Complexity Analysis of Resting State Functional Magnetic Resonance Imaging (rsfMRI) Data as an Early Diagnostic Tool for Alzheimer's Disease (AD)

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Introduction

AD is a progressively debilitating neurodegenerative disorder that impairs an individual's cognitive functions, including memory and critical thinking. Despite the fact that it is possible to identify AD by the characteristic accumulation of certain compounds in the brain, such as beta amyloid (Aβ) plaques, there are still gaps in the understanding of the pathogenesis of the disease; particularly the pathophysiological changes to the structure of the brain [1]. Additionally, at time of clinical diagnosis with current methods, a significant portion of the brain has Aβ plaques, which have irreparable cognitive effects; a tool for earlier diagnosis would greatly impact patients and families lives, and would result in huge cost savings of healthcare dollars.

Biologically based time-varying signals (e.g. resting state fMRI) can be classified as statistical fractals, since, at a physiologically limited scaling range, they will express self-similarity and self-invariance. As such, it is possible to calculate brain regional voxel-wise fractal dimension (FD), in other words spatially determine the physiological temporal complexity. Additionally, once D is known, the Hurst exponent ($0<H\leq1$), which relates to a fractal's scale-invariance, can be determined [2,3].

Previous work by our group has shown reduced time domain complexity in AD [4]. The central hypothesis of the current work is that AD characteristically impacts particular regions of the brain, creating a unique complexity signature, evident in frequency domain variants in H for those regions. We hypothesize that brain frequency complexity is reduced in AD and thus could be a metric for earlier diagnosis and possibly severity.

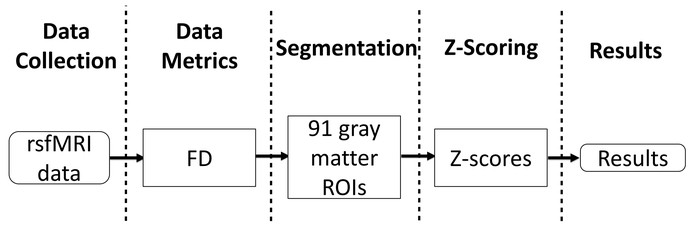
Materials and Methods

- 66 individuals (suspected early onset AD and healthy age/sex matched controls) from previously acquired data were analyzed.
- The data includes anonymized resting state fMRI and high resolution 3D T1-weighted structural MRI.
- Scans were reviewed by a neuroradiologist to remove patients with confounding conditions (e.g. stroke, normal pressure hydrocephalus, small vessel disease, etc.)
- Open source software was used to:
  - Convert raw fMRI data to Neuroimaging Informatics Technology Initiative (NIfTI) format
  - Correct for any distortions from subject motion and eddy currents generated during scanning
  - Correct inherent inhomogeneities in the main magnetic field (B_0)
  - Extract the brain from the surrounding skull/tissue
- Home-written MATLAB scripts were applied to:
  - Perform voxel-wise fractal analysis on each element of the preprocessed 4D brain matrices
  - Compare AD to healthy controls using severity scores

Data Preprocessing Specifics

- The FMRIB Software Library (FSL) is a repository of imaging tools that was used [5]. Analysis involved motion/eddy correction, extraction of brains from tissues, & warping to MNI152 atlas [7,8]
- The *dcm2niix* code, freely available from the Rordenlab GitHub, was used to convert raw MRI Digital Imaging and Communications in Medicine (DICOM) images from each scan to a singular NIfTI file [6].
- Matlab was used to convert rsfMRI signals from time to power spectral density, perform detrended fluctuation analysis, & calculate FD.
  - ROI-based analysis compared 91 regions with brain regional Z-score ($\boldsymbol{Z_{FD}}$) of ≤ -1.68 defined as clinically important

Data Processing



Brain Region	FD Z-Score
GM Primary motor cortex BA4a Left	-3.709953
GM Primary motor cortex BA4a Right	-5.990572
GM Primary motor cortex BA4p Left	-3.311505
GM Primary motor cortex BA4p Right	-5.263596
GM Primary somatosensory cortex BA1 Left	-1.135757
GM Primary somatosensory cortex BA1 Right	-3.01606
GM Primary somatosensory cortex BA2 Left	-1.884404
GM Primary somatosensory cortex BA2 Right	-2.955067
GM Primary somatosensory cortex BA3a Left	-2.256508
GM Primary somatosensory cortex BA3a Right	-4.39945
GM Primary somatosensory cortex BA3b Left	-1.812209
GM Primary somatosensory cortex BA3b Right	-3.512752

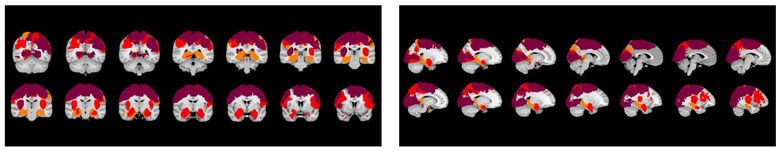


Figure 1: Workflow for the functional complexity analysis of rsfMRI data is shown above. Below are results for an example patient displaying the $\boldsymbol{Z_{FD}}$ values for the respective brain regions. Images are MNI brain masks with rsfMRI analysis overlayed in axial and coronal views.

Results

- The most affected regions were secondary somatosensory cortex (73.7%), Broca's area (63.2%), amygdala (52.6%), insula (42.1%), and hippocampus (36.8%). For predicting ODB, significant metrics included hippocampal volume (P<0.004), sex (P<0.04), and age (P<0.0005), with interaction terms of age:sex (P<0.02) and age:hippocampal volume (P<0.002).

Results

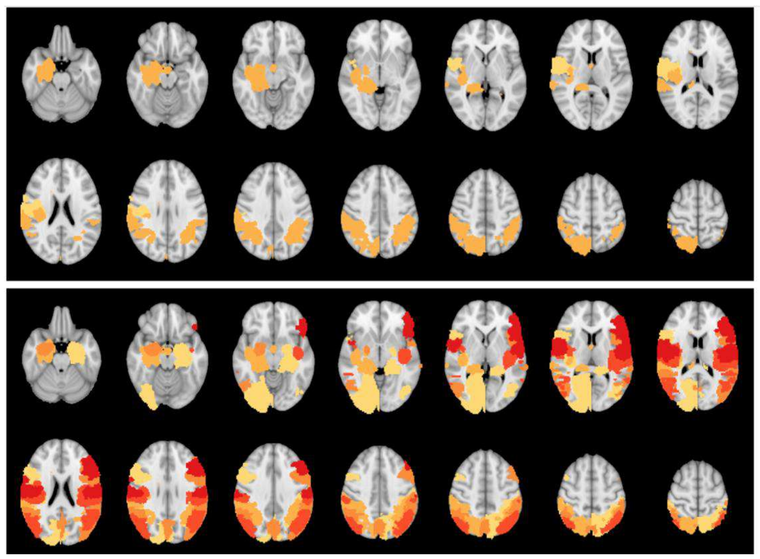


Figure 2: Results from mild (top) and severe (bottom) subjects showing:
A) Axial views with regions that have a $\boldsymbol{Z_{FD}}$ that is significantly decreased ($\boldsymbol{Z_{FD}}$ ≤ -1.68 standard deviations) from the healthy controls
B) Highlighted regions are colour coded to indicate severity of reduction in temporal complexity
→ It is possible to distinguish between the earlier/more advanced subjects by visual inspection alone.

- The algorithm was able to successfully map the spatial variation in Hurst exponent. Group statistical analysis was able to spatially localize and highlight common brain regions among AD patients that were starting to lose their temporal complexity.

Conclusions

- FD may be a useful metric in the assessment of suspected AD. Future analysis will include neurocognitive scores (e.g., MMSE) and additional brain volumetric measures.

References

1. Iliff J., et al. (2012) Sci Transl Med. 15;4(147):147ra111.
2. Eke A., et al. (2000) Eur Jrnl Phys. 439(4):403-15.
3. Eke A., et al. (2002) Phys Msrmnt. 20(1):1-38.
4. Warsi M., et al. (2012) Magn. Reson. Matls Phys. Biol. Med. (MAGMA) 25(5):335-344.
5. Smith S., et al. (2009) NroImg. 45:S173-86.
6. Rorden C., et al. (2016) J Neurosci Methods. 264:47-56.
7. Smith S., (2002) Hmn Brn Mpng, 17(3):143-155.
8. Andersson J., and Sotiropoulos S., (2016) NroImg. 125:1063-1078.

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I am a PhD candidate in McMaster's Biomedical Engineering department. My supervisor is Dr. Michael Noseworthy and I am studying how medical imaging technology (magnetic resonance imaging) can be used to earlier diagnose and develop severity metrics for neurodegenerative disorders, particularly Alzheimer's Disease. I am passionate about improving the lives of patients and their families through the application of engineering in healthcare specifically regarding neuropathologies. My goal is to pursue a career in the interdisciplinary field of biomedical engineering that synergistically merges research and industry to improve the health and well-being of individuals in society through advancing patient care.