FMRI using non-Gaussian γ-stretched exponential maps

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Purpose: Recent works suggested that the signal arises from diffusion-weighted (DW) functional magnetic resonance imaging (fMRI) at high *b* values might be affected by physiological phenomena following neuronal activity[1-3]. In principle, this approach might provide a more direct measure of brain activity and represent a notable advancement in fMRI investigation. Pampel and coworkers[3] showed that the interaction between DW gradients and susceptibility-induced background gradient fields around vessels has an impact on apparent diffusion coefficient (*ADC*) measurements and fMRI experiments. Thanks to this dependence, DW fMRI activation maps are coherent with conventional BOLD fMRI derived activation maps and, notably, they are more "localized"[1-3]. A recent study[1], measuring the vascular component of DW fMRI under hypercapnia, which induces blood flow changes in the absence of a change in neuronal firing, has suggested that a large component of diffusion fMRI signal at high *b* value is vascular rather than neuronal effects. Other recent works have produced controversial explanations for the mechanisms underlying changes in the apparent diffusion coefficient (ADC) during brain activation.

In the present work we investigated the signal source and spatial specificity of DW fMRI changes in the visual cortex by using an innovative approach based on non-Gaussian description of water diffusion[4]. The working hypothesis of the study was to demonstrate that non-Gaussian diffusion fMRI might represent a real advance in fMRI. Moreover, this study aimed at clarifying the biophysical process underpinning the observed changes in ADC during brain activation, employing the most recent results we obtained in the field of non-Gaussian diffusion MRI[4,5]. Indeed, we have recently shown that the stretched exponent, γ, of the non-Gaussian stretched exponential model is strongly affected by local magnetic susceptibility variations, $\Delta\chi$[5]. Here we suggest exploiting this dependence to localize brain activation areas more accurately.

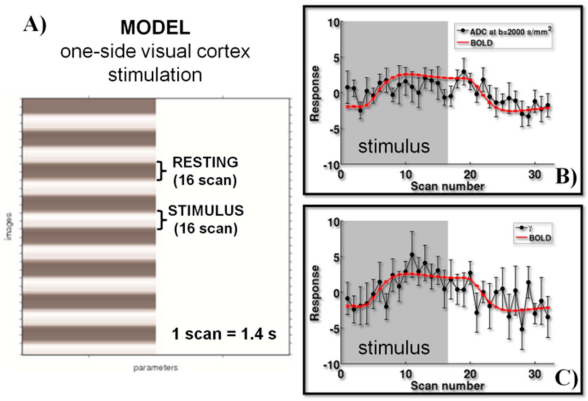

Fig.1 Representative results from one subject. *A)* time scheme of the model used to produce the one-side visual cortex stimulation. *B)* Time courses of Gaussian diffusion (b=2000 s/mm^2) and BOLD fMRI signals. *C)* Time courses of non-Gaussian diffusion and BOLD fMRI signals. Gray swathes in *B)* and *C)* indicate stimulation and rest blocks (time expressed in scan units; 1 scan = 1.4 s). Error bars represent the standard deviation of the response across the corresponding eight epochs.

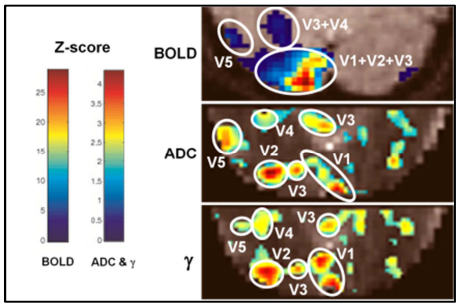

Fig.2 Representative results from one subject. BOLD fMRI, Gaussian diffusion fMRI (ADC) and non-Gaussian diffusion fMRI (γ) activation maps. Voxels were classified as significantly activated at *p values uncorrected* < 0.005.

Methods: four volunteers (males, age: 26±1) participated in this study after giving informed consent, according to the national laws and the local ethics committee guidelines. All imaging was obtained by using a 3.0T scanner (Siemens Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany), equipped with a circularly polarized transmit-receive coil. The maximum gradient strength was 40 mT m^{-1}, with a maximum slew rate of 400 mT m^{-1} ms^{-1}. Eight oblique slices centered on the calcarine fissure were selected from a rapid localization scan. Using a block-design paradigm of visual stimulation we investigated the visual cortex by comparing Gaussian and non-Gaussian diffusion fMRI acquisitions to standard BOLD dependent experiments. Therefore, 256 volumes of diffusion weighted segmented echo planar images (DW SE-EPI) were acquired using the following parameters: *TR*/*TE* = 1400 / 107 ms, slice thickness 3 mm, with 50% gap, matrix size 64x64, in plane resolution of 3x3 mm^2. The diffusion encoding gradients were applied along readout direction using five different *b* values: 0, 500, 1500, 2000, 3000 s/mm^2. BOLD fMRI images were acquired by using a gradient-echo sequence with the same TR, 24 slices of 1mm thickness. For all fMRI experiments, visual stimulation was obtained from a flickering half-dartboard presented in the right visual field (frequency, 8 Hz), via projection on a semi-opaque screen within the MRI scanner room. The activation paradigm consisted of eight epochs of 16 scan = 22.4 s separated by a 16 scan = 22.4 s interval (**Fig.1A**). Activation maps were calculated individually for each subject. Images were first corrected for motion artifacts and registered to the high-resolution anatomical images followed by spatial smoothing with a Gaussian filter of 6 mm full width at half maximum. Usual BOLD fMRI activation maps were reconstructed, for each subject, using a first level analysis in SPM8 (www.fil.ion.ucl.ac.uk/spm). Conventional Gaussian diffusion activation maps (ADC-maps) were obtained from the b = 2000 s/mm^2 diffusion-sensitized fMRI images using SPM8 and following the data processing employed in ref.[**1**]. Non-Gaussian diffusion maps were calculated using the full range of b-values. A nonlinear Levenberg-Marquardt algorithm was used to estimate, from the diffusion-sensitized signal, S, at each b value, voxel-by-voxel, the non-Gaussian diffusion parameter, γ, according to the stretched exponential model: $S=S_0Exp[-(b\ ADC)^{\gamma}]+\eta$. The corresponding non-Gaussian diffusion activation maps (γ-maps) were obtained using SPM8, and following the same procedure employed for calculating ADC-maps. In all imaging modalities (BOLD, ADC and γ maps) voxels were classified as significantly activated at *p values uncorrected* <0.005.

Results: First we examined the time-course of BOLD, ADC and γ within a volume of interest (VOI), separately for each subject. The VOIs were defined by thresholding activation maps at $Z_{score}\geq10$ for BOLD maps and $Z_{score}\geq3$ for ADC and γ maps. As expected[1,2], the ADC expansion time course showed a feeble increase at stimulus onset, and overall, the BOLD and ADC expansion time courses were similar in shape (**Fig.1B**). However, the most important and novel result concerns the γ expansion time course analysis (**Fig.1C**). BOLD and γ expansion time courses were compared to each other, and revealed a better matching than that observed between ADC and BOLD (**Fig. 1B** and **C**).

ADC and γ activation maps directly calculated from the raw diffusion-sensitized MRI signals clearly showed activation of primary as well as secondary visual areas, such as the visual motion area MT/V5 which is typically activated by flickering stimuli[6] (**Fig.2**). Voxels detected as activated from Gaussian and non-Gaussian diffusion MRI were well located along the cortical ribbon. In contrast, BOLD fMRI identified were much broader areas of activation, encompassing large subcortical areas beyond the cortex (**Fig.2**). Finally, activated voxels from γ maps overlapped with those from ADC maps, but, in addition, they revealed a higher contrast-to-noise ratio (CNR) and statistical significance (e.g. see time-courses in **Fig.1** and V1 regions in **Fig.2**).

Discussion: the time course analysis (**Fig.1**) performed in this study shows that non-Gaussian diffusion response to brain activation matches well to the BOLD activation, and is more pronounced than that observed by conventional ADC methods. This result is in full agreement with recent work concerning Gaussian diffusion fMRI[1,3] and with recent findings on non-Gaussian diffusion MRI[4,5]. Indeed, we have recently shown that non-Gaussian γ parameter is strongly affected by local $\Delta\chi$[4,5]. Results reported in **Fig.1C** demonstrate that it is possible to exploit this dependence to monitor time-varying local $\Delta\chi$ due to brain activation. Moreover, the overlap of activated voxels between γ and ADC maps (**Fig.2**) suggests that the vascular contribution, and thus local $\Delta\chi$ time variations, are predominant contributors to ADC changes of voxels activation detected by γ maps (**Fig.2**) indicates that non-Gaussian diffusion fMRI might provide a better anatomical localization of brain activation when compared to BOLD and conventional Gaussian diffusion fMRI. Finally, according to Miller and coworkers[1], we found that vascular contribution (in capillaries and small veils) is predominant in ADC variations, and that non-Gaussian, compared to conventional diffusion MRI techniques are more sensitive and spatially specific to the signal source.

Conclusion: in this work we exploit the recent evidence of the strong dependence of non-Gaussian γ parameter on local $\Delta\chi$ in order to show: 1) vascular contribution (in capillaries and small veils) is predominant in the ADC variations found in Gaussian diffusion fMRI; 2) non-Gaussian diffusion fMRI is more sensitive and spatially localized to the signal source than Gaussian diffusion fMRI; 3) it is possible to use non-Gaussian diffusion fMRI to localize brain activation areas more accurately than usual BOLD fMRI. Here we show that non-Gaussian diffusion fMRI could represent an advance in functional neuroimaging.

References: [1]KL Miller et al., *PNAS* **104** (2007); 20967–20972. [2]T Jin et al. *NeuroImage* **41** (2008); 801-812. [3]A Pampel et al., *NMR in Biomedicine* **23** (2010); 610-618. [4]M Palombo et al., *J Chem Phys* 135 (2011); 034504. [5]M Palombo et al., *J Magn Reson* **216** (2012); 28-36. [6]R.B. Buxton et al., *Magn Reson Med* **39** (1998); 855–864. [7]Z Kubova et al., *Vision Res* **35** (1995); 197–205.