Klinikum rechts der Isar

Christine Preibisch[1,2,3], Mario E. Archila-Melendez[1,2], Stephan Kaczmarz[1,2], Christian Sorg[1,2]

[1] Technical University of Munich, Department of Neuroradiology, Munich, Germany, [2] Technical University of Munich, TUM Neuroimaging Center, Munich, Germany, [3]Technical University of Munich, Clinic of Neurology, Munich, Germany

Studying the impact of impaired perfusion and oxygen metabolism on resting-state fMRI-based functional connectivity by simulating blood oxygenation fluctuations

Introduction

Blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) at rest is widely used to map human brain functional connectivity (BOLD-FC).[1, 2] Alterations in BOLD-FC[3-6] are commonly interpreted in terms of neuronal impairments. The validity of this interpretation requires a tight coupling between neuronal activity and subsequent vascular-hemodynamic processes underlying the BOLD effect. Significant impact of healthy hemodynamic response function variability on BOLD-FC has been demonstrated.[7] More pronounced effects are expected when cerebrovascular reactivity, oxygen metabolism or perfusion are reduced in neurological[8-12] and psychiatric disorders.[13-15]

Materials & Methods

BOLD signal simulations using Simulink and MATLAB R2019b (MathWorks).

Our adapted Balloon model[16-18] essentially follows Simon and Buxton[19] and allows for independent changes in $CMRO_2$ and CBF. Synthetic input neuronal activity N(t) (Fig. 1a) was generated by exploiting power-to-power cross-frequency coherence[20] between time series with three different frequencies (60 Hz, 10 Hz, 0.05 Hz). The BOLD reference signal (Fig. 1c) was kept identical across all FC simulations. Fig. 2 summarizes BOLD signal time curves (BOLD-TCs) simulated across a wide range of possible (patho-) physiological alterations in oxygen metabolism and perfusion.

BOLD-FC analyses: Using an identical neuronal input (N(t)) throughout, the dependence of BOLD-FC on alterations in hemodynamic parameters was explored by adopting a seed-based BOLD-FC-approach. Fig. 3 (left) illustrates the basic idea: Correlation coefficients (CC) were calculated between the green-rimmed intrinsic signal portions of the reference signal (seed S, Fig.1c) and the simulated BOLD-TCs of target regions across a range of parameters (Fig. 2).

For each pair of parameters, BOLD-FC values were calculated for 16x16 different realizations of added random white noise at constant signal-to-noise-ratio (SNR_0=250), which were then represented as matrices of CC and p-values for each scenario (Fig.3, middle, right).

Aim

The aim of our simulation study was to investigate how distinct alterations in neurovascular coupling influence blood oxygenation level dependent functional connectivity (BOLD-FC) measures at rest. To this end, we simulated BOLD-FC for three distinct scenarios, with independent changes in cerebral metabolic rate of oxygen ($CMRO_2$), cerebral blood flow (CBF) and cerebral blood volume (CBV) amplitudes and delays as well as CBF-CBV coupling (Figure 1).

Findings

Using BOLD time course (TC) simulations across a wide range of conditions, we demonstrate crucial impact of neuro- vascular coupling on resting-state fMRI-based functional connectivity measures. Our results (Figure 4) suggest that modeling of hemodynamic coupling might help to gain insights on the crucial interplay between vascular-hemodynamic components that should be taken into account when interpreting BOLD-FC especially in patients with potential vascular pathologies.

Simulations & Results

Three different scenarios were explored with respect to effects of independent changes in

1) $CMRO_2$ and CBF amplitudes (m1, f1)
2) $CMRO_2$ and CBF delays (τ_m, τ_f)
3) CBV-CBF coupling and delay (α_v, τ_v)

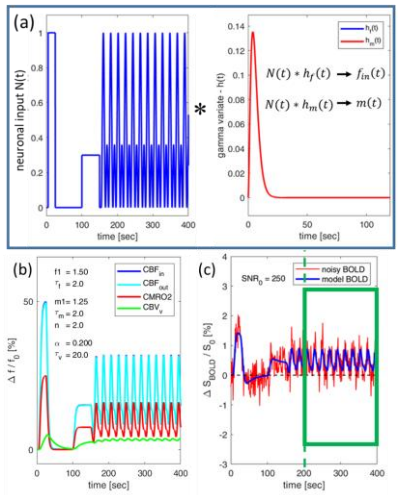

Figure 1: Simulation of BOLD reference signal
(a) Convolution of neuronal input N(t) with gamma variate functions $h_f(t)$ and $h_m(t)$ yields independent CBF ($f_{in}(t)$) and $CMRO_2$ (m(t)) input functions. **(b)** Simulated outflow CBF_{out} (≈ CBF_{in}) and CBV_v. **(c)** Green-framed BOLD signal portions (blue) with random white noise (red, SNR_0 = 250) are used for BOLD-FC calculations.

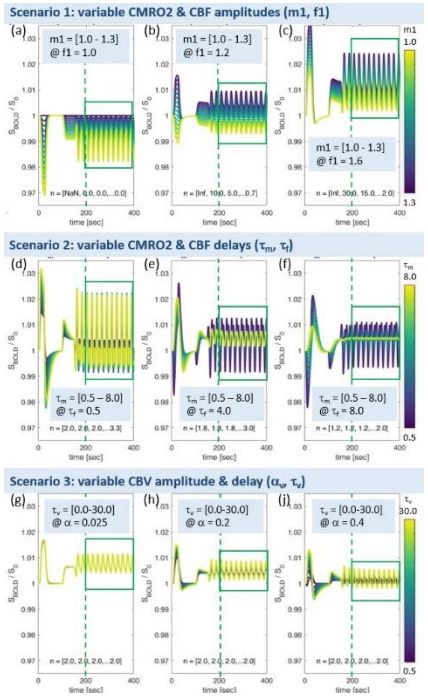

Figure 2. Simulated 'impaired' BOLD-TCs for ranges of (top) $CMRO_2$ amplitudes at 0% (a), 20% (c) and 60% CBF change (c); (middle) $CMRO_2$ delays at 0.5s (d), 4s (e), and 8s CBF delay (f); (bottom) CBV delays at flow-volume coupling exponent α_v=0.025 (g), α_v=0.2 (h) and α_v=0.2 (i). Line colors change from dark blue to yellow along given ranges of m1 (a-c), τ_m (d-f) and α_v (g-i) (color bars).

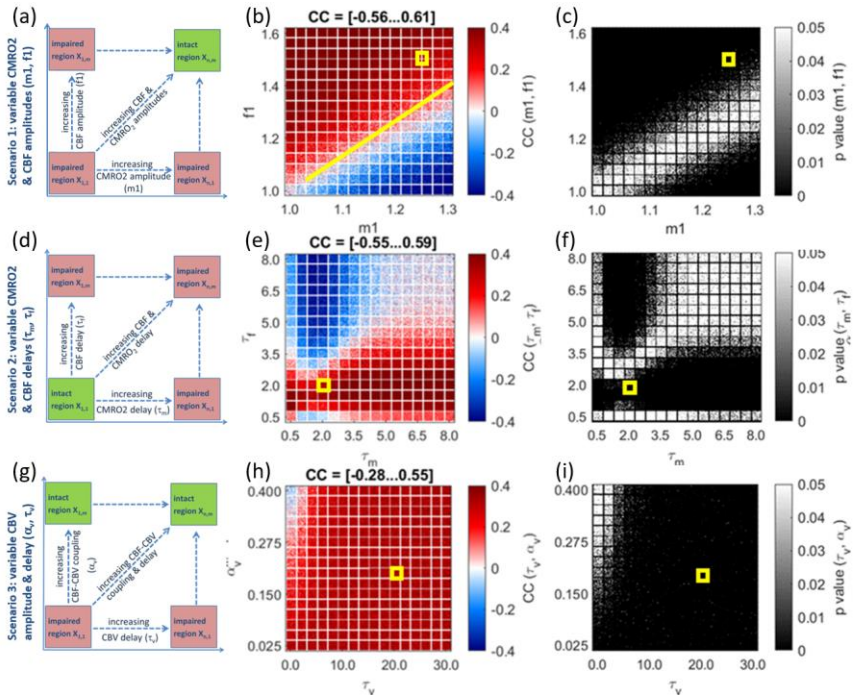

Figure 3. Overview on simulated scenarios and BOLD-FC results. Investigates scenarios (left) comprise independent changes in $CMRO_2$ and CBF amplitudes (a), $CMRO_2$ and CBF delays (d) as well as CBF-CBV coupling (g). Correlation coefficients (CC) (middle) and p-values (right) reflect the BOLD-FC (b, e, h) between the seed BOLD-TC (Fig.1c) and target BOLD-TCs (Fig.2) simulated across three different scenarios (left). At SNR_0 = 250, 16x16 different random white noise realizations were calculated for each pair of investigated parameters. Yellow squares indicate the location of the reference seed TC in the respective parameter spaces. CC matrices are scaled between -0.4 and 0.4. Minimum and maximum values are noted in the titles. Maps of p-values are truncated at p = 0.05, rendering insignificant voxels white.

Results

For scenario 1 (Fig.3b,c), we found 'linear' influences of $CMRO_2$ and CBF amplitudes on BOLD-FC: for a given $CMRO_2$ amplitude, BOLD-FC changes from negative to positive FC with increasing CBF amplitude, and increasing $CMRO_2$ amplitude shifts this dependence linearly.

For scenario 2 (Fig.3e,f), $CMRO_2$ and CBF delays had a complex 'nonlinear' effect on BOLD-FC: for small $CMRO_2$ delays, we found that BOLD-FC changes from positive to negative BOLD-FC with increasing CBF delays, but for large $CMRO_2$ delays positive BOLD-FC diminishes with increasing CBF delay.

For scenario 3 (Fig.3h,i), changes in CBF-CBV coupling have little effect on BOLD-FC.

Discussion

Our finding of highly significant positive correlations for BOLD-TCs simulated with high CBF amplitudes fit well with previous work.21 Similarly, low and insignificant correlations fit with observations of reduced BOLD/FC in areas of hypoperfusion.22 In addition, our simulations imply a distinct dependence of BOLD-FC on relative delays in CMRO2, and CBF, which has not yet been demonstrated

Acknowledgments

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