Supplementary material

Functional and Structural Brain Network Correlates of Visual Hallucinations in Lewy Body Dementia

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1. Validation of the source localization pipeline

To validate the implemented cortical source estimation, we used the EEG data collected for a different study involving a motor task paradigm, where participants were asked to maintain isometric contraction by opposition of thumb and index. We randomly chose four subjects, pre-processed the respective EEG task data, estimated the cortical sources, and generated the power spectrum topographies. For the source localization pipeline being deemed correct, we expected a prominent power activation across time points within the β-band over sensory-motor areas. This was in fact the case, as shown in Figure S1.

Figure S1 – Topographies of power spectra during a motor task. Topographies were obtained on four randomly chosen healthy control subjects; they all show a prominent activation over the sensorimotor areas.
2. Age as a nuisance covariate in the Network Based Statistics

To address the potential concern on the possible effect of age on the statistics, we also performed the NBS by including age as nuisance covariate and tested the difference in EEG network patterns between groups. As expected, we found a network component which largely resembled the one we reported in the main text (14 edges, 15 nodes, $P = 0.033$, Figure SII), confirming the robustness of our results.

**Figure SII – Results of the NBS with inclusion of age as a nuisance covariate.** The obtained connectome resembles the results reported in the main text.
3. Validation of MMSE as cognition-related score

A potential limitation of our analysis lies in the choice of the MMSE as a cognition-related behavioural score. This score reportedly shows low sensitivity in characterizing the cognitive phenotype of patient groups, and may poorly represent executive function. To address any potential concern, we additionally tested whether any significant difference in the CAMCOG subdomain scores between groups exists. We first compared the CAMCOG total score, and no significant result emerged \((P = 0.6442)\). By including the CAMCOG total score as a nuisance covariate in the NBS, we obtained a differential subnetwork which resembled the one we reported in the main text \((P = 0.027, 17 \text{ edges, } 18 \text{ nodes})\). By testing the individual subdomains, we found a significant difference only for the orientation score \((P = 0.033)\), which was higher for the NVH group. With the inclusion of this score as a covariate in the NBS we still found a resemblant significant component, although with a weaker effect and only by choosing a more permissive primary threshold \((t_{th} = 13, P = 0.046)\). Although not significantly different between groups, we also performed the NBS by including the CAMCOG visuo-perceptual score, as we believed this variable to be pertinent for the purpose of our research. As a result, we found the same network component as the one we reported in the main article. The outcome of this additional analysis confirms the robustness of our results. The detected components are shown in Figure SIII.

![CAMCOG TOTAL](image1.png) ![CAMCOG ORIENTATION](image2.png) ![CAMCOG PERCEPTION](image3.png)

**Figure SIII – Results of the NBS with inclusion of CAMCOG scores as a nuisance covariate.** The obtained connectomes resemble the results reported in the main text.

4. Potential effect of cholinergic medication on the functional connectivity analysis

To address the potential concern on the effect of cholinergic medication on the functional connectivity analysis, we additionally performed the NBS analysis also including the medication state as a
nuisance covariate. Although we obtained a significant network component, this shows a reduced significance and number of connections compared to the one we reported in the main analysis ($P = 0.045$, 11 edges, 12 nodes, Figure SIV). This outcome might be due to the low statistical power associated with the imbalance between participants’ medication states, as majority of participants were taking cholinesterase inhibitors. Future studies with larger cohorts should better address the effect of this type of medication on functional connectivity alterations associated with LBD-VH as detected with EEG.

**Figure SIV – Results of the NBS with inclusion of medication state as a nuisance covariate.** The obtained connectome resembles the results reported in the main text, although with a lower number of connections.
5. DLB and PDD groups

In our work we grouped DLB and PDD participants together and divided them in two groups based on the existence of the visual hallucination feature. For exploratory purpose, we investigated whether any difference between DLB and PDD groups existed in terms of functional connectivity. By performing the NBS analysis, we did not find any significant differential network component. This result is in agreement with our previous publication where we investigated EEG-network properties of different types of dementia in the sensor domain. Demographics of the two diagnostic groups are reported in Table SI.

Table SI - Demographic data and clinical scores.

| Demographic information               | DLB (N=18) | PDD (N=24) | Statistics |
|----------------------------------------|------------|------------|------------|
| Age                                    | 76.28 ±6.64| 71.83 ±4.99| P = 0.023T |
| Male/Female                            | 14/4       | 23/1       | P = 0.074I (df=1) |
| MMSE                                   | 23.00 ±4.10| 24.38 ±3.83| P = 0.288I T |
| Duration of dementia (years)           | 1.0 ±0.7   | 4.4 ±5.4   | P = 0.014T |
| NPI hall total (frequency x severity)  | 1.56 ±1.79 | 1.42 ±1.74 | P = 0.832T |
| UPDRS III                              | 15.50 ±8.10| 30.96 ±15.84| P < 0.001T |
| AChel (yes/no)                         | 17/1       | 15/8*      | P = 0.054I (df=2) |
| LEDD                                   | 163 ±213   | 822 ±432   | P < 0.001T |

df: degrees of freedom
T Unpaired Mann-Whitney U test
χ² test
* One PDD patient was on Memantine.

6. EEG network differences: theta and beta frequency bands

We focused our analyses on the EEG alpha frequency band, since it is reportedly the most linked to lower level visual processing, whilst other frequency ranges such as beta are likely associated with higher level attentional processes. In addition, abnormal alteration of EEG alpha rhythm features has been reported to be associated with Lewy body dementia and to show high specificity in discriminating this syndrome against other forms of dementia and the healthy condition. For completeness, we used the Network Based Statistics (NBS) to test whether any significant differential network component emerged within the other frequency bands; specifically we tested theta (4.6-7 Hz) and beta (15-20 Hz), and no significant components were detected (P > 0.05). We also did not find any significant difference in the modularity measure.
7. Alternative measures of structural connectivity

In our work we chose the number of white matter streamlines as a measure of structural connectivity strength between brain regions, as we hypothesized it to be associated with the degree of pathological degeneration. However, this choice comes with some advantages. For instance, it might be biased by the persistence of atrophied white matter fibres. With an exploratory purpose, we measured the fractional anisotropy and mean diffusivity of the fibres connecting the NBM to the NBS-detected cortical regions, as these produced our most significant result when compared between groups and correlated with the functional connectivity strength. Unfortunately, by comparing the white matter properties along the reconstructed tracts between groups and testing whether any correlation existed with functional connectivity strength, we did not find any significant result (Figure SV). It is possible that a higher statistical power, i.e. larger sample size, might lead to the outcome obtained by solely measuring the number of streamlines, although several reasons might influence the correct interpretation of the contrasting results. This should be investigated in future studies.
Figure SV – NBM-cortex connectivity: FA and MD. No significant results emerged from the between-group comparison and correlation with EEG connectivity.

8. EEG network coordinates

For visualization purpose, node coordinates were obtained as mass centroids of the ICBM152 head-model\(^1\) vertices within each of the 148 ROIs.\(^2\) Coordinates in the MNI space are reported in Table SII.

| Label                                      | x         | y         | z         |
|--------------------------------------------|-----------|-----------|-----------|
| 'Pole_occipital_L'                         | -16.856895| -100.1667 | -5.6742534|
| 'Pole_occipital_R'                         | 18.1147846| -95.929877| -2.8385904|
| 'G_occipital_sup_L'                        | -13.980972| -92.103146| 30.6393072 |
| 'S_oc_middle_and_Lunatus_L'                 | -31.049869| -89.221256| 6.53669457 |
| 'G_occipital_sup_R'                        | 18.3290267| -87.948505| 35.1847473 |
| 'G_occipital_middle_L'                     | -40.138361| -87.491509| 13.4534898 |
| 'S_oc_middle_and_transversal_L'             | -25.742421| -84.568726| 20.9439325 |
| 'G_and_S_occipital_inf_L'                  | -38.461317| -83.414618| -11.446184 |
| 'G_cuneus_L'                               | -3.3468657| -81.646603| 17.567933 |
| 'S_oc_middle_and_Lunatus_R'                | 37.2338349| -81.03735 | 9.2765386 |
| 'S_oc_sup_and_transversal_R'               | 30.1793647| -80.346951| 22.179264 |
| 'S_collat_transv_post_L'                   | -24.259606| -79.935652| -7.833175 |
| 'G_occipital_middle_R'                     | 46.3450485| -79.025415| 15.236103 |
| 'S_collat_transv_post_R'                   | 27.3908389| -78.88232 | -8.866538 |
| 'G_cuneus_R'                               | 5.90665408| -78.013931| 19.829762 |
| 'G_oc-temp_med-Lingual_L'                  | -9.5373903| -74.11454 | -5.9839477 |
| 'G_and_S_occipital_inf_R'                  | 44.2472872| -74.053108| -12.27754 |
| 'S_calcarine_L'                            | -15.496666| -72.070582| 4.7100384 |
| 'S_parieto_occipital_L'                    | -15.504848| -69.375785| 25.815665 |
| 'G_pariet_infAngular_L'                    | -45.302616| -68.591351| 42.219665 |
| 'S_occipital_ant_L'                        | -43.101425| -68.519245| 4.1523196 |
| 'G_oc-temp_med-Lingual_R'                  | 9.37101745| -67.3593   | -3.6127028 |
| 'S_parieto_occipital_R'                    | 17.3258766| -66.76767 | 27.365577 |
| 'S_calcarine_R'                            | 17.2170709| -66.715428| 6.1039833 |
| 'S_occipital_ant_R'                        | 47.6111792| -62.243474| 4.3389048 |
| 'G_parietal_sup_L'                         | -23.406961| -61.896369| 59.818168 |
| 'G_pariet_infAngular_R'                    | 49.5164272| -60.790665| 42.767234 |
| 'G_precuneus_L'                            | -4.134602 | -60.289891| 43.610005 |
| 'G_precuneus_R'                            | 4.79367477| -60.271867| 46.5138273 |
| 'S_intrapariet_and_P_trans_L'              | -30.657589| -59.100794| 41.7982714 |
| 'G_parietal sup_R'                         | 25.1441688| -57.872513| 63.2070373 |
| 'S_intrapariet_and_P_trans_R'              | 30.5651545| -56.858196| 44.7500326 |
| Region                        | X   | Y   | Z   |
|-------------------------------|-----|-----|-----|
| 'S_interm_prim-Jensen_L'      | -52.21148 | -55.547456 | 36.9375096 |
| 'G_oc-temp_lat-fusfor_L'      | -38.018595 | -54.096665 | -20.14663 |
| 'G_oc-temp_lat-fusfor_R'      | 34.2769577 | -51.637045 | -20.75457 |
| 'S_oc-temp_lat_L'             | -44.815804 | -51.018649 | -11.938669 |
| 'S_oc-temp_lat_R'             | 43.8580055 | -48.834051 | 14.267307 |
| 'S_subparietal_L'             | -9.5142274 | -48.27462 | 35.7512872 |
| 'S_subparietal_R'             | 8.9537357 | -48.226819 | 37.5207114 |
| 'G_cingul-Post-ventral_L'     | 7.09224502 | -46.656395 | 5.58728157 |
| 'S_oc-temp_med_and_Lingual_L' | -28.407234 | -46.364172 | 13.258884 |
| 'S_oc-temp_med_and_Lingual_R' | 29.0422694 | -45.597104 | 12.87741 |
| 'G_cingul-Post-ventral_L'     | -7.6501913 | -44.821491 | 3.14296627 |
| 'S_interm_prim-Jensen_R'      | 53.4322737 | -43.416018 | 35.9316095 |
| 'S_temporal_sup_L'            | -49.801234 | -42.712461 | 7.05405015 |
| 'G_temporal_inf_L'            | -55.181424 | -40.845183 | -21.999078 |
| 'G_temporal_inf_R'            | -2.2440024 | -40.328792 | 30.7762786 |
| 'G_temp_sup-Plan_tempo_L'     | -60.074589 | -39.214686 | 21.6403281 |
| 'S_temporal_sup_R'            | 50.8477299 | -38.19845 | 9.12947461 |
| 'G_cingul-Post-dorsal_R'      | 1.85359023 | -38.108126 | 33.1704614 |
| 'G_temporal_inf_R'            | 55.1884657 | -38.095535 | -24.232985 |
| 'S_cingul-Marginalis_L'       | -13.062979 | -36.829735 | 48.9899383 |
| 'G_and_S_paracentral_L'       | -7.3626139 | -36.226501 | 69.8499747 |
| 'G_pariet_inf-Subparam_L'     | -61.114305 | -35.991977 | 33.2433335 |
| 'G_and_S_paracentral_R'       | 7.88003389 | -35.652382 | 71.5312243 |
| 'S_cingul-Marginalis_R'       | 11.9953128 | -35.555264 | 49.2884566 |
| 'S_temporal_inf_R'            | 56.0866664 | -34.854645 | -14.660639 |
| 'Lat_Fis-post_L'              | -4.1857889 | -34.072207 | 19.4094988 |
| 'S_postcentral_L'             | -40.476822 | -33.284302 | 46.1508686 |
| 'S_temporal_inf_L'            | -55.519184 | -31.191312 | -18.6941 |
| 'G_pariet_inf-Subparam_R'     | 58.3919828 | -30.067496 | 37.0142107 |
| 'S_postcentral_R'             | 39.559387 | -29.737032 | 46.4406676 |
| 'G_temporal_middle_L'         | -62.091079 | -28.564557 | -11.401692 |
| 'G_temp_sup-Plan_tempo_R'     | 60.8702299 | -28.49692 | 21.4961563 |
| 'Lat_Fis-post_R'              | 40.1730677 | -24.817006 | 18.5781316 |
| 'G_postcentral_L'             | -47.507469 | -24.046153 | 55.9848725 |
| 'S_temporal_transverse_L'     | -53.333727 | -22.0591 | 5.73130557 |
| 'G_temporal_middle_R'         | 62.3925978 | -21.611309 | -15.007033 |
| 'G_postcentral_R'             | 47.0899879 | -21.027259 | 56.1218101 |
| 'G_temp_sup_G_T_transv_L'     | -47.5505 | -20.574775 | 9.92095113 |
| 'S_central_L'                 | -38.25244 | -20.149708 | 46.0067886 |
| 'S_collat_transv_ant_L'       | -42.103808 | -19.177564 | -28.981915 |
| 'S_central_R'                 | 37.3316732 | -18.272409 | 46.4338759 |
| 'S_temporal_transverse_R'     | 52.3678114 | -18.024797 | 9.32791289 |
| 'S_collat_transv_ant_R'       | 41.7743007 | -17.738935 | -29.330809 |
| 'G_oc-temp_med-Parahip_L'     | -25.057202 | -17.490021 | -26.242779 |
| 'G_oc-temp_med-Parahip_R'     | 23.8832041 | -13.10857 | -27.340384 |
| 'G_temp_sup_G_T_transv_R'     | 48.2852039 | -12.302355 | 7.36303752 |
| 'G_and_S_subcentral_L'        | -57.601796 | -10.807142 | 14.2693463 |
| 'S_precentral-sup-part_L'     | -27.848176 | -10.494424 | 56.7640435 |
| 'G_ins_lg_and_S_cent_ins_L'   | -41.825645 | -10.458351 | 2.23362653 |
Table S1 | Network node coordinates based on the Destrieux atlas\(^2\) in the MNI space. Nodes are computed as mass centroids within each parcellated region.

| Node Description                              | X    | Y    | Z    |
|-----------------------------------------------|------|------|------|
| G_front_middle_L                              | -38.591993 | 35.7733403 | 33.0580822 |
| G_front_inf-Orbital_R                         | 51.1508807 | 36.9698238 | -13.594139 |
| S_orbital-H_Shaped_L                          | -27.354868 | 37.6675795 | -16.42051 |
| G_rectus_L                                    | -4.1211068 | 38.1418317 | -23.422932 |
| G_front_middle_R                              | 38.6936979 | 38.2369656 | 32.078083 |
| S_orbital-H_Shaped_R                          | 26.8075877 | 38.7712856 | -16.740152 |
| S_suborbital_R                                | 3.15998605 | 41.9296244 | -16.421215 |
| G_and_S_cingul-Ant_R                          | 5.85787713 | 42.3592462 | 4.55362515 |
| G_and_S_cingul-Ant_L                          | -7.2514034 | 42.3919445 | 6.63595362 |
| S_suborbital_L                                | -5.220484 | 43.9476634 | -12.708837 |
| S_orbital_lateral_L                           | -43.648027 | 45.4283591 | -5.5656196 |
| S_orbital_lateral_R                           | 43.6923782 | 46.5803129 | -3.1078501 |
| S_front_middle_L                              | -28.307357 | 47.0646389 | 19.3032746 |
| S_front_middle_R                              | 28.9039738 | 47.4571278 | 17.8662803 |
| G_and_S_frontomargin_L                        | -25.310918 | 60.9520505 | -9.0834118 |
| G_and_S_frontomargin_R                        | 21.2763927 | 63.2872608 | -11.452679 |
| G_and_S_transv_frontopol_L                    | -16.838447 | 68.2448486 | -2.3301895 |
| G_and_S_transv_frontopol_R                    | 17.4681568 | 68.4477277 | 0.18827672 |

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