Functional Liver Imaging Using Inter-Pixel Cross Correlation (IPCC): A Brute Force Univariate Approach

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Introduction: BOLD (blood oxygen level dependent) contrast, well known as the basis behind brain fMRI, can be applied to the functional assessment of other bodily organs. For example we have previously shown liver BOLD contrast can vary between the pre- and postprandial states **[1]**. However, over a single slice the liver BOLD response to a standardized meal challenge appeared heterogeneous: there was no obviously apparent and uniform "ideal" BOLD signal response that could be used to correlate with BOLD signal physiologic modulation. Indeed, choosing an "ideal" haemodynamic response function (HRF) that best described postprandial liver function seemed at best something to do on a per-subject basis. Here, we present a novel approach to analyzing liver BOLD response to a standardized meal challenge, hypothesized to better classify the global liver meal-response.

Theory and Methods: A novel BOLD analysis approach has previously been demonstrated for investigating resting-state brain functional connectivity **[2]**. Briefly, in a task-identified region (using cross-correlation with an ideal box-car waveform), each pixel time-course from a 2-D resting-state BOLD image set is used as a reference waveform and cross-correlated with all other task-identified pixel time-course on a pixel-by-pixel basis, and the pixels exhibiting similar time-varying behavior are considered connected. In the case of liver, if there is a global BOLD signal dynamic response to a controlled meal, the inter-pixel cross-correlation (IPCC) analysis may be similarly employed to derive it (**Fig. 1**). Specifically, each liver pixel time course provides an ideal HRF to correlate with all other pixel time-courses. Using a correlation coefficient (*cc*) threshold of 0.7, the number of correlating time-courses was assigned to the corresponding pixels in a new matrix called the correlation number weighted (*cnw*) map.

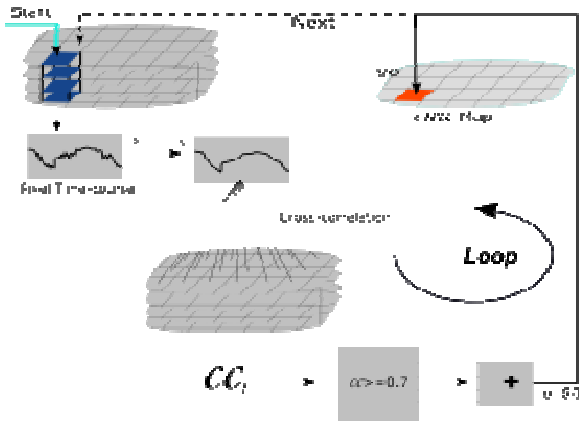

Fig. 1. IPCC procedure

In this study, approved by our local ethics committee, 9 healthy fasted human subjects were scanned using a GE Signa HDX 3T short-bore MR scanner and 8-channel torso phased array coil during free breathing. Following localization of the hepatic portal bifurcation, a sagittal multiphase T2*-weighted GRE EPI sequence was employed (α=90°, 1 NEX, TR/TE=1000/35ms, 24cm FOV, 64×64 matrix, 1 slice of 8mm thick, 864 phases, 36 discarded acquisitions, total time=15 min) with intake of a controlled meal (235mL of Ensure Plus **[1]**) initiated 2.4 minutes into scanning. Image post-processing first involved motion correction, based on the correlation coefficient template matching algorithm **[3],** followed by reduction in respiratory noise through a band-stop digital filter, using Matlab. The motion-compensated BOLD image sets were finally analyzed using this IPCC procedure using "3dfim+", of AFNI (http://afni.nimh.nih.gov/).

Results: An inter-pixel correlation *cnw* map was obtained for each liver. It was found that a lower *cc* threshold, e.g. 0.4, was not sensitive to the highly inter-correlated regions (*cc* of about 40% liver area was above 0.4), while an overly high threshold, e.g. 0.9, might give a pseudo *cnw* map by chance. 0.7 seemed to be appropriate. In the *cnw* map at *cc*=0.7, the maximum pixel value represented the maximum number of liver pixels correlated with each other throughout the liver slice. An ROI placed at the maximum correlation region gave a mean BOLD signal time-course (**Fig. 2**). The maximum pixel value normalized by the total liver pixel number (here, called max. correlation degree) was on average 8.49±2.97%.

Discussion: The IPCC procedure seems to be a reasonable apaproach to address the complex nature of a liver HRF. The HRF is likley complex due to the dual blood supply (hepatic artery and hepatic portal vein) as well as drainage from the spleen. In addition differing meal absorption would also contribute to HRF complexity. We suggest an ROI located at the maximum-valued pixel on the *cnw* map represents a global response of the liver to the controlled meal. The variability of this response indicates the complex BOLD modulation in the liver. Furthermore, the maximum correlation degree, as a normalized value, may allow direct comparison of meal-induced liver activation, and hence liver function, between subjects.

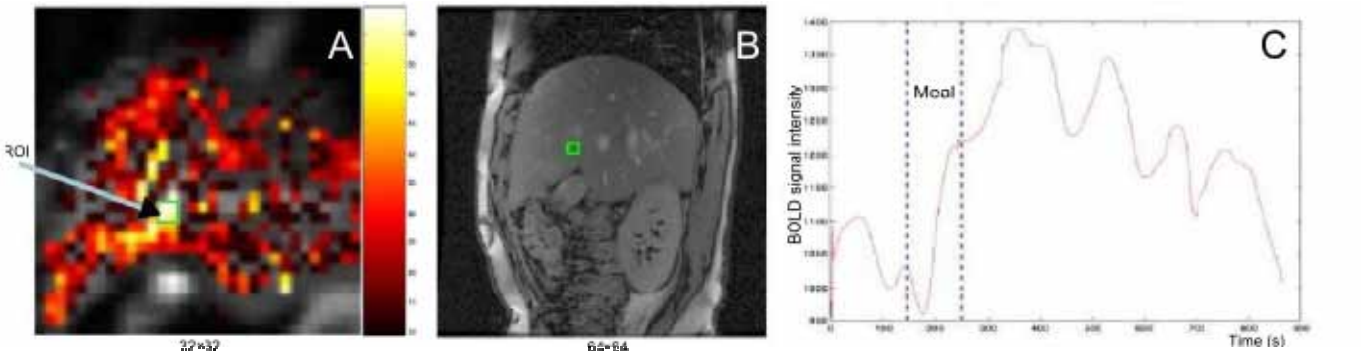

Fig. 2 A) BOLD image overlaid with a *cnw* map; **B)** Anatomic image and an ROI with the highest corr. Degree; **C)** ROI BOLD signal time-course (denoised)

References: [1] Fan *et al.* (2006) ISMRM *abs.*14:3249; **[2]** Biswal *et al.* (1995) Magn. Reson. Med. 34:537; **[3]** Sussman *et al.* (2003) *IEEE Trans Med. Img.* 22:206.