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Cardiac cycle-induced EPI time series fluctuations in the brain: Their temporal shifts, inflow effects and T_2* fluctuations

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ABSTRACT

The cardiac-induced arterial pressure wave causes changes in cerebral blood flow velocities and volumes that affect the signals in echo-planar imaging (EPI). Using single-echo EPI time series data, acquired fast enough to unalias the cardiac frequency, we found that the cardiac cycle-induced signal fluctuations are delayed differentially in different brain regions. When referenced to the time series in larger arterial structures, the cortical voxels are only minimally shifted but significant shifts are observed in subcortical areas. Using double-echo EPI data we mapped the voxels' "signal at zero echo time", S_0, and apparent T_2^* over the cardiac cycle. S_0 pulsatility was maximised for voxels with a cardiac cycle-induced timing that was close to the arterial structures and is likely explained by enhanced inflow effects in the cortical areas compared to subcortical areas. Interestingly a consistent T_2^* waveform over the cardiac cycle was observed in all voxels with average amplitude ranges between 0.3-0.55% in grey matter and 0.15–0.22% in white matter. The timing of the T_2^* waveforms suggests a partial volume fluctuation where arteriolar blood volume changes are counterbalanced by changes in CSF volumes.

1. Introduction

Echo-planar imaging (EPI) with sampling after multiband excitation achieves temporal resolution in the sub-second regime whilst maintaining a good slice coverage and spatial resolution (Feinberg and Setsompop, 2013; Feinberg et al., 2010; Moeller et al., 2010). In combination with improved signal-to-noise ratio (SNR) at ultra-high magnetic field, these fast acquisition techniques facilitate the study of spatio-temporal phenomena at finer scales and higher frequencies (Setsompop et al., 2016). The ability to depict higher frequency regimes without alias turns cardiac cycle-induced fluctuations, typically recorded as nuisance signal, from "physiological noise" into a valuable signal that may carry information about cerebrovascular mechanisms. So far, studies have addressed the *spatial* pattern of cardiac cycle-related fluctuations in EPI time series (Dagli et al., 1999; Tong et al., 2014; Kiviniemi et al., 2016), but little is known about the *temporal* signatures and underpinning contrast mechanisms. Generically referred to as "pulsatility" these fluctuations are of interest for research into cerebral compliance in response to the arterial pressure wave and the impact of pulsatility changes on tissue (Robertson et al., 2010; Webb et al., 2012). A better understanding of cardiac cycle-induced EPI signals might further be of use to improve fMRI physiological noise cleaning.

This work aims to investigate the timing of cardiac cycle-induced EPI signal fluctuations in the brain, and their associated MR parameters. Here, the voxel's signal at zero-echo time, S_0, and its apparent transverse decay constant, T_2^*, underpin these fluctuations. Two types of data set were acquired:

1. **Single-echo EPI** with a repetition time (TR) of 328 ms. These scans recorded the unaliased EPI time series up to the cardiac frequency regime. We used these data to calculate the temporal shifts in the cardiac cycle-induced signal fluctuations.
2. **Double-echo EPI.** These scans were acquired to fit S_0 and the apparent T_2^* values. Each measurement time point was phase-locked to an externally measured cardiac trigger signal to subsequently create voxel-wise S_0 and T_2^* waveforms over the cardiac unit cycle.

The single-echo EPI data revealed temporal shifts in the cardiac cycle-related time series between and within tissue types and between brain areas, which we refer to as "cardiac phase shift". We relate the S_0 and T_2^* pulsatility over the cardiac cycle from the double-echo EPI data to these shifts. For the remainder of this text we will refer to "pulsatility" as the

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fluctuation of a variable around its mean value over the course of the cardiac period. We will further use the term "phase" exclusively to denote the temporal position within the cardiac cycle (not to be confused with complex k-space or image phase).

2. Theory

The arterial pressure wave propagation speed is on the order of 10 m/s (Asmar et al., 1995). It is therefore beyond the temporal resolution of EPI time series and can be regarded as being experienced by all parts of the brain instantaneously. However, the brain is confined by the skull and the pressure wave is tightly coupled to much slower changes in local cerebral blood volume (CBV) and flow velocity (CBFV) (Wagshul et al., 2011; Van De Vosse and Stergiopulos, 2011). These CBV and CBFV changes affect the MR signal and manifest in cardiac frequency fluctuations in the EPI time series.

2.1. EPI signal model

Let τ_c be the systole-to-systole time period that spans the *cardiac unit cycle* τ with $\tau \in (0, \ldots, \tau_c]$. We assume that cardiac cycle-induced fluctuations are independent of the absolute cycle duration, but nevertheless have a fixed phase relationship to the unit cycle (Hu et al., 1995). The voxel signal is a combination of intra- and extravascular signals (Marques and Bowtell, 2008) and can be expressed as a multi-exponential decay (Obata et al., 2004; Zhao et al., 2007; Uludag et al., 2009)

$$S_{multi}(\tau) = \sum_i v_i(\tau) \cdot \rho_i \cdot M_{z,i}(\tau) \cdot \exp\left\{\frac{-\mathrm{TE}}{T^*_{2,i}}\right\} \quad (1)$$

where TE denotes the echo time and i the compartments of grey matter, white matter, arterioles, capillaries, venules and CSF. v_i, ρ_i and $M_{z,i}$ are the respective partial volume fractions, proton densities and longitudinal magnetisations. We explicitly stated v_i as a function of the cardiac cycle τ as blood volumes within a voxel may change from systole to diastole. The magnetisation $M_{z,i}(\tau)$ will vary with inflow effects (see discussion of S_0 in the following section). Further, $M_{z,i}$ could fluctuate with variations in the longitudinal relaxation constant T_1 due to oxygenation changes. Eq. (1) assumes that $T^*_{2,i}$ for a given compartment does not vary over the cardiac cycle, as baseline oxygen extraction rates are not related to the cardiac cycle to our knowledge.

An experimental measurement of all components in the multi-exponential model is difficult and often a simplified mono-exponential decay is used instead (Zhao et al., 2007; Bianciardi et al., 2016)

$$S_{mono}(\tau) = S_0(\tau) \cdot \exp\left\{\frac{-\mathrm{TE}}{T^*_2(\tau)}\right\} \quad (2)$$

The above model allows a measurement of the voxel's S_0 and apparent T^*_2 using double- or multi-echo data. An approximation $S_{mono} \approx S_{multi}$ will be limited to voxels with small partial volume contamination. If partial volume contamination is large, e.g. in a voxel consisting of half grey matter and half CSF, the mono-exponential decay becomes inaccurate because of the large difference in T^*_2 values between the compartments. We use simulations to calculate the theoretical error of estimating apparent S_0 and T^*_2 values from the mono-exponential fit for different partial volume combinations and test to what extent an approximation $S_{mono} \approx S_{multi}$ is valid (see Methods).

Different physiological mechanisms cause fluctuations in the $S_0(\tau)$ and $T^*_2(\tau)$ parameters. Inflow effects and partial volume fluctuations will manifest in $S_0(\tau)$. This can be written more explicitly as $S_0(T_1, M_0, \mathrm{TR}, \alpha, \mathrm{CBV}(\tau), \mathrm{CBFV}(\tau))$ (Bianciardi et al., 2016), where M_0 is the equilibrium magnetisation and α the radio-frequency (RF) flip angle. $\mathrm{CBV}(\tau)$ and $\mathrm{CBFV}(\tau)$ determine the amount of already RF-excited spins being replaced with fresh ones in the voxel. CBFV pulsatility will only affect S_0 if the spins experience multiple RF-excitations. In a classical single-slice acquisition, this is determined by the minimum blood velocity to traverse the slice. This simple theory will not hold for multiband acquisitions, where slower spins can experience fewer RF-pulses than faster ones if their position is out of synchrony with the slice acquisition order. Complicated vascular pathways through the slices require modelling of the vascular tree which is beyond the scope of this paper. However, it must be acknowledged that inflow-related magnetization enhancement due to CBFV still occurs with multiband excitation. In our experiments we used TRs of 328 ms (single-echo data) and 405 ms (double-echo data). Blood spins in large arterial structures, such as the middle cerebral artery (MCA) travel at about half a metre per second (Meckel et al., 2013) and traverse the imaging slab within one TR. Hence, S_0 pulsatility in voxels containing these structures should be induced by CBV and not CBFV pulsatility (see Bianciardi et al. for a detailed discussion (Bianciardi et al., 2016). Blood flow velocities are reduced in the smaller arterial branches, for example velocities in arteries in the basal ganglia are on the order of 3–6 cm/s (Bouvy et al., 2016) and here a mixed contribution of CBV and CBFV pulsatility to the inflow S_0 effect is expected. Blood flow velocities at the arteriolar and capillary level are on the order of less than a millimetre per second and spins will be saturated, rendering inflow effects negligible.

Arterioles, capillaries and venules should not alter their oxygen extraction rate between systole and diastole, i.e. single compartment T^*_2-values are assumed to be constant at each vascular level (although oxygen saturation will decrease down the vascular tree). However, we do expect the intravoxel microvascular and CSF partial volumes to fluctuate from systole to diastole, which should change the apparent voxel T^*_2.

2.2. Temporal shifts in the cardiac cycle-related signals

Fig. 1 shows a schematic presentation of the cardiac cycle-induced shifts in EPI time courses. A shift at the cardiac frequency f_c between two voxels can be obtained via the phase angle of their Fourier-transformed complex signals (more details will be presented in the Methods section). These phase shifts are likely related to underlying $S_0(\tau)$ and $T^*_2(\tau)$ variations that differ between tissues and brain areas, depending on levels of vascularisation and timing of cardiac cycle-induced variations in inflow and partial volume effects. Additionally, cardiac cycle-induced tissue displacement varies in magnitude and timing in different brain areas. Non-rigid brain motion is known to be maximal in the brain stem and propagates radially towards the outer parts of the brain (Poncelet et al., 1992; Zhong et al., 2009; Soellinger et al., 2009) and could cause timing variations in the EPI signals.

3. Methods

3.1. Single-echo EPI: Cardiac phase mapping

We calculated each voxel's phase ϕ at the cardiac frequency f_c using the following steps:

1. A high temporal resolution external cardiac trace (e.g. pulse-oximetry) is measured during fMRI acquisition. It is sub-sampled to the acquired TR and then Fourier-transformed to obtain the expected cardiac power spectrum. The cardiac frequency f_c is then defined as the component with the maximum power amplitude.
2. The EPI time series $S(t)$ in each voxel is Fourier-transformed into the frequency domain to yield $\widetilde{S}(f)$.
3. An arbitrary voxel r is selected to serve as a fixed phase reference (absolute phase values are re-referenced to the dominant value in an arterial mask at a later stage, see Post-processing section).
4. The phase ϕ_k at voxel k is calculated as the angle between the complex values using the four-quadrant inverse tangent: