

Quantitative mapping of cerebrovascular reactivity using resting-state BOLD fMRI: Validation in healthy adults



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ABSTRACT

In conventional neuroimaging, cerebrovascular reactivity (CVR) is quantified primarily using the blood-oxygenation level-dependent (BOLD) functional MRI (fMRI) signal, specifically, as the BOLD response to intravascular carbon dioxide (CO₂) modulations, in units of [%ΔBOLD/mmHg]. While this method has achieved wide appeal and clinical translation, the tolerability of CO₂-related tasks amongst patients and the elderly remains a challenge in more routine and large-scale applications. In this work, we propose an improved method to quantify CVR by exploiting intrinsic fluctuations in CO₂ and corresponding changes in the resting-state BOLD signal (rs-qCVR). Our rs-qCVR approach requires simultaneous monitoring of PETCO₂, cardiac pulsation and respiratory volume. In 16 healthy adults, we compare our quantitative CVR estimation technique to the prospective CO₂-targeting based CVR quantification approach (qCVR, the “standard”). We also compare our rs-CVR to non-quantitative alternatives including the resting-state fluctuation amplitude (RSFA), amplitude of low-frequency fluctuation (ALFF) and global-signal regression. When all subjects were pooled, only RSFA and ALFF were significantly associated with qCVR. However, for characterizing regional CVR variations within each subject, only the PETCO₂-based rs-qCVR measure is strongly associated with standard qCVR in 100% of the subjects ($p \leq 0.1$). In contrast, for the more qualitative CVR measures, significant within-subject association with qCVR was only achieved in 50–70% of the subjects. Our work establishes the feasibility of extracting quantitative CVR maps using rs-fMRI, opening the possibility of mapping functional connectivity and qCVR simultaneously.

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Introduction

Cerebrovascular reactivity (CVR) is an important indicator of vascular reserve (Ito et al., 2003) and autoregulatory efficiency (Nur et al., 2009). CVR refers to the degree of vasodilatation or constriction in response to a vascular agent or respiratory task. Clinically, impaired CVR has been associated with risk for stroke and transient ischemic attacks (Liu et al., 2012; Zirak et al., 2014). Given similar diagnoses, individuals with CVR impairment have a much higher risk of disabling stroke than those without (Blaser et al., 2002; Bokkers et al., 2011; Kuroda et al., 2004; Mandell et al., 2011; Mandell et al., 2008; Markus and Cullinane, 2001; Schoof et al., 2007; Silvestrini et al., 2000; Tsvigoulis and Alexandrov, 2008). In addition, reduced CVR has also been cited as a marker for lacunar infarction (Birns et al., 2009; Mandell et al., 2011), microbleeding (Birns et al., 2009; Conijn et al., 2012), as well as cortical atrophy (Fierstra et al., 2010) and cognitive decline in individuals at risk of stroke (Hurford et al., 2014; Kovács et al., 2010). Furthermore, CVR is

of direct diagnostic value in patient management (Mandell et al., 2011; Mandell et al., 2008). However, conventional forms of CVR measurement are often inappropriate for those with severe disease risk.

CVR is commonly measured from the fMRI response to vasodilating agents. Approaches generally include acetazolamide injection and respiratory manipulations. While acetazolamide injections are invasive and have been associated with adverse and potentially long-lasting side effects (Asghar et al., 2011; Mancino et al., 2011), respiratory manipulations are relatively non-invasive and safe. They induce changes in the subject's end-tidal CO₂ pressure (PETCO₂), a surrogate for intravascular CO₂ (Mark et al., 2010; Poulin et al., 1996). CO₂ is a potent vasodilator, triggering changes in vascular tone through the arterial baroreflex. PETCO₂ changes can be induced through manually adjusted administration of blended gases (Bandettini and Wong, 1997; Cohen et al., 2004; Yezhuvath et al., 2009), end-tidal forcing (Poulin et al., 1996) or more recently, computerized PETCO₂ targeting (Conklin et al., 2011; Han et al., 2011; Mandell et al., 2011; Mandell et al., 2008; Mark et al., 2010; Mikulis et al., 1989; Mutch et al., 2012; Prisman et al., 2008; Slessarev et al., 2007; Spano et al., 2013; Vesely et al., 2001). The latter method provides immediate and robust PETCO₂ changes, and we have used it extensively in our own work (Chen and Pike, 2010a; Chen and Pike, 2010b; Halani et al., 2015). More recently,

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breath-holding (Murphy et al., 2011) and deep breathing (Bright et al., 2009) have been proposed as alternatives to modulate PETCO₂, although CO₂ manipulation through breathing circuits is still the dominating approach.

The vascular response to CO₂ is well established (Battisti-Charbonney et al., 2011). Typically, CVR is measured as the ratio between the blood-oxygenation level dependent (BOLD) signal change and PETCO₂ change (by virtue of CBF-BOLD coupling). Generally, respiration-challenge based conventional quantitative CVR measurement (qCVR) approaches require lengthy subject preparations and strict subject cooperation, and are particularly challenging in patients (Lu et al., 2011; Magon et al., 2009; Mandell et al., 2008). In addition, the various styles of breath-holding can introduce difficulties in comparing CVR values across populations. Moreover, undesirable perturbations in neuronal activity (Jain et al., 2011; Xu et al., 2011) due to the sometimes large PETCO₂ changes (Chen and Pike, 2010a) can compromise the accuracy of conventional CVR measures. More concerning are unwanted side effects of conventional CVR tasks, which may be harmful in certain patient types (Karakaya et al., 2006; Laine et al., 1986). Often, patients do not fulfill the inclusion criteria for the existing CVR measurement approach. Based on prior literature, even within those undergoing CVR mapping, as many as 24.3% are unable to complete the respiratory challenges (Spano et al., 2013). These considerations significantly limit the clinical applicability of conventional CVR techniques, and are particularly prohibitive to those at risk of disease.

This work is motivated by the need to overcome this pressing challenge, and introduces a novel approach to quantify CVR based solely on resting-state fMRI (rs-fMRI), without the need for invasive agents, breath-holding or inhalation manipulations. The rs-fMRI family of techniques (Biswal et al., 1995; Fox and Greicius, 2010; Hedden et al., 2009; van Dijk et al., 2010) is commonly used to capture an intrinsic brain activity. However, the rs-fMRI signal also encompasses substantial non-neural contributions (Biswal and Kannurpatti, 2009; Biswal et al., 2007; Kannurpatti et al., 2008; Tong and Frederick, 2010), notably through intrinsic physiological processes. These non-neural components constitute the majority of the rs-fMRI signal variability. While these indirect contributions are commonly discarded, we propose to exploit the vascular nature of physiological rs-fMRI as the foundation for extracting quantitative CVR entirely using rs-fMRI (rs-qCVR). In this context, the term “quantitative” will be used to represent CVR values with units of [%ΔBOLD/mmHg CO₂].

The vascular nature of the rs-fMRI signal is well described in a recent review (Liu, 2013). Specifically, the potential of rs-fMRI and PETCO₂ to offer CVR information has been suggested in a number of previous works (Kannurpatti et al., 2014; Kannurpatti et al., 2010, 2011; Wise et al., 2004). In particular, Wise et al. illustrated, for the first time, the strong influence of the rs-fMRI signal by instantaneous fluctuations in PETCO₂ (Wise et al., 2004). In our recent work, building on the

biophysical model proposed by Chang et al. (2009a), we modeled the effects of spontaneous PETCO₂ fluctuations on the rs-fMRI BOLD signal (Golestani et al., 2015). Furthermore, we isolated the PETCO₂ effects from those of other prominent physiological processes including cardiac-rate variability (CRV) and respiratory-volume variability (RVT). It bears mentioning that the rs-fMRI signal is inherently modulated by endogenous fluctuations in PETCO₂ through a similar mechanism to that modulating the fMRI signal in respiratory manipulations. In this study, we (1) capture and exploit the rs-fMRI signal component due to PETCO₂ variability as a means to estimate quantitative CVR (qCVR); (2) compare our resting-state qCVR measurements to those obtained using the prospective CO₂-targetting method (referred to as the de facto “standard”); (3) compare the performance of our qCVR method to that of alternative rs-fMRI based non-quantitative CVR methods.

Methods

Participants

All experiments were performed on 16 healthy young adults (age = 26.5 ± 6.5 years, 7M/9F). Screening questionnaires were used to ensure that participants do not suffer from diseases or take medications that might compromise brain function or hemodynamics (Chen et al., 2011). All participants were recruited from the Rotman Research Institute Research Participants Database, and were asked to refrain from strenuous exercise for 24 h and to avoid caffeine/alcohol consumption for 4 h (Mort and Kruse, 2008) prior to the scans. Written informed consent, in accordance with the Baycrest Research Ethics Board, was obtained from all participants.

Physiological monitoring

Our experimental set up is outlined in Fig. 1. During the rs-fMRI sessions, we recorded heart rate using the scanner’s built-in finger oximeter, attached to the left index finger. This would provide estimates of cardiac variability. We also recorded the respiration pattern using a pressure-sensitive respiration belt, connected to the Biopac™ (Biopac Systems, Inc. California). The belt was attached just below the ribcage. The belt recordings are linearly proportional to lung expansion, and reflect respiration. PETCO₂ was passively monitored using a breathing circuit connected to a RespirAct™ system (Thornhill Research, Toronto).

Imaging protocol

We performed the scans at Baycrest using a Siemens TIM Trio 3 Tesla system (Erlangen, Germany) and a 32-channel matrix head coil. Participants were immobilized using head constraints (including a vacuum bag under the chin to control pitch motion).

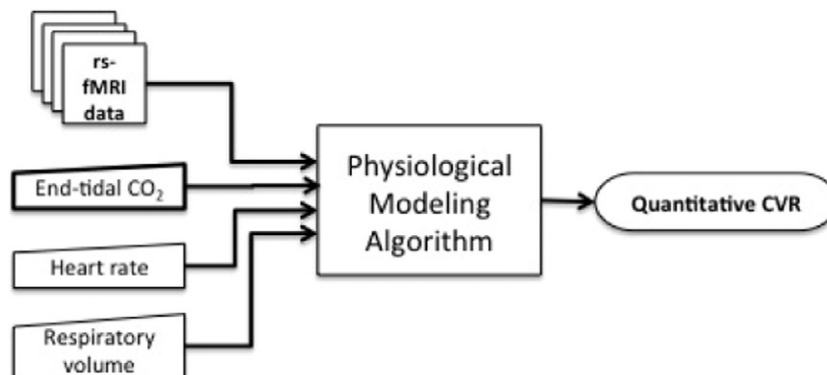


Fig. 1. Experimental set up. In addition to rs-fMRI data, our proposed CVR quantification methodology also relies on the recording of end-tidal CO₂ (PETCO₂), heart-rate and respiratory-volume traces during the rs-fMRI acquisition. These inputs are processed through our physiological modeling algorithm to produce quantitative CVR values.

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