Disruption of regional brain network activity by amyloid plaques in prodromal Alzheimer’s disease

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1. Introduction:
The default mode network (DMN) is a set of functionally connected brain regions comprising the posterior cingulate, precuneus, inferior parietal and medial prefrontal cortex. Its integrity, being impaired even in prodromal Alzheimer’s disease (pAD), is essential e.g. for autobiographical memory retrieval. Interestingly, amyloid plaque (AP) deposition - a critical hallmark of AD - overlaps with the DMN to a great extent and is associated with a decrease of its functional connectivity (FC) [1,2]. However, it is still unclear if DMN malfunction is present consistently during rest and task and whether AP deposition also affects other overlapping intrinsic connectivity networks (ICNs) being involved in higher cognitive processes. This would reflect a network-independent mechanism of AP effects on brain activity.

2. Questions:
(1) Is FC of ICNs altered consistently during rest and an attention demanding task?
(2) Is rest-FC in these regions related to the degree of cognitive impairment in pAD?
(3) Does patients’ AP deposition predict rest-FC in disrupted regions?

3. Methods:
Participants: Patients with pAD (n=24) and healthy controls (n=16). FMRl: BOLD-image acquisition during a 10-minutes rest (re-MRI) and a 17-minutes block task period (t-MRI). Independent component analysis (ICA, GIFT-toolbox) was performed to identify the posterior and anterior DMN (pDMN & aDMN), left, right and dorsal attention network (lATN & rATN) and the primary auditory network (pAN) during rest and task. Outcome: z-maps reflecting ICNs’ functional connectivity. Analysis: group comparisons (two-sample-t-tests) in order to identify networks with spatially consistent FC-changes (Δ FC) during rest and task (p<0.05, FWE corrected on cluster level). Sig. Δ FC-clusters are depicted with p<0.05, uncorrected, for visual presentation (see results).

PET: Pittsburgh Compound B – Positron emission tomography (PIB-PET) to identify individual regional, fibrillar amyloid plaque density. Analysis: two-sample-t tests between groups (p<0.001, uncorrected) and ROI-based calculation of standardized uptake value ratios (SUVR) relative to the cerebellum in patients, representing semiquantitative degree of AP deposition.

4. Results:
4.1. Altered intrinsic connectivity networks (ICNs) during rest and task.

ICNs and group differences in functional connectivity (Δ FC) during rest and task:
A. posterior DMN (pDMN; Δ FC located in the precuneus for rest [controls>poments] and task [patients>controls]) & anterior DMN (aDMN) C right attention network (rATN) & FC in the right inferior parietal lobule/angular gyrus, again control>patients during rest and patients>controls during task D. left attention network (lATN) & FC dorsal attention network (lATN) & FC (patients>controls) in the angular gyrus only during task F primary auditory network (pAN)

4.2. Spatially consistent group differences in the posterior default mode network and right attention network during rest and task.

 Approach analysis

Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>MRI</th>
<th>PET</th>
<th>Pittsburgh Compound B (PIB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>68(8)</td>
<td>68(5)</td>
<td>66(6)</td>
</tr>
<tr>
<td>62(4)</td>
<td>62(5)</td>
<td>62(6)</td>
</tr>
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<td>Gender (F/M)</td>
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<td>9/7</td>
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<td>CDR</td>
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<td>0.0 (0.0)</td>
</tr>
<tr>
<td>CERAD-total</td>
<td>66.3 (10.8)</td>
<td>68.5 (6.5)</td>
</tr>
<tr>
<td>CERAD-CERAD-total</td>
<td>66.3 (10.8)</td>
<td>68.5 (6.5)</td>
</tr>
<tr>
<td>Δ FC during rest and task &amp; FC during task and task</td>
<td>A spatial maps of controls’ and patients’ pDMN and group differences (Δ FC) during rest and task. The overlap of Δ FC regions was used as a ROI whose mean FC is shown in the chart. B spatial maps of controls’ and patients’ rATN and Δ FC during rest and task. Again, mean FC of the overlap region is depicted in the chart.</td>
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4.3. Altered functional connectivity during rest correlates with severity of cognitive impairment in patients.

Voxelwise correlation of patients’ altered resting-state FC (Δ FC rest) with the pDMN and, on the second brain, the sig. correlating voxels (p<0.05). The chart depicts the averaged correlation across all voxels (r=0.04, p=0.201). B Correlating voxels of the rATN’s Δ FCrest with the CERAD-total score in patients. Averaged correlation: r=0.67, p=0.001.

4.4. ICN changes overlap with increased PIB in patients and show negative correlations during rest.

The figure shows the overlap of patients’ elevated PIB levels (Δ PIB) with the controls’ ICNs, and the group differences during rest (Δ FCrest). A voxelwise correlation of patients’ altered resting-state FC with the CERAD-total score. Averaged correlation: r=0.36, p=0.005.

5. Conclusion:
Here we revealed overlapping regions of altered FC during rest and task. In pAD, disrupted FC during rest predicts the degree of cognitive impairment and correlates with local amyloid deposition. These findings are not restricted to the DMN only, but can also be observed in a right fronto-parietal network/lateralized attention network indicating a general mechanism of regional amyloid plaque effects on ICN integrity. Conclusively, results provide evidence that amyloid plaques may impact brain activity and cognition via disordered regional activity in PIB.

6. References:

7. Acknowledgements:
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