Baseline-dependent neurovascular coupling and its implications for resting-state fMRI

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INTRODUCTION

Spatiotemporal correlations of resting-state BOLD signals between different brain regions provide the basis of emerging paradigm of resting-state functional connectivity with fMRI [1]. The BOLD signal fluctuation is wildly believed to originate from the concurrent neural activity, but their exact relations – the neurovascular and neurometabolic couplings – are not well understood. The central dogma of neurovascular coupling is that the increased neural activity triggers a hemodynamic response, a hypothesis which is generally accepted for stimulus evoked responses. Recently we proved that this hypothesis is valid not only for continuous but also for very short stimuli [2,3]. Extending the same logic for resting state, this hypothesis should be valid for baseline neural activity and hemodynamic fluctuations. Indeed increasing number of studies show certain correlations between the neural activity and fluctuations of spontaneous hemodynamic signals (BOLD, CBF, or CBV) [4,5,6]. These studies even describe time-lagged correlations, albeit not very strong ones, between components (e.g. frequency range) of neural signals and the hemodynamic signals. But surprisingly, the correlations between the raw activity and hemodynamic signals are not significant in the majority of studies. There is an apparent contradiction of the main hypothesis that neural activity and hemodynamic signals are related to each other. We propose a non-linear convolution approach to resolve this apparent paradox. Using convolution to model the neurovascular coupling we found that there is very strong dependence between the neural and hemodynamic signals, even in resting state but because of its high non-linearity, the linear correlation methods are not feasible. We examined the relationship between neocortical spontaneous activity and the concurrently measured local blood flow in head-fixed awake, lightly-, and deeply-anesthetized rodents.

METHODS

Animal preparations: For the anesthesia studies we used Sprague-Dawley rats, which were tracheotomized and artificially ventilated (70% N_2O, 30% O_2) with 55-80 beat/minute rates. The anesthesia was switched to i.p. α-chloralose (80mg initial dose, then 40 mg/kg/hr) in group I (n=9) or s.c. Domitor (0.1mg/kg/h) in group II (n=12) from Isoflurane (1-2%) after the surgery. A femoral arterial line was used for monitoring blood pressure, acid-base balance and blood gases throughout the experiment. For awake studies we used black cbl57 mice (n= 7, 25-33 g, Jackson Labs). They were surgically prepared for restraint by attaching a head post to the skull and temporally closed craniotomies were created over somatosensory area. Following surgery, animals were closely monitored for a week during which they recovered from surgery. ***Neural and blood flow measurements:*** The animal was placed in a stereotaxic holder on a vibration free table inside a Faraday cage. For awake animals the chambers were open while for anesthetized animals tiny burr holes were made above left and right somatosensory regions (S1) [4.4 mm lateral and 1.0 mm anterior to bregma] and tungsten microelectrodes (FHC Inc, Bowdoinham, ME) together with a micro laser-Doppler probe (200 μm in diameter) (Oxford Optronics, Oxford, UK) were inserted up to layer 4 (~1mm depth) with stereotaxic manipulators. The multi-unit activity (MUA) was extracted from the raw signal with a band-pass (300-3000Hz), the local field potentials (LFP) with a low pass (<150 Hz) electronic filter (Krohn-Hite, Inc). ***Analysis:*** 300s long epochs without movement artifacts were selected for analysis. Spiking activities were extracted from the MUA signals. The individual spiking events were used as input signals for the convolution analysis, while the LDF signals were considered as output. Since both signal, can be contained undetermined noise injection (including physiological noises, as heart rate), the deconvolution was unpractical, therefore we applied the following method. We defined the transfer function as a modified gamma variate function (GVF) [7]. We systematically changed the parameters of GVF, from a minimum level, to create series of transfer function (n=80000), which were individually convolved on the input signal to calculate simulated output signal. The Pearson's correlation between the simulated signal and the output signal was calculated and recorded as a function of the appropriate GVF parameters,. The maximum Pearson's correlation in this set defined the parameters of transfer function for the analyzed experimental record.

RESULTS

The GVF has three parameters: the amplitude (A), the peak time (t_p) and the exponential decay parameter (α), which defines the width of the function. The higher α is the narrower the transfer function (Figure 1). We used normalized signals, therefore A=1 considered as constant, while t_p and α are significantly different in awake than in anesthetized states ($p<0.002$) and shows difference between anesthetic states ($p<0.06$). The parameters of the averaged transfer functions were t_p=4.77s, α=5.4 for α-chloralose anesthesia, t_p =3.83s, α=9.5 for domitor anesthesia and t_p =3.1s, α =20, for awake animals (Figure 1). Using these parameters, the state dependent transfer functions create such simulated signals which correlation to the measured signal is above 0.5, two times higher than the frequency power based correlations [5].

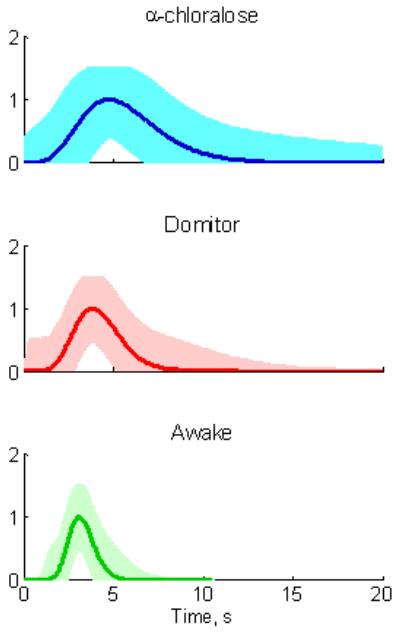

Figure 1. Gamma variate model of resting state neurovascular coupling between the spiking activity and spontaneous blood flow fluctuations. The average functions of deep, light and lack of anesthesia (α-chloralose, domitor, and awake) are indicated with SDs.

DISCUSSION

Spontaneous rhythmic fluctuations of neural activities and cerebral blood flow signals are correlated only if the neurovascular transfer function is fast and narrow. In that case the neurovascular transformation can be without significant bias and in some cases linear correlations are observable. Indeed the fastest and narrowest neurovascular connection is in awake state, where we could see correlations between the native neural and flow signals. The slower transfer function of anesthetized states can completely eliminate the coherent connection between neural and vascular signals. The same decreased correlation was observed when the same transfer function was applied for different anesthetic depth [6]. However this calculation of resting state neurovascular coupling model is phenomenological because of the lack of definite time related connections (e.g. stimuli) and the high noise injection (including heart rate) into the measured signals. Future analyses are required to develop transfer functions based on actual physiological mechanisms. In summary, depth of anesthesia attenuates not only the intensities of neurovascular signals, but the dynamic of their coupling as well.

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