Intrinsic connectivity networks and compensation in prodromal Alzheimer's disease

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Introduction: In Alzheimer's disease (AD) declarative memory deficits constitute a hallmark symptom. Declarative memory is related to the hippocampal system. In AD the hippocampi (HC) are early affected by tau-pathology, atrophy and changed activation during memory tasks. During encoding the HC interacts with widespread neocortical areas. Intrinsic connectivity networks (ICN), which functionally organize the neocortex, are selectively changed in early AD. ICNs are defined by synchronized BOLD-oscillations across remote brain areas.
Question: Are AD-induced changes of HC-neocortex interactions during encoding related to changes of the neocortical ICN-organization in AD?
AD-induced interaction changes comprise reduced and increased interaction magnitudes when compared with healthy controls. We interpret increased interactions as representative for **compensation**-related processes.

2. Methods:

Measurement: BOLD-fMRI
Subjects: Patients with amnestic mild cognitive impairments (MCI) and healthy elderly (normal controls, NC); patient group PG1 consists of 24 patient with MCI see Table 1; patient group PG2 is a subgroup of PG1 with patients, who progressed to AD within 2 years after scanning.
Paradigm 1 (Resting-state; Analysis of ICNs): patient group PG1; 4 minutes of rest-fMRI. Data-Analysis: *Independent Component Analysis* (ICA, GIFT toolbox). Group comparison: two-sample T-Test, p<0.05, FDR corrected (see Sorg, Riedl et al. PNAS 2007).
Paradigm 2 (Encoding; comparing HC-neocortex interaction and ICNs): PG2; encoding of words in two conditions; each condition is suggested to represent a distinct degree of HC-neocortex interaction: elaborated ("create a sentence for the shown word") – non-elaborated ("repeat the shown word"); blocked-design.

Table 1. Subject demographic information

	NC	MCI
n	16	24
Age (years)	68.1 ± 3.8	69.3 ± 8.1
Sex (male/female)	10/6	13/11
Education (< / >12 years)	10/6	14/10
CDR-Sum of Boxes	0 ± 0	2.2 ± 0.9 *
MMSE	29.6 ± 0.5	27.7 ± 1.1 *
CERAD (delayed recall)	7.4 ± 1.3	4.3 ± 2.1 *

Data Analysis 2: *Psychophysiological interaction (PPI)* with the psychological factor „elaboration of encoding" and the physiological factor time series of left and right HC, respectively. Group comparison: For each ICN we performed a two-sample T-test restricted for the according network as ROI; p=0.001 uncorrected; *subsequently* we compared AD-related changes of PPI patterns with AD-related ICN changes

3. Results:

3.1. Analysis of ICNs (Fig1): We found 8 ICNs, spatially consistent across both groups: amongst others the default network (**DN**) and the executive attention (**EA**) (Fig1, left: above the DN represented by one IC (independent component), left for the NCs, right for the patients, glass brain across all subjects p<0.05 FDR; below the EA). Only for the DN and EA significant group differences were found with reduced co-activity in the patients (Fig1, right).

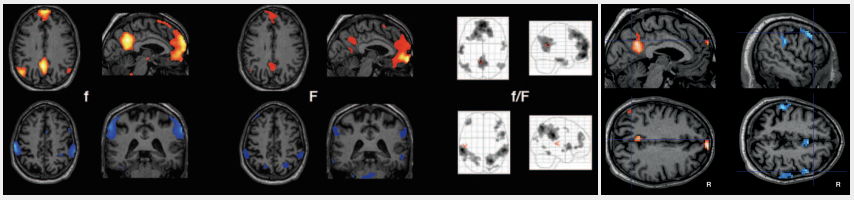

Figure 1

3.2.1. Encoding, PPI (Psychological factor "Elaboration of Encoding", seeds are left and right HC, respectively):
Fig. 2 left, PPI restricted to the DN-ROI: For the right HC we found reduced PPI-connectivity with bilateral medial prefrontal areas of the DN for the patients compared with healthy controls (shown in red). For the left HC we found increased – compensatory – PPI-connectivity with left lateral temporal and inferior parietal areas of the DN (shown in green). p<0.001 uncorrected. For visualization purpose, SPM maps with threshold p<0.01 uncorrected.
Fig. 2 right, PPI restricted to the EA-ROI: For the right HC we found reduced PPI-connectivity with right lateral areas of the EA for the patients compared with healthy controls (shown in red). For the left HC we found increased – compensatory – PPI-connectivity with bilateral lateral parietal areas of the EA (shown in green). p<0.001 uncorrected. For visualization purpose, SPMs are thresholded at p<0.01 uncorrected.
For the **further ICNs** we found no relevant PPI-connectivity changes across groups neither for the right nor for the left HC.

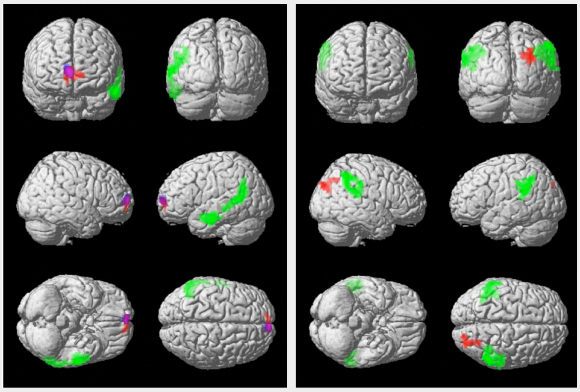

Figure 2

3.2.2. Comparison between group-changes of PPI maps and group-changes of ICN maps (Fig3):
For the DN we found slight regional overlap of medial prefrontal regions with reduced co-activation in the patient group and reduced PPI-connectivity for the right HC in the patient group (not shown).
For the EA (Fig3) we found regional overlap of lateral parietal regions with reduced co-activation in the patient group (in red) and compensatorily increased PPI-connectivity for the left HC in the patient group (in green). For visualization purpose, SPMs are thresholded at p<0.01 uncorrected.

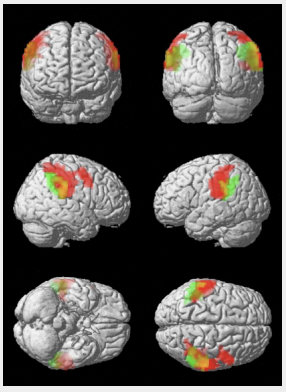

Figure 3

4. Conclusion:

In this study of patients with prodromal AD we found regional overlap of both changed connectivity patterns of the HC during encoding and reduced co-activity patterns of ICNs. Changes of encoding-related connectivity are in both directions – reduced connectivity and compensatorily increased connectivity. Reduced co-activity in ICNs might reflect compensation-related connectivity increases in an early stage of progressive AD.