# Analyzing Differences of Static BOLD-sensitive whole Brain MR Images: Application in Dementia

S. A. Rombouts[1], P. Scheltens[2], J. Kuijer[1], F. Barkhof[3]

[1]Physics & Medical Technology, VU University Medical Center, Amsterdam, Netherlands, [2]Neurology, VU University Medical Center, Amsterdam, Netherlands, [3]Radiology, VU University Medical Center, Amsterdam, Netherlands

## Introduction

The majority of FMRI studies apply T2* weighted imaging, sensitive to blood oxygenation level dependent (BOLD) contrast [1], to subtract images acquired during a reference condition from activation images. In FMRI studies of group differences, these subtraction images are compared between groups to assess differences in brain activation between groups. However, the reference image itself may also be different between groups, although this is usually not analyzed.

There are several possible explanations for a difference in T2* weighted reference images between patients and controls. Recent BOLD FMRI data show structured network activity during a resting state [2-7], which might be altered in patients with Alzheimer's disease (AD) [8]. In Parkinson's disease, an increase in iron deposition is supposed to decrease the putaminal signal on T2 weighted scans [9, 10]. Region of interest analyses of hippocampal regions showed that the resting state T2* weighted signal was diminished in AD in the hippocampus, probably caused by decreased resting metabolism [11]. These hippocampal ROI analyses have not been extended to whole brain analyses. Whole brain, static (hence no time series) resting state T2* weighted signal analyses in dementia is the topic of the current study.

Previously we reported on altered activation and deactivation in early dementia (that is mild cognitive impairment (MCI) and AD [12, 13]). In the current study we re-analysed those data and determined the average rest whole brain static T2* weighted signal in each subject of the same dataset. We aimed to determine whether there are any regions with an altered T2* weighted signal in dementia, and how these relate to atrophy.

## Methods

Eighteen AD, 28 MCI patients and 41 healthy elderly controls performed an on/off task (face encoding vs. fixation) during T2* weighted EPI FMRI scanning on 1.5 T (Sonata, Siemens) [12, 13]. A T1-weighted structural MRI-scan was also acquired. Image analysis was carried out using FSL 3.2 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) [14]. The first five T2* weighted volumes were deleted. Ten whole brain T2* weighted scans acquired during the 21 seconds fixation period at the beginning of the face encoding paradigm were used [13].

Data preprocessing included motion correction and removal of non-brain structures [14]. In each subject, the 10 EPI scans during fixation (control condition) were then averaged to create the static BOLD reference state image, which was registered to the structural image. Structural images were segmented into grey matter probability maps (GMPs), white matter and CSF [15]. EPI scans were normalized by dividing each voxel's signal by the average CSF signal in the EPI image. Both these normalized EPI images and the GMP images were put in standard space, and spatially smoothed using FWHM=8mm.

Normalized EPI signal was compared between patients and controls voxel-wise using FSL with a two sample t-test ($p<0.001$). Of each region that was significantly different between patients and controls, both EPI and GMP signal was averaged, giving EPI and GMP variables. These two variables per region were then further analysed using a general linear model testing for group differences per region. Further, interactions between the two variables were tested to determine whether one variable would show a significantly larger group difference than the other.

## Results and Conclusion

Patients showed increased T2* weighted signal near the ventricles in the whole brain voxel-wise analysis (Figure 1). This is because CSF has highest signal intensity on T2* weighted scans, and ventricles are enlarged in patients. Compared to controls, patients showed decreased T2* signal in the left hippocampus, middle and posterior cingulate cortex / precuneus, left and right insula / putamen, and left parietal cortex (Figure 1). In all these regions, except the bilateral insula/putamen, patients also had decreased GMP as compared to controls. In two of these regions (left hippocampus and posterior cingulate cortex), there was an interaction between EPI and GMP variables: the group differences were significantly greater for GMP than EPI signal.

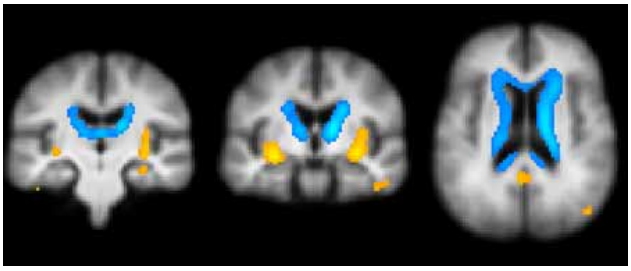

*Figure 1: Coronal and transverse sections showing significant signal differences of static BOLD EPI images between controls and patients, projected on the average structural scan of all subjects ($p<0.001$, uncorrected). In blue: signal increase in patients; in orange/yellow: signal decreases in patients. Signal increases are located at the borders of ventricles. Signal decreases are located in left hippocampus (image on the left), insula/putamen bilateral (image on left and in middle) and posterior cingulate cortex / precuneus (image on the right).*

We conclude that in FMRI studies of dementia, not only the dynamic BOLD signal (activation, deactivation or resting state connectivity), but also the static signal during the reference condition is diminished in certain regions. Most of these differences are likely caused by GM atrophy, although decreased metabolism [11], or perhaps iron deposition [9, 10] are also factors that may contribute. This technique may provide an easy to apply, whole brain imaging method to study early changes in dementia, as previously shown for the hippocampal region [11]. Further, it may be used in task related BOLD FMRI and add to the understanding of the mechanism of task related group differences.

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### References

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