

Functional Connectivity Changes of the *Locus Coeruleus* in Alzheimer's Disease

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1. Background

- The *Locus Coeruleus* (LC) is a nucleus situated in the pons, and the primary source of central nervous system noradrenaline, with widespread projections and rich connectivity with multiple brain regions.
- Studies have shown that the earliest pathology associated with Alzheimer's Disease (AD) is the presence of neuro-fibrillary tangles within LC neurons¹, accumulating decades before the onset of clinical AD².
- Neuromelanin-sensitive MRI (NM-MRI) allows visualisation of both the LC and *substantia nigra*³, however this imaging technique has been largely restricted to Parkinson's Disease.
- Despite it being well-documented in the literature that degeneration of the LC is closely associated with AD^{4,5}, current studies employing NM-MRI have been testing LC signal intensity, rather than the functional connectivity of the LC.
- In this study we used a combination of NM-MRI, structural MRI and resting-state functional MRI to test the functional connectivity of the LC in AD patients and controls.

2. Methods

- NM-MRI, structural MRI and resting state functional MRI scans were acquired for 25 well-matched healthy aging controls and 23 AD patients in an Alzheimer's Research UK funded project. Two of the controls were excluded due to poor quality MRI scans. Therefore, the data from 23 AD patients and 23 controls entered into final analysis
- Of the 23 AD patients, 11 were classified as Mild AD patients and 12 were classified as Moderate AD patients
- All eligible participants gave their written, informed consent before taking part in assessments in the Memory Assessment Research Centre, Department of Medical Physics at University Hospital Southampton, and the School of Psychology, including measurements of inflammatory markers and genetic measures and completion of a standardised questionnaire assessing cognitive function, before completion of structural, NM and resting state functional MRI scans.
- The scans were skull-stripped, registered and normalised to the MNI152_t1_2mm_brain template using the FMRIB Software Library.
- LC masks were created using the NM-MRI scans, allowing isolation of these voxels for analysis
- The subsequent data were processed using the CONN toolbox on MATLAB
- Seed-to-voxel and ROI (region-of-interest) to ROI analyses were used to produce connectivity maps and comparisons were conducted between AD and controls, left and right LC, mild and moderate AD, and resting state networks

Figure 1: ROI-to-ROI connectivity maps for AD patients and controls

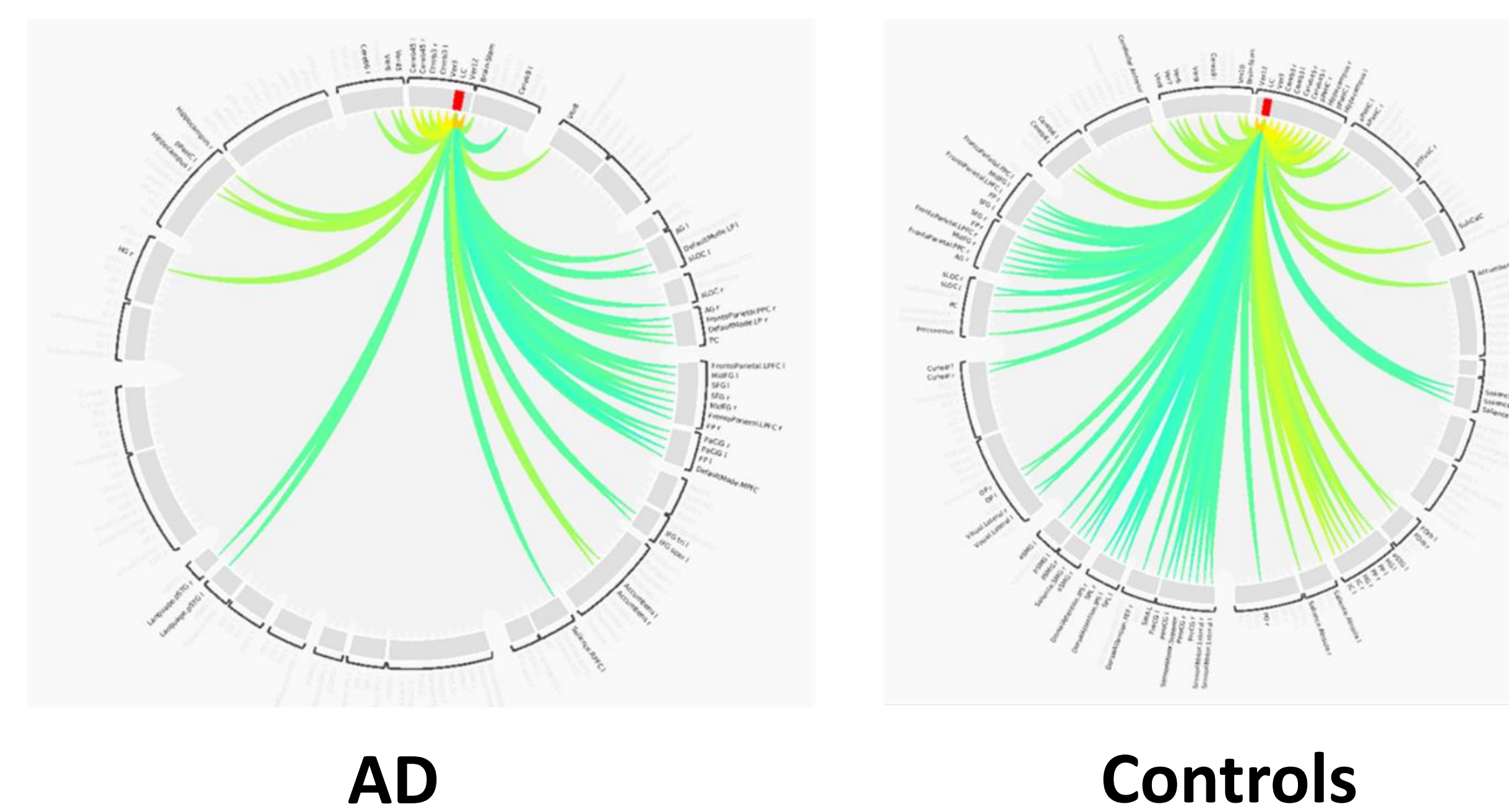


Figure 2: Seed-to-voxel connectivity maps for AD patients and controls

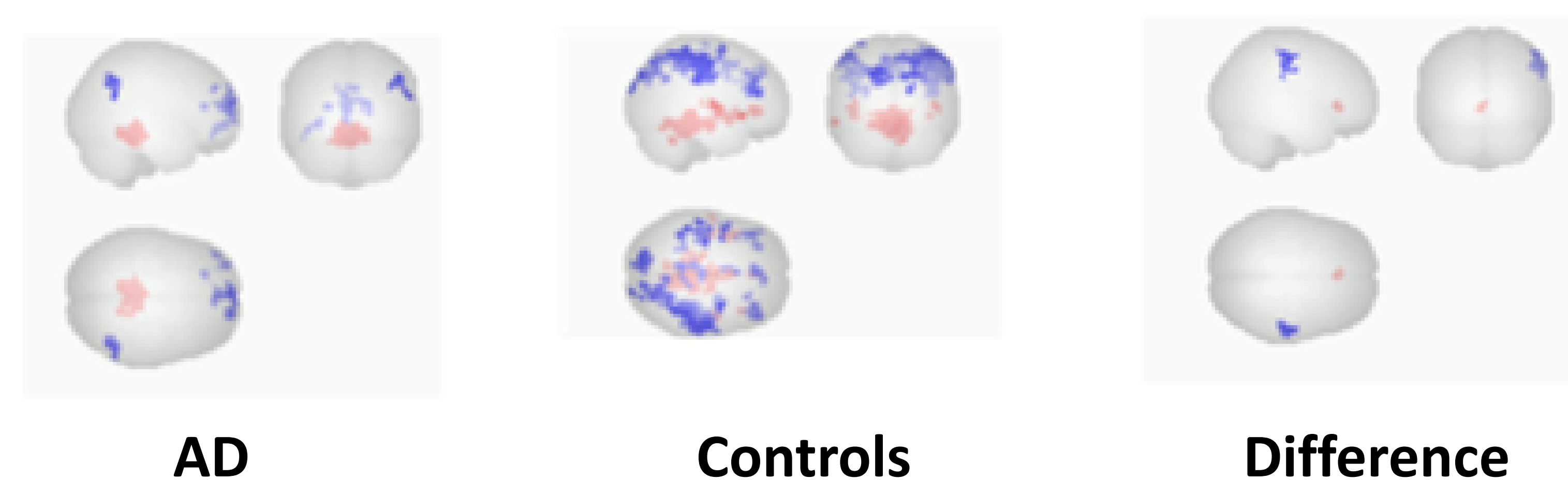
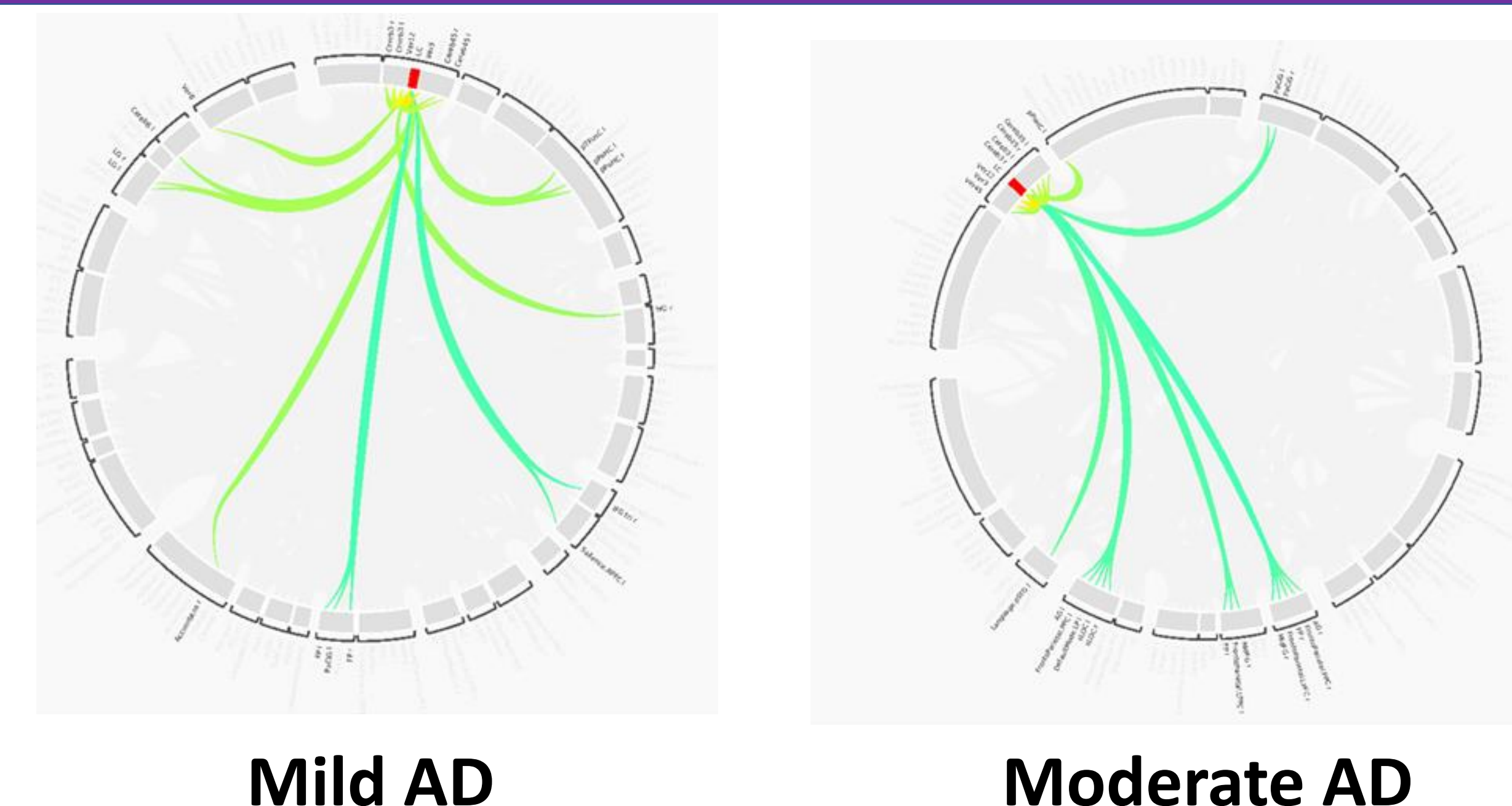


Figure 3: ROI-to-ROI connectivity maps for Mild AD and Moderate AD



3. Results

- AD patients had connections from the LC to only 43 brain regions, compared to 80 brain regions in the controls (Figure 1)
- In comparison to controls, AD patients had reduced LC connectivity in the subcallosal cortex (p-FDR=0.016417), increased LC connectivity in the right supramarginal and postcentral gyri (p-FDR=0.000002), and reduced connectivity in the default mode network (p-FDR=0.000286) and sensorimotor network (p-FDR=0.027524) (Figure 2).
- The left LC in the AD patients had significant connections to only 56 brain regions compared to the 81 brain regions in the right LC.
- In particular, the left LC had decreased number of significant connections to the amygdala and vermis, compared to the right LC.
- The number of significant connections from the LC to other brain regions decreased with progression from controls to mild AD patients to moderate AD patients.
- The default mode network and sensorimotor networks showed loss of connectivity in AD, in regions consistent with previous studies.

4. Conclusions

- This study provided new evidence of reduced connectivity of the LC in AD patients.
- There was also an asymmetrical reduction in the connectivity of the left LC compared to the right.
- Further research into the connectivity of the LC in mild and moderate AD patients is required as our seed-to-voxel and ROI-to-ROI analyses had conflicting results.
- A reduction in functional connectivity of the LC could indicate pathogenesis and progression of AD, aiding prediction of disease progression and development of novel intervention targets.
- Our recommendation is a future longitudinal study with a larger sample size to allow for greater investigation into the causality of the correlation between LC degeneration and AD, which this study has helped to support.

5. References

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