TRIAL-WISE INVESTIGATION OF CEREBRAL BLOOD VOLUME CHANGE IN HUMAN BRAIN AT 7T

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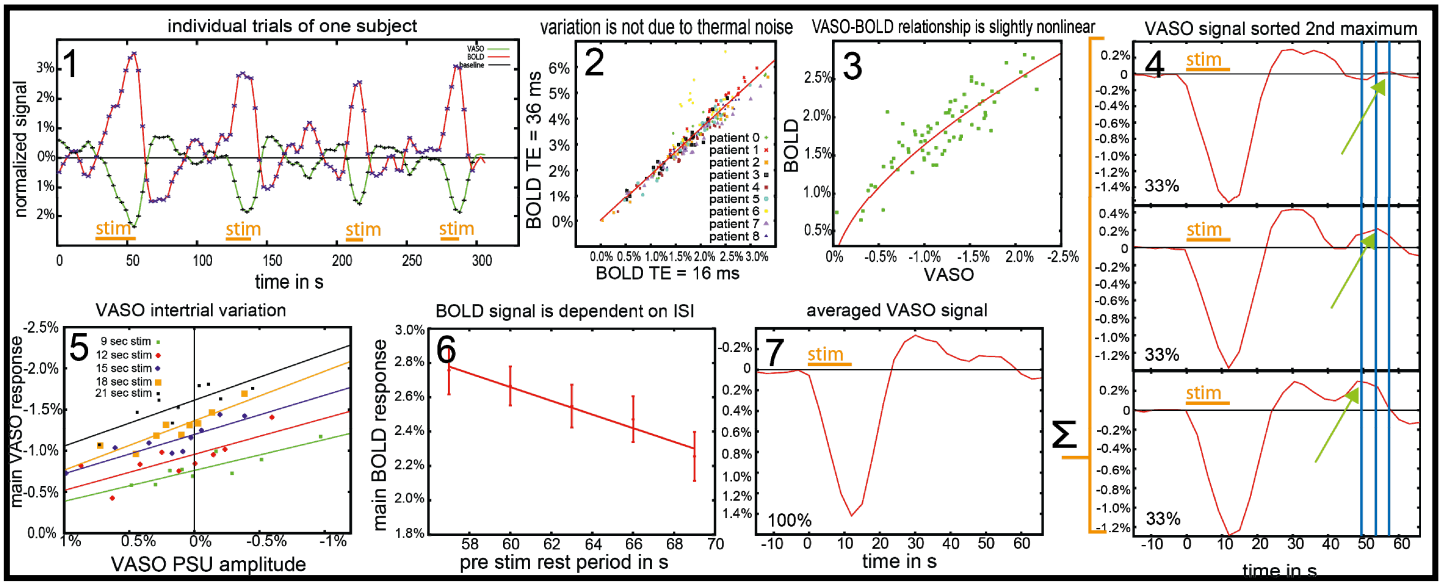
Purpose: Magnitude variations in stimulus evoked blood oxygenation level dependent (BOLD) signal change can be due to modulations in baseline physiology (e.g. blood pressure, end-tidal CO_2, arterial oxygenation etc.) and/or in the neural response (e.g. stimulus type, attention, interference with background activity). These variations, apparent both across subjects and inter-trial within a single subject (Fig 1), represent a confound in the interpretation of BOLD in terms of underlying neuronal activity. The purpose of this study was to use a high-SNR fMRI method in order to simultaneously investigate BOLD and cerebral blood volume (CBV) changes on a trial-by-trial basis to help improve our understanding of neurovascular coupling. CBV measurements are more suitable for investigation of the mechanisms underlying inter-trial response variations since this variable is much less affected by the exact physiological baseline state than the BOLD response[a]. Furthermore, the arterial vessels, visible in CBV measurements, are actively controlled and might have a closer temporal coupling to the neural response than the passively-controlled venous vessels dominating the BOLD response, enabling better investigation of the post-stimulus signal evolution.

Methods: A multi-echo, slice-saturation slab-inversion VASO sequence[b] was used to obtain time series acquired interleaved with and without blood nulling at three echo times (TE = 16/36/56 ms) at 7T, sensitive to CBV and BOLD signal changes. Further experimental parameters were: TR/TI1/TI2 = 3/1/2.5 s, nominal resolution (2 mm)^3, N = 9. We used a flickering checkerboard visual stimulation paradigm which consisted of 39 activation-rest periods. Stimulus duration was 9/12/15/18/21 s and inter stimulus interval (ISI) was 57/60/63/66/69 s presented in a randomized order. Respiration was recorded to ensure its independence of the results.



Results: Inter-trial variations are large (coefficient of variation = 30% - 40%). Figure 2 which compares magnitude size as a function of TE suggests that the variations are not caused by thermal noise but are predominantly physiologically based. Relationship of BOLD and VASO responses show small nonlinearities (Fig. 3), as expected from the deoxyhaemoglobin dilution model[c]. On an individual trial basis, the sustained post-stimulus undershoot (PSU) is very different compared to the mean time course averaged across all acquired trials. In individual trials, the post stimulus signal follows an oscillatory pattern (Fig. 4). The well-described shape of PSU seems to appear only after averaging over several oscillation frequencies (Fig. 7). The correlation of main response and amplitude of PSU is positive for a given stimulus duration (slope of lines in Fig. 5). However, when the response is increased externally by using longer stimulus durations, it has not much effect on the PSU amplitude (parallel lines of fit in Fig. 5). Even with ISIs above 57 s, BOLD signal has not yet returned to baseline, and the response depends on the preceding ISI (Fig. 6).

Discussion: This study shows that the inter-trial variations of BOLD and CBV signals are not due to noise, but reflect underlying neural vascular mechanisms that can be isolated by correlating features of individual trial responses[d] (e.g. initial response vs. undershoot). For example, the mechanism controlling the interplay of initial response vs. PSU amplitude is different for exogenous response variations (e.g. stimulus duration) and endogenous variations (with same stimulus type). The different stimuli in Fig. 5 can be separated neither by their amplitude nor by their PSU amplitude. However, by combining both variables each stimulus can be separated along the diagonal line in Fig. 5. The post-stimulus oscillation can be interpreted as a feature of a damped oscillator, or as an effect of correlation with resting state oscillation[e]. The post-stimulus oscillation is slightly stronger in the CBV than in the BOLD response, perhaps due to the filtering caused by the passively responding venous vessels that dominate BOLD signal.

Conclusion: The high-SNR fMRI method used here enabled a new approach for investigating neurovascular coupling in healthy human volunteers by considering inter-trial variations. The results shown here suggest that averaging over trials is associated with a loss of specific neural information, such as post-stimulus oscillations visible in almost all trials but disappearing after averaging. Since BOLD signal baseline is not approached after resting periods under 60s, the interpretation of fMRI responses using smaller ISIs can be confounded. Combining several features of individual responses can offer additional characterization of underlying activation.

References: a Lu, MRM, 2008. **b** Huber, MRM, 2013. **c** Davis, PNAS 1998. **d** Mullinger, PNAS. 2013. **e** He, J NeuroSci, 2013.