# Investigating the role of axonal strain in brain white matter damage using biomechanical modelling of normal pressure hydrocephalus

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## I. INTRODUCTION

Mechanical loading of the brain, such as in traumatic brain injury (TBI) or normal pressure hydrocephalus (NPH), can damage brain tissue and the axons within it. Axon-oriented strain has been suggested as a superior biomechanical predictor of brain injury compared to the conventional maximum principal strain (MPS). However, this superiority has only been evaluated against binary injury classifications (e.g., concussion). To date, axon-oriented strain has not been evaluated against quantitative, in-vivo measures in human brain, limited by the lack of paired mechanical and neuroimaging data. Idiopathic NPH (iNPH), characterised by ventricular enlargement and white matter degeneration, provides a clinically relevant scenario in which such data are available [1-2]. Here we use iNPH data to evaluate whether axon-oriented strain better explains in-vivo white matter alterations, measured with diffusion imaging, than MPS. We also resolve this strain into tensile and compressive modes to explore their links with measured white matter abnormalities.

## II. METHODS

MRI scans of 22 NPH patients (8 females, age = 71.91 ± 7.06) and 30 healthy controls (HC) (14 females, age = 73.80 ± 5.71) were acquired and averaged to generate anatomical templates, from which a finite element (FE) brain model was developed [1][ 3]. Mechanical loading was applied at the ventricular linings using displacement fields derived from FE-based registration between the HC and NPH ventricles. The model predicted brain deformation, including changes in morphology and the distribution of Green–Lagrange strain.

Diffusion-weighted MRI scans from the HC cohort were averaged to generate a template representing the axonal anatomy of the brain. This template was used to extract voxel-wise axonal orientations and construct local coordinate systems with corresponding rotation matrices (Fig. 1). These matrices were used to project the global strain tensors predicted by the FE model into axon-based local coordinates, yielding strain tensors aligned with the local axonal direction. In addition, the MPS, a commonly used mechanical metric for predicting tissue damage, was calculated for comparison.

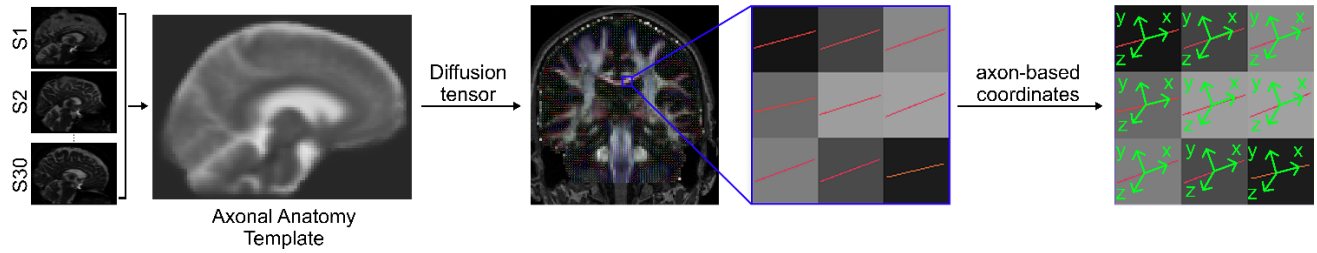


Fig. 1. Workflow of diffusion-weighted MRI processing and extraction of axonal orientations.

Fractional anisotropy (FA), a clinical metric reflecting the integrity of white matter tracts, was calculated for all subjects. FA maps were then averaged within each group to generate representative templates for HC and NPH. The voxel-wise difference between these templates was computed to quantify FA abnormalities in NPH patients (ΔFA). Finally, the associations between mechanical metrics predicted by the model, including MPS and axon-oriented strain, and ΔFA were evaluated using parcel-based Pearson's correlation.

## III. INITIAL FINDINGS

The model accurately reproduced the anatomical deformation and morphological changes associated with NPH, particularly change in the callosal angle and ventricular relative expansion in z axis (z-Evans) (Fig. 2(A)). The

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model reproduced the callosal angle and z-Evans index with relative errors of 0.7% and 1.8%, respectively.

Large MPS was concentrated in peri-ventricular regions (Fig. 2(B)). Axonal strain was changing from tensile to compressive in these regions, with corpus callosum (CC) fibres mostly in tension and corticospinal tracts fibres under both tension and compression. We found significant correlations between MPS and ΔFA in the corticospinal tract ($r = 0.62$, $p < 0.001$) and CC ($r = -0.55$, $p < 0.001$). We found stronger correlations between axonal strain and ΔFA, with $r = 0.73$ ($p < 0.001$) for corticospinal tract and $r = -0.60$ ($p < 0.001$) for CC (Fig. 2(C)).

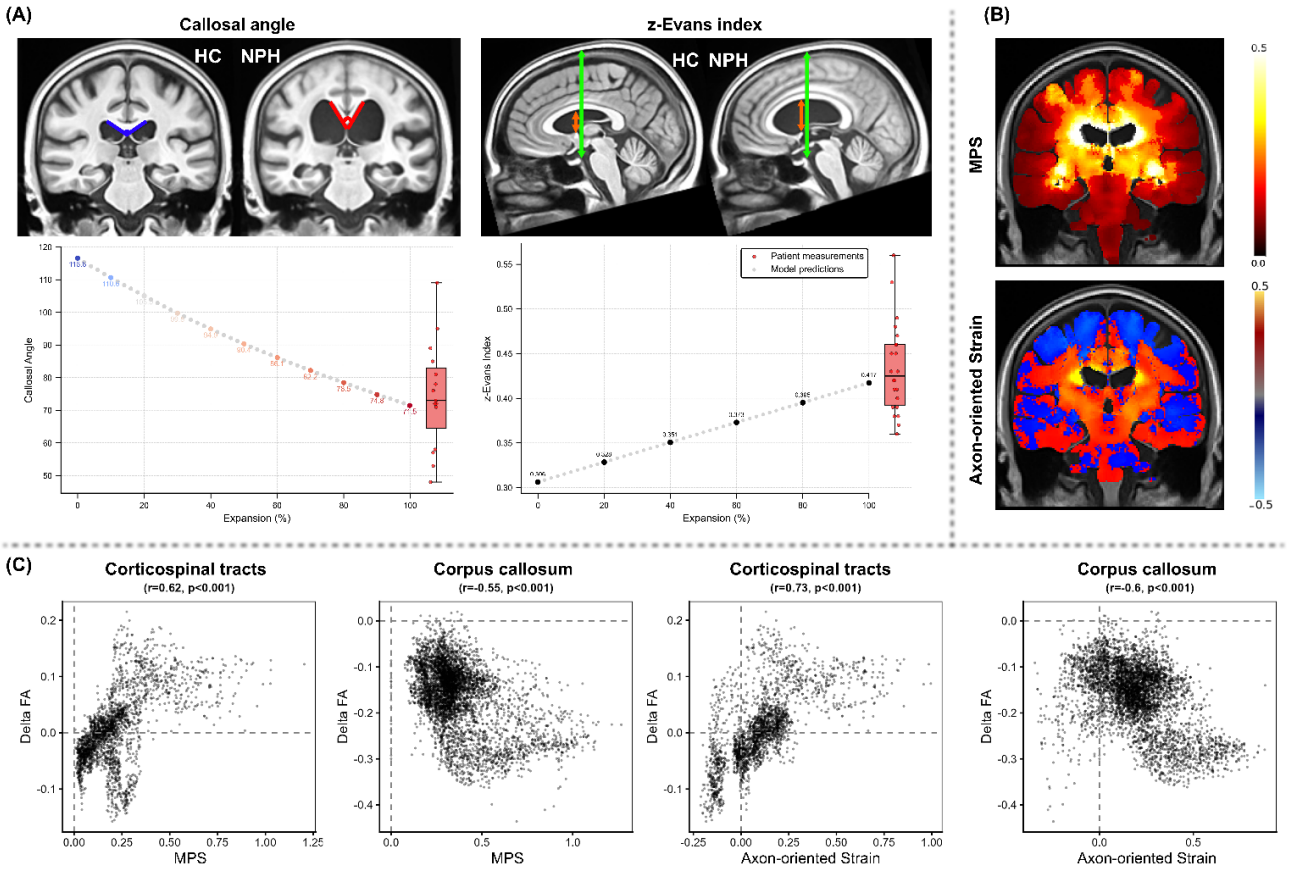


Fig. 2. (A) Model reproduction of key anatomical features of NPH. (B) Predicted strain distributions in the brain. (C) Correlation analysis between strain metrics and ΔFA.

## IV. DISCUSSION

The developed brain model for NPH demonstrated a strong ability to reproduce the morphological changes observed clinically, supporting its accuracy and validity. Strain concentration was predicted in the corticospinal tract and corpus callosum, which are also regions where FA abnormalities were observed in NPH patients.

Correlation analysis showed that both MPS and axonal strain were associated with ΔFA in both tracts, suggesting that mechanical loading may contribute to the observed FA abnormalities. However, axon-oriented strain consistently showed stronger correlations with ΔFA compared with MPS, and distinguishing between tensile and compressive modes indicated a greater ability to explain the specific mechanisms of axonal microstructural alterations. The different correlation patterns observed in corticospinal tract and corpus callosum may be due to the higher strain levels in the corpus callosum, which may have exceeded an injury threshold and lead to localised FA alterations, though understanding these patterns require further study. These initial findings suggest that axonal strain may provide a better mechanical metric for predicting white matter FA abnormalities due to mechanical loading, such as in NPH and TBI. To our knowledge, this is the first evidence in a living human brain that axon-oriented strain explains white matter abnormality (ΔFA) more closely than MPS, extending a superiority previously inferred only from predicting concussion as a binary, non-specific outcome in acute TBI. While correlating tract-specific strains with individual clinical outcomes is a critical next step, this requires future patient-specific modelling, as the current framework utilises a group-averaged head model.

## V. REFERENCES

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