NCAI Canada
Dr. Ahmad Farooq
Semester 2024-2025

KNN graph – Inspired by Marcus Volg

Research – fMRI and Amyloid PET Common Factors

Phase 1: `Literature Review & Theoretical Foundation`

Zainab Jamil

November 03, 2025

Table of Contents

1 – Summarize the key fMRI metrics relevant to AD

1.1 – Functional Connectivity (FC)

The correlations between spatially remote neurophysiological events. In neuroimaging, this typically refers to a temporal correlation between regional fluctuations in cerebral blood flow or BOLD signal.

1.1.1 – Role of FC in AD :

crucial for understanding cognitive decline and is being explored as a biomarker for early diagnosis and monitoring disease progression. In Alzheimer's, there are often changes like reduced connectivity within brain networks and altered patterns of connectivity, which are linked to specific cognitive deficits, such as memory, executive control, and visuospatial impairments. Studies using methods like resting-state fMRI and EEG show that these altered connections can predict cognitive symptoms and may provide targets for potential future therapies.

1.2 – DMN

The Default Mode Network (DMN) is a network of interconnected brain regions that is most active when a person is not focused on the outside world and is instead engaged in internally-focused thoughts, such as self-reflection, daydreaming, and recalling memories. It is also active during quiet wakefulness and is considered the "default" mode because it is suspended when the brain needs to focus on external, goal-directed tasks. The DMN is crucial for cognition and is implicated in conditions like depression, where there is a failure to suppress its activity appropriately.

1.2.1 – FC within DMN

Functional connectivity within the default mode network (DMN) is a promising biomarker for Alzheimer's disease (AD), characterized by reduced connectivity in key regions like the posterior cingulate cortex and precuneus. This reduced connectivity is associated with AD pathology, including amyloid-beta and tau deposition, and can predict future cognitive decline in cognitively unimpaired individuals. While studies show promising results at a group level, current static measurements lack the sensitivity for standalone use. Still, dynamic and subcortical DMN analyses show potential for early detection and monitoring.

==Resting-state networks (RSNs) Resting-state networks (RSNs) are used as a biomarker for Alzheimer's disease (AD) by measuring altered functional connectivity in the brain during rest using techniques like resting-state functional magnetic resonance imaging (rs-fMRI). The most significant finding is a reduced functional connectivity within the default mode network (DMN), particularly in the posterior regions like the posterior cingulate cortex and precuneus. These functional changes can appear even before cognitive symptoms develop, suggesting that rs-fMRI is a promising, non-invasive tool for early detection and tracking disease progression.

1.2.2 – 1. Degree Centrality

Degree centrality is a graph metric used as a biomarker for Alzheimer's disease (AD) because it measures brain network connectivity, and its alterations can indicate early stages of the disease. Specifically, studies show that individuals with AD or mild cognitive impairment (MCI) have abnormal degree centrality values, such as decreased connectivity in regions like the left inferior temporal gyrus and increased connectivity in areas like the right fusiform gyrus. These changes can be detected using functional magnetic resonance imaging (fMRI) and may precede the development of more severe clinical symptoms, making it a potentially useful tool for early diagnosis and monitoring

1.2.3 – Network Hubness

Network hubness refers to the degeneration of highly connected brain regions, known as hubs, and serves as a biomarker for Alzheimer's disease (AD) because these hubs are selectively and severely affected in the disease. As AD progresses, these crucial hubs experience increased amyloid-beta deposition, regional atrophy, and functional connectivity dysfunction, which can be detected through imaging

techniques. The disruption of these central nodes is directly correlated with cognitive decline and can be a very early indicator of AD, even preceding other pathological markers

1.2.4 – Graph Theory Measures

Graph theory measures can serve as biomarkers for Alzheimer's by quantifying the disruption of brain network topology, showing that patients with AD have a more random and disconnected network compared to healthy individuals. Key metrics include a longer characteristic path length, lower global efficiency, and decreased clustering coefficient in AD patients, indicating that the brain's functional and structural connections are less integrated and more disorganized.

1.3 – Amplitude of Low Frequency Fluctuations (ALFF)

Amplitude of Low Frequency Fluctuations (ALFF) and fractional Amplitude of Low Frequency Fluctuations (f/ALFF) are neuroimaging methods used to measure spontaneous fluctuations in BOLD-fMRI signal intensity for a given region in the resting brain. Electrophysiological studies suggest that low-frequency oscillations arise from spontaneous neuronal activity. Though ALFFs have been researched extensively in fMRI-based theoretical models of brain function, their actual significance is still unknown

1.4 – regional homogeneity (ReHo)

Regional Homogeneity (ReHo) is a method used in resting-state functional MRI (rs-fMRI) to measure the local coherence of spontaneous brain activity. It works by calculating the similarity of a voxel's blood oxygen level-dependent (BOLD) time series to the time series of its nearest neighbors, providing insight into local functional connectivity. A higher ReHo value indicates greater similarity, suggesting strong local synchronization of neuronal activity.

1.5 – The most relevant metrics to AD :

TODO Functional Connectivity

AD is characterized by error communication between brain zones, especially those related to memory and cognition. FC in DMN is very linked to episodic memory, which is what most people think of as memory, and includes information about recent or past events and experiences, and self-referential thinking, which is the cognitive process of relating information to oneself, such as using your own experiences, beliefs, and self-concept as a filter to interpret the world. In addition, changes in FC appear before major structural atrophy, making it a sensitive early biomarker.

TODO Amplitude of Low-Frequency Fluctuations (ALFF) ALF reflects automatic neuronal activity in resting-state networks, and in AD, reduced ALFF in DMN regions consists to functional hypoactivity, while irregular increases may reflect compensatory hyperactivity. This metric helps capture early functional changes that are not visible structurally.

TODO Graph Networks It shows widespread networks' disorganisation. Provide a whole-brain view of functional impairment, beyond specific regions.

2 – Amyloid PET Quantification, Accumulation, Scan Interpretation

2.1 – Types of Amyloid PET :

Static Amyloid PET: Static imaging provides a single, snapshot measure (often the standard for clinical diagnosis).

Dynamic Amyloid PET: Dynamic imaging provides more detailed kinetic data over time, which is often used for research or specific quantification.

`Quantification` of static amyloid PET scans can be performed using software packages to calculate both regional and composite levels of amyloid burden.

2.2 – Standardised uptake value ratio

The most widely used measure for quantifying amyloid burden is the SUVr. It is a nuclear medicine term, used in positron emission tomography (PET) as well as in modern calibrated single photon emission tomography (SPECT) imaging for a semiquantitative analysis. Its use is particularly common in the analysis of fluorodeoxyglucose images of cancer patients. It is a simplified method based on computing the ratio of tracer uptake between an image-derived radioactivity concentration, cimg, and the whole body concentration of the injected radioactivity cinj. It can also be used with other PET agents, especially when no arterial input function is available for more detailed pharmacokinetic modeling. Otherwise, measures like the fractional uptake rate (FUR) or parameters from more advanced pharmacokinetic modeling may be preferable.

2.3 – Centiloid scaling

a standardized quantitative scale used for interpreting amyloid positron emission tomography (PET) scans, primarily for Alzheimer's disease.

2.4 – Reference-based z-scores :

Reference-based Z-scores in Alzheimer's disease are a way to standardize and compare an individual's cognitive or biomarker data against a reference group of healthy individuals, allowing for a more objective measure of impairment.

2.5 – Where does amyloid accumulate first in Brain Regions?

Based on the **Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity** research paper, it shows that Aβ accumulation preferentially starts in the `precuneus, medial orbitofrontal, and posterior cingulate cortices` , i.e., several of the core regions of the default mode network (DMN). The results suggest that Aβ fibrils start to accumulate predominantly within certain parts of the DMN in preclinical AD and already then affect brain connectivity.

From the **Early Brain Amyloid Accumulation at PET in Military Instructors Exposed to Subconcussive Blast Injuries** research , they found that Amyloid accumulates first in the `inferomedial frontal lobe, precuneus, blast-exposed individuals` none observed in controls.

2.6 – How a "positive" or "negative" scan is defined

1. A scan is considered "positive" if the SUVR in the target brain regions exceeds a pre-determined threshold, indicating abnormal levels of amyloid plaque accumulation.
2. A scan is "negative" if the SUVR is below this threshold.
3. While visual interpretation is still the standard in clinical practice, quantitative methods are often used in research. A common threshold for some tracers (like PiB) is an SUVR of 1.5 to signify a positive scan, though thresholds can vary depending on the specific tracer and analysis method.

3 – Linking fMRI Metrics (DMN Integrity) with Global/Regional Amyloid Burden: Does Amyloid Disrupt Networks or Do Networks Accelerate Amyloid Deposition?

Amyloid Beta deposition is detected with Amyloid PET, disrupting the Default Mode Network (DMN), which includes: Posterior cingulate cortex (PPC) and precuneus; a part of PPC, medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex, and hippocampus. These areas are strongly interconnected and active during rest and memory retrieval,s and other activities in which the brain is in a rest state.

Amyloid accumulation, specifically in association cortices like precuneus, posterior cingulate, and lateral temporal areas, leads to a decrease in the functional synchrony between these regions, in addition to the communication between posterior and anterior brain regions tends to be weak.

However, not all studies show only decreased connectivity; sometimes, increased connectivity is seen in other networks, like the frontoparietal or salience networks. This can be explained as the brain tries to recruit extra resources. The relationship between amyloid and connectivity depends on the disease stage, the presence of tau pathology, and individual variability.

4 – Find and summarize research papers that have already analyzed paired fMRI and Amyloid PET data. What were their main findings and methodological approaches

TODO

4.1 – Predicting brain amyloid-β PET phenotypes with graph convolutional networks based on functional MRI and multi-level functional connectivity Research paper

1. **Main Findings :**

Using non-invasive functional magnetic resonance imaging (fMRI) to predict Aβ-PET phenotypes in the AD continuum with graph learning on brain networks with high accuracy (78.8%), suggesting fMRI as a potential surrogate for PET in amyloid detection. Combining longitudinal amyloid PET and MRI data enhances the prediction of conversion from mild cognitive impairment (MCI) to AD, with integrated shape features providing the highest predictive accuracy. Dual PET-fMRI studies show that microglial activation (neuroinflammation) in the posterior cingulate cortex is associated with increased task-related brain activity in AD, independent of amyloid load PET-MRI methods, especially those using deep learning for segmentation, outperform PET-only approaches in predicting amyloid positivity, particularly in non-demented adults.

1. **Methodological Approaches :**

Deep Learning and Graph Convolutional Networks: Used to predict amyloid PET grades from fMRI-derived functional connectivity networks, often employing clustering and classification techniques Longitudinal Multimodal Analysis: Integration of PET and MRI biomarkers over time, with quantitative measures such as SUVR, brain atrophy indices, and shape features, analyzed using receiver operating characteristic curves. Spatially Constrained ICA: fMRI components serve as spatial priors to guide the estimation of PET connectomes, enabling direct comparison of network-level patterns across modalities. Dual-Tracer PET-fMRI: Simultaneous acquisition of amyloid and neuroinflammation PET tracers with fMRI during cognitive tasks to assess the interplay between pathology and brain function. Automated Quantification and Segmentation: PET-MRI methods utilize deep learning-based segmentation for more anatomically precise SUVR calculation and amyloid status prediction. Image Synthesis Models: Convolutional neural networks and joint diffusion attention models are used to generate PET-like images from MRI or low-dose PET, validated against full-dose PET images

TODO

4.2 – Longitudinal Analysis of Amyloid PET and Brain MRI for Predicting Conversion from Mild Cognitive Impairment to Alzheimer's Disease: Findings from the ADNI Cohort Research paper

1. **Methods :**

- Included 180 patients with MCI from the Alzheimer's Disease Neuroimaging Initiative, with baseline and 2-year follow-up scans obtained using F-18 florbetapir PET and MRI.
- Patients were categorized as converters (progressing to AD) or nonconverters based on a 6-year follow-up.
- Quantitative analyses included the calculation of amyloid burden using SUVR, brain amyloid smoothing scores (BASSs), brain atrophy indices (BAIs), and their integration into shape features.
- Longitudinal changes and receiver operating characteristic analyses assessed the predictive power of these biomarkers.

2. **Main Findings :**
   - Among 180 patients with MCI, 76 (42.2%) were converters, who exhibited significantly higher baseline and 2-year follow-up values for SUVR, BASS, BAI, and shape features than nonconverters ($p < 0.001$).
   - Shape features demonstrated the highest predictive accuracy for conversion, with areas under the curve of 0.891 at baseline and 0.898 at 2 years.
   - Percent change analyses revealed significant increases in brain atrophy; amyloid deposition changes showed a paradoxical decrease in converters.
   - Strong associations were observed between longitudinal changes in shape features and neuropsychological test results.

TODO

4.3 – A Comparative Analysis of Two Automated Quantification Methods for Regional Cerebral Amyloid Retention: PET-Only and PET-and-MRI-Based Methods research Paper

1. **Methodologies:**
   - A large sample of 1180 participants in the Catholic Aging Brain Imaging (CABI) database was analyzed to calculate the regional standardized uptake value ratio (SUVR) using both methods.
   - The logistic regression models were employed to assess the discriminability of amyloid-positive and negative groups through 10-fold cross-validation and area under the receiver operating characteristic (AUROC) metrics.
   - The parietal, frontal, and cingulate regions importantly contributed to the prediction.
2. **Main Findings:**
   - The two methods showed a high correlation in calculating SUVRs, but the PET-MRI method, incorporating MRI data for anatomical accuracy, demonstrated superior performance in predicting amyloid-positivity.
   - They compared the two established pieces of quantification software and demonstrated that PET-MRI methods with a pre-trained deep learning model could have a superior ability to identify Aβ-positivity.
   - The parietal, frontal, and cingulate areas were important to predict Aβ-positivity, especially in non-demented adults.
   - To detect the early AD continuum and intervene promptly, using the PET-MRI method would be beneficial to efficiently and accurately quantify Aβ accumulation in these regions.

TODO

4.4 – MRI-based Deep Learning Assessment of Amyloid, Tau, and Neurodegeneration Biomarker Status across the Alzheimer's Disease Spectrum

1. **Methodologies :**
   - MRI and PET data were retrospectively collected from the Alzheimer's Disease Imaging Initiative.
   - PET scans were paired with MRI scans acquired within 30 days, from August 2005 to September 2020.
   - Pairs were randomly split into subsets as follows: 70% for training, 10% for validation, and 20% for final testing.
   - A bimodal Gaussian mixture model was used to threshold PET scans into positive and negative labels. MRI data were fed into a convolutional neural network to generate imaging features.
   - Combined, these features in a logistic regression model with patient demographics, APOE gene status, cognitive scores, hippocampal volumes, and clinical diagnoses to classify each ATN biomarker component as positive or negative.
   - Area under the receiver operating characteristic curve (AUC) analysis was used for model evaluation.
2. **Main Findings :**

There were 2099 amyloid, 557 tau, and 2768 FDG PET and MRI pairs. Model AUCs for the test set were as follows: amyloid, 0.79 (95% CI: 0.74, 0.83); tau, 0.73 (95% CI: 0.58, 0.86); and neurodegeneration, 0.86 (95% CI: 0.83, 0.89). Within the networks, high gradients were present in key temporal, parietal, frontal, and occipital cortical regions. Model coefficients for cognitive scores, hippocampal volumes, and APOE status were highest.

5 – Bibliographie

Sheline, Yvette I., and Marcus E. Raichle. “Resting State Functional Connectivity in Preclinical Alzheimer’s Disease.” Biological Psychiatry, vol. 74, no. 5, Sept. 2013, pp. 340–347, https://doi.org/10.1016/j.biopsych.2012.11.028.

ScienceDirect. “Functional Connectivity - an Overview | ScienceDirect Topics.” Sciencedirect.com, 2016, www.sciencedirect.com/topics/medicine-and-dentistry/functional-connectivity.

Xiong, Jing, et al. “Altered Brain Network Centrality in Patients with Mild Cognitive Impairment: An FMRI Study Using a Voxel-Wise Degree Centrality Approach.” Aging, vol. 13, no. 11, 9 June 2021, pp. 15491–15500, https://doi.org/10.18632/aging.203105. Accessed 28 Dec. 2022.

Cañete-Massé, Cristina, et al. “Abnormal Degree Centrality and Functional Connectivity in down Syndrome: A Resting-State FMRI Study.” International Journal of Clinical and Health Psychology, vol. 23, no. 1, 6 Oct. 2022, pp. 100341–100341, https://doi.org/10.1016/j.ijchp.2022.100341. Accessed 4 May 2025.

Yu, Meichen, et al. “Selective Impairment of Hippocampus and Posterior Hub Areas in Alzheimer’s Disease: An MEG-Based Multiplex Network Study.” Brain, vol. 140, no. 5, 16 Mar. 2017, pp. 1466–1485, academic.oup.com/brain/article/140/5/1466/3072777?login=true, https://doi.org/10.1093/brain/awx050.

Brier, Matthew R., et al. “Functional Connectivity and Graph Theory in Preclinical Alzheimer’s Disease.” Neurobiology of Aging, vol. 35, no. 4, Apr. 2014, pp. 757–768, https://doi.org/10.1016/j.neurobiolaging.2013.10.081. Accessed 2 Feb. 2020.

Sharma, Rakhi, and Shiv Dutt Joshi. “Graph Theoretical Measures for Alzheimer’s, MCI, and Normal Controls: A Comparative Study Using MRI Data.” Annals of Neurosciences, vol. 32, no. 1, 1 Sept. 2023, pp. 21–28, https://doi.org/10.1177/09727531231186503. Accessed 28 Mar. 2025.

Cordes, D., et al. “Frequencies Contributing to Functional Connectivity in the Cerebral Cortex in “Resting-State” Data.” AJNR. American Journal of Neuroradiology, vol. 22, no. 7, 1 Aug. 2001, pp. 1326–1333, pubmed.ncbi.nlm.nih.gov/11498421/.

Adhikari, Bhim M, et al. “Cerebral Blood Flow and Cardiovascular Risk Effects on Resting Brain Regional Homogeneity.” Biological Psychiatry, vol. 91, no. 10, 15 Nov. 2022. UK Biobank (UKBB).

University of California. “Memory.” Memory and Aging Center, 2025, memory.ucsf.edu/brain-health/memory.

Nejad, Ayna Baladi, et al. “Self-Referential Processing, Rumination, and Cortical Midline Structures in Major Depression.” Frontiers in Human Neuroscience, vol. 7, no. 666, 2013, https://doi.org/10.3389/fnhum.2013.00666.

Ayaz A, Nisar I, Muhammad A, Ahmed K, Chand P, Jehan F. Structural Changes in the Brain on Magnetic Resonance Imaging in Malnourished Children: A Scoping Review of the Literature. Pediatr Neurol. 2023 Dec;149:151-158. doi: 10.1016/j.pediatrneurol.2023.08.020. Epub 2023 Aug 29. PMID: 37890309.

Sarver, Dustin E., et al. “Hyperactivity in Attention-Deficit/Hyperactivity Disorder (ADHD): Impairing Deficit or Compensatory Behavior?” Journal of Abnormal Child Psychology, vol. 43, no. 7, 12 Apr. 2015, pp. 1219–1232, link.springer.com/article/10.1007/s10802-015-0011-1, https://doi.org/10.1007/s10802-015-0011-1.

Pemberton, Hugh G., et al. “Quantification of Amyloid PET for Future Clinical Use: A State-of-The-Art Review.” European Journal of Nuclear Medicine and Molecular Imaging, vol. 49, no. 10, 7 Apr. 2022, pp. 3508–3528, www.ncbi.nlm.nih.gov/pmc/articles/PMC9308604/, https://doi.org/10.1007/s00259-022-05784-y.

Wikipedia Contributors. “Standardized Uptake Value.” Wikipedia, Wikimedia Foundation, 4 Oct. 2025, en.wikipedia.org/wiki/Standardized_uptake_value.

Palmqvist, Sebastian, et al. “Earliest Accumulation of β-Amyloid Occurs within the Default-Mode Network and Concurrently Affects Brain Connectivity.” Nature Communications, vol. 8, no. 1, 31 Oct. 2017, https://doi.org/10.1038/s41467-017-01150-x.

Leiva-Salinas, Carlos, et al. “Early Brain Amyloid Accumulation at PET in Military Instructors Exposed to Subconcussive Blast Injuries.” Radiology, vol. 307, no. 5, 1 June 2023, https://doi.org/10.1148/radiol.221608.

Ingala, Silvia, et al. “Amyloid-Driven Disruption of Default Mode Network Connectivity in Cognitively Healthy Individuals.” Brain Communications, vol. 3, no. 4, 2021, p. fcab201, pubmed.ncbi.nlm.nih.gov/34617016/, https://doi.org/10.1093/braincomms/fcab201. Accessed 11 Dec. 2022.

Kim, Do-Hoon. “Longitudinal Analysis of Amyloid PET and Brain MRI for Predicting Conversion from Mild Cognitive Impairment to Alzheimer’s Disease: Findings from the ADNI Cohort.” Tomography, vol. 11, no. 3, 19 Mar. 2025, p. 37, https://doi.org/10.3390/tomography11030037. Accessed 28 Apr. 2025.

Kim, Sunghwan, et al. “A Comparative Analysis of Two Automated Quantification Methods for Regional Cerebral Amyloid Retention: PET-Only and PET-And-MRI-Based Methods.” International Journal of Molecular Sciences, vol. 25, no. 14, 12 July 2024, pp. 7649–7649, www.mdpi.com/1422-0067/25/14/7649, https://doi.org/10.3390/ijms25147649. Accessed 3 Nov. 2025.

Lew, Christopher O, et al. “MRI-Based Deep Learning Assessment of Amyloid, Tau, and Neurodegeneration Biomarker Status across the Alzheimer Disease Spectrum.” Radiology, vol. 309, no. 1, 1 Oct. 2023, https://doi.org/10.1148/radiol.222441.