Resting or fluctuating activity?
A resting state fMRI study in Lewy Body Dementia

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Introduction

Dementia with Lewy Bodies (DLB) is a common age-related neurodegenerative disorder, causing considerable disability and distress. Named after the deposits of protein seen within the nerve cells, their presence is linked to low levels of acetylcholine and dopamine and to a loss of inter-neuron connectivity. Characterised by the classical triad of symptoms: Parkinsonism, complex visual hallucinations and cognitive fluctuations (CF's). Relatively speaking the latter symptom is the least studied, although reasoning suggests that it holds great promise. CF's are particularly common in DLB, as well as being qualitatively different, in comparison to other dementia's such as Alzheimer's Disease (AD).

Resting state fMRI was used to test the hypothesis that CF's are related to alterations in the brain's dynamics. This involves the evaluation of interactions that occur whilst not performing an explicit task; many anatomically separated whilst functionally connected regions have been identified using this approach. The prominent Default Mode Network (DMN) and Attentional System most notable in relation to AD and DLB respectively.

Aims

- Assess the stability of the RSN's with a notion towards correlating the temporal differences with cognitive fluctuations. Previous research has shown a significant negative correlation between the DMN and Attentional system; the initial aim was therefore to reproduce these findings using our data.
- The hypothesis was that DLB displayed an altered, possibly unpreserved, negative correlation between the two RSN's in comparison to the control group.

Methods

Patient selection: 3 distinct cohorts of subjects were selected from the CAtFieLD database (data collected according to the CAtFieLD protocol); 16 with DLB, 16 with AD and 16 healthy controls (HC), all matched for age and the dementia groups matched for degree of cognitive impairment.

fMRI preprocessing: The raw data required preprocessing prior to any analysis. This included cleaning, filtering of artifacts and coregistration to MNI152 standard space steps, and was carried out using the FMRIB Software Library (FSL).

Analysis: To investigate the dynamics of the RSN's another FSL tool called Dual Regression was used. A group concatenated (groups being DBL, AD and healthy control) MELODIC approach was used to obtain RSN maps. Using these maps dual regression was used to extract a time series from each subject's fMRI for comparison and correlation with clinical variables.

Discussion

The negative correlation evident in previous research was not present in the control group. In fact, the two RSN's were positively correlated and hence the initial research question was made redundant.

Following this group comparisons were done using an alternate approach on the preprocessed data, highlighted below.

Method

The REST Toolbox for Matlab was used to perform first level analysis on the data, using the two separate computations Regional Homogeneity (ReHo) and Amplitude of Low Frequency Fluctuations (ALFF)

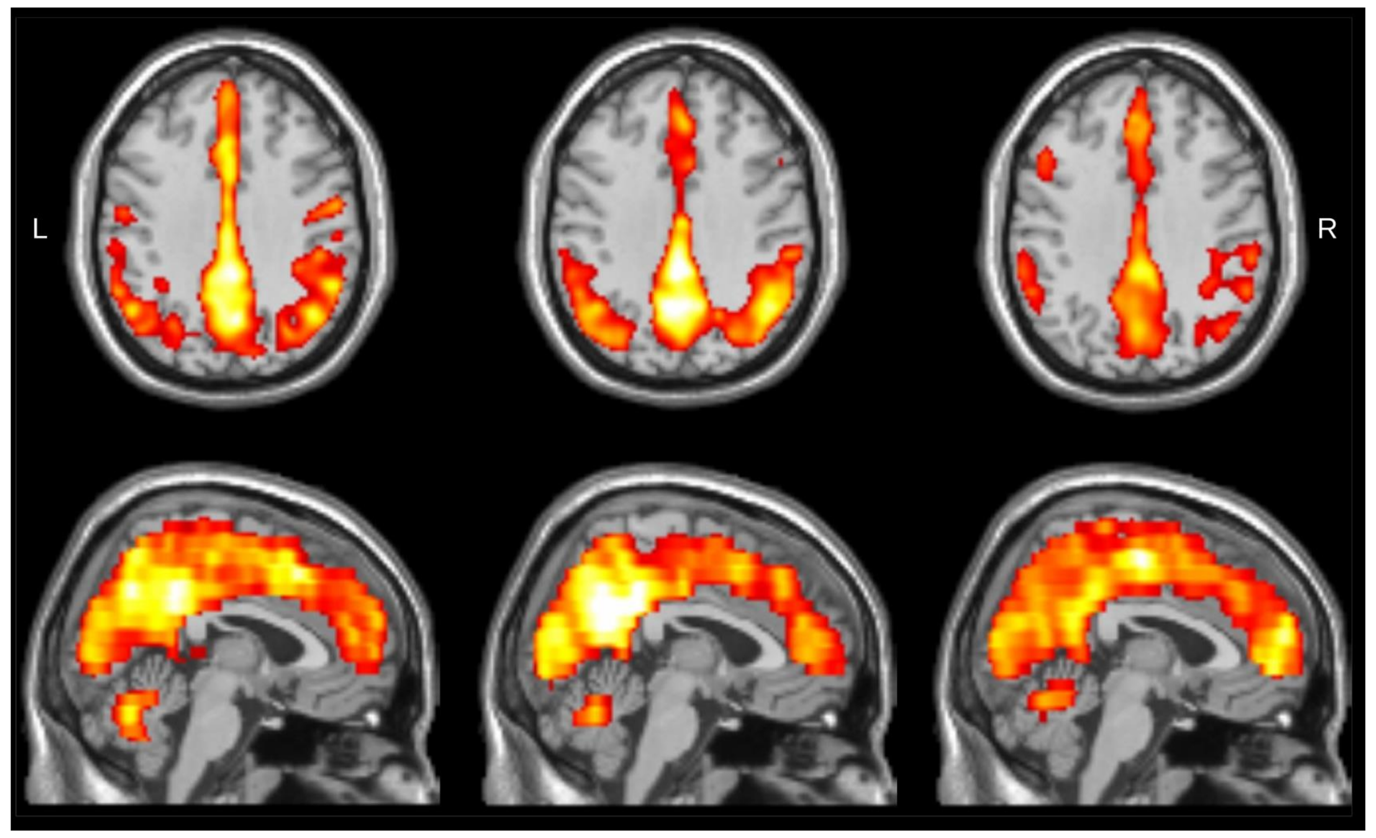
ReHo: This measure determines the similarity between one point and it's nearest neighbours, given the hypothesis that intrinsic brain activity is manifested by clusters of voxels rather than a single point.

ALFF: Low frequency fluctuations in activity are a fundamental feature of the resting brain, and their presence is key to determining correlated activity between certain regions. ALFF is defined as the total power within this low frequency range and thus implies the strength of these important low frequency fluctuations.

These results were taken forward to second level, between group, analysis within the SPM toolbox. Comparisons were made between the 3 subject groups as well as between those who hallucinate and those who don't within the DLB group, using two-sample T tests. Complementing this, ReHo and ALFF mean results were produced for each of the 3 subject groups. Results were visualised using MRIcron.

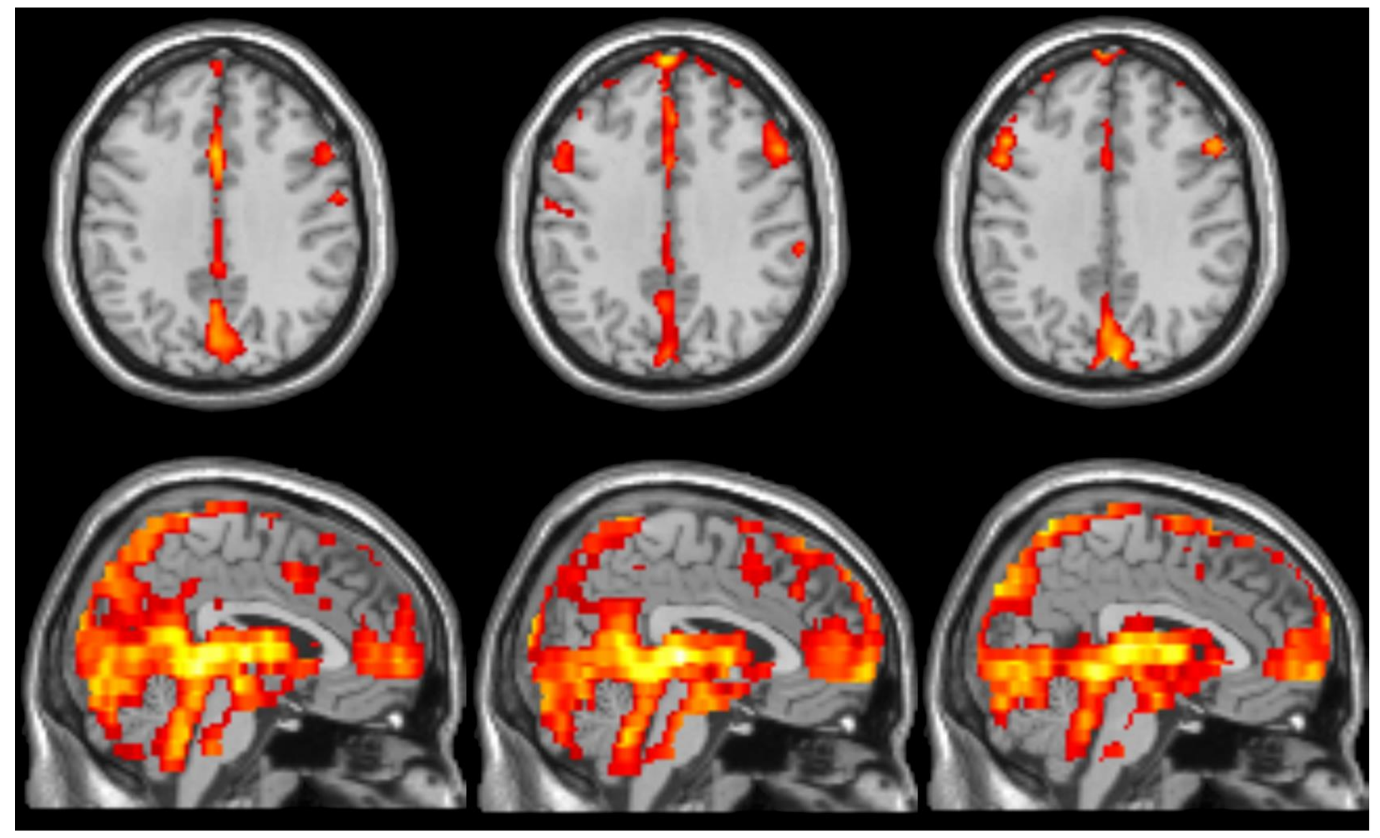
Results

The figures below show the results, firstly of the means, followed by an example of the comparisons



Axial

Sagittal



HC DLB AD

HC DLB AD

Figure A; ReHo: The axial view prominently shows the DMN with a reduction in activity within the AD cohort.

Figure B; ALFF: High levels of activity in the primary visual cortex seen in the sagittal view. This is due to the fact that the data was collected with the subject's eyes open.

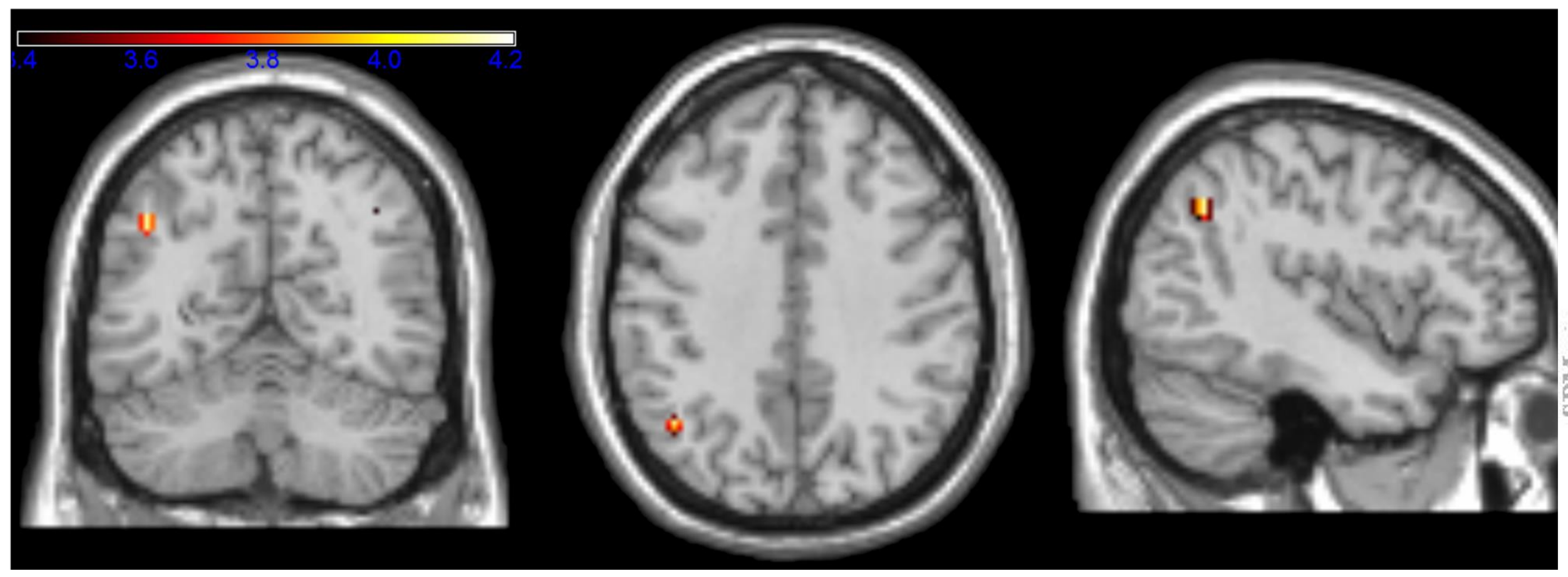
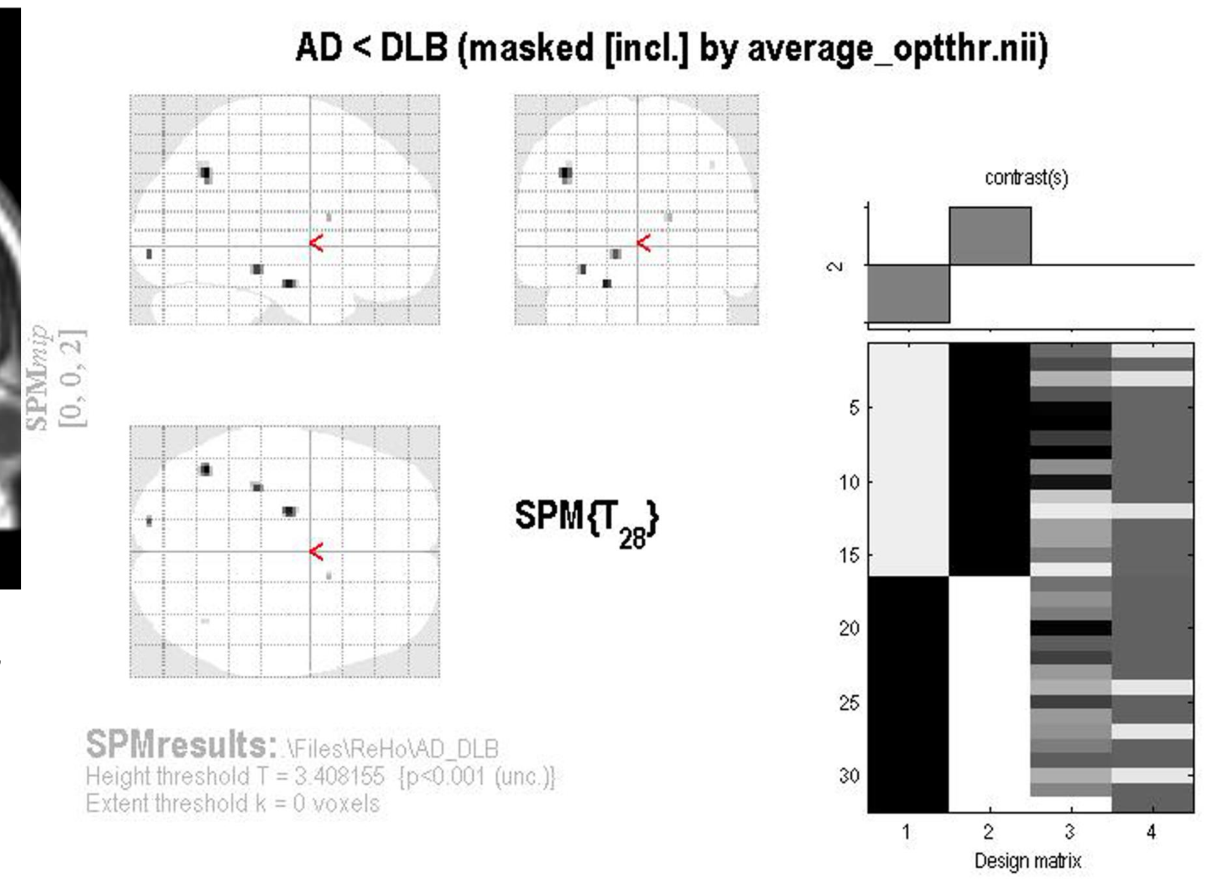


Figure C; Comparison between the AD and DLB groups: Showing one cluster (MNI -42, -60, 38) of activity where the DLB group were bigger than the AD. For each of the four comparisons T contrasts were used to illustrate greater activity.



Statistics: *p-values adjusted for search volume*

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	$(Z_{\equiv})$	p_{uncorr}	
0.990	6	0.995	0.838	12	0.396	0.967	0.833	4.13	3.62	0.000	-42 -60 38
		0.999	0.838	7	0.524	0.985	0.833	4.03	3.55	0.000	-20 -14 -22
		1.000	0.838	5	0.597	0.995	0.833	3.90	3.45	0.000	-32 -32 -14
		1.000	0.838	3	0.693	0.998	0.833	3.83	3.41	0.000	-14 -92 -6
		1.000	0.838	2	0.756	1.000	0.998	3.56	3.21	0.001	16 8 14
		1.000	0.838	2	0.756	1.000	0.998	3.42	3.10	0.001	40 -60 42

Figure D; the SPM result of the comparison between AD and DLB, where DLB had significantly greater activity: Using this clusters could be identified for further inspection using the MRIcron viewer.

Conclusions

- Positive correlation seen between the two RSN's within our data. Possible reasoning being that in previous research only young patients were used or, most likely, that only the best cases were published e.g. at intervals where the negative correlation was seen.
- Unfortunately the four comparisons did not produce results with high significance, even with the use of a number of different approaches.

Future work

- Fully interpret the comparison results with identification of brain regions involved using the MNI coordinates. Try to replicate the findings to a higher significance level.

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