SINGLE-SUBJECT HEMODYNAMIC REFRACTORY EFFECTS IN HEALTHY VOLUNTEERS

B. Descamps[1], P. Vandemaele[1], K. Paemeleire[2,3], L. Leybaert[3], and E. Achten[1]

[1]Neuroradiology, Ghent University Hospital, Ghent, Belgium, [2]Neurology, Ghent University Hospital, Ghent, Belgium, [3]Neurophysiology, Ghent University, Ghent, Belgium

Introduction

As the hemodynamic response (HR) to a single stimulus lasts for several seconds, successive stimulus presentation leads to an addition of the second response to the first. In 1998, Friston et al. proposed that this hemodynamic response is not fully linear. Successive stimulus-presentation results in an almost perfect linearly additive effect, except for stimuli-pairs which have a short interstimulus interval [1]. Huettel et al. demonstrated this non-linearity for interstimulus intervals (ISI) of 1s, 2s, 4s and 6s [2]. For an ISI of 6s the effect has nearly disappeared. Huettel's data processing led to across-subject results. In order to optimize the processing, in this work several processing methods were compared to achieve robust single-subject results. From the literature it is known that patients with migraine show a potentiation of event-related potentials (ERP) amplitude in response to repeated visual stimulation compared to a decrease in ERP amplitude in healthy volunteers [3]. Therefore, the hypothesis for this study is that the HR in patients with migraine will show a different adaptation effect in response to stimulus repetition while the known effects will be present in normals. The results reported here are the acquisition and post-processing optimization for single-subject analysis in normal subjects.

Methods

Design. Visual stimuli (single and paired stimuli) consisted of a 500ms lasting full-screen reversing checkerboard pattern, presented through goggles. Pairs had an ISI (onset-to-onset) of 1s, 2s or 6s; the fixed intertrial interval was 20s. Every condition was randomly repeated 30 times (120 repetitions in total). The paradigm included also 60 prescans. The total paradigm took 45'30" of acquisition time.

Data acquisition. All imaging was performed on a 3T system (MAGNETOM Trio, Siemens AG, Erlangen, Germany). Anatomical images were T1 weighted images (MPRAGE) with isotropic voxels (0.9 x 0.9 x 0.9 mm³). Functional images were acquired using a T2* weighted echo planar sequence sensitive to BOLD contrast with voxel size 3.5 x 3.5 x 3.0 mm³, TR = 1000 ms, TE = 35 ms, FoV = 224 mm, 15 slices with 0.5 mm gap.

Processing. All data from six healthy volunteers were preprocessed in SPM5 (FIL, London, UK): slice time correction, realignment, coregistration of anatomical and functional images, normalization and smoothing. Design was set up with the four conditions (0, 1, 2 and 6 seconds ISI) and realignment parameters as covariates of no interest. Four additional t-contrasts (one for each condition) were added. For each t-contrast, the time course of activation for all voxels above threshold were averaged, fitted to a canonical HR and plotted. A region of interest (RoI) analysis on Brodmann areas 17 and 18, selected with WFU Pick Atlas (http://fmri.wfubmc.edu/cms/software), was also performed, using MarsBaR (http://marsbar.sourceforge.net) with the same design as for the SPM processing. Resulting curves contain data points without any fitting. Furthermore, Matlab (The MathWorks, Natick, USA) was used to process the data: baseline calculation, determining onset times, extracting all activated voxels for each condition, subtracting the mean 0s response and after a time shift plotting the data as such (no fitting with a canonical HR function was done); percent signal changes are plotted in relation to the calculated baseline.

Because several subjects reported difficulties with attention due to the long scanning time, the analysis was repeated using the first half of the acquisition data.

Results

Figures 1 to 3 present results for a single subject after subtraction of the response to the first stimulus, for own software, SPM5 and MarsBaR, respectively. The response to the second stimulus in a stimulus pair with a short interstimulus interval (less than 6s) shows a latency and a decreased amplitude (1s ISI: overall mean normalised amplitude 0.822 ± 0.15, overall mean latency 1.63s ± 1.08; 2s ISI: overall normalised amplitude 0.958 ± 0.12, overall mean latency 1.06s ± 0.73). In the 6s condition the response to the second stimulus follows the first one remarkably well (overall mean normalised amplitude 1.175 ± 0.40, overall mean latency -0.494s ± 0.33). Figure 2 is an SPM plot of the time course in the most significant voxel; responses to all conditions are superposed. Plotted realignment parameters in figure 4 show this subject started moving his head in the second half of the long scanning session (45'30" in total). Despite using only 60 repetitions we could still extract the refractory effects for the subjects (data not shown).

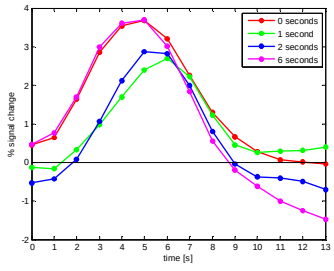

Figure 1

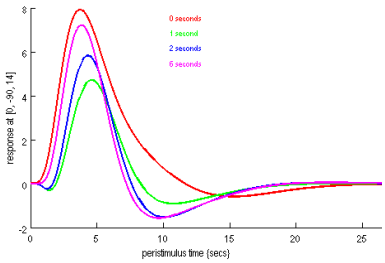

Figure 2

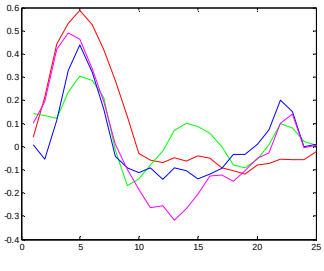

Figure 3

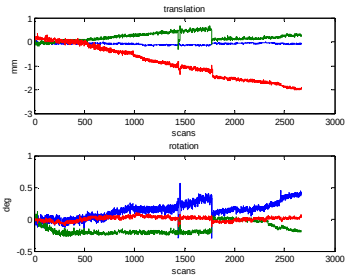

Figure 4

Superposed conditions, all but the first after subtraction of the first (0s) stimulus response, with own software (figure 1), SPM5 (figure 2) and MarsBaR (figure 3). Figure 4: a subject's realignment plot: major movements – apart from scanner drift – appear in the second half of the scan session.

Discussion and conclusion

We demonstrate that even in a single subject, non-linearity of the hemodynamic response can be revealed.

Fig. 1 shows for a single subject that, after subtraction, the hemodynamic response to the 6s condition looks like a 0s response. In the same figure, signals at onset (t = 0s) for the 1s and 2s conditions start lower than in the 0s and 6s conditions. This observation can be explained by neurovascular reasons: the expanding vascular bed has its limitations. If a second stimulus is presented shortly after the first one, an additional increase in blood flow and blood volume (and thus more oxyhemoglobin) is not possible. If the first response is subtracted, this may result in the time courses seen in figure 1.

In SPM, a plot of the four conditions provides similar results: figure 2 also shows the latency and the decrease in amplitude of responses to shorter ISI, but SPM models the data using a canonical HR function, though in this particular situation the hemodynamic response does not follow linearity as proposed by SPM. Using fast event-related designs one should take into account that modelling the measured HR possibly induces estimation errors, e.g. decreased power. We propose to determine the HR function for each condition in each individual subject and then use these data for modelling.

Despite using only 60 repetitions we were still able to extract the refractory effects for the subjects; although the data provide decreased power due to less data points, refractory effects remain detectable, while otherwise data are less useful. This indicates total acquisition time can be reduced to 23'15".

Further investigation with patients with migraine will now be required to determine whether and how patients' data differ from healthy volunteers. In order to determine the origin of the refractory period (neuronal or vascular or both) event related potentials and fMRI data for the same subject should be compared.

References

[1] Friston, K. J., O. Josephs, et al. (1998). Magn Reson Med 39(1): 41-52; [2] Huettel, S. A. and G. McCarthy (2000). NeuroImage 11(5): 547-553; [3] Schoenen, J., W. Wang, et al. (1995). Eur J Neurol 2(2): 115-122.