

Novel Relaxation-diffusion MRI Biomarkers for Early Detection of Alzheimer's Disease

Ning Hua¹, Lee E. Goldstein¹, Richard J. Rushmore¹, Yogesh Rath², Lipeng Ning²

¹Boston University, Boston, MA, USA, ²Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

1 Introduction

The Challenge: Early detection of AD is clinically vital but severely limited by current methods:

- Biofluids: Lack spatial resolution. CSF sampling is invasive, and blood biomarkers rely on delayed leakage from the CNS to the periphery.
- PET Imaging: Requires radioactive tracers that typically only detect late-stage, insoluble A β or tau deposits.
- Contrast MRI: Requires exogenous tracers that pose safety concerns regarding brain deposition.
- Structural MRI: Only detects macroscopic brain atrophy prominent in late-stage AD, missing early microstructural changes.

The Solution: Relaxation-diffusion MRI (rdMRI) samples multiple echo times and diffusion weightings to probe biochemical and microstructural heterogeneity.

Our Approach: By generating relaxation-diffusion distributions (RDD) to map joint transverse relaxation (R_2) and diffusion (D) profiles, we pioneered *in vivo* rdMRI to simultaneously and non-invasively detect these early AD biomarkers (A β , tau, and microvascular leakage).

2 Method

Animals: 3xTg-AD mice were bred and maintained at Boston University. Age- and sex-matched non-transgenic wild-type mice served as controls.

MRI Acquisition: Scans were conducted under 1–2% isoflurane anesthesia using a 9.4T/20cm Bruker BioSpec scanner equipped with a 23mm volume coil. A 2D-EPI sequence was employed with the following parameters: TR = 3200ms, FOV = 20 $\times$ 12.48mm², matrix = 128 $\times$ 80, and slice thickness = 0.5mm. Data included eight echo times (TE = 22 – 72ms) and eight diffusion weightings (b = 0 – 2500s/mm², 3 directions).

Data Processing: Relaxation-diffusion distribution (RDD) maps were estimated using a maximum-entropy algorithm.

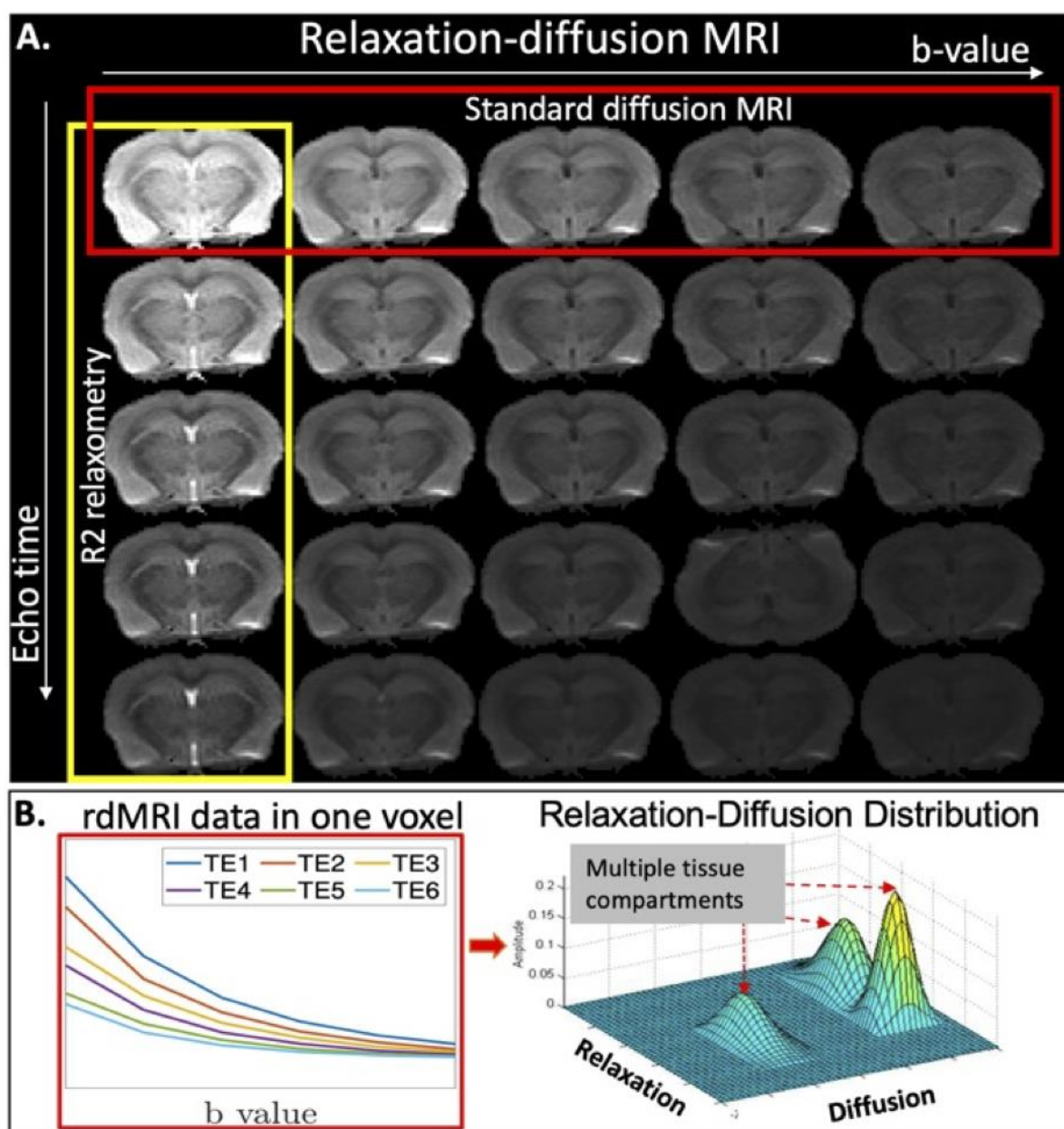
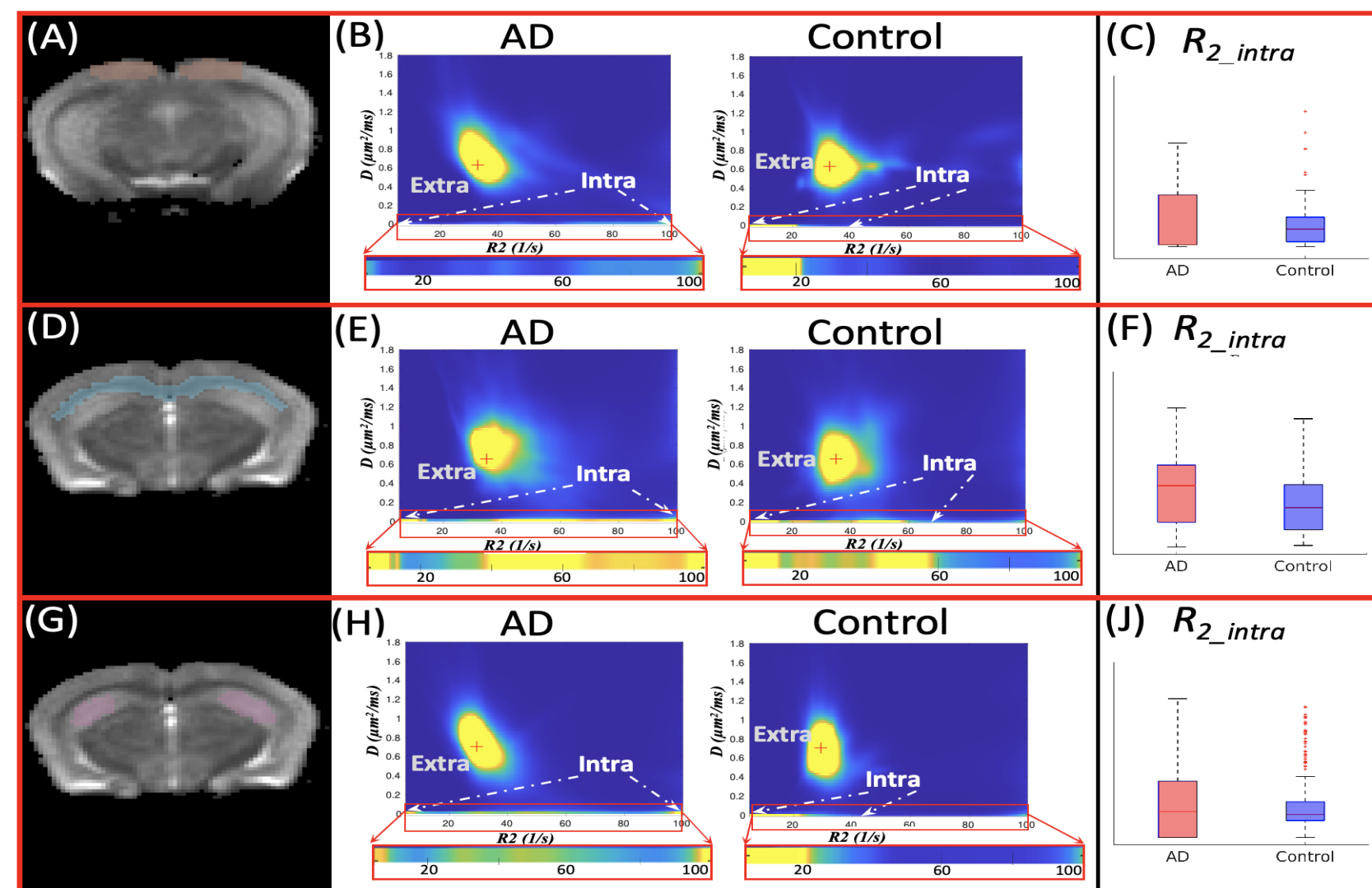


Figure: (A) illustrates the relaxation-diffusion MRI method that probes variable contrast in the joint space of b -values and echo times (TE s), which include the standard diffusion MRI and R_2 relaxometry as special cases. (B) shows the relaxation-diffusion distribution method that probes the intra-voxel microstructure of different tissue compartments.

3 Results

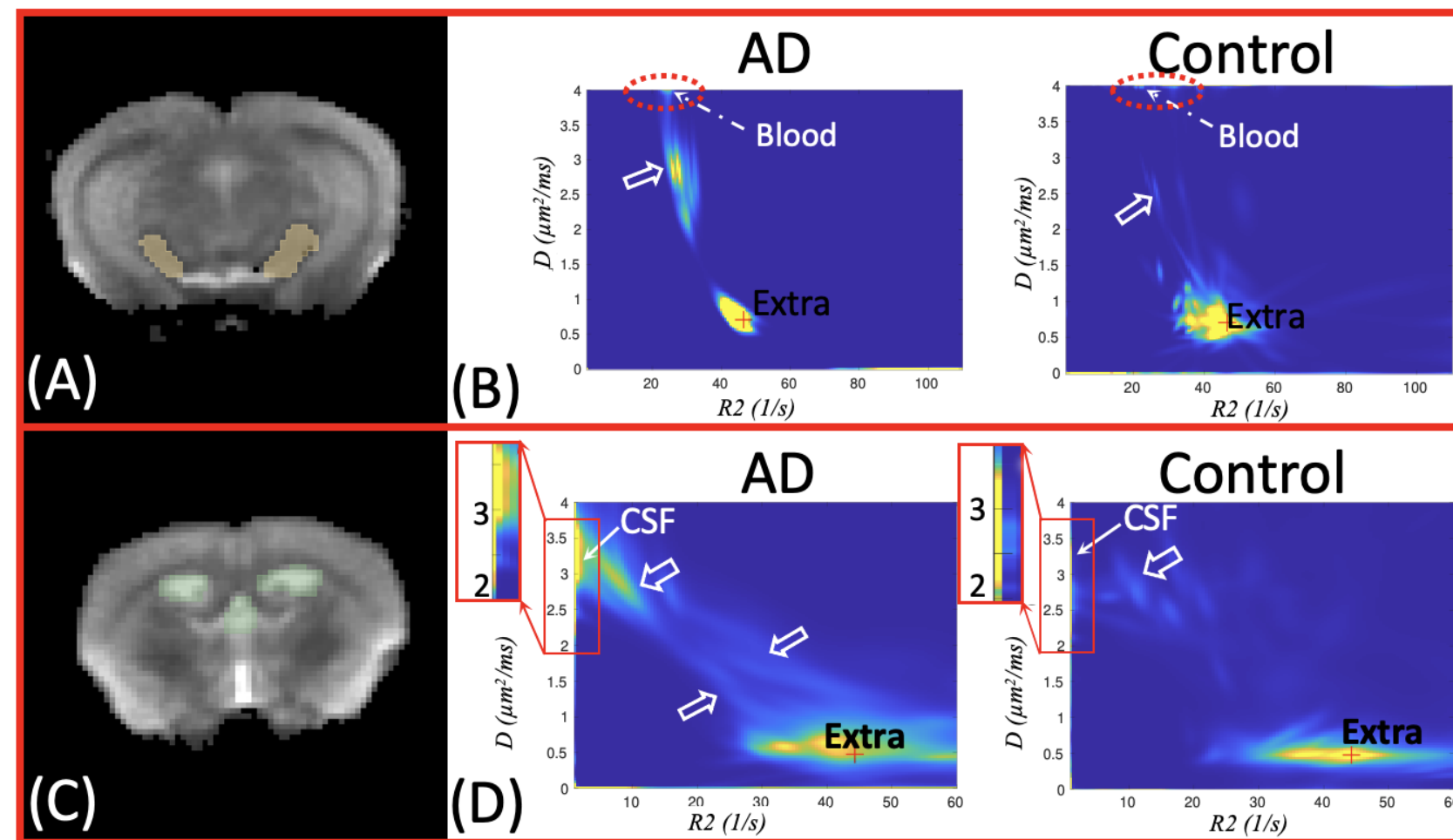
Pilot data (verify feasibility):

- One 3xTg-AD vs one wide-type control mouse (20 months old)



Results show:

- In cortex, white matter, and hippocampus, AD mice show broader/right-shifted intra- and extra-cellular R_2 .
- Elevated R_2 is consistent with greater macromolecular content in AD tissue.
- RDD localizes this effect to different tissue compartments instead of averaging the voxel.

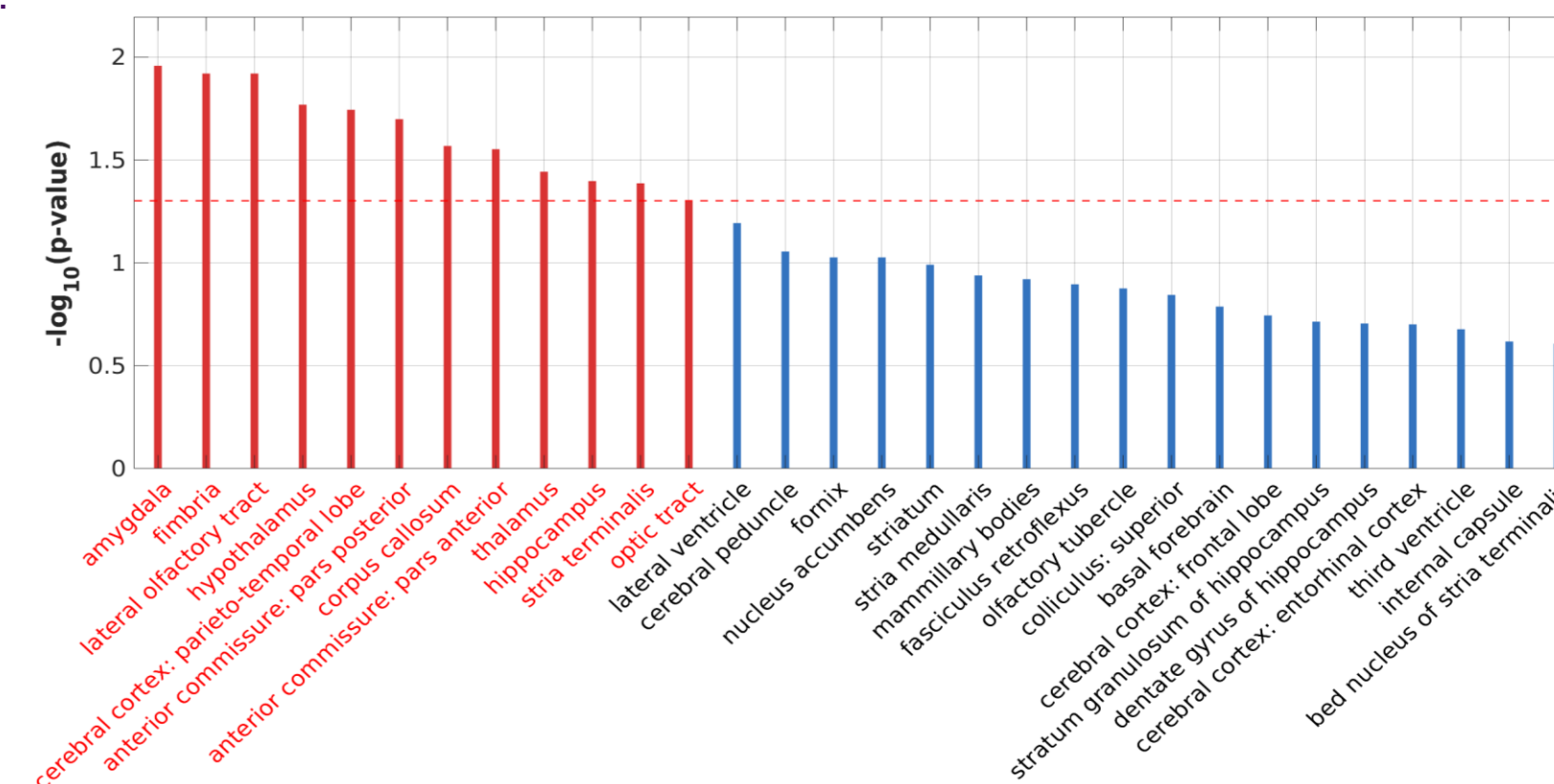


Results show:

- Vascular-rich regions and ventricles reveal CSF, extracellular, and blood-associated components.
- AD mouse shows increased water exchange components (hollow arrows), consistent with BBB/BCSFB disruption.

We expanded the study to focus on early detection of AD (3 months old):

- 3xTg-AD (n = 15, male = 8, female = 7) vs B6129F1 (n = 14, male = 7, female = 7)
- Random permutation tests based on J-Divergence between RDD.
- RDD Differences Between AD and Control Groups by Anatomical ROIs in Dorr atlas [Dorr et al., 2008].



Average RDD distribution from selected ROIs:

- AD show clear separation between intra and extra cellular spaces
- Enhanced "exchange water" compartments