Figures and figure supplements

Cortical tau deposition follows patterns of entorhinal functional connectivity in aging

Jenna N Adams et al
Figure 1. Functional connectivity (FC) of the different entorhinal seeds in healthy young adult (YA) participants. (a) The full entorhinal seed (EC, green), including transentorhinal, lateral, and medial regions, was derived from FreeSurfer segmentation of each participant’s native space T1, and time series were extracted from native space fMRI data. (b) The anterolateral EC (aIEC, red) and posteromedial EC (pMEC, blue) seeds were applied in template space, and time series were extracted before smoothing to preserve the spatial resolution of the seeds. (c–e) Seed-to-voxel FC analyses were performed for each seed with semi-partial correlations. Group level FC results were derived from one-sample t-tests controlling for age and sex, and thresholded at the voxel (p<0.001 uncorrected) and cluster level (p<0.05, FDR corrected). Results reflect t-statistics. (c) FC of the EC seed included medial temporal, lateral temporal, and limbic regions. (d) FC of the aIEC seed included anterior temporal regions, such as medial and lateral temporal lobe. (e) FC of the pMEC seed included posterior medial regions, such as the parahippocampal gyrus and posterior cingulate. (f) Binary maps of aIEC (red) and pMEC (blue) FC show little spatial overlap (purple) between the FC patterns. See Figure 1—figure supplement 1 for parallel results using OA FC. See Figure 1—figure supplement 2 for a visualization of gray matter voxels removed due to signal dropout, and aIEC and pMEC seeds overlaid on the group-mean functional image.

DOI: https://doi.org/10.7554/eLife.49132.005
Figure 1—figure supplement 1. Functional connectivity (FC) of the different entorhinal seeds in older adult (OA) participants. Seed-to-voxel FC analyses were performed for each seed. Group level FC results were derived from one-sample t-tests controlling for age and sex, and thresholded at the voxel (p<0.001 uncorrected) and cluster (p<0.05 FDR corrected) levels. Results reflect t-statistics. (a) FC of the EC seed included medial temporal, lateral temporal, and limbic regions. The dice similarity coefficient (DSC) between the YA and OA EC maps was 0.45, reflecting moderate overlap. (b) FC of the alEC seed included anterior temporal regions, as well as some posterior medial regions such as the posterior cingulate cortex. DSC between YA and OA alEC maps was 0.36, reflecting fair overlap. (c) FC of the pmEC seed included posterior medial regions, although reduced in scope compared to YA FC patterns. DSC between YA and OA pmEC maps was 0.53, reflecting moderate overlap. (f) Binary maps of the alEC (red) and pmEC (blue) FC show spatial overlap (purple) between the FC patterns, especially in posteromedial cortex.

DOI: https://doi.org/10.7554/eLife.49132.006
Figure 1—figure supplement 2. Signal drop out demonstrated with group-mean functional images. (a) A group-level explicit mask (yellow) was created by removing GM voxels of low signal (<40% of the mean signal across the gray matter; shown in brown) from a gray matter mask. This explicit mask was applied to all functional connectivity analyses to ensure regions of low signal did not contribute to results. (b) aIEC (red) and pmEC (blue) template space seeds are overlaid on the group-mean functional image to visually demonstrate the average signal in these regions. For functional connectivity analyses, voxels of low signal were removed from each ROI on a participant-level basis.

DOI: https://doi.org/10.7554/eLife.49132.007
Figure 2. Tau preferentially deposits within regions of functional connectivity (FC) with entorhinal cortex. Tau deposition, defined as the proportion of suprathreshold FTP voxels (>1.4 SUVR), was measured in each FC mask and in cortical regions that did not demonstrate FC with the seeds ('Outside'). Tau deposition in each region was contrasted with repeated measures ANCOVAs and post-hoc t-tests. (a) Tau preferentially deposited within regions of EC FC (green) compared to outside cortical regions (gray). Region by Aβ status interactions were driven by an increased mean difference between the EC and outside cortical regions in the Aβ+ compared to the Aβ- group. (b) Tau preferentially deposited within regions of aIEC FC (red) compared to both pmEC FC (blue) and outside cortical regions (gray), and in pmEC FC compared to outside cortical regions. Region by Aβ status interactions were driven by an increased mean difference between aIEC FC and outside cortical regions in the Aβ+ compared to the Aβ- group. See Figure 2—figure supplement 1 for parallel results using OA FC. ***p<0.001, **p<0.01, *p<0.05; ‘x’ indicates the drivers of significant Aβ status interactions (p<0.05); Error bars indicate the standard error of the mean.

DOI: https://doi.org/10.7554/eLife.49132.008
Figure 2—figure supplement 1. Tau deposition within regions of functional connectivity (FC) with entorhinal cortex derived from FC from the older adult (OA) participants. Tau deposition, defined as the proportion of suprathreshold FTP voxels (>1.4 SUVR), was measured in each FC mask and in outside cortical regions that did not demonstrate FC. Tau deposition in each region was contrasted with repeated measures ANCOVAs and post-hoc t-tests. (a)Tau preferentially deposited within regions of significant EC FC (green) compared to outside cortical regions (gray). Region by Aβ status interactions were driven by an increased mean difference between the EC and outside cortical regions in the Aβ+ compared to the Aβ- group.  (b) Tau preferentially deposited within regions of alEC FC (red) compared to both pmEC FC (blue) and outside cortical regions (gray), and in pmEC FC compared to outside cortical regions. Region by Aβ status interactions were reduced to a trend. ***p<0.001, **p<0.01, *p<0.05; ‘x’ indicates the drivers of significant Aβ status interactions (p<0.05). Error bars indicate the standard error of the mean.

DOI: https://doi.org/10.7554/eLife.49132.009
Figure 3. Stronger FC with a region is associated with higher levels of tau deposition in that region. (a-c) To examine associations between tau and FC strength, group level YA FC masks for each EC seed were clustered into regions of low, medium, and high FC based upon the mean YA FC strength.*

*Figure 3 continued on next page
Figure 3 continued
(b) The proportion of suprathreshold FTP voxels (>1.4 SUVR) was calculated for each FC strength region (‘tau deposition’). Repeated measures ANCOVAs and post-hoc t-tests were performed to contrast tau deposition between each FC strength region. (d) EC FC strength was significantly related to tau deposition in a stepwise pattern, with tau increasing in low < medium < high FC regions. Aβ status interactions were observed between all comparisons. (e) Increasing aIEC FC strength was also related to higher tau deposition in a stepwise fashion, and Aβ interactions were driven by the difference between high-medium and high-low FC regions. (f) Increasing pmEC FC strength was associated with decreases in tau deposition, and Aβ interactions were driven by the difference between high-medium and high-low FC regions. See Figure 3—figure supplement 1 for parallel results using OA FC. ***p<0.001, **p<0.01, *p<0.05; ‘x’ indicates the drivers of significant Aβ interactions (p<0.05). Error bars indicate the standard error of the mean.

DOI: https://doi.org/10.7554/eLife.49132.012
Stronger older adult (OA) functional connectivity (FC) to a region is associated with higher levels of tau deposition to that region. (a-c) Group level FC masks from the OA participants for each seed were divided into regions of low, medium, and high FC based upon the

---

Figure 3—figure supplement 1 continued on next page
mean FC strength (beta value) of each voxel with one-dimensional k-means clustering. (d-f) The proportion of suprathreshold FTP voxels (>1.4 SUVR) was calculated in each FC strength region (‘tau deposition’). Repeated measures ANCOVAs and post-hoc t-tests were performed to contrast tau deposition in each FC strength region. (d) EC FC strength was significantly related to tau deposition in a stepwise pattern, with tau increasing in low < medium < high FC regions. Aβ status interactions were observed between all comparisons. (e) Regions of high aIEC FC strength had more tau deposition than regions of medium or low FC. Aβ interactions were driven by the difference between high-medium and high-low FC regions. (f) Regions of low pmEC FC strength had more tau deposition than regions of medium or high FC. Aβ interactions were reduced to a trend. ***p<0.001, **p<0.01, *p<0.05; ‘x’ indicates the drivers of significant Aβ interactions (p<0.05). Error bars indicate the standard error of the mean.

DOI: https://doi.org/10.7554/eLife.49132.013
**Figure 4.** EC-cortical tau associations and relationships with FC strength. (a) Voxelwise regressions were performed across OA participants between the mean EC FTP SUVR predicting voxelwise FTP. One-sample t-tests show a group level map depicting voxels that had strong positive associations between their FTP and the amount of FTP in the EC. (b–d) YA average FC strength per voxel (beta) was correlated with each voxel’s EC-cortical tau association strength (beta). FC of the EC (b) and aEC (c) seeds demonstrated positive associations, where stronger FC to a voxel was correlated with a stronger association between EC FTP and that voxel’s FTP. The pmEC (d) showed a weak association. See Figure 4—figure supplement 1 for parallel results using OA FC. ***p<0.001.

DOI: https://doi.org/10.7554/eLife.49132.016
**Figure 4—figure supplement 1.** EC-cortical tau associations and relationships with functional connectivity (FC) strength from older adult (OA) participants. (a-c) Group average FC strength per voxel derived from the OA participants was correlated with each voxel’s EC-cortical tau association strength, where stronger FC to a voxel was correlated with a stronger association between EC FTP and that voxel’s FTP. The EC (a) and aIEC (b) demonstrated positive associations that were of similar strength to the YA FC data, while the pmEC (d) had a stronger positive association than found in the YA data. ***p<0.001.

DOI: https://doi.org/10.7554/eLife.49132.017