water undergoing free diffusion.* ***(B)*** *The compartments defined in A are combined to visually represent the different cell types constituting the parenchyma in our model: microglia, astrocytes, neurons, extracellular space. Reproduced with permission from the publisher, American Association for the Advancement of Science* (Garcia-Hernandez et al., 2022).

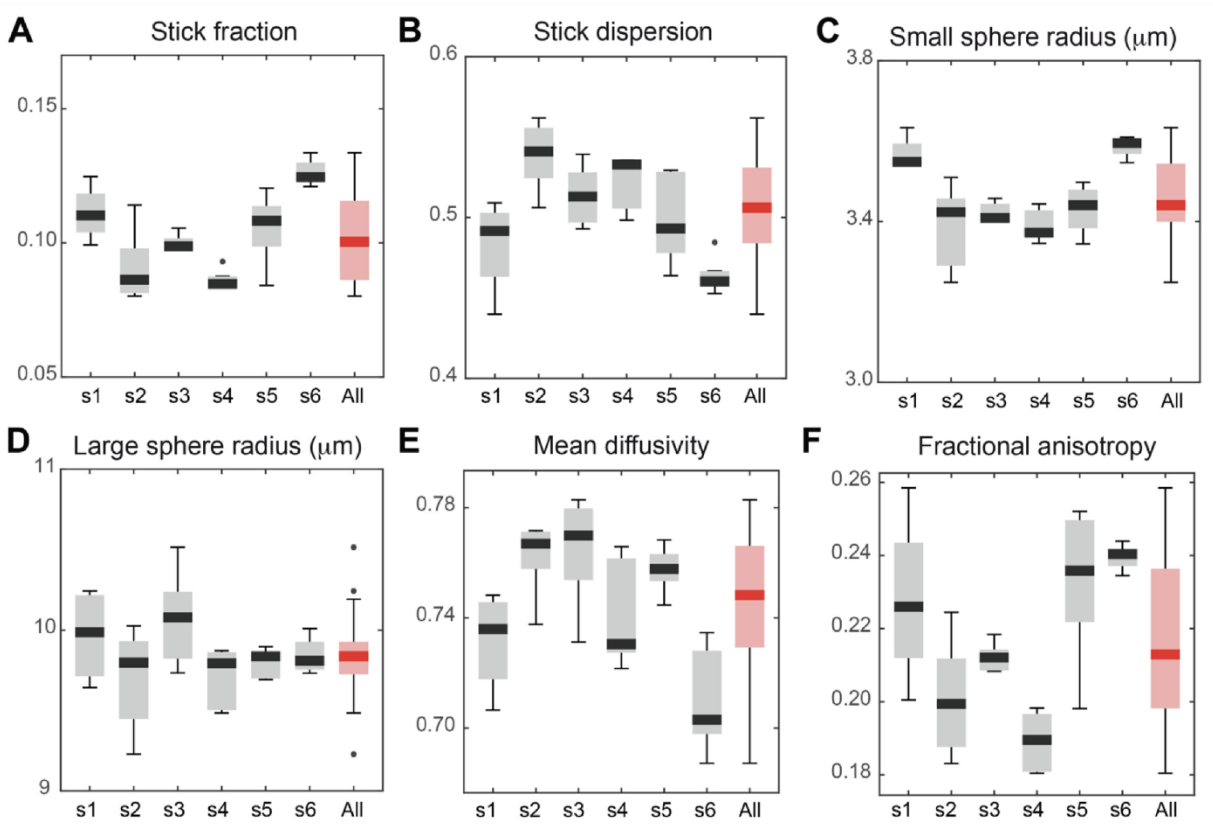


Figure 20 Feasibility of the framework translation to human

(A) *Boxplot of stick fraction as measured separately in the hippocampus of six subjects scanned five times (s1 to s6) and pooling all subjects together (red). The same is shown for the stick dispersion parameter* ***(B)****, small sphere radius* ***(C)****, large sphere radius* ***(D)****, mean diffusivity* ***(E)****, and fractional anisotropy* ***(F).*** *Reproduced with permission from the publisher, American Association for the Advancement of Science* (Garcia-Hernandez et al., 2022)***.***

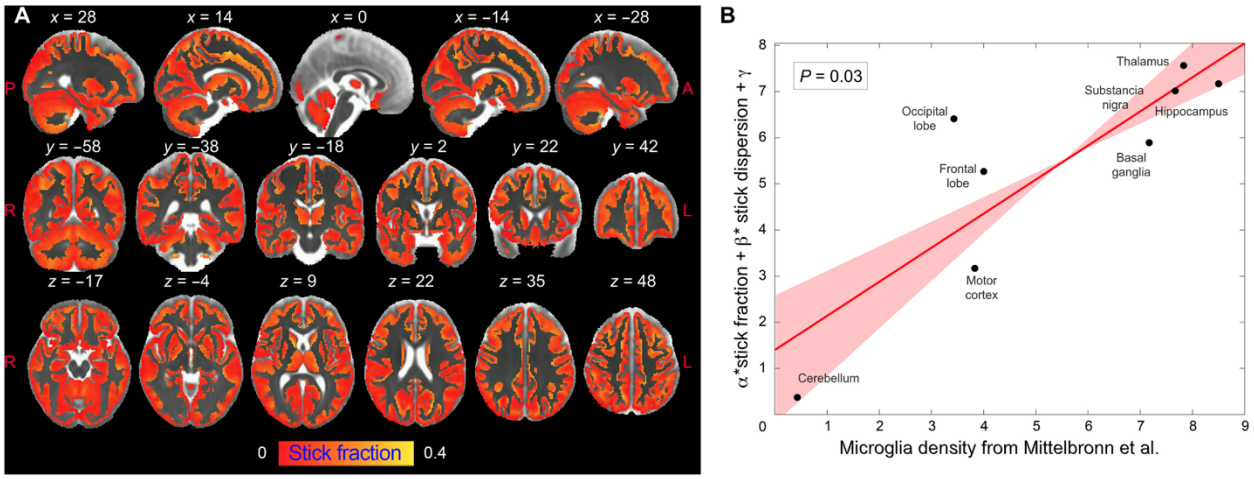


Figure 21 Correlation between the stick fraction and microglia density in the human brain.

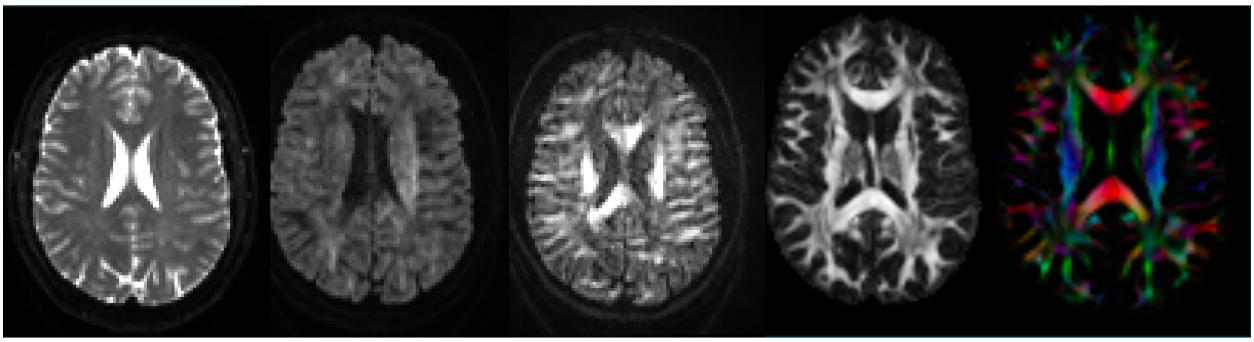
(A) *Stick fraction according to the MCM normalized to the brain template masked for gray matter tissue, and averaged across subjects.* ***(B)*** *Multiple linear regression using stick fraction and dispersion to explain microglia density measured using histological staining of postmortem human tissue in eight gray matter regions (hippocampus, cerebellum, substantia nigra, basal ganglia, thalamus, motor, frontal, and occipital cortices) as reported in (Mittelbronn et al., 2001). Regression confidence intervals are calculated using bootstrap. Reproduced with permission from the publisher, American Association for the Advancement of Science* (Garcia-Hernandez et al., 2022).

5.5.2 The Role of High-Gradient Diffusion MRI

Another critical frontier in diffusion imaging is the use of ultra-strong gradient systems, such as the Connectome scanner and more recently the Cima.X systems, which enable improved sensitivity to small scale tissue features. High-gradient diffusion MRI allows for shorter diffusion times and higher b-values, enhancing the ability to probe restricted diffusion and resolve smaller cellular compartments.

Recent advances in high-gradient hardware, including the emerging Cima.X systems, further extend these capabilities by enabling rise time in diffusion gradients to reach speeds allowing for improved characterization of complex tissue architecture. Figure 22 illustrated representative high-gradient diffusion imaging acquired on a T3 Cima.X system using a short diffusion time sequence (17ms) that has previously been demonstrated primarily on specialized Connectome platforms. These findings highlight the potential for translating advanced diffusion

approaches previously restricted to ultra-high performance research systems into a more clinically accessible system. Access to shorter rise times leading to shorter diffusion times may be particularly important for inflammation selective diffusion models as they increase sensitivity to smaller spatial scales and more restricted cellular environments. In combination with biologically informed multicompartment approaches, these advances could improve the ability to characterize glial morphology and other cellular scale tissue properties in vivo.



With Tom Liu, David Berry, Ryan Barnes (UCSD)

Figure 22 **Implementation of high-gradient diffusion MRI acquired on a 3T Cima.X system.**

Representative diffusion imaging acquired using a short diffusion-time (17 ms) high-gradient sequence implemented on a 3T Cima.X platform. Panels illustrate diffusion-weighted image contrast and derived fiber orientation information from the acquisition. This sequence was adapted from methodologies previously demonstrated on specialized 7T Connectome systems.

Recent studies using high-gradient diffusion systems further support this framework, demonstrating improved estimation of microstructural parameters such as cell size and compartment specific diffusion properties (Lee et al., 2024; Ramos-Llordén et al., 2026). In the context of neuroinflammation, this increased sensitivity may be particularly valuable for detecting subtle changes in glial morphology and density that are not accessible with standard clinical scanners. The integration of high-gradient diffusion MRI with biologically informed models represents a promising avenue for advancing inflammation imaging. For example, combining high-gradient acquisitions with multicompartment models of glial morphology could enable more precise quantification of microglial proliferations, astrocyte hypertrophy, and other hallmarks of neuroinflammatory processes.

5.5.3 Toward Multimodal and Longitudinal Models of Disease

Future work should also focus on integrating diffusion MRI with other imaging modalities to better capture the complex interplay between inflammation, pathology and neurodegeneration. Combining diffusion measures with positron emission tomography (PET) markers of amyloid, tau, and neuroinflammation as well as vascular-sensitive imaging approaches, could provide a more comprehensive understanding of disease mechanisms.

Longitudinal studies will be particularly important for determining whether inflammation related changes in WM microstructure precede, accompany, or follow the accumulation of AD pathology. Additionally, incorporating repeated measures of systemic inflammation over time may help clarify how chronic immune activation contributes to disease progression and individual variability in disease trajectories.

These approaches also provide a foundation for advancing precision medicine in AD. Multimodal and longitudinal data can be leveraged to identify biologically meaningful subtypes of individuals who are most likely to benefit from specific interventions. In this context, diffusion derived measures of WM microstructure may serve as sensitive biomarkers for detecting early treatment effects and monitoring disease modification over time.

Importantly, integrating these approaches into clinical trial design could enable more targeted and efficient studies, including the use of biomarker-based enrichment strategies to select participants with specific biological profiles, as well as the incorporation of microstructural imaging metrics as intermediate outcome measures. Together, these advances may support the development of more personalized therapeutic strategies aimed at modifying inflammation-related pathways in AD.

5.6 Closing Thoughts

This dissertation advances a framework where WM microstructure serves as a central link between systemic biology and cognitive function in aging and Alzheimer's disease. By leveraging advanced diffusion MRI techniques, this work demonstrates that WM alterations are not simply a downstream consequence of neurodegeneration but instead reflect biologically meaningful processes that may contribute directly to disease progression. Importantly, these findings challenge the traditional view of neuroinflammation as a diffuse and nonspecific process. Instead, they support a model in which inflammation acts selectively on limbic white matter pathways, driving microstructural degeneration within networks that are both critical for memory and particularly vulnerable in AD.

Looking forward, continued advances in diffusion MRI, including high-gradient systems and cell-specific modeling approaches, offer the potential to transform our ability to image neuroinflammation in vivo. By integrating these methods with multimodal and longitudinal frameworks, future research may enable earlier detection of disease, improved characterization of individual risk, and the development of targeted therapeutic strategies.

Ultimately, understanding how systemic inflammation shapes brain microstructure represents a critical step toward bridging the gap between molecular pathology and cognitive decline, and developing more effective approaches for preventing and treating Alzheimer's disease. By resolving the microstructural signatures of neuroinflammation, we move closer to a precision-medicine approach that recognizes Alzheimer's not just as a disease of plaques and tangles, but as a complex, systemic failure of neural resilience.

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