Reduced Regional Integration in the Default Network of Patients with Very Mild Alzheimer's Disease Detected by Bootstrapping Rest-fMRI Data

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Alzheimer's Disease (AD) is the most prevalent cause of progressive dementia in older adults. Early Alzheimer's disease (AD) is associated with prominent changes of the default network (DN). AD has impact on inter-regional but also on intra-regional neuronal communication processes i.e. on brain integration at distinct levels. Based on the intuition that blood oxygenation level dependent (BOLD) signal variations of a given region might reflect functional aspects of regional integration, we proposed a novel marker *BV(r) (Regional BOLD Variation)* for the characterization of regional integration changes within the DN of patients with amnestic mild cognitive impairment (aMCI), a risk state for AD.

1. Subjects and Data Acquisition

• resting state fMRI of 24 patients with amnestic MCI (aMCI) and 16 healthy controls

• subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep;

1. Selection of Regions of Interest

• 10 ROIs within the default network
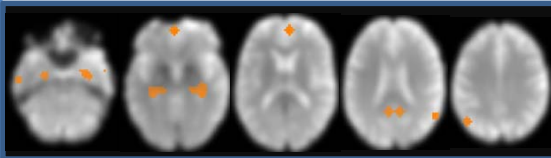
• medial temporal gyri, hippocampi,
• left superior frontal gyrus, hippocampi,
• right superior frontal gyrus,
• left and right posterior cingulate cortex, right superior marginal gyrus,
• left superior marginal gyrus;
• coordinates of ROI-centers derived from ICA (Sorg et al. 2007);

2. Evaluation of Regional BOLD Variation

• bootstrapping the BOLD activity allows detecting minor variations in regional integration;

• for each time point the mean BOLD activity is computed for a large number of samples with replacement;

• width of the 95% confidence interval of all bootstrapping samples is the base of our marker;

• to obtain single robust measure of homogeneity, we average this quantity among all time points;

Voxel time courses of right PCC

Variation of mean BOLD activity at arbitray time point
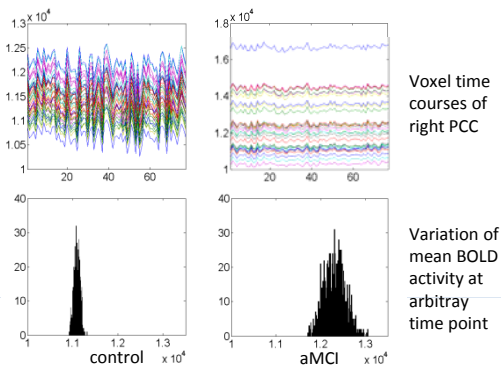
3. Results

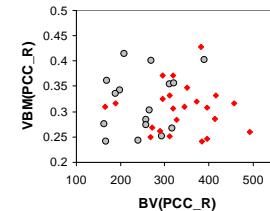**• Significant group differences**

(α = 95%, Mann-Whitney-U, Westfall-Young Correction)

○ HC
◆ aMCI
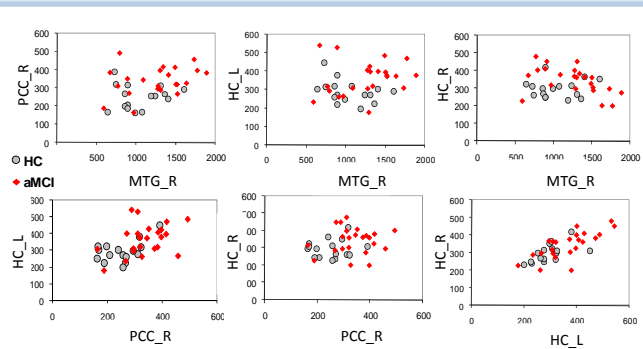
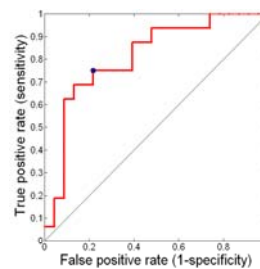• which **can not be explained by grey matter loss;**

• only slight correlation to grey matter loss in hippocampi;

-> differences of **functional** type

• most pronounced difference in BOLD Variation in **right posterior cingulate cortex** is a good test to identify aMCI;

(area under ROC curve 0.81)

4. Conclusion

• regional integration in rest-fMRI captured by bootstrapping plays an important role for aMCI identification;

• significant regions within the DN correspond well to previous findings (Grecius et al., 2004, Sorg et al. 2007);

• on the data of our study, our novel marker performs superior than previously proposed measures for regional integration (Li et al., 2002, Zang et al., 2004, Xu et al., 2008);

• comparison with VBM demonstrates that the differences are functional in nature;

• Li, S.-J., Zhu L., Wu, G., Zhang, M.-J., Franczak, M., Antuono, P.G. (2002), Alzheimer Disease: Evaluation of a Functional MR Imaging Index as a Marker. *Radiology*, vol. 225, no. 1, pp. 253-259.
• Sorg C., Riedl V., Mühlau M., Calhoun VD., Eichele T., Läer L., Drzezga A., Förstl F., Kurz A., Zimmer C., Wohlschläger A.M. (2007), Selective changes of resting-state networks in individuals at risk for AD. *Proc Natl Acad Sci USA.*, vol. 104, no. 47, pp.18760-5.
• Xu Y., Xu G., Wu G., Antuono P., Rowe, D.B., Li S.-J. (2008), The phase shift index for marking functional asynchrony in Alzheimer's disease patients using fMRI. *Magn Reson Imaging*, vol. 26, no. 3, pp. 379-92.
• Zang Y., Jiang T., Lu Y., He Y., Tian L. (2004), Regional homogeneity approach to fMRI data analysis. *Neuroimage*, vol. 22, no. 1, pp. 394-40