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# MRI-Derived Markers of Disease Progression in Early Versus Late PSP and CBS

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## Objective

***To determine which MRI biomarkers are sensitive to disease progression early in disease course as compared to later, for progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS).***

## Background

Future tau-targeted clinical trials will need sensitive biomarkers of disease progression. The utility of some biomarkers may depend on disease stage. Here we investigate the rates of change in measures derived from T1- weighted images and diffusion tensor imaging (DTI) data from the 4 Repeat Tau Neuroimaging Initiative (4RTNI). 4RTNI is a multicenter dataset of longitudinal multimodal data for the pure tauopathy FTLD syndromes of PSP and CBS. Volumetric measures of white matter (WM) and grey matter (GM) atrophy may be obtained from the T1 images, and measurements reflecting WM microstrostructure can be derived from the DTI data. Previous longitudinal studies in PSP and CBS have demonstrated overall greater DTI changes in CBS as compared to PSP[1], greater supratentorial DTI change in CBS and greater infratentorial DTI change in PSP[2], as well as continued progression of supratentorial white matter degeneration and midbrain atrophy in PSP[3]. However, the rate of focal degenerative change over the full disease timespan remains unclear[4,5,6]. Better understanding the rate of change of microstructural (DTI) versus macrostructural (volumetrics) MRI biomarkers in early versus late stage diseases will help to clarify appropriate use of these imaging biomarkers. Since disease staging for PSP and CBS is still an open question, here we use symptom duration as a proxy for disease stage.

**Hypothesis 1:** Patients with a shorter disease duration will show more rapid rate of change on MRI measures than patient with a longer disease duration.

**Hypothesis 2:** There will be greater rate of change in WM measures than GM measures, regardless of disease stage.

## Methods

*Participants*

| PSP Subjects (at Baseline) | SHORT | LONG | p-value* |
|---|---|---|---|
| n | 8 | 12 | |
| Age (mean (sd)) | 66.12 (8.59) | 71.64 (7.84) | 0.164 |
| Sex | 3M , 5F | 4M , 8F | |
| Years of Education (mean (sd)) | 13.88 (1.55) | 16.08 (3.82) | 0.141 |
| CDR Global (mean (sd)) | 0.62 (0.23) | 0.71 (0.58) | 0.707 |
| PSP-RS Total (mean (sd)) | 23.75 (5.04) | 42.10 (15.43) | 0.005 |

| CBS Subjects (at Baseline) | SHORT | LONG | p-value* |
|---|---|---|---|
| n | 8 | 10 | |
| Age (mean (sd)) | 62.25 (5.28) | 67.10 (6.97) | 0.123 |
| Sex | 4M , 4F | 4F , 6M | |
| Years of Education (mean (sd)) | 20.38 (4.60) | 16.00 (2.49) | 0.020 |
| CDR Global (mean (sd)) | 0.56 (0.32) | 0.55 (0.37) | 0.941 |
| PSP-RS Total (mean (sd)) | 19.88 (6.73) | 23.78 (12.07) | 0.432 |

*** by t-test**

Patients from the 4RTNI data were dichotomized into two groups:
**SHORT: disease duration ≤ 2yr LONG: 5yr ≤ disease duration < 10yr**

*Imaging*

T1 images were processed using the Freesurfer longitudinal pipeline[7] and the brainstem structures segmentation pipeline[8]. DTI images were preprocessed using publicly available preprocessing scripts[9], and diffusion metrics were quantified via nonlinear registration of FA images to the JHU-ICBM atlas via ANTs[10]. ROIs were selected for analysis based on prior studies[1,3,11]: Total WM, total GM, precentral and postcentral gyrus, midbrain (T1 only), superior cerebellar peduncles. Five subjects had useable DTI but not useable T1 imaging data (3 PSP-LONG, 1 CBS-SHORT, 1 PSP-SHORT)

*Analysis*

For subjects with 2 or 3 time points of useable data, a linear model was fitted and the slope was extracted. Group differences in slope were then assesed via t-test. All statistical analyses were performed using R.

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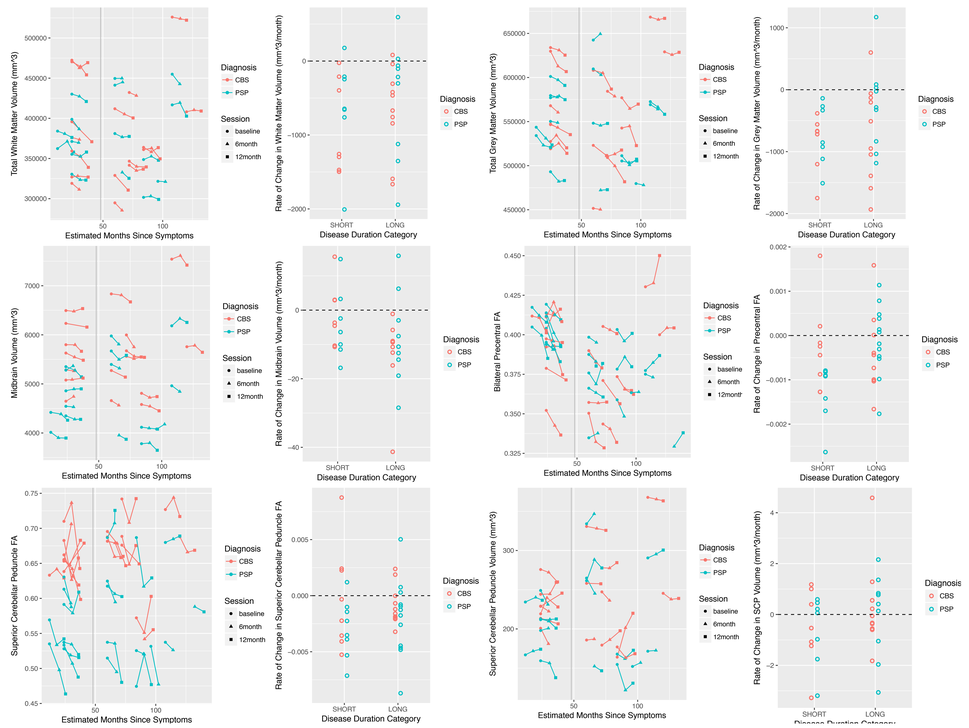


***Figure 1:*** *Plots showing the timecourse of MRI-derived measures, based on reported symptom duration at baseline, along with their rates of change by a two- or three-point linear fit.*

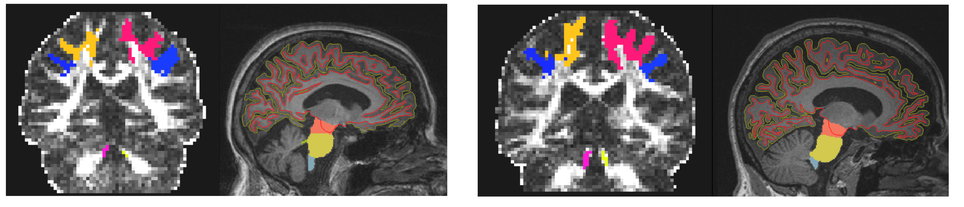

***Figure 2:*** *Example DTI and T1 parcellations for a PSP-LONG subject (left) and a CBS-LONG subject (right)*

## Results

- Precentral FA shows a greater rate of change in PSP-SHORT than PSP-LONG (p= 0.0025)
- Midbrain volume shows a greater rate of change in CBS-LONG than CBS-SHORT (p= 0.036)
- Rates of change for total WM and GM volume appear comparable for long and short disease durations, in both PSP and CBS

## Conclusions

- Rapid precentral change occurs early and is specific for PSP
- There appears to be a trend for more rapid change in early disease stages
- Late midbrain atrophy in CBS may be indicative of underlying PSP pathology

## Future Directions

- Inspect additional supratentorial white matter tracts including the corpus callosum
- Add ROIs for caudate and cerebellar subregions
- Await pathologic confirmation (3 PSP cases confirmed)

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