Progress Report

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Title of Project: Screening for *de novo* brain morphology changes in frontotemporal dementia

Summary*:*
Frontotemporal dementia (FTD) refers to a collection of younger-onset dementia syndromes which strike individuals in their 50-60's, producing stark changes in behaviour and personality, language and/or motor skills. These changes reflect the progressive atrophy of frontal and/or temporal brain regions, that support complex functions such as decision-making, personality, social cognition, and language. With no treatments to halt or slow the progression of FTD, individuals become severely impaired in everyday functioning and increasingly dependent on family members.

A major barrier to the accurate diagnosis and management of FTD is its common misdiagnosis as a psychiatric problem or as an atypical variant of Alzheimer's disease (AD). Reliable *in vivo* diagnostic markers of dementia are scarce, with most available only in research settings (e.g., PiB-PET imaging) or requiring invasive procedures (e.g., CSF examination). As such, neuroimaging techniques are becoming increasingly important for the early diagnosis of FTD. Current imaging metrics, however, only partially capture the structural complexity of the cerebral cortex and show poor sensitivity to detect subtle brain changes in early stages of the disease course.

With the support of the Brain Foundation, we leveraged current advances in neuroimaging to improve the specificity and sensitivity for a diagnosis of FTD. We proposed that the natural folding of the cerebral cortex represents a clinically useful biomarker for the early detection of FTD. In collaboration with Dr. Christopher Madan at the University of Nottingham, we sought to establish whether a measure of cortical folding (fractal dimensionality) could serve as a biomarker to assess structural brain changes in FTD. Dr. Madan's pioneering work on cortical fractal dimensionality demonstrates age-related and inter-individual brain differences in comparison with traditional measures of cortical thickness. Moreover, the fractal dimensionality method shows superior detection of subtle changes within relatively small subcortical structures, reinforcing its utility in dementia screening.

Study objectives:
We proposed that subtle changes in the folding of the cortical ribbon, as detected by fractal analysis, would afford increased sensitivity in detecting FTD. Leveraging **CI Irish's** expertise in clinical and cognitive characterisation of FTD and **CI Madan's** experience in the development of computational neuroanatomy methods, we employed fractal analyses to determine the morphometric footprint of well-characterised cases of clinically established FTD versus clinically probable Alzheimer's disease.

We recruited 30 behavioural variant frontotemporal dementia (bvFTD), 30 Alzheimer's disease (AD) patients, and 30 healthy older Controls for inclusion in this study. Participants were matched for age, sex, and years in formal education. Patient groups were matched for level of cognitive and functional impairment. All participants underwent comprehensive cognitive assessment and structural T1-weighted neuroimaging using the following sequences: coronal orientation, matrix 256 x 256, 200

slices, 1 x 1 mm in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8ms, flip angle α=8°. These scanning sequences were chosen as optimal for examining cortical thickness, and the new fractal analysis techniques.

Analytic techniques:

MRI data was processed using FreeSurfer and MATLAB toolboxes developed by Madan, in particular, calcFD, which estimates fractal dimensionality. This measure of brain structure has been shown to be sensitive to aging and other individual-difference factors, but also particularly robust to confounding factors including head position (test-retest reliability) and head motion. The fractal dimensionality method measures the relative size of a structure across multiple resolutions to calculate the complexity of the structure based on the relative change in spatial fidelity.

Hypothesis vs Findings

We hypothesised that overall fractal dimensionality would be significantly lower in both patient groups versus Controls, but that disease-specific differences would be evident in distinct regions of interest. Specifically, we predicted that alterations in cortical folding would be most pronounced in frontal and insular cortices in the FTD group.

Our work is still in progress, but we observe clear differences in the surface topology of the two types of dementia, with Alzheimer's disease changes particularly pronounced in temporal and parietal regions, while FTD changes were most pronounced in frontal and temporal regions (Figures 1 & 2).

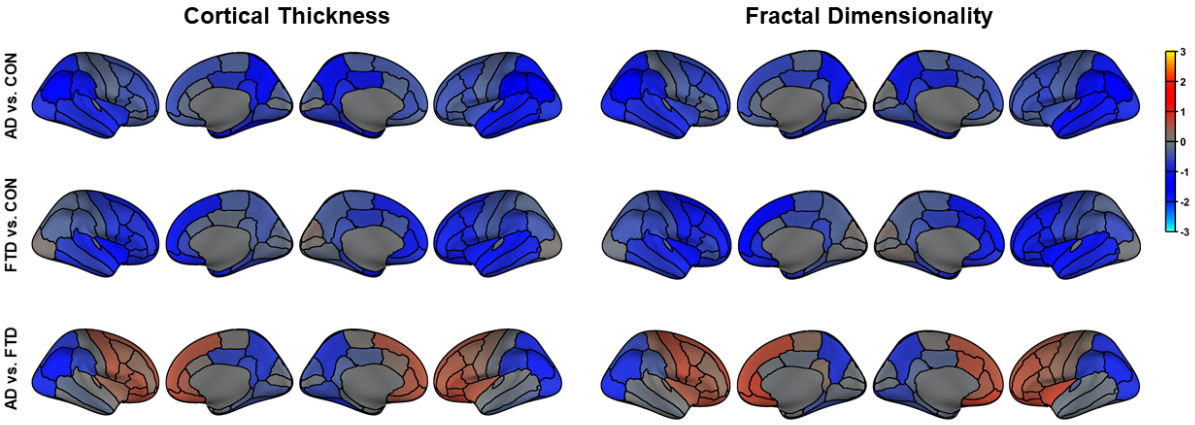

Figure 1. Changes in cortical thickness and fractal dimensionality in AD and FTD patient groups. Effects are present in both cortical thickness and gyrification. Differences are plotted as Z-scores of the relevant sample estimates, to make the two measures more comparable. As visible in the last row, the two patient groups have distinct topologies.

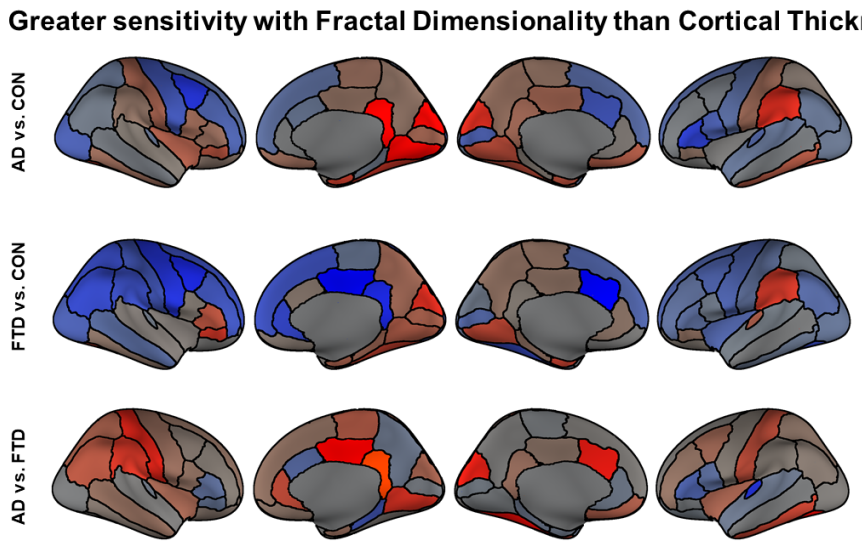

Figure 2. Direct comparison of cortical thickness and fractal dimensionality measures in AD and FTD. Colour scale adjusted to provide greater sensitivity. Fractal dimensionality demonstrates relatively global differences in the topology of the two types of dementia. These differences correspond to differences in regional complexity of the underlying cortical brain structure that are not apparent with conventional measures of cortical thickness and gyrification (gyrification not shown here).

Unanswered Questions

Our findings demonstrate that changes in superior frontal and medial regions represent a potential morphometric footprint of FTD, however it remains unclear at what point in the disease trajectory these changes occur. We are currently exploring these questions in genetically "at-risk" individuals and hope to soon present new data on the predictive efficacy of fractal dimensionality to detect subtle changes in prodromal phases of FTD.

What these research outcomes mean

Despite significant advances in the field, we currently lack a gold-standard imaging biomarker that can reliably detect the earliest pathological signatures of FTD. The current findings extend our understanding of changes in brain morphology in FTD, which distinguish it from disease-matched cases of AD. We are currently working on other characterisations of brain morphology, such as measurements of sulcal morphology and novel shape properties (e.g., texture and topological spatial frequency) of cortical and subcortical brain regions. Given the intense global effort to discover clinically sensitive imaging biomarkers, our findings contribute an essential missing piece of the puzzle regarding the morphometric footprint of FTD that will enable us to improve the diagnostic screening process, and to better monitor and predict disease progression.