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Hunting for Neuronal Currents: Absence of Rapid MRI Signal Changes During Visual Evoked Response

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Introduction
Recently, the use of MRI to detect changes in neuronal currents (NCs) during human brain activation has been suggested [1-4]. NC based fMRI could have tremendous impact on neuroscience, complementing existing measurement methods of microscopic (e.g. single-cell recordings) and macroscopic (EEG/MEG) electrical activity. However, so far it has not been demonstrated convincingly that: 1) MRI can separate NC-effects from other (e.g. BOLD) effects; 2) MRI has adequate sensitivity to detect NC in vivo. Here we introduce a method that can separate rapid (e.g. NC) from slow (e.g. BOLD) processes, and apply this method to investigate whether MRI allows detection of the NC response to a visual stimulus.

Materials and Methods
To improve fMRI sensitivity, we combined an efficient stimulus method (binary m-sequence [5]) with a highly-sensitive 16-channel MRI detector [6]. To allow detection of fast neuronal responses, the stimulus was controlled by a rapid m-sequence (2 s length, 100 ms bins). This sequence was used repetitively (150x), and its amplitude was modulated with a second, slower m-sequence (2 s bins) to allow simultaneous and separable measurement of the BOLD signal (Fig. 1). M-sequence 1's corresponded to 50 ms checkerboard display followed by 50 ms darkness (0's = 100 ms darkness). Per subject (n=6) 2-4 runs were performed, two of which incorporated a 50 ms delay between stimulus and MRI acquisition. Single-shot EPI MRI was performed on a GE 3 T using an oblique slice, centered on the calcarine fissure (81 ms TE; 100 ms TR; 25^{o} flip angle; 4x4x5 mm^3 nominal resolution). MEG (275-channel system: CTF, Inc.) was performed with the same stimulus on the same subjects. MRI and MEG data were analyzed in identical fashion using correlation analysis [5]. MRI data were analyzed for signal intensity (magnitude) and phase effects. The BOLD signal was extracted by correlation with a zero-filled slow m-sequence. Subsequent correlation of the 0-2 s lag bins in the correlogram (fig. 3) with the rapid m-sequence resulted in a BOLD-free signal sensitive to rapid processes such as NC effects. Pixels (MRI) or sensors (MEG) with t-scores exceeding 3.5 were considered activated. Average t-scores were determined over all activated pixels.

Results and Discussion
All subjects showed highly significant BOLD fMRI (t=5.90) and MEG (t=6.73) activation (see table). Despite the excellent (< 1%) ROI-averaged temporal standard deviation (TSD, see Table 1) no significant NC (rapid fMRI) activation was found either in magnitude (table) or phase (results not shown). Average t-scores in 0-100-ms-lag (t-score rapid 1) and 100-200-ms-lag (t-score rapid 2) were below 0.12 in all subjects. An example of single subject data is shown in Figs 2-3, demonstrating the insignificant rapid fMRI response (red curve). Despite the superior sensitivity of the methodology used in these experiments, and otherwise similar conditions, previous results [4] could not be reproduced. We conclude that under the conditions described above, the sensitivity of MRI to detect evoked responses through NCs is at least an order of magnitude below that BOLD-based fMRI or MEG.

References
[1] Kamei, IEEE Trans Magn. 1999; [2] Bodurka, MRM 2002; [3] Konn, MRM 2003; [4] Xiong, HBM 2003; [5] Kellman, Neuroimage 2003; [6] de Zwart, MRM 2004

Table 1: fMRI and MEG results

	MRI data						MEG data		
subject	**# MRI runs**	**TSD**	**TSD ROI**	**# active voxels**	**average t-score slow**	**average t-score rapid 1/2**	**# MEG runs**	**# active sensors**	**average t-score MEG**
1	1	3.91	0.95	43.0	3.83	-0.10/-0.09	2	13.0	6.62
2	1	3.96	0.68	84.0	4.58	-0.11/0.02	2	21.0	5.73
3	2	4.45	0.60	111.0	7.45	0.04/-0.12	3	14.7	4.95
4	4	3.19	0.41	131.0	6.82	-0.05/0.00	3	33.3	10.09
5	2	2.56	0.32	97.5	6.73	0.03/0.03	3	16.3	6.56
6	4	3.10	0.52	73.8	6.00	0.01/-0.02	3	21.0	6.44
average	**2.3**	**3.52**	**0.58**	**76.7**	**5.90**	**-0.03/-0.03**	**2.7**	**19.9**	**6.73**
SD	*1.4*	*0.70*	*0.22*	*46.9*	*1.14*	*0.07/0.06*	*0.5*	*7.3*	*1.77*

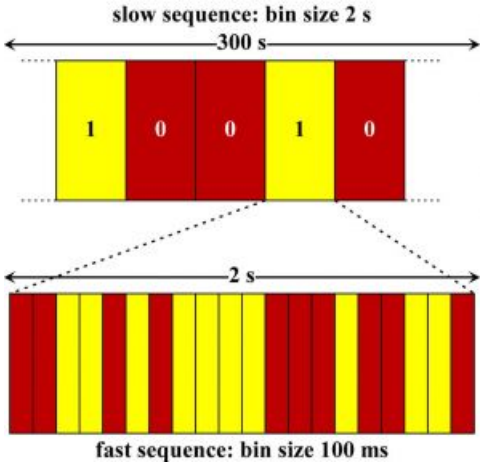

Figure 1: The modulated binary m-sequence used to simultaneously map slow (BOLD) and rapid (neuronal) effects.

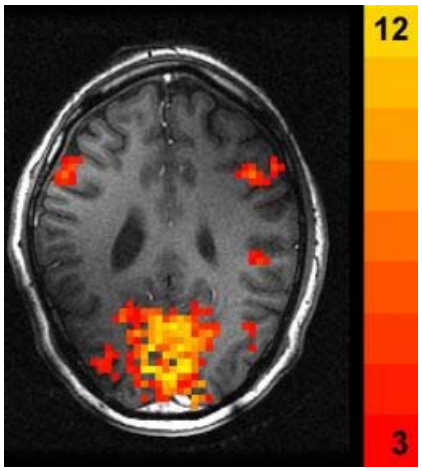

Figure 2: T-score map of the BOLD activation.

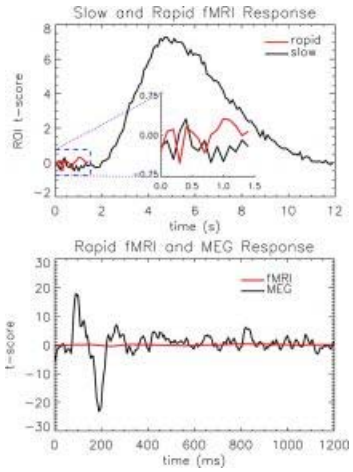

Figure 3: Average t-score in the slow and fast fMRI response (top). The bottom plot shows a comparison of the fast fMRI response with the response of an

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