Shape Changes in the Dentate Nucleus in Individuals with Friedreich Ataxia Assessed using Quantitative Susceptibility Mapping

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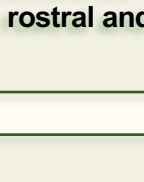
BACKGROUND

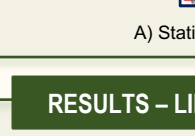
Friedreich ataxia (FRDA) is the most common inherited spinocerebellar disease.[1]

1. Individuals with FRDA experienced loss of muscle control and poor balance. [1]

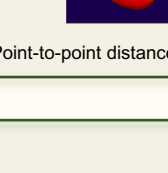
2. 

Caused by GAA multiplication on FXN gene, leads to nervous system damage. [1]

3. 
Pathology primarily in the cerebellar dentate nucleus, showing general volume reduction.[2,3,4]

4. 
Dentate nucleus (DN) is divided into motor and non-motor regions. [5]

5. 
Examining the DN may offer a better evaluation of disease progression. [1,3,4]

6. 
Shape analysis as a novel and sensitive approach to understand structural changes.[3,4]

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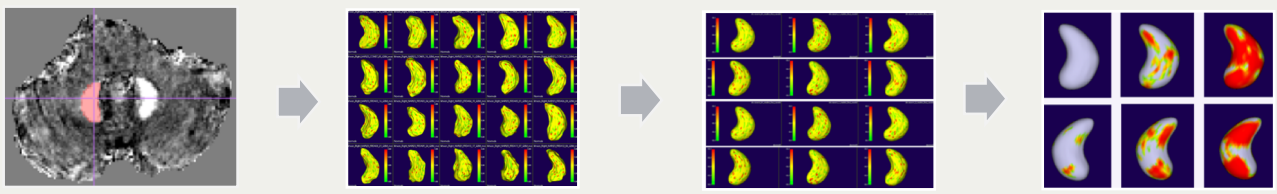
OBJECTIVES

1. Examine the **regional structural changes** of dentate nucleus in individuals with Friedreich Ataxia relative to healthy controls.

2. Examine the **correlations** between **regional structural changes** and **clinical parameters** (disease severity, disease duration, GAA repeat length, age at onset) within the dentate nucleus in individuals with Friedreich Ataxia.

METHODOLOGY

- Retrospective cross sectional study with data collected from three studies, using MRI technique called **Quantitative Susceptibility Mapping** (QSM).
- QSM images of **51 FRDA** patients and **47 controls,** with clinical data (disease severity, disease duration, GAA repeat length, age at onset) from FRDA cohort.
- **Shape analysis** to examine regional structural changes.
- Statistical analysis using Student's T-test and Spearman's correlation test.



Step 1: Manual segmentations of the dentate nucleus (FSL software)

Step 2: Construction of the 3D surface map (SlicerSALT software)

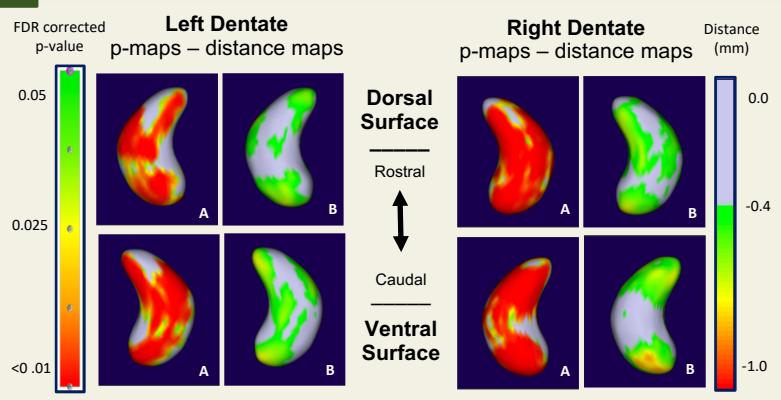
Step 3: Anatomical orientation and mean shape creation

Step 4: Statistical analysis of group difference and correlations

RESULTS – MEAN GROUP DIFFERENCES

Mean Group Differences

- **Atrophy** in patients relative to controls (p_{FDR}<0.05)
- Located on both the **left** and **right** dentate nuclei across almost all of the **dorsal** and **ventral** surfaces.
- Difference was largest in the **rostral and caudal** portions.

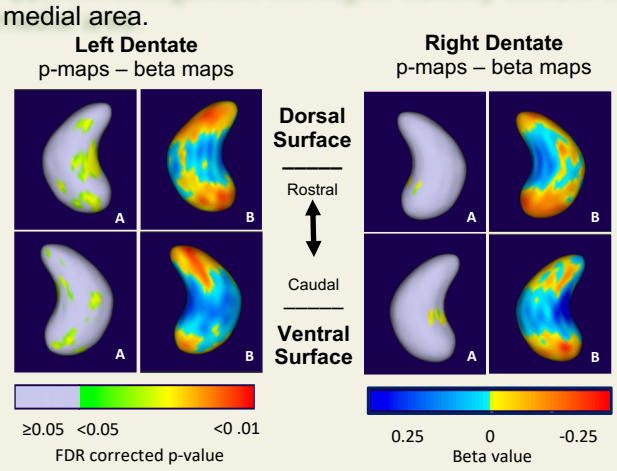


A) Statistically significant area of atrophy; B) Point-to-point distance of specific surface points

RESULTS – LINEAR CORRELATIONS

Clinical Correlations with Disease Severity

- **Limited correlation area**, left lateralised (p_{FDR}<0.05).
- **Greater atrophy with higher severity score** in the rostral and caudal portions.
- Apparent enlargement with higher severity score in the medial area.



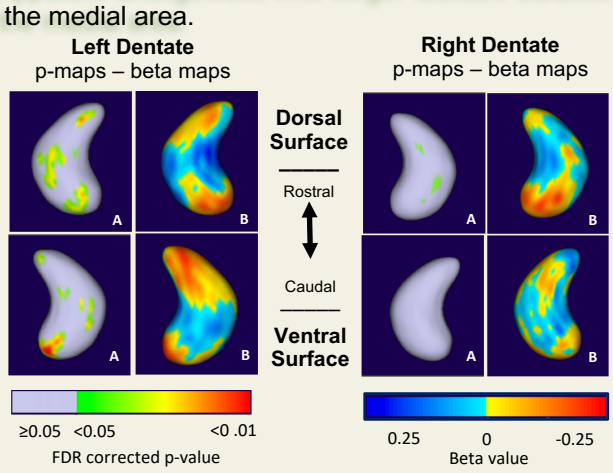
A) Area of correlation; B) Gradient of shape changes

Clinical Correlations with GAA Repeat Length

- **No correlation** with shape changes was found in either dentate (p_{FDR}<0.05).

Clinical Correlations with Disease Duration

- **Limited correlation area**, left lateralised (p_{FDR}<0.05).
- **Greater atrophy with longer disease duration** in the rostral and caudal portions.
- Apparent enlargement with longer disease duration in the medial area.



A) Area of correlation; B) Gradient of shape changes

Clinical Correlations with Age at Onset

- **No correlation** with shape changes was found in either dentate (p_{FDR}<0.05).

DISCUSSION

Dentate Shape Abnormalities

- Heterogeneous atrophy throughout the dentate nucleus was **not specific to motor regions**.
- Areas of atrophy likely corresponds to the dentate nucleus grey matter.

Correlations with Neurodegenerative Aspect

Correlations with degenerative processes were represented by disease severity and duration.

- Progressive atrophy might correspond to cellular degeneration (grey matter) of the dentate nucleus.
- Apparent expansion in medial areas likely to occur as an epiphenomenon in FRDA.
- Lateralised correlation toward the left dentate nucleus might indicate differential susceptibility to progressive degeneration between the left and right side in FRDA.

No Correlations with Neurodevelopmental Aspect

Correlations with developmental aspect were reflected by GAA repeat length and onset age.

- This study found no evidence in favour of a strong developmental component in the dentate nucleus.
- The developmental abnormalities might have subtle impact relative to the degenerative processes.

CONCLUSION

This is the **first study** to examine regional shape changes in the dentate nucleus in FRDA individuals using shape analysis.

- There are **non-homogeneous atrophy**, particularly in the grey matter of the dentate nucleus, among individuals with FRDA.
- The regional shape changes of the dentate nucleus are **associated** with the **neurodegenerative** process in FRDA.
- These findings demonstrated the potential of shape analysis as a **marker of disease progression**.
- Longitudinal observations would be helpful to assess shape changes as the disease progresses.

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