

ESPRIT SCHOOL OF ENGINEERING

AI Project · CBL Method · 2025–2026

Brain Understanding

INVESTIGATE PHASE REPORT

ESSENTIAL QUESTION

“What if the brain holds more information than we ever learned to see?”



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Aligned with UN SDGs: Goal 3 – Good Health & Well-being · Goal 4 – Quality Education · Goal 9 – Innovation & Infrastructure

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1 Introduction

Neurological disorders often involve subtle, distributed, or early-stage brain alterations that escape routine visual inspection. MRIs may appear non-specific, functional disruptions may precede anatomical degeneration, and physiological dysregulation may remain undetected without quantitative modeling.

The central challenge of this project is therefore making the invisible visible in brain imaging. Across multiple investigative axes, we examine how artificial intelligence and advanced neuroimaging methods can extract meaningful, interpretable biomarkers from brain imaging.

Each axis explores a different dimension of brain organization, yet all converge toward a unified objective: to transform hidden neural patterns into structured, clinically interpretable evidence.

1.1 Investigative Framework

This Investigate Phase follows the CBL methodology and is structured around seven complementary axes exploring structural, functional, physiological, and network-level brain organization. Each axis addresses a different dimension of the central challenge while maintaining alignment with the essential question.

2 Axis 1 – MRI-based correlation of cognitive decline in Alzheimer's disease and vascular dementia

Alzheimer's disease and vascular dementia both cause cognitive decline, often through overlapping brain alterations. This axis examines how structural MRI markers of atrophy and vascular injury relate directly to cognitive performance in each condition.

2.1 Guiding Questions

WHO

- Who are the affected populations?
- Who is most at risk of rapid progression or loss of independence?
- Who are the key stakeholders?
- Who ensures governance, compliance, and ethical oversight?
- Who develops, validates, and monitors the AI system?
- Who will annotate/verify imaging markers (radiologist/neurologist), and how much time is feasible?

WHAT

- What distinguishes AD from VCI/VaD (mechanisms + MRI patterns)?
- What MRI markers define vascular burden (WMH, lacunes, microbleeds, PVS) and neurodegeneration (atrophy, hippocampus)?
- What short-term cognitive effects differ (memory vs executive dysfunction/processing speed)?
- What long-term outcomes are predicted (major NCD, loss of independence, institutionalization)?
- What imaging sequences are required (T1, FLAIR, SWI/T2*) and what if one is missing?
- What clinical data are essential (diagnosis, MMSE/MoCA, vascular risks, meds, education)?
- What is missing in current literature about mixed pathology and explainability?
- What will be the project outputs (models, biomarkers report, explainability maps, dashboard/report)?
- What tools/software will we use for conversion, preprocessing, segmentation, and modeling?
- What computational resources are required and what is realistically available?
- What skills are required in the team and how will we cover gaps?

WHERE

- Where are structural alterations most predictive of decline?
- Where do neurodegenerative and vascular processes overlap in the brain (mixed pathology “hotspots”)?
- Where are WMH most clinically impactful (periventricular vs deep, strategic tracts)?
- Where can region-level explainability give actionable insight to clinicians (which regions / outputs)?

WHY

- Why is differential diagnosis difficult in mixed pathology?
- Why does small vessel disease accelerate cognitive decline?
- Why are mixed dementia cases underrepresented in research datasets?
- Why do many AI models prioritize classification over cognition correlation?
- Why is explainability essential for clinical adoption?
- Why must Tunisian data protection compliance be strictly ensured?

HOW

- How can we quantify the relative contribution of atrophy vs vascular burden?
- How can we align MRI markers with NIA-AA (AD) and STRIVE (vascular) frameworks in practice?
- How can MRI features be correlated with cognitive scores (MMSE/MoCA + domains)?
- How can we handle constraints (small sample size, missing scores, scanner variability)?
- How can preprocessing be standardized?
- How can bias be controlled (age, sex, education, comorbidities, scanner/protocol)?
- How can AI remain interpretable and clinically trustworthy (XAI method + clinician validation)?
- How can governance ensure ethical approval, anonymization, secure on-site analysis, and controlled publication?
- How will we document and version-control the pipeline for reproducibility (Git, experiment tracking)?
- How will we evaluate the model clinically (what metrics + clinician feedback process)?

2.2 Guiding Activities

2.2.1 Team Structure

Weekly meetings (clinical + technical alignment).

Roles:

Modeling Lead

- Develop statistical baseline models.
- Implement deep learning models (if feasible).
- Control bias and validate performance.

Explainability & Reporting Lead

- Produce Grad-CAM visualizations.
- Generate ROI-level importance maps.
- Translate outputs into clinician-friendly reports.

Governance & Documentation Coordinator

- Manage ethics approval.
- Maintain compliance documentation.
- Ensure reproducibility (Git, logs, data dictionary).

2.2.2 Causes and Effects

Alzheimer's Disease (AD)

- Progressive neurodegeneration → medial temporal atrophy → hippocampal shrinkage → memory impairment.

Vascular Cognitive Impairment (VCI/VaD)

- Small vessel disease, infarcts, chronic ischemia → white matter hyperintensities (WMH), lacunes, microbleeds → executive dysfunction and slowed processing.

Mixed Pathology

- Coexistence of atrophy + vascular burden → accelerated cognitive decline.

Short-Term Effects

- Executive dysfunction (vascular-related).
- Slowed information processing.
- Memory encoding/retrieval impairment (AD-related).

Long-Term Effects

- Progression to major neurocognitive disorder.
- Loss of independence.
- Increased institutionalization risk.
- Higher caregiver burden.

2.2.3 Stakeholders

Patients & caregivers

- Need diagnostic clarity.
- Planning for care and quality of life.

Neurologists, radiologists, neuropsychologists

- Clinical interpretation.
- Differential diagnosis in mixed cases.

El Razi Hospital

- Data governance.
- Legal compliance.
- Publication oversight.

AI Research Team

- Model development.
- Validation and monitoring.
- Clinical translation.

2.2.4 Ethical Considerations

Patient Rights & Ethics

- Informed consent OR ethics-approved waiver for retrospective anonymized data.
- Strict privacy protection (minimum necessary data use).
- Data stored in secure on-site hospital environment.
- Ethics committee approval prior to data access.

Responsible AI

- Avoid pure black-box systems.
- Provide explainable outputs: ROI-level volumetric importance; Saliency/Grad-CAM maps.
- Bias control: Age, sex, education; Scanner variability; Comorbidities.
- Model strictly decision-support, not diagnostic replacement.

2.2.5 Limitations

The present project complies with Tunisian constitutional and legislative provisions governing personal and health data protection.

- **Article 24 of the 2014 Tunisian Constitution** and **Article 30 of the 2022 Constitution** guarantee the protection of personal data and privacy.
- **Organic Law No. 2004-63 of 27 July 2004 on the Protection of Personal Data** classifies health data as sensitive data and imposes strict conditions for processing, including confidentiality, purpose limitation, and security safeguards.
- **Law No. 91-21 of 13 March 1991 regulating the medical profession** establishes that only licensed physicians are legally authorized to issue medical diagnoses.

Accordingly:

- All MRI, EEG, ECG, and clinical data will be anonymized prior to analysis.
- Data processing will occur within a secure institutional environment.
- The AI system will function strictly as a **clinical decision-support tool**, without replacing medical judgment.

Institutional Constraints

- Restricted access to raw MRI.
- On-site analysis requirement.
- Approval process before publication.

2.2.6 Constraints

Data Constraints

- Limited sample size per class (AD / VaD / mixed).
- Missing cognitive scores.
- Incomplete MRI sequences.
- Temporal mismatch between MRI and cognitive testing.

Technical Constraints

- Scanner variability.
- Motion artifacts.
- Skull stripping and normalization errors.
- WMH segmentation variability.
- Limited availability of SWI for microbleeds.

Time Constraints

- Limited clinician availability.
- Need for minimal manual annotation.
- Reliance on standardized markers (STRIVE + atrophy scales).

2.2.7 Data

2.2.7.1 Primary Imaging Data

Structural MRI Recommended sequences:

- T1-weighted: Atrophy, Hippocampal volume, Cortical thickness
- FLAIR: White matter hyperintensities (WMH)
- T2/SWI (if available): Microbleeds

Format:

- DICOM → NIfTI conversion.
- De-identification before processing.
- Quality control prior to analysis.

Core Imaging TargetsAD-Related Markers:

- Medial temporal atrophy.
- Hippocampal volume.
- Global brain volume.
- Cortical thinning (temporal/parietal).

Vascular Markers (STRIVE Framework):

- White matter hyperintensities (WMH).
- Lacunes.
- Microbleeds.
- Perivascular spaces.

2.2.7.2 Clinical / Cognitive Data

- Age, sex, education
- Diagnosis (AD / VaD / mixed / control).
- Vascular risk factors (HTN, diabetes, smoking).
- Medication history (if available).
- Cognitive tests: MMSE, MoCA, Executive function tests, Memory scores

2.2.7.3 Early Availability Questions

- How many cases per class?
- Are MRI and cognitive scores temporally aligned?
- Are repeated scans available?
- Are scanner/protocol differences documented?

2.2.8 Study of Existing Work

2.2.8.1 Literature Anchors

- **NIA-AA framework:** AD defined biologically (A/T/N model). MRI supports “N” (neurodegeneration).
- **STRIVE criteria:** Standardized definitions for vascular lesions.
- **Meta-analyses:** WMH burden linked to dementia risk. Hippocampal atrophy predicts cognitive decline.

Identified Gap

- Most studies analyze AD or VaD separately.
- Mixed pathology underrepresented.
- Limited region-level explainability.
- Classification prioritized over cognitive correlation.

Added Value of Our Project

- Real-world Tunisian dataset (El Razi).
- Direct MRI ↔ cognition correlation.
- Combined: AD atrophy markers; STRIVE vascular markers; Clinician-validated explainable outputs.

2.2.8.1 Concrete Workflow

1. Ethics & Governance: Draft protocol → Submit for hospital + ethics approval → Define data access levels → Secure storage and anonymization workflow.
2. Data Engineering: DICOM → NIfTI conversion → De-identification → Quality control → Metadata documentation.
3. Preprocessing (Standardized Pipeline): Skull stripping → Registration to template space → Intensity normalization → WMH segmentation (FLAIR) → Hippocampal / atrophy measurement (T1) → Extraction of structured biomarkers.
4. Modeling (Progressive Strategy) Baseline: ROI volumetry + WMH burden; Regression / correlation with cognition; Adjustment for age, sex, education. Advanced (If Data Allows): 3D CNN or hybrid model (structured + imaging); Separate modeling of atrophy contribution and vascular burden contribution; Optional mixed-effect modeling (if repeated scans).
5. Explainability: ROI importance ranking → Grad-CAM for deep models → Region-level summary tables → Clinician validation session (“Does this make sense medically?”).
6. Validation: Stratified cross-validation → Subgroup analysis (age, sex) → Bias checks → Plausibility verification → Error analysis (mixed cases vs pure cases).

2.2.10 Tools, Resources & Skills

Software (Open-Source Priority): Python, PyTorch, MONAI, NiBabel, SimpleITK, FreeSurfer / FSL, ANTs (registration). Institutional installation approval may be required.

Compute Resources: Local workstation (baseline models). GPU recommended for 3D CNN. Optional Colab/Kaggle (if allowed). Secure hospital storage for MRI.

Required Skills: MRI preprocessing, Neuroimaging interpretation, Statistical modeling, Machine learning, Bias and confounding control, Data governance & documentation.

Skill gaps addressed via: Internal training sessions; MOOCs on neuroimaging ML; Structured team knowledge-sharing.

2.2.11 Budget & Resources

Training: Optional MOOCs on neuroimaging ML; Internal sessions on MRI preprocessing; Literature review workshops.

Software: Mostly open-source tools. No major licensing costs expected.

Compute: Existing workstation. GPU access if available. Secure hospital infrastructure.

2.3 References

Akoudad, S., Wolters, F. J., Viswanathan, A., de Bruijn, R. F., van der Lugt, A., Hofman, A., Koudstaal, P. J., Ikram, M. A., & Vernooij, M. W. (2016). Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurology*, 73(8), 934–943.

Summary: Association of Cerebral Microbleeds With Cognitive Decline and Dementia

What is this article about? Sometimes, on MRI, doctors can see tiny spots of old bleeding in the brain. They're called cerebral microbleeds. The study asks: Do people with these spots get worse in thinking/memory over time? Do they have higher risk of dementia?

What did the researchers do? They used data from a big real-life population study (Rotterdam Study). They scanned 4,841 people with MRI (age 45+). For 3,257 people, they had cognitive tests twice, around 6 years apart. They also followed people to see who developed dementia.

What did they find?

- Having “a few” microbleeds (1 to 4) didn't change much the decline wasn't clearly different from people with none.
- People with more than 4 microbleeds tended to get worse over time in: executive functions (planning, organizing, focusing), processing speed (how fast the brain handles information), sometimes memory, sometimes motor speed (hand/coordination tasks).
- Location matters: Lobar microbleeds (outer parts of brain/cortex often linked to amyloid problems) were more linked to decline in executive function, processing speed, memory. Deep/infratentorial microbleeds (deeper brain areas often linked to high blood pressure damage) were more linked to decline in motor speed.
- Dementia risk: People with microbleeds had about ~2× higher risk of developing dementia compared to those without microbleeds (after adjusting for age/sex/education). This also applied to Alzheimer-type dementia risk.

Why this article is useful for our project: It supports the idea that MRI vascular markers (like microbleeds) can relate to cognitive decline, connect vascular damage and Alzheimer mechanisms, and help explain mixed dementia (both vascular + Alzheimer changes).

Important limitations: MRI detection depends on machine settings (some microbleeds can be missed). Not many people developed dementia in the follow-up → some results become less stable. Microbleeds may not directly cause decline; they might be a sign of bigger underlying disease.

Twait, E., Gerritsen, L., Moonen, J., Verberk, I., Teunissen, C., Visser, P. J., van der Flier, W. M., & Geerlings, M. I. (2024). Plasma Alzheimer's disease markers and MRI load of vascular pathology and neurodegeneration: The SMART-MR Study. *Cerebral Circulation – Cognition and Behavior*, 6, 100232.

Summary: SMART-MR Study

What is this study about? There are two main causes of dementia: (1) Alzheimer's disease → caused by abnormal proteins in the brain; (2) Vascular disease → caused by blood vessel problems in the brain. This study asks: Can we detect signs of these brain problems using a simple blood test? And do these blood markers match what we see on MRI scans?

Who did they study? 594 people, around 64 years old, who did NOT have dementia but had arterial (blood vessel) disease. So these are people at risk, but not yet demented.

What did they measure? In the blood: Amyloid-beta, p-tau 181, NfL, GFAP “brain damage signals” detectable in blood. On MRI: White Matter Hyperintensities (WMH), Infarcts (small strokes), Total brain volume, Hippocampus volume.

What did they find?

- Higher p-tau → more white matter damage: People with higher p-tau had more WMH on MRI, suggesting a link between Alzheimer-type protein changes and vascular brain damage.
- Higher NfL → smaller brain volume: NfL seems to reflect brain shrinkage (neurodegeneration).
- Higher NfL and GFAP → more strokes (infarcts): These markers may reflect vascular brain injury.

Conclusion: Blood markers of Alzheimer's disease are linked to brain damage seen on MRI even before dementia appears. It supports the idea that Alzheimer's disease and vascular damage interact, not act separately. Blood biomarkers + MRI together give stronger information.

Nguyen, T. T., Rahman, M. M., Tan, H. J., Lee, J. H., & Yeo, T. T. (2025). Comparing deep learning CNN method with traditional MRI-based hippocampal segmentation and volumetry for early Alzheimer's disease diagnosis across diverse populations. Scientific Reports, 15, Article 29366.

Summary: CNN vs. Traditional Hippocampal Segmentation

What is the study about? In Alzheimer's disease, the hippocampus shrinks. Doctors measure its size on MRI scans to help detect early Alzheimer's. This study compares: (1) Traditional method (VBM) → older MRI analysis method; (2) AI method (CNN – HippoDeep) → deep learning automatic segmentation. Which method is better at detecting early Alzheimer's? Does it work in different populations (Caucasian vs Southeast Asian)?

What did they find?

- CNN was better: In the Caucasian dataset, CNN accuracy (AUC) ≈ 0.91 vs. Traditional method ≈ 0.71 . CNN still better in Southeast Asian dataset.
- Stronger link with cognition: CNN hippocampal volumes more strongly related to MMSE scores: CNN correlation $r = 0.65$ vs. Traditional method $r = 0.41$. CNN measurements better reflect real cognitive decline.
- Works across populations: Both Western and Southeast Asian populations tested successfully.

Comparison with Our Solution:

This Article	Our Project
Focus: Only hippocampus	Hippocampus + white matter + vascular lesions
Disease: Alzheimer's only	Alzheimer's + Vascular dementia
Imaging: T1 MRI	Likely T1 + FLAIR
AI task: Segmentation + classification	Correlation + explainable AI
Biomarker: Hippocampal volume	Atrophy + WMH + infarcts
Goal: Early AD detection	Understand overlap & cognitive decline

How This Article Helps Us: We can use it to (1) justify using CNN segmentation for hippocampus, (2) show hippocampal volume correlates with cognition, (3) support using automated MRI analysis, (4) compare segmentation vs multimodal biomarker approach. While CNN-based hippocampal segmentation improves early AD detection, it does NOT include white matter hyperintensities, vascular lesions, or mixed dementia analysis. Our project fills that gap.

Zhang, Y., Liu, X., Wang, J., Chen, H., & Li, Z. (2024). Vision transformer-equipped convolutional neural networks for automated Alzheimer's disease diagnosis using 3D MRI scans. *Frontiers in Neuroscience*, 15, 1490829.

Summary: VECNN Vision Transformer + CNN

What is this study about? Researchers built an AI model called VECNN (Vision Transformer + CNN). CNN is good at detecting local patterns (like small brain shrinkage). Vision Transformer is good at understanding global context (how different brain areas relate). This study combines both.

What data did they use? ADNI dataset (big international Alzheimer's dataset), 2,248 MRI scans, 3 groups: Healthy (HC), Mild Cognitive Impairment (MCI), Alzheimer's (AD). They used 3D MRI scans, not just 2D slices.

Results: 3-class classification (HC vs MCI vs AD): Accuracy 92.14%, Sensitivity 93.27%, Specificity 89.95%, Precision 86.84%. For Alzheimer's specifically: Accuracy $\approx$ 95.63%.

Comparison with Our Solution:

This Article (VECNN)	Our Project
Disease: Alzheimer only	Alzheimer + Vascular dementia
Task: Classification (HC/MCI/AD)	Correlation + explainable analysis
Focus: Whole brain 3D patterns	Specific damaged regions
Vascular lesions: Not included	Important part of our analysis
Mixed dementia: No	Yes (possible)

How We Can Use This Article: While VECNN demonstrates high performance in automated AD classification using 3D MRI, it does not incorporate vascular pathology markers. Our project extends beyond pure classification by integrating both neurodegenerative and vascular MRI features to better explain cognitive decline across Alzheimer's and vascular dementia. Their innovation: Combining CNN + Vision Transformer in 3D. Our innovation: Integrating neurodegeneration, vascular pathology, cognitive scores, and Explainable AI.

3 Axis 2 – Early Differentiation of PD vs Atypical Parkinsonism

Parkinson's disease and atypical parkinsonian syndromes share early symptoms and often look similar on MRI. Subtle structural differences must be extracted computationally to improve early and reliable differentiation.

3.1 Guiding Questions

WHO

- Who are the target patient groups (early-stage PD, PSP, MSA, $\pm$ CBD)?
- Who are the key stakeholders (patients/families, neurologists, radiologists, hospital governance, AI research team)?
- Who is responsible for ethical oversight, data governance, and secure analysis?

WHAT

- What early clinical features overlap across syndromes (bradykinesia, rigidity, postural instability, autonomic dysfunction)?
- What MRI-visible structural markers are expected for each syndrome (brainstem, cerebellum, basal ganglia, cortex) even if subtle?
- What quantitative MRI measures are most informative (volumes, cortical thickness, asymmetry indices, midbrain/pons ratios)?
- What short- and long-term effects arise from early diagnostic uncertainty (trial-and-error management, patient anxiety, inconsistent prognosis, reduced cohort reliability)?
- What gaps exist in the literature regarding early-stage differentiation, explainability, and subgroup performance?

WHERE

- Where are the most discriminative regions for each syndrome?
 - PSP: midbrain, superior cerebellar peduncles, frontal regions
 - MSA: pons, cerebellum (vermis/hemispheres), putamen
 - PD: subtle basal ganglia/brainstem changes
 - CBD: asymmetric frontoparietal cortex + basal ganglia
- Where do structural changes overlap or remain too subtle for visual detection?
- Where can region-level explainable outputs improve clinical interpretability?

WHY

- Why is early-stage MRI often non-specific despite underlying pathology?
- Why does misclassification matter clinically (prognosis, treatment planning, follow-up strategy)?
- Why are research cohorts impacted by noisy labels and heterogeneous groups?
- Why is ethical and privacy compliance critical in real-world hospital datasets?
- Why is explainability essential for AI adoption in clinical decision support?

HOW

- How can subtle early structural changes be detected quantitatively (morphometry, ratios, ICV normalization)?
- How can scanner/protocol variability, motion artifacts, and small structure challenges be mitigated?
- How can MRI features be directly correlated with clinical/cognitive metadata (symptom duration, UPDRS/MDS-UPDRS, key symptom flags)?
- How can AI pipelines remain interpretable, clinically trustworthy, and strictly decision-support? (e.g., Grad-CAM, SHAP, uncertainty reporting)
- How can data constraints (limited sample size, class imbalance, missing early-stage markers) be addressed?
- How can reproducible, secure, on-site analysis pipelines be established (preprocessing → segmentation → modeling → explainability)?
- How can rare classes or heterogeneous labels be handled for baseline feasibility without compromising validation?
- How can outputs be aligned with neuroanatomy and artifact auditing to ensure biological plausibility?

3.2 Guiding Activities

3.2.1 Team Structure & Collaboration

Meetings: Daily async: Messenger; Weekly technical sync + screen share: Discord; Periodic in-person: Razi/El Razi Hospital (clinical alignment, MRI review)

Roles: Clinical Liaison: define criteria, red flags, follow-up confirmation; Data Engineering Lead: DICOM → NIfTI conversion, anonymization, QC; Modeling Lead: baseline ML & 3D CNN; Explainability/Reporting Lead: Grad-CAM, SHAP, clinician review

3.2.2 Concrete Workflow & Tasks

3.2.2.1 Ethics & Governance

- Draft protocol with aims, data fields, anonymization plan
- Submit for hospital ethics and approval workflow
- Ensure decision-support only (no autonomous diagnosis)
- Explainability, ROI evidence, bias control (age/sex/scanner/site)
- Confidentiality, minimal necessary data extraction, on-site secure storage

3.2.2.2 Data Engineering & Preprocessing

- DICOM → NIfTI conversion; de-identification; secure folder structure
- Quality Control: exclude corrupted scans / severe motion artifacts
- Preprocessing: N4 bias correction, skull stripping, optional MNI normalization
- Automated segmentation: FreeSurfer/FastSurfer/SynthSeg, cerebellar parcellation if supported
- Feature Extraction: Regional volumes, cortical thickness; Brainstem/cerebellar ratios, asymmetry indices; ICV normalization, age/sex correction; FLAIR lesion load as confounder (if available)

3.2.2.3 Modeling

Baseline: Tabular ML on ROI features: logistic regression, random forest, SVM

Advanced: 3D CNN on preprocessed T1 volumes (MONAI); Optional hybrid: CNN features + clinical metadata

Explainability & Validation: Grad-CAM 3D saliency maps, SHAP importance for tabular features; Artifact audit: verify model focuses on plausible neuroanatomy; Train/validation/test split: patient-level, stratified k-fold; Metrics: accuracy, sensitivity, specificity, F1, AUC (one-vs-rest for multiclass); Error analysis: subtypes + early-stage subgroup

3.2.3 Data & Clinical Metadata

- Structural MRI: Required T1 3D (morphometry, cortical thickness, volumetry); optional FLAIR
- Regions of interest: midbrain, pons, cerebellum (vermis/hemispheres), putamen, caudate, pallidum, optional cortex (frontal/parietal)
- Clinical metadata: age, sex, diagnosis (follow-up confirmed), symptom duration/stage, key flags (falls early, autonomic dysfunction, gaze palsy, asymmetry), UPDRS/MDS-UPDRS
- Labels: multi-class (PD vs PSP vs MSA vs $\pm$ CBD); rare classes optionally collapsed for baseline feasibility
- Early availability checks: number of cases per class, MRI protocol consistency, longitudinal follow-up confirmation

3.2.4 Literature Anchors & Gaps

- Clinical/MRI frameworks for PSP/MSA/CBD (midbrain vs pontocerebellar patterns)
- AI pitfalls: data leakage, no external validation, early-stage subgroup performance
- Identified gap: early-stage MRI often non-specific, subtle patterns missed visually, limited explainability
- Added value: hospital dataset with follow-up confirmed labels, two-level modeling (interpretable morphometry + 3D CNN), early-stage evaluation, explainable outputs aligned with neuroanatomy, artifact auditing

3.2.5 Budget & Resources

Training (Internal sessions): MRI preprocessing workflow; Structural biomarkers in parkinsonism; MONAI 3D CNN basics; Explainability + auditing

Software (Open-source): Neuroimaging: dcm2niix, ANTs, FreeSurfer/FastSurfer/SynthSeg; AI: scikit-learn, PyTorch, MONAI; Explainability: Captum (Grad-CAM), SHAP; Reproducibility: Git + experiment logs

Compute: Baseline ML: CPU workstation (16–32 GB RAM); 3D CNN: 1 GPU $\geq$ 8 GB VRAM; Estimated GPU time: 50–150 hours; Storage: 0.5–1 TB secure hospital storage

3.3 References

A) Levin et al. Clinical Review of Atypical Parkinsonism

This review clarifies the clinical and pathological foundations of atypical parkinsonian syndromes (PSP, MSA, CBD) and their differentiation from Parkinson's disease (PD).

It highlights that early clinical overlap (bradykinesia, rigidity, postural instability) makes diagnosis challenging, particularly in early stages where structural MRI can appear “non-specific.”

The paper emphasizes distinct pathological mechanisms:

- **Synucleinopathies** (PD, MSA)
- **Tauopathies** (PSP, CBD)

PSP shows midbrain atrophy, MSA shows pontocerebellar atrophy, while PD often lacks specific early structural changes

The Differential Diagnosis and Treatment of Atypical Parkinsonism

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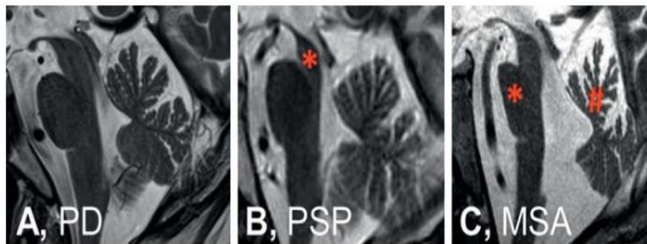
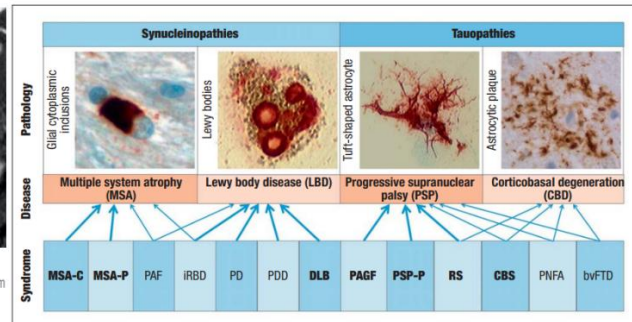


Figure 2: Imaging results. On magnetic resonance imaging, the midsagittal plane of the brainstem does not show a specific atrophy pattern in Parkinson's disease (PD) (A), whereas in progressive supranuclear palsy (PSP) (B) midbrain atrophy (*) is visible, and in multiple system atrophy (MSA) (C), atrophy of the pons (*) and in the upper portion of the cerebellar vermis (#) can be seen. Further characteristic imaging findings of atypical parkinsonian syndromes are shown in the eFigure



B) McFarland Diagnostic Approach to Atypical Parkinsonian Syndromes

The paper provides a structured clinical approach to differentiating PSP, MSA, CBD, DLB from idiopathic Parkinson's disease (PD). Parkinsonian syndromes are classified based on which abnormal protein accumulates in the brain:

- **Tauopathies:** abnormal tau protein builds up inside neurons and glial cells → includes PSP and CBD.
- **Synucleinopathies:** abnormal alpha-synuclein protein accumulates → includes PD, MSA, and DLB.

These proteins damage different brain regions, which explains why each disease shows distinct structural patterns on MRI.

Clinical Message: Early PD and atypical syndromes overlap clinically. MRI can show supportive signs (midbrain vs pontocerebellar atrophy). However, imaging may be subtle early, and diagnosis remains primarily clinical. Neuropathology remains the gold standard.

- **MSA (hot cross bun / putamen changes):** supports that MSA primarily involves pontocerebellar and basal ganglia degeneration, distinguishing it from typical PD.
- **PSP (hummingbird sign):** supports that PSP predominantly affects the midbrain and superior cerebellar peduncles, differentiating it from PD.
- **Neuropathology (PSP – tau inclusions):** confirms that PSP is a tauopathy where abnormal tau accumulation leads to selective degeneration of midbrain structures visible on imaging.



FIGURE 5-4 Sagittal T1-weighted MRI of a patient with progressive supranuclear palsy-Richardson syndrome. Marked midbrain atrophy is present, suggesting the appearance of a hummingbird or penguin sign. Inset shows atrophy of the superior cerebellar peduncles (arrows).

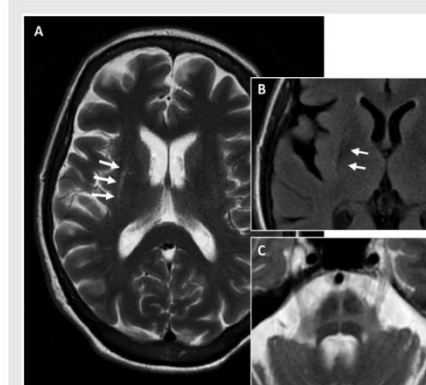


FIGURE 5-6 Axial T2-weighted MRI of a patient with multiple system atrophy-parkinsonian type demonstrating slitlike hyperintensity (A, arrows) at the rim of the right putamen, fluid-attenuated inversion recovery (FLAIR) hyperintensity of posterior putamen (B, arrows), and typical hot cross bun sign representing atrophy and gliosis of the pons (C).

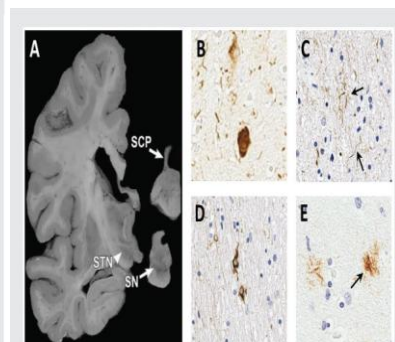


FIGURE 5-3 Typical neuropathologic findings in progressive supranuclear palsy. The macroscopic photo shows atrophy of the superior cerebellar peduncle (SCP) and midbrain structures including the subthalamic nucleus (STN) and loss of pigmented cells in the substantia nigra (SN) (A). The photomicrographs show classic pathologic findings including neurofibrillary tangles (B), neurofibrillary threads (C, arrows), coiled bodies (D), and tufted astrocyte (E, arrow) stained with Phf1 antibody to human tau.

C) Salvatore et al. Machine learning on brain MRI data for differential diagnosis of Parkinson's disease and Progressive Supranuclear Palsy

Salvatore et al. used normal T1-weighted structural MRI which often appears visually unremarkable in early stages. Instead of looking at obvious atrophy, they:

- Applied Voxel-Based Morphometry (VBM) → measures subtle gray matter differences across the whole brain.
- Used PCA (Principal Component Analysis) → reduces thousands of brain voxels into main structural patterns.
- Trained an SVM (Support Vector Machine) → to separate PD from PSP.

The important part is that the separation was not based on visible lesions it was based on distributed subtle structural patterns across the brain. And the model successfully separated PD and PSP with high accuracy.

- Each dot represents one patient. After reducing whole-brain MRI measurements into main structural patterns (PCA), PD and PSP patients begin to separate in feature space, showing that subtle brain differences exist even when MRI appears visually normal.
- The SVM algorithm learns an optimal separating boundary between PD and PSP patients based on structural MRI patterns, achieving high classification accuracy.
- The highlighted regions show that midbrain and pontine areas contribute strongly to PD vs PSP classification, consistent with known PSP-related neurodegeneration. Warm and cool colors represent regional gray matter differences between groups, with PSP showing more pronounced brainstem atrophy compared to PD.

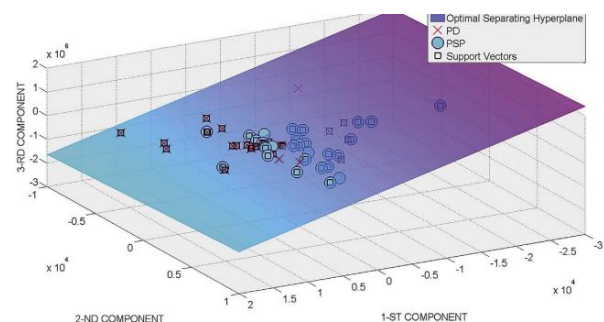
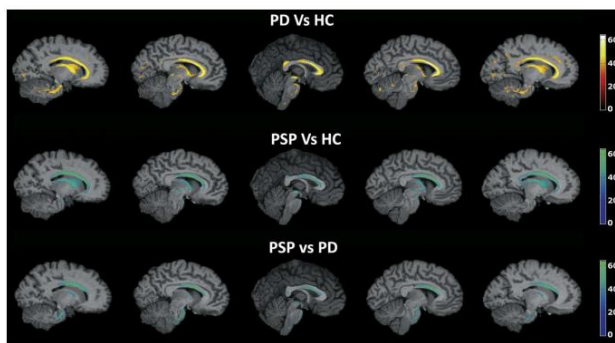


Fig. 2. Optimal separating hyper-plane for the PSP versus PD binary labeled group (1st, 2nd and 3rd components).

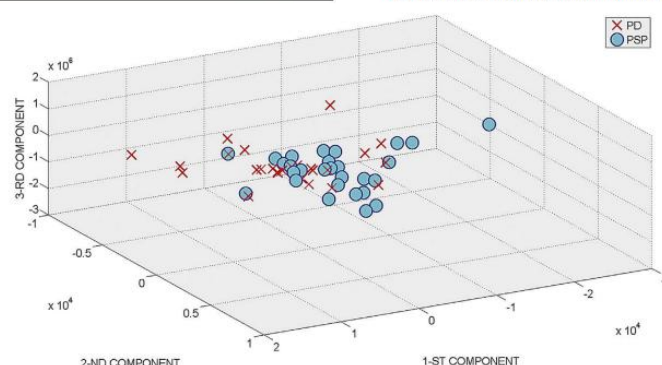


Fig. 1. PCA coefficients for the PSP versus PD binary labeled group (1st, 2nd and 3rd components).

4 Axis 3 – EEG/ECG-based Analysis of Stress Recovery Speed

Two people can experience the same stress but recover at different speeds. Measuring brain and heart signals together can reveal hidden regulatory differences not visible on structural imaging.

4.1 Guiding Questions

WHO

- Who are the individuals affected by chronic stress or fatigue?
- Who are the key stakeholders in monitoring and analyzing stress recovery?

WHAT

- What physiological markers indicate stress recovery speed?
- What EEG rhythms and ECG metrics should be considered for analysis?
- What skills are required to process and analyze EEG/ECG signals effectively?
- What tools and software are most suitable for signal processing and AI modeling?

WHERE

- Where in the brain or which EEG channels are predictive of fast vs slow recovery?
- Where are the HRV indices reflecting autonomic recovery?
- Where can brain–heart interactions be measured?

WHY

- Why do individuals with similar stress levels recover differently?
- Why is early detection of stress dysregulation important?
- Why is research on multimodal biomarkers limited and important?
- Why do demographic factors (age, sex, health conditions) influence recovery speed?
- Why is it important to store sensitive physiological data securely and ethically?

HOW

- How can EEG and ECG features be combined to quantify recovery speed?
- How can AI models be made interpretable and clinically useful?
- How should artifacts and synchronization across participants be handled?
- How can preprocessing of EEG/ECG signals affect recovery analysis?
- How can training and online resources improve team performance and best practices?
- How can sensitive physiological data be stored securely and ethically?

4.2 Guiding Activities

4.2.1 Team Structure & Collaboration

Meetings:

Weekly clinical + technical meetings

Roles:

Clinical Liaison: protocol definition, ethics, recruitment; Data Engineering Lead: signal preprocessing, artifact removal, synchronization; Modeling Lead: AI pipeline (baseline regression, neural networks); Explainability/Reporting Lead: feature analysis, visualization, interpretability

4.2.2 Concrete Workflow & Tasks

4.2.2.1 Ethics & Governance

- Draft protocol with aims, data fields, anonymization plan
- Submit for ethics approval
- Decision-support only (no autonomous diagnosis)
- Ensure bias control (age, sex, health conditions), interpretability, and privacy compliance

4.2.2.2 Data Engineering & Preprocessing

- EEG/ECG preprocessing: filtering, artifact removal, segmentation
- Synchronization of EEG/ECG with stress/recovery events
- Feature extraction: EEG: alpha/beta/theta power, recovery slopes; ECG: HRV metrics (RMSSD, LF/HF), recovery time constants; Brain–heart coupling: coherence or correlation decay

4.2.2.3 Modeling

- Baseline ML: regression of recovery speed on EEG/ECG features
- Advanced: neural networks integrating EEG + ECG temporal patterns
- Explainability: feature importance, interpretable outputs
- Validation: cross-validation, bias and plausibility checks

4.2.3 Data & Clinical Metadata

- Primary data: EEG multi-channel scalp signals, event-related potentials; ECG: HR, HRV, R-R intervals
- Secondary data: demographics, stress protocol, cognitive performance, subjective stress scores
- Format: time-series, DICOM/EDF or standard EEG/ECG formats
- Early availability checks: number of participants, signal quality, synchronization with tasks

Example datasets: Resting-state EEG, EEG Dataset, Complete EEG Dataset, EEG Signals for Anxiety Levels Detection

4.2.4 Literature Anchors & Gaps

- HRV reflects autonomic regulation; EEG rhythms change with stress
- Brain–heart coupling measurable via coherence, correlation, or decay metrics
- AI models can predict recovery speed, but most focus on static stress levels
- Gap: limited multimodal, interpretable AI for recovery dynamics
- Added value: focus on dynamic recovery, combine EEG + ECG, extract interpretable biomarkers

4.2.5 Budget & Resources

- Training: online courses on EEG/ECG processing, HRV, AI for biosignals
- Software: Python, MNE, NeuroKit2, TensorFlow/PyTorch
- Compute: local workstation or cloud GPU
- Storage: secure, anonymized EEG/ECG datasets

4.2.6 Skills, Tools & Resources

- Skills: EEG/ECG signal processing, HRV analysis, time-series analysis, machine learning, neural networks, data visualization, AI explainability, ethics & privacy in healthcare data
- Tools: Python, MNE, NeuroKit2, TensorFlow, PyTorch, NumPy, Pandas, Matplotlib, Seaborn
- Resources: Kaggle datasets, published literature, online courses (Coursera, edX), GitHub code repositories, secure cloud storage for medical data

4.3 References

McEwen (2007). Physiology and neurobiology of stress. Physiol Rev. Thayer et al. (2012). Heart-brain interaction and HRV. Biol Psychol.

McEwen (2007): Stress is not harmful by itself. What is harmful is repeated or prolonged activation of stress systems. McEwen shows that stress is adaptive in the short term (allostasis), but repeated or poorly regulated stress leads to allostatic load increasing long-term brain vulnerability.

How stress becomes harmful when recovery fails:

- Stress activates the HPA axis (cortisol) and Autonomic nervous system
- Chronic stress causes “wear and tear” = allostatic load
- Poor recovery increases vulnerability to disease.

Thayer et al. (2012): HRV is linked to brain regions involved in threat and safety evaluation, such as the amygdala and medial prefrontal cortex (mPFC). HRV reflects the integrated functioning of the mPFC–brainstem system that regulates the heart. The vagus nerve plays a central role in connecting the brain and heart, supporting the neurovisceral integration theory. Therefore, HRV can serve as a marker of stress, adaptability, and overall health.

5 Axis 4 – Uneven Brain Aging (Structural MRI)

Brain aging does not occur evenly across all regions. Some areas age faster than others, and identifying these regional differences may reveal early vulnerability.

5.1 Guiding Questions

WHO

- Who are the populations of interest?
- Who are the key stakeholders?
- Who is responsible for ethical governance and oversight?

WHAT

- What does “uneven brain aging” mean biologically?
- What structural MRI markers reflect age-related brain changes? (Cortical thickness, Hippocampal volume, Regional gray matter volume, Subcortical volumes, Atlas-based parcellation metrics)
- What is brain-age gap?
- What is regional age deviation?
- What are the consequences of relying only on global brain-age models? (Masking localized vulnerability, Reduced clinical interpretability, Poor decision-support usability)
- What data constraints exist? (Scanner variability, Sample size imbalance, Age distribution skewness, Sex imbalance, Motion artifacts)
- What existing approaches already attempt brain-age modeling?
- What are their limitations in regional explainability?

WHERE

- Where do age-related structural changes appear first?
- Where can accelerated aging be detected in at-risk individuals?
- Where can region-level visualization improve clinical decision-making?

WHY

- Why is brain aging heterogeneous rather than uniform?
- Why can global brain-age models obscure regional imbalance?
- Why is early detection of structural vulnerability important? (Prevention, Monitoring, Risk stratification)
- Why is interpretability essential for clinical adoption?
- Why must outputs remain decision-support only and not diagnostic?

HOW

- How can DICOM images be converted to NIfTI?
- How will MRI preprocessing be standardized?
- How can regional volumetry be extracted?
- How can chronological age be predicted using regression or CNNs?

- How can explainability methods visualize regional importance? (Saliency maps, SHAP, Heatmaps)
- How will model robustness be validated? (Cross-validation, Bias checks, Age-group robustness)
- How will scanner heterogeneity be mitigated?
- How will secure and reproducible pipelines be implemented?

5.2 Guiding Activities

5.2.1 Team Structure & Collaboration

Meetings: Weekly sync (clinical + technical); Interpretation validation sessions with clinicians; Daily async communication

Roles: Data Preprocessing Lead; Modeling Lead; Interpretability Lead; Clinical Validation Liaison

5.2.2 Concrete Workflow Tasks

5.2.2.1 Ethics & Governance

- Define legal constraints for MRI data usage
- Draft protocol (objectives, inclusion criteria, anonymization)
- Submit to ethics committee if using clinical data
- Ensure system is decision-support only
- Implement bias monitoring (age, sex, scanner)

5.2.2.2 Data Engineering & Preprocessing

- Convert DICOM → NIfTI
- Quality control (motion, artifacts)
- Skull stripping
- Registration to MNI template
- Intensity normalization
- Atlas-based parcellation
- Cortical thickness extraction (optional FreeSurfer)

5.2.2.3 Modeling

Baseline: Regional volumetry; Linear regression / Random Forest; Brain-age gap computation

Advanced: 3D CNN structural MRI model; 2D slice-based CNN; Multi-input model (regional + image)

Explainability: Regional importance maps; Age deviation heatmaps; Atlas-overlay visualization

Validation: K-fold cross-validation; External validation (if dataset allows); Bias testing (sex, age group, scanner)

5.2.3 Data & Clinical Metadata

Imaging Data: T1-weighted structural MRI; Cortical thickness; Hippocampal volume; Regional gray matter volume; Atlas-based segmentation

Clinical Metadata: Chronological age, Sex, Education, Cognitive scores

5.2.4 Literature Anchors & Identified Gaps

Foundational Work: Cole & Franke (2017) – Brain-age modeling review; UK Biobank large-scale brain-age studies; 3D CNN structural MRI models

Known Limitations: Focus on global brain age; Limited regional explainability; Accuracy > interpretability; Rare visualization of imbalance patterns

Identified Gap: Few frameworks quantify regional heterogeneity, provide interpretable heatmaps, link deviation patterns to vulnerability, or audit biological plausibility.

5.2.5 Budget & Resources

Training: Neuroimaging preprocessing workshops; ML / Deep Learning MOOCs; Explainable AI tutorials

Software: Python, NiBabel, MONAI, PyTorch, FreeSurfer (optional)

Compute: Local workstation (CPU baseline); GPU (≥ 8 GB VRAM) for 3D CNN; Secure storage

5.3 References

Cole, J. H., & Franke, K. (2017). Predicting age using neuroimaging: Innovative brain ageing biomarkers. Trends in Neurosciences, 40(12), 681–690.

This paper reviews how structural MRI and machine learning can be used to estimate “brain age” and define the brain-age gap as a biomarker of biological brain aging. It shows that deviations between predicted brain age and chronological age may indicate early vulnerability or disease-related changes.

Franke, K., & Gaser, C. (2019). Ten years of BrainAGE as a neuroimaging biomarker of brain aging: What insights have we gained? Frontiers in Neurology, 10, 789.

This figure shows that the researchers analyzed 42,075 participants (ages ~45 to 83) and divided them into 84 age groups of 500 subjects each. For each group, they computed a structural covariance matrix (brain structure relationships across regions), allowing them to study how brain structural organization changes progressively with aging.

UK Biobank Brain Imaging Consortium publications (structural MRI aging studies).

6 Axis 5 – Brain Load & Hidden Effort (fMRI Functional Connectivity)

A brain can look structurally normal while working inefficiently. Functional connectivity analysis can reveal hidden cognitive effort and compensatory network imbalance.

6.1 Guiding Questions

WHO

- Who are the target populations experiencing hidden cognitive effort despite structurally normal MRI?
- Who are the patients reporting fatigue, cognitive overload, or post-stroke compensation without visible lesions?
- Who are the key stakeholders (patients, neurologists, radiologists, rehabilitation specialists, hospital governance, AI research team)?

WHAT

- What does it mean for a brain to be structurally normal but functionally imbalanced?
- What types of connectivity alterations may indicate hidden effort (hyperconnectivity, hypoconnectivity, altered global efficiency)?
- What measurable fMRI-based indicators can reflect network imbalance?
- What graph theory metrics (degree, clustering coefficient, modularity, hub centrality, global efficiency) best capture functional inefficiency?
- What short- and long-term consequences arise from unrecognized functional imbalance (diagnostic delay, chronic fatigue, increased vulnerability)?
- What are the data-related constraints (sample size, scanner heterogeneity, motion artifacts)?
- What existing approaches already attempt to model functional connectivity in clinical contexts?

WHERE

- Where in the brain are connectivity alterations most likely to manifest?
- Are large-scale networks such as the Default Mode Network, frontoparietal control network, and salience network particularly vulnerable?
- Where does post-stroke compensation alter network topology?
- Where can region-level explainable outputs improve clinical interpretability?

WHY

- Why does structural MRI often fail to capture early functional dysfunction?
- Why do patients report severe effort despite “normal” scans?
- Why is early detection of network inefficiency important for prevention and rehabilitation?
- Why is explainability essential for clinical adoption of AI-based connectivity tools?

HOW

- How can hidden neural effort be quantified using resting-state fMRI?
- How can BOLD signal correlations be transformed into connectivity matrices?
- How can connectivity markers be correlated with fatigue scores or cognitive performance?
- How can motion artifacts, scanner variability, and small sample size be mitigated?
- How can reproducible and secure pipelines be implemented?
- How will the imaging and clinical data be obtained?

6.2 Guiding Activities

6.2.1 Team Structure & Collaboration

Meetings: Weekly technical sync with our professors; Interpretation sessions with clinicians; Daily async: Messenger; Weekly technical sync + screen share: Discord

Roles: Clinical Liaison: symptom definition, fatigue scoring, interpretation validation; Data engineering Lead: preprocessing pipeline, connectivity computation; Modeling Lead: graph modeling, GNN training; Explainability Lead: SHAP, saliency visualization; Clinical Validation coordinator: session planning, results review

6.2.2 Concrete Workflow Tasks

6.2.2.1 Ethics & Governance

- Define juridical constraints regarding medical data usage and publication.
- Identify the responsible authority for ethical oversight (hospital ethics committee / academic board).
- Submit for ethics approval before data processing.
- Submit for ethics approval before data processing.
- Ensure the system is strictly decision-support only.
- Implement bias monitoring (age, sex, scanner type).
- Secure storage on encrypted local/cloud infrastructure.

6.2.2.2 Data Acquisition

Data Sources: Public repositories: OpenNeuro, Human Connectome Project, Public resting-state fMRI datasets

Inclusion Criteria:

- Structurally normal T1 MRI
- Resting-state fMRI available
- Acceptable motion threshold (<0.5 mm framewise displacement)
- Fatigue or cognitive performance measures available
- Control group without reported fatigue

6.2.2.3 Data Engineering & Preprocessing

- DICOM $\rightarrow$ NIfTI conversion
- Motion correction
- Slice timing correction
- Temporal filtering (<0.1 Hz)
- ROI parcellation (atlas-based)
- Extract BOLD time-series per ROI
- Connectivity matrix extraction
- Fisher Z-transformation

6.2.2.4 Modeling

Baseline Analysis Compute: Global efficiency, Modularity, Node strength, Hub centrality; Compare patients vs controls; Correlate network metrics with fatigue scores and cognitive performance

Advanced Modeling: Connectivity-based classifiers; Regression predicting fatigue severity; Graph Neural Networks (if feasible); Dynamic connectivity analysis (sliding windows)

6.2.3 Explainability & Validation

- ROI-level importance ranking
- SHAP-based feature importance
- Network saliency visualization
- Cross-validation (patient-level split)
- Robustness testing against motion/scanner bias

6.2.4 State of the Art & Identified Gaps

6.2.4.1 Resting-State Functional Connectivity Foundations

Marcus E. Raichle demonstrated that spontaneous BOLD fluctuations form organized resting-state networks such as the Default Mode Network (DMN). This established that resting activity is structured and functionally meaningful rather than noise.

Ed Bullmore and Olaf Sporns introduced graph-theoretical modeling of brain networks, defining nodes and edges and quantifying efficiency, modularity, and hub structure. These works justify modeling functional imbalance even in the absence of structural lesions.

6.2.4.2 Functional Connectivity & Compensation

Studies in post-stroke and fatigue populations suggest: Hyperconnectivity may reflect compensatory effort. Network reorganization may precede structural degeneration. Functional inefficiency may exist despite normal structural imaging.

However, most existing studies: Focus on group-level statistics. Rarely correlate network imbalance with subjective fatigue. Do not translate findings into interpretable decision-support tools.

6.2.4.3 AI & Connectivity Modeling

Recent machine learning approaches attempt automated connectivity modeling, including joint connectivity-classification frameworks and dynamic graph-based architectures.

Limitations of current approaches: Emphasis on classification accuracy over interpretability; Limited clinical validation; Minimal focus on hidden cognitive effort or fatigue; Black-box modeling without neurobiological plausibility checks.

6.2.4.4 Identified Gap

- Hidden cognitive effort is under-modeled in network neuroscience.
- Fatigue and compensation are rarely treated as primary outcomes.
- Few frameworks combine: Graph theory; Clinical correlation; Explainable AI; Biological plausibility auditing

6.2.4.5 Added Value of This Axis

- Focus on hidden effort rather than disease labeling.
- Correlation with fatigue and cognitive scores.
- Graph-based interpretable biomarkers.
- Explainable AI aligned with neuroanatomy.
- Potential application in rehabilitation monitoring.

6.2.5 Data

Imaging Data: Resting-state fMRI (primary); Optional task-based fMRI; BOLD signal time-series; Connectivity matrices

Regions of Interest: Default Mode Network; Frontoparietal control network; Salience network; Motor networks (post-stroke); Fronto-subcortical circuits

Clinical Metadata: Fatigue scales; Cognitive test scores; Processing speed; Demographics (age, sex, education)

6.2.6 Budget & Resources

Training: Internal sessions on fMRI preprocessing; Graph theory workshops; Explainable AI sessions

Software (Open Source): Python, Nilearn, NetworkX, PyTorch, SHAP

Computational Resources: CPU workstation for baseline models; GPU (≥ 8 GB VRAM) for advanced models; Secure storage infrastructure

6.3 References

Fox & Raichle (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging.

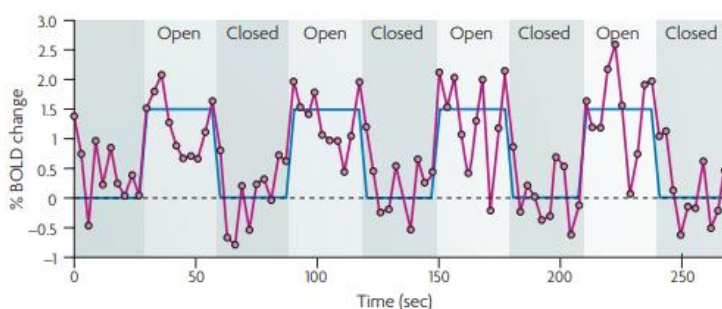
This article shows something very important: even when we are doing nothing, the brain is highly active. This article shows that this “noise” is actually: Spontaneous brain activity, Organized, Structured and Functionally meaningful.

What is the BOLD signal? BOLD = Blood Oxygen Level Dependent. It is the signal used in fMRI. It measures blood flow, oxygen consumption, and changes in deoxygenated hemoglobin.

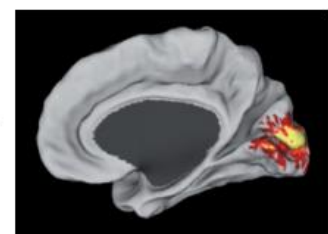
When researchers looked at slow fluctuations in the BOLD signal (< 0.1 Hz), they discovered:

- The left motor cortex fluctuates with the right motor cortex
- Visual areas fluctuate together
- Memory areas fluctuate together
- Attention networks fluctuate together
- The default mode network fluctuates together

This means that brain regions that work together during tasks are also synchronized at rest. More neural activity $\rightarrow$ more oxygenated blood $\rightarrow$ stronger BOLD signal. The brain consumes 20% of the body's energy. Task-related increases are less than 5%. This means that most of brain activity is spontaneous. So if we ignore resting activity, we ignore most of the brain.



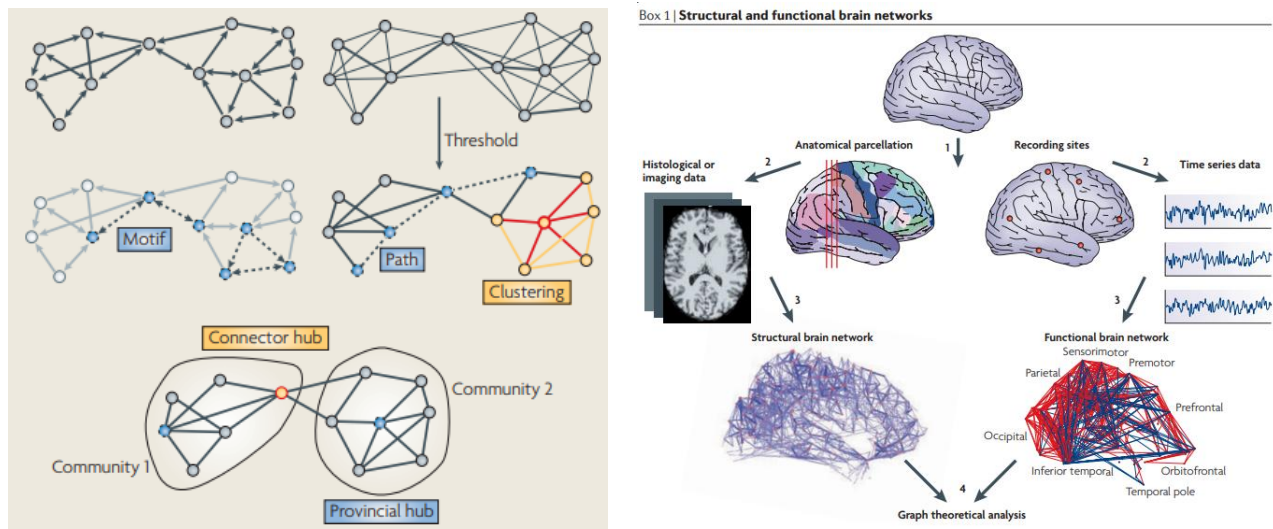
Open - Closed =



Bullmore & Sporns (2009). Complex brain networks: graph theoretical analysis of structural and functional systems.

This article shows that the brain can be modeled as: Nodes → neurons or brain regions; Edges → structural connections (white matter tracts) or functional connections (correlations in activity). This abstraction allows the brain to be studied mathematically using graph theory.

The brain is organized as: Locally clustered modules; Connected globally through hubs; With short paths for efficient communication. This balance enables efficient, robust, and flexible information processing, a principle relevant to AI network design.



Zhao, J., & Others (2023). Jointly Learning Connectivity and Classification: A Deep Neural Network for Functional Connectivity.

This article presents a deep learning framework that simultaneously learns functional connectivity representations and performs classification. Unlike methods that treat connectivity extraction and classification as separate steps, the model jointly optimizes both, improving the alignment between learned features and classification outcomes. Importantly, the network also identifies which brain regions contribute most to decisions, offering some degree of interpretability. For our project, this paper provides a useful example of how machine learning can be directly applied to functional connectivity matrices and how models can be structured to yield biomarkers that relate network patterns to clinical outcomes.

Anonymous Authors (2023). Spatial-Temporal DAG Convolutional Networks for fMRI Connectivity.

This preprint introduces a spatial-temporal deep learning architecture designed to learn effective connectivity patterns from fMRI data while accounting for both spatial relationships (region-to-region) and temporal dynamics (how connectivity evolves over time). The use of Directed Acyclic Graph (DAG) convolutional networks allows the model to capture causal influences in network signals. Although still in the preprint stage, it is highly relevant to this axis because it offers a way to model not just static connectivity but dynamic network changes a component that may underlie hidden brain load or compensatory effort.

Anonymous Authors (2024). DSAM: Deep Learning Framework for Brain Network Dynamics.

This recent preprint proposes a deep learning framework aimed at capturing goal-specific functional connectivity dynamics and performing network-informed classification. The model learns specialized embeddings of brain networks that reflect task-related or resting-state patterns, enabling classification or pattern discovery across subjects. Although still under review, DSAM is notable because it focuses on learning networking dynamics rather than treating connectivity as static snapshots. For this project on hidden effort and functional imbalance, this work presents an advanced architecture that could be adapted to identify connectivity patterns associated with compensatory effort, fatigue, or early inefficiencies especially when paired with explainability techniques.

7 Axis 6 – Cerebellar Subtle Dysfunction (MRI ± fMRI)

The cerebellum contributes to coordination and cognition but is often overlooked in early disease. Subtle changes in cerebellar regions may explain instability not visible on routine scans.

7.1 Guiding Questions

WHO

- Which patients show motor or cognitive symptoms without obvious cerebellar lesions?
- Are cerebellar changes present in: Parkinsonian syndromes? Early cognitive decline? Subtle coordination disorders?
- Do asymmetries differ between clinical groups?

WHAT

- Are there measurable volumetric differences in cerebellar lobules?
- Are asymmetry indices altered?
- Is vermis volume reduced in specific motor profiles?
- Does cerebellar volume correlate with: UPDRS scores? Balance/coordination measures? MMSE / MoCA scores?

WHERE

- Which lobules are most implicated? (Lobule VI, Lobule VIII, Crus I / II, Vermis)
- Are hemispheric differences clinically meaningful?
- Is cerebellar involvement isolated or linked to brainstem/subcortical structures?

WHY

- Why are cerebellar contributions often underestimated in early disease?
- Could subtle cerebellar modulation explain: Timing instability? Executive slowing? Postural imbalance?
- Does quantifying the cerebellum improve differentiation between close pathologies?

HOW

- How can cerebellar lobules be segmented reliably?
- How to compute normalized volumetric asymmetry?
- How to correlate morphometry with clinical scores?
- How to ensure AI focuses on cerebellar regions (not artifacts)?
- Can explainability confirm biological plausibility?

7.2 Guiding Activities

7.2.1 Clinical Alignment

Meet neurologists to define:

- Subtle cerebellar symptom profiles
- Relevant motor scales (UPDRS, coordination tests)
- Relevant cognitive scales (MoCA, executive tests)

Define inclusion subgroup:

- Patients without overt cerebellar lesion
- Structural MRI T1 available

7.2.2 Structural MRI Pipeline

Preprocessing: DICOM → NIfTI; N4 correction; Skull stripping; MNI normalization

Segmentation (Automated cerebellar parcellation): Extract Lobular volumes, Vermis volume, Hemispheric volumes

Quantitative Metrics: Volume normalization (ICV-adjusted); Asymmetry index calculation; Volume-to-score regression

7.2.3 AI Modeling

Baseline: Regression models linking cerebellar volumes to motor/cognitive scores

Advanced: 3D CNN with cerebellum-focused ROI masking

Task type: Score prediction; Subgroup differentiation

7.2.4 Explainability & Validation

- 3D Grad-CAM maps
- SHAP contribution ranking
- Artifact audit
- Clinical validation session: Do highlighted regions match neurological expectations?

7.3 References

Schmahmann (2019). The cerebellum and cognition. Brain.

Jeremy Schmahmann Cerebellar cognitive affective syndrome. This study confirmed the cerebellum's role beyond motor control, establishing the cerebellar cognitive affective syndrome (CCAS).

Bilateral Cerebellar Lobule Study fMRI and tDCS in bilingual language control

This study investigated the distinct roles of bilateral cerebellar lobules in bilingual language control using fMRI and tDCS. fMRI results revealed symmetrical activation in the posterolateral cerebellum (lobules VI and VIII) during language switching, with effective connectivity analysis showing a cerebrocerebellar network involving the dACC/pre-SMA, left lobule VI as a core node, and ipsilateral pathways to frontal and subcortical regions. Specification curve analysis linked specific intracerebellar and thalamic connections to switch costs. Experiment 2 demonstrated that anodal tDCS over the right, but not left, posterolateral cerebellum significantly reduced language switch costs, with greater effects in higher-proficiency bilinguals. Together, these findings reveal a functional asymmetry: the right cerebellum is causally involved in language control, while the left cerebellum supports broader cognitive control networks.

Buckner (2013). Cerebellar functional connectivity. Trends Cogn Sci.

Randy Buckner Cerebellar connectivity and cognitive mapping. This review shows that the cerebellum is largely connected to cognitive brain networks, not just motor areas. Early PET scans found cerebellar activity during language tasks, and viral tracing confirmed links to prefrontal cortex. Resting-state fMRI revealed that most of the human cerebellum maps to association networks in a mirrored, organized layout. The cerebellum also mirrors cerebral asymmetries (e.g., right-sided for language). Its cognitive role is now widely accepted, though related deficits can be subtle.

These works support:

- Cerebellar role beyond motor control
- Cerebro-cerebellar network organization
- Functional lateralization

8 Axis 7 – Epilepsy Vulnerability (Network Instability)

Epilepsy is increasingly understood as a disorder of unstable brain networks rather than solely a focal structural lesion. Seizure vulnerability may be present even when structural MRI appears normal, suggesting that hidden connectivity instability must be quantitatively modeled.

8.1 Guiding Questions

WHO

- Which patients show seizure vulnerability without clear structural lesions on MRI?
- Are instability patterns present in specific subtypes such as focal epilepsy, temporal lobe epilepsy, genetic generalized epilepsy, or drug-resistant epilepsy?
- Do network instability markers differ between clinical subtypes?
- Can vulnerability be detected during interictal (non-seizure) periods?

WHAT

- Are there measurable differences in:
 - Functional connectivity strength?
 - Phase-locking value (EEG)?
 - Network synchrony?
 - Connectivity variability over time?
 - Network entropy?
 - Graph metrics (clustering coefficient, path length, modularity)?
- Are hypersynchrony-prone regions identifiable?
- Does connectivity instability correlate with seizure frequency, disease duration, drug resistance, or surgical outcome?
- Is seizure vulnerability measurable even when no seizure occurs?

WHERE

- Which brain regions are most implicated?
- Are epileptogenic zones localized or network-wide?
- Is instability focal or distributed?
- Are hub regions more vulnerable?

WHY

- Why is epilepsy increasingly understood as a network disorder rather than a focal lesion disorder?
- Can quantifying network instability improve seizure prediction or surgical planning?
- Why might structural MRI appear normal while network instability persists?

HOW

- How can functional connectivity be reliably estimated from EEG and resting-state fMRI?
- How can dynamic connectivity and instability be quantified over time?
- How can graph theory metrics be computed and interpreted clinically?
- How can instability markers be standardized across patients and recording sessions?
- How can machine learning models differentiate subtypes or predict drug resistance?
- How can explainability methods identify critical nodes and edges driving predictions?
- How can biological plausibility be validated with neurologists?
- How can reproducibility be ensured through standardized preprocessing and cross-validation?

8.2 Guiding Activities

8.2.1 Clinical Alignment

Neurologists will define epilepsy subtype classification (focal, temporal lobe, generalized, MRI-negative, drug-resistant) to ensure proper subgroup comparison. Clear clinical endpoints will be standardized, including seizure frequency, disease duration, medication response, and surgical outcome.

Inclusion criteria will prioritize patients with available interictal recordings to determine whether instability markers are detectable outside seizure events. Subgroup analysis will ensure that network vulnerability patterns are compared across epilepsy types and resistance profiles.

This alignment ensures that connectivity instability is interpreted within accurate clinical context and that predictive modeling reflects real-world neurological decision-making.

8.2.2 Data Acquisition & Preprocessing

Resting-state EEG and resting-state fMRI will be used to quantify functional connectivity and dynamic network behavior.

EEG preprocessing will include band-pass filtering, artifact removal using Independent Component Analysis (ICA), re-referencing, and segmentation into clean interictal epochs. This ensures that connectivity measures reflect neural activity rather than noise.

fMRI preprocessing will include motion correction, spatial normalization, temporal filtering, and ROI time-series extraction to produce standardized connectivity matrices.

All preprocessing steps will be documented and version-controlled to guarantee reproducibility and minimize inter-subject variability.

8.2.3 Connectivity Estimation & Network Quantification

Functional connectivity will be estimated using:

For EEG: Phase-Locking Value (PLV), coherence, imaginary coherence, and cross-frequency coupling to quantify synchronization and excitability patterns.

For fMRI: Pearson correlation matrices and dynamic sliding-window connectivity to assess temporal variability of networks.

Graph theory metrics will be computed, including clustering coefficient, characteristic path length, global efficiency, modularity, hub centrality, small-world index, and network entropy.

Instability markers such as connectivity variability over time, network state transitions, and hypersynchrony indices will be extracted to quantify vulnerability even during interictal periods.

This step operationalizes seizure vulnerability into measurable, biologically interpretable metrics.

8.2.4 Modeling Strategy

Baseline machine learning models (logistic regression, SVM, Random Forest) will classify epilepsy vs controls and differentiate subtypes based on network features. Feature importance analysis will identify the most discriminative instability markers.

Advanced approaches may include Graph Neural Networks (GNNs) applied directly to connectivity matrices and temporal CNN/LSTM models for dynamic instability modeling.

Predictive tasks will include drug-resistance prediction, subtype differentiation, seizure vulnerability scoring, and estimation of epileptogenic network regions.

Where feasible, computational modeling inspired by Viktor Jirsa's "Virtual Epileptic Patient" framework may be explored to simulate network fragility.

8.2.5 Explainability & Clinical Validation

Node-level importance ranking and edge contribution analysis will identify vulnerable hubs and unstable pathways.

SHAP-based attribution and graph-level interpretability techniques will ensure that predictions are biologically plausible and not driven by noise.

Stability across recording sessions will be tested to evaluate robustness.

A clinical validation session will compare model-identified hubs with neurologist-defined seizure onset zones and surgical findings to confirm medical coherence.

8.2.6 Validation & Robustness

Cross-validation will be performed at the subject level to prevent data leakage.

External dataset testing will assess generalizability.

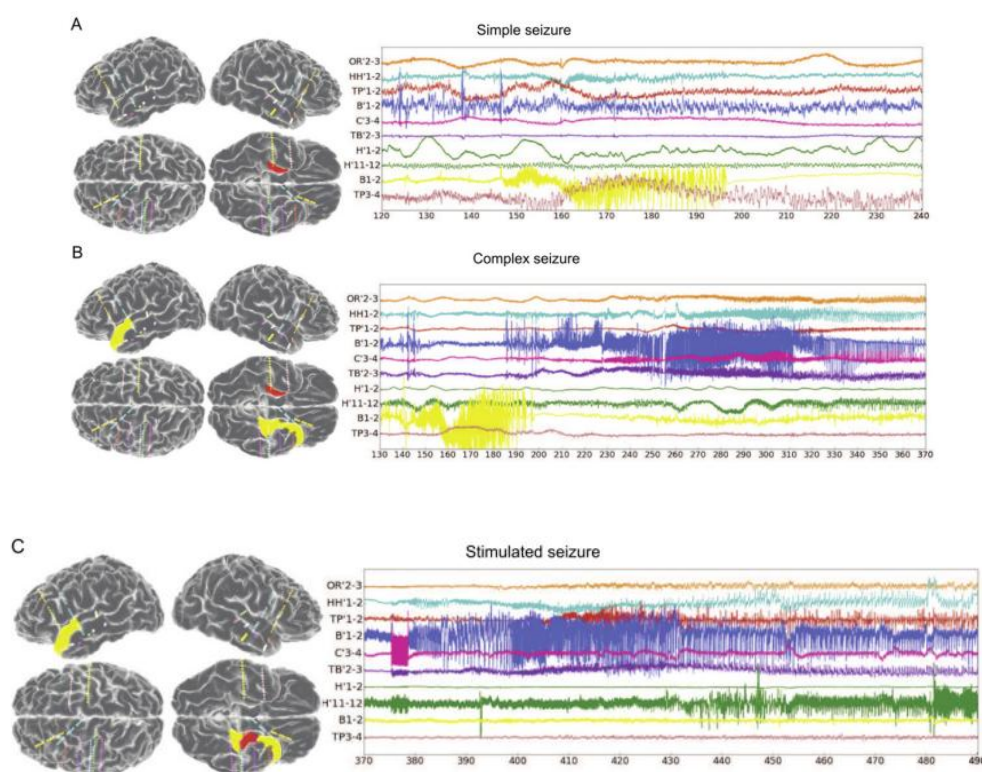
Robustness to noise, test-retest reliability, and subgroup stability analysis will be conducted to ensure clinical reliability.

Error analysis will examine whether instability patterns differ between MRI-negative and lesion-positive patients.

8.3 References

Viktor Jirsa — *The Virtual Epileptic Patient*

Jirsa and colleagues introduced a personalized whole-brain computational model that simulates seizure propagation using patient-specific structural connectivity. Their work demonstrates that epilepsy is a network disorder in which seizures emerge from unstable large-scale brain dynamics rather than from a single focal lesion. This supports our axis approach of measuring network instability and vulnerability as biomarkers, even during interictal (non-seizure) periods.



Mark Kramer & Sydney Cash — *Epilepsy as a disorder of cortical network organization*

This review reconceptualizes epilepsy as a disorder of large-scale cortical network organization rather than solely a focal structural abnormality. The authors describe how seizures involve dynamic changes in functional connectivity across different phases: interictal state, onset, propagation, and termination. Using graph theory metrics such as clustering coefficient and path length, they show that seizure activity is not simply hypersynchronous but characterized by evolving patterns of coupling and decoupling across brain regions. The study highlights how network analysis of EEG/ECOG data can improve understanding of seizure mechanisms, localization of epileptogenic zones, and potentially guide surgical planning.

9 Synthesis and Global Analysis

9.1 Synthesis of Main Findings Across All Axes

Across the seven investigative axes, a coherent pattern emerges: meaningful brain dysfunction is often present before it becomes visually obvious. Routine inspection may fail to detect early or distributed alterations, yet quantitative analysis reveals measurable structural, functional, physiological, and network-level signatures.

Axis 1 – Alzheimer’s Disease & Vascular Dementia

Cognitive decline does not arise from isolated lesions but from interacting processes: neurodegeneration (atrophy) and vascular burden (WMH, microbleeds, infarcts). Quantitative MRI markers allow us to correlate these mechanisms directly with cognitive performance, especially in mixed pathology.

Axis 2 – Parkinson’s Disease vs Atypical Parkinsonism

Early-stage parkinsonian syndromes often appear radiologically “non-specific.” However, subtle morphometric differences in brainstem, cerebellum, and basal ganglia can be computationally extracted to improve differentiation and reduce diagnostic uncertainty.

Axis 3 – Stress Recovery Speed

Physiological dysregulation may exist without structural abnormalities. Recovery speed reflects the efficiency of brain–heart regulatory systems, demonstrating that vulnerability can be functional and dynamic rather than anatomical.

Axis 4 – Uneven Brain Aging

Brain aging is regionally heterogeneous. A global brain-age score may obscure localized vulnerability. Regional deviation analysis provides a more interpretable and clinically actionable understanding of accelerated aging patterns.

Axis 5 – Brain Load & Hidden Effort (fMRI)

A structurally normal brain may still operate inefficiently. Functional connectivity analysis reveals compensatory hyperconnectivity, network imbalance, and hidden cognitive effort that cannot be detected through anatomy alone.

Axis 6 – Cerebellar Subtle Dysfunction

The cerebellum contributes to motor coordination and higher cognition but is frequently overlooked. Subtle lobular asymmetries and altered cerebro-cerebellar coupling may explain instability not visible as overt lesions.

Axis 7 – Epilepsy Vulnerability (Network Instability)

Epilepsy is increasingly understood as a disorder of unstable brain networks rather than a purely focal lesion. Network instability, hypersynchrony tendencies, and dynamic connectivity fluctuations can be measurable even during interictal periods, revealing seizure vulnerability beyond visible structural abnormalities.

Together, these findings confirm that the brain indeed contains measurable information that traditional inspection methods do not fully capture.

9.2 Cross-Axis Convergence

Although each axis investigates a different condition or modality, four foundational principles unify the investigation:

9.2.1 Hidden Patterns Require Quantification

Across neurodegeneration, movement disorders, stress regulation, aging, network imbalance, cerebellar modulation, and epilepsy, dysfunction frequently manifests as distributed or dynamic patterns rather than gross lesions. Quantitative morphometry, connectivity modeling, graph theory, and multimodal signal analysis are therefore essential.

9.2.2 Regional & Network Vulnerability Matter

Brain dysfunction rarely affects the brain uniformly. Instead, vulnerability often appears as:

- Regional asymmetry
- Localized atrophy
- Selective lobular deviation
- Hub instability
- Network-level imbalance

Understanding these patterns requires models that preserve anatomical and network specificity.

9.2.3 Structure and Function Interact

Structural degeneration, vascular injury, physiological dysregulation, and connectivity instability are not independent phenomena. Several axes demonstrate that functional disruption may precede structural loss, and network inefficiency may amplify anatomical vulnerability. A hybrid analytical framework is therefore required.

9.2.4 Necessity of Explainability

Across all axes, interpretability is not an optional enhancement but a clinical necessity. For responsible integration into hospital workflows, AI outputs must:

- Highlight anatomically meaningful regions
- Provide node- or ROI-level importance
- Demonstrate biological plausibility
- Remain strictly decision-support

Explainability bridges computational modeling and clinical trust.

9.3 Analysis

The Investigate Phase directly shapes the architecture of the eventual system.

9.3.1 Hybrid Modeling Strategy

Given the diversity of mechanisms observed, the solution must support:

- ROI-based quantitative morphometry
- Whole-brain pattern learning
- Functional connectivity modeling
- Graph-theoretical network analysis
- Multimodal integration (structural + functional + physiological)

No single modeling paradigm is sufficient.

9.3.2 Emphasis on Subgroup & Early-Stage Sensitivity

Multiple axes demonstrate that early stages may appear radiologically normal. Therefore, validation must prioritize:

- Early-stage subgroup evaluation
- Subtle effect detection
- Robust cross-validation
- Bias monitoring (age, sex, scanner variability)

9.3.3 Regional Interpretability as a Core Requirement

The system must produce structured, clinician-readable outputs such as:

- Region-level importance maps
- Lobular asymmetry indices
- Network centrality markers
- Connectivity instability scores
- Feature contribution rankings

This ensures outputs are medically interpretable and clinically actionable.

9.3.4 Governance & Real-World Constraints

Hospital-based research introduces non-negotiable constraints:

- Strict data anonymization
- On-site secure analysis
- Ethical approval and oversight
- Controlled publication procedures
- Minimal manual annotation burden

These constraints shape the pipeline toward reproducibility, transparency, and compliance with Tunisian data protection law.

9.4 Unified Strategic Insight

Across all seven axes, the investigation confirms a central insight:

Brain dysfunction is often subtle, distributed, dynamic, and network-dependent.

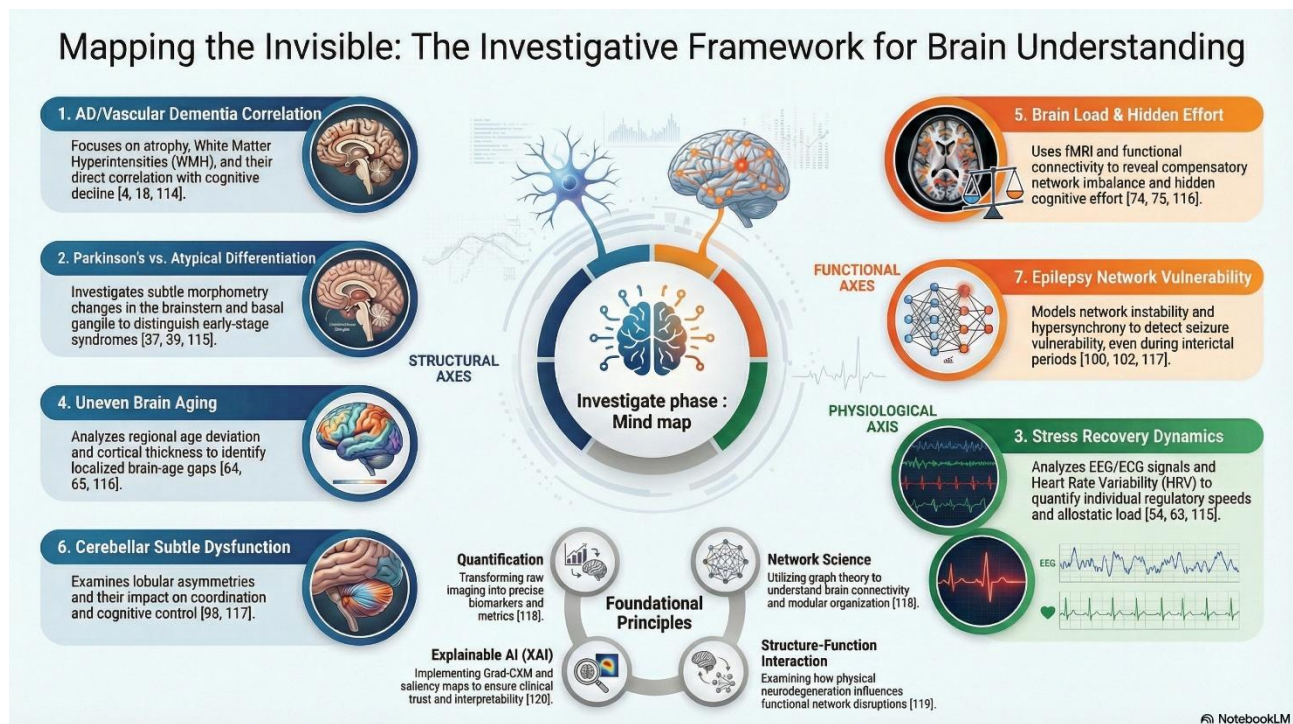
Structural imaging alone is insufficient. Functional imbalance may precede anatomical loss.

Regional asymmetry may signal early vulnerability. Network instability may persist despite normal scans. Physiological dysregulation may reveal hidden stress. Cerebellar modulation may influence cognition beyond motor control.

Therefore, making the invisible visible requires:

- Quantitative neuroimaging
- Network science
- Physiological modeling
- Explainable artificial intelligence
- Clinical co-validation

9.5 Mind Map: Cross-Axis Synthesis



9.6 Final Synthesis Statement

The Investigate Phase demonstrates that the brain holds significantly more information than routine observation reveals. By integrating structural morphometry, vascular burden analysis, functional connectivity modeling, cerebellar assessment, physiological regulation metrics, and network instability quantification, this project establishes a unified and clinically responsible framework for transforming hidden neural patterns into interpretable biomarkers.

In doing so, the investigation directly answers the essential question: the brain does hold more information than we have learned to see and through quantitative, explainable AI, that information can become visible, measurable

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