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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 cortex¹. Its integrity, being impaired even in prodromal Alzheimer's disease (pAD)^{2,3,4}, is essential e.g. for autobiographical memory retrieval¹. Interestingly, amyloid plaque (AP) deposition - a critical hallmark of AD - overlaps with the DMN to a great extent⁵ and is associated with a decrease of its functional connectivity (FC)^{6,7,8}. 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).

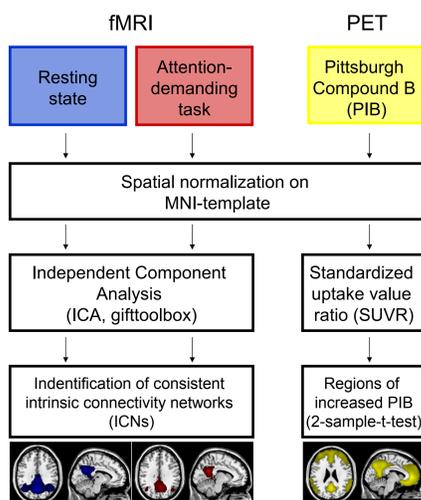
fMRI: BOLD-image acquisition during a 10-minutes *rest* (rs-fMRI) and a 17-minutes block *task* period (t-fMRI). Independent component analysis (ICA, GIFT-toolbox) was performed to identify the posterior and anterior DMN (pDMN & aDMN), left, right and dorsal attention network (IATN, rATN & dATN) and 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 (ΔFC) during rest and task ($p < 0,05$, FWE corrected on cluster level). Sig. ΔFC -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, fibrillary amyloid plaque density. **Analysis:** two-sample-t-test 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.

Approach of analysis

Demographic and clinical characteristics

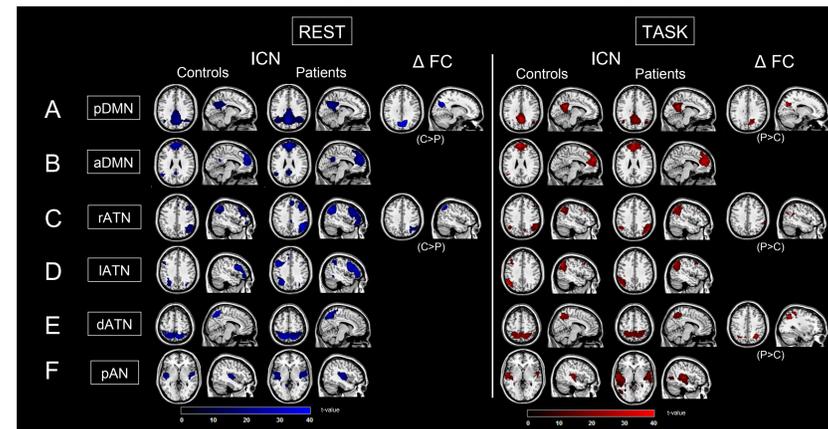


	Patients	Controls
N	24	16
Age	68.2 (8.4)	64.8 (5.4)
Gender (F / M)	10/14	9/7
CDR	0.5 (0)	0 (0)*
CERAD-total	66.3 (10.8)	88.1 (6.8)*

CDR: Clinical Dementia Rating; CERAD: battery of the Consortium to Establish a Registry for Alzheimer's disease; CERAD-total: summary of CERAD sub-tests; group comparisons: χ^2 (gender), two-sample t-test (age, CDR, CERAD-total); * indicate significant group difference with $p < 0.05$.

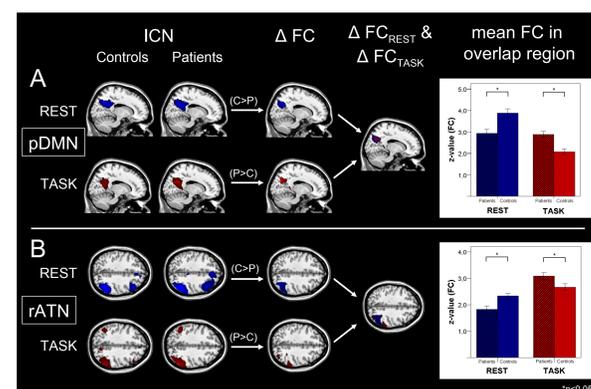
4. Results:

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



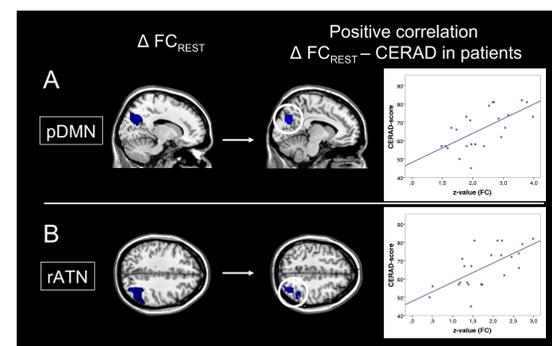
ICNs and group differences in functional connectivity (ΔFC) during rest and task: **A** posterior DMN (pDMN); ΔFC located in the precuneus for rest (controls>patients) and task (patients>controls) **B** anterior DMN (aDMN) **C** right attention network (rATN); ΔFC in the right inferior parietal lobule/angular gyrus, again controls>patients during rest and patients>controls during task **D** left attention network (IATN) **E** dorsal attention network (dATN); ΔFC (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.



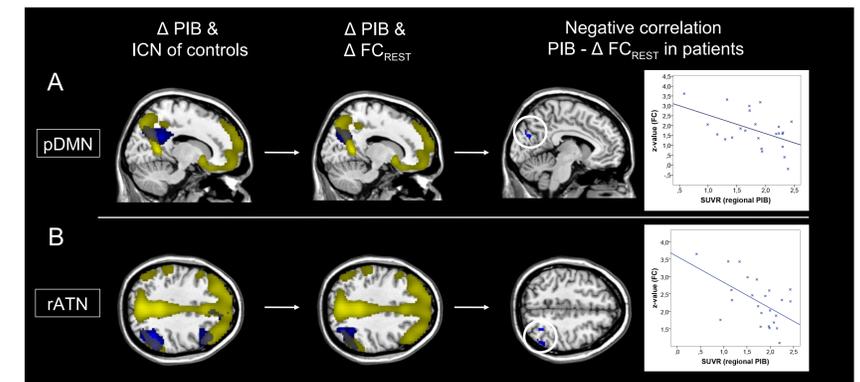
A spatial maps of controls' and patients' pDMN and group differences (ΔFC) during rest and task. The overlap of ΔFC regions was used as a ROI whose mean FC is shown in the chart. **B** spatial maps of controls' and patients' rATN and ΔFC during rest and task. Again, mean FC of the overlap region is depicted in the chart.

4.3. Altered functional connectivity during rest correlates with severity of cognitive impairment in patients.



Voxelwise correlation of patients' altered resting state-FC (ΔFC_{REST}) with the individual CERAD-total score. **A** shows the regions of ΔFC_{REST} for the pDMN and, on the second brain, the sig. correlating voxels ($p < 0,05$). The chart depicts the averaged correlation across all voxels ($r = 0,64$; $p = 0,001$). **B** Correlating voxels of the rATN's ΔFC_{REST} 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 (ΔPIB) with the controls' pDMN/rATN and the group differences during rest (ΔFC_{REST}). A voxelwise correlation of patients' altered resting state-FC with the local mean PIB was performed for **A** the pDMN (averaged correlation: $r = -0,50$; $p = 0,013$) and **B** the rATN (averaged correlation: $r = -0,56$; $p = 0,005$)

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 network activity in pAD.

6. References:

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