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A novel technique for quantitative bedside monitoring of neurovascular coupling

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HIGHLIGHTS

- A novel method using EEG and NIRS to characterize continuous neurovascular coupling.
- Method validated using a stochastic model.
- Method applied to infants on therapeutic hypothermia for neonatal encephalopathy.
- Method found neurovascular coupling in infants with no detectable brain injury.

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ABSTRACT

Background: There is no current method for continuous quantification of neurovascular coupling (NVC) in spontaneous brain activity. To fill this void, we propose a novel method to quantify NVC using electroencephalogram (EEG) and near-infrared spectroscopy (NIRS) data.
New method: Since EEG and NIRS measure physiologic changes occurring at different time scales, we bring them into a common dynamical time frame (DTF). To achieve this, we partition both signals into one-second epochs and calculate the standard deviation of the EEG and the average value of the NIRS for each epoch. We then quantify the NVC by calculating spectral coherence between the two signals in the DTF. The resulting NVC will have a low resolution with all of its content localized below 1 Hz.
Results: After validating this framework on simulated data, we applied this approach to EEG and NIRS signals collected from four term infants undergoing therapeutic hypothermia for neonatal encephalopathy. Two of these infants showed no evidence of structural brain injury, and the other two died during the course of the therapy. The intact survivors showed emergence of NVC during hypothermia and/or after rewarming. In contrast, the two critically ill infants, who subsequently died, lacked this feature.
Comparison with existing methods: Existing methods quantify NVC by averaging neurovascular signals based on certain events (for example seizure) in the EEG activity, whereas our approach quantifies coupling between spontaneous background EEG and NIRS.
Conclusion: Real-time continuous monitoring of NVC may be a promising physiologic signal for cerebral monitoring in future.

1. Introduction

Neurovascular coupling (NVC) is a neural activation support mechanism involving synergistic interactions between the metabolic and vascular systems. The concept of NVC dates back to 1890, when Roy and Sherrington first proposed that the brain possesses an intrinsic mechanism by which the vascular supply can be varied locally in response to local variations in neural activity (Roy and Sherrington, 1890). With the advent of

Abbreviations: NVC, neurovascular coupling; DTF, dynamical time frame; FRP, fluctuating rhythmic pattern; HbD, oxygenated (HbO_2) and dexoygenated hemoglobin (Hb) difference; BSP, burst suppression pattern; NIRS, near-infrared spectroscopy; LDF, LASER Doppler flowmetry; HIE, hypoxic ischemic encephalopathy.

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modern imaging techniques, it is possible to quantify the NVC by simultaneous measurement of cerebral hemodynamic changes and electrocortical signals. Some commonly used techniques to measure cerebral hemodynamics include functional magnetic resonance imaging (fMRI), optical imaging spectroscopy, and LASER Doppler flowmetry (LDF). LDF is an invasive technique reserved for in vivo measurements in animal models, whereas the optical technique is used in animal and human studies. FMRI measures cerebral hemodynamic changes through blood oxygen-level dependent (BOLD) signals. Though these techniques offer high spatial resolution, they are not transferable to bedside application in their current state. Another optical technique with many applications in cerebral hemodynamic monitoring is near-infrared spectroscopy (NIRS). The portable and noninvasive features of NIRS make it suitable for long-term bedside cerebral hemodynamic monitoring (Brady et al., 2008, 2007; du Plessis, 1995; Govindan et al., 2013; O'Leary et al., 2009; Soul et al., 2007). Animal models have shown that the cerebral hemoglobin difference [HbD, oxygenated hemoglobin (HbO_2) minus deoxygenated hemoglobin (Hb)] is a reliable surrogate for cerebral blood flow (CBF) (Tsuji et al., 1998). The standard technique to measure electrocortical activity is electroencephalography (EEG), which is used in routine clinical practice for critically ill patients because it can be performed at the bedside.

Previous studies quantified NVC by associating cerebral hemodynamic changes with certain spontaneous changes in brain activity, such as the discontinuous patterns in the EEG of preterm infants (Roche-Labarbe et al., 2007). Simultaneous changes in EEG and NIRS have also been observed during electrocortical seizures in infants (Roche-Labarbe et al., 2008). In addition, NVC has also been studied using auditory (Devor et al., 2003; Dunn et al., 2003; Sheth et al., 2003) or visual stimuli (Cooper et al., 2009). However, conducting an auditory or visual response paradigm is difficult at the bedside in an intensive care unit setting. Further, reliable techniques are needed to identify the spontaneous events in the brain signals of the infant to time lock and average the vascular signals. Thus, in this work we decided to quantify NVC in the spontaneous brain activity and NIRS signals.

Our understanding of the integrity of NVC and its relevance to clinical care and long-term outcome remains impeded by the lack of a real-time quantitative and continuous technique to measure the cerebral hemodynamic responses to electrocortical activation. This void in our understanding is more glaring in cases where such information might have the greatest clinical utility, namely at the bedside of critically ill patients. To fill this void, we propose a novel approach using spectral coherence to quantify NVC in resting brain activity. We validate our approach using data from a numerical simulation. Finally, we demonstrate the application of this approach to quantify the NVC using EEG and NIRS signals obtained from four infants that were undergoing therapeutic hypothermia for neonatal encephalopathy.

Hypoxic ischemic encephalopathy (HIE) occurs in about 4–6 out of every 1000 births (Sarnat and Sarnat, 1976). It is a clinical syndrome characterized by disturbed neurological function and/or seizures (Sarnat and Sarnat, 1976). Newborns with HIE have a high propensity to develop cerebral palsy. Characteristic EEG background patterns have been well described in the setting of neonatal HIE and established as reliable predictors of neurodevelopmental outcome (Howard et al., 2011). In particular, burst suppression patterns (BSP), characterized by bursts of neural activity interspersed with quiescent periods, have shown to be predictive of adverse outcomes in HIE infants (Sinclair et al., 1999). In the foregoing discussion, we will call BSP – or discontinuity, its improved variant – 'fluctuating rhythmic patterns' (FRP). Simultaneous EEG and NIRS monitoring may help to characterize the vascular responses to FRP and define its prognostic value in newborn infants with HIE.

2. Materials and methods

2.1. Converting EEG and NIRS to a common time scale

Because NVC is defined as the association between CBF and electrocortical activity, we used HbD to characterize vascular changes and EEG to measure the electrocortical activity. HbD quantifies slow dynamics (vascular changes) in the order of seconds, while EEG quantifies fast dynamics (brain function) in the order of a few milliseconds. To reliably quantify the covariation between EEG and NIRS, we converted HbD and EEG to a common time scale which we called the dynamical time frame (DTF). To achieve this, we partitioned the HbD and EEG signals into one-second epochs and calculated the standard deviation of the EEG and average HbD for each epoch. We computed spectral coherence between HbD and EEG in the DTF to quantify NVC. Note that the sample rate of HbD and EEG in the DTF is 1 Hz. Thus, DTF not only brings both EEG and HbD into a common time scale but also allows us to investigate the dynamical interaction between them. We would like to mention that the standard deviation of HbD for one-second epoch as calculated for EEG did not allow correct quantification of the NVC in our physiological signals. Hence, we used the mean value of the HbD in each one-second epoch to convert HbD into a common time scale.

2.2. Quantification of NVC

The normal impulse-response time for NVC is on the order of 5–10 s. To quantify NVC, we used 40 min of HbD and EEG signals in the DTF. We partitioned the signals into 1-min, non-overlapping epochs. Prior to the calculation of the coherence spectrum, the data in 1-min epoch were convolved with a rectangular window in the time domain to avoid spectral leakage. Coherence was calculated using Welch periodogram approach (Govindan et al., 2013, 2005; Halliday et al., 1995). In short, this approach involved calculating the cross-spectrum between EEG and HbD ($S_{EEG,HbD}$), and the power spectra of EEG (S_{EEG}) and HbD (S_{HbD}) in 1-min epochs and averaging those quantities over all epochs to get the estimates of the same. Coherence was defined as: $C(\omega) = \frac{|\bar{S}_{EEG,HbD}(\omega)|^2}{\bar{S}_{EEG}(\omega) \cdot \bar{S}_{HbD}(\omega)}$, with ω being the frequency in Hz, and the overline indicates an estimate of that quantity (Halliday et al., 1995).

The confidence level derived under the hypothesis of independence between EEG and HbD at the $100\alpha\%$ level is given by $1-(1-\alpha)^{1/(M-1)}$, with M being the number of non-overlapping epochs used in the estimation of spectral quantities for the coherence estimation (Halliday et al., 1995). $C(\omega)$ is a normalized measure. It takes on a value of one in cases of perfect synchrony between two signals and a value of zero in cases of complete asynchrony. $C(\omega)$ was considered statistically significant at a frequency of ω if $C(\omega)$ was greater than the confidence limit (which we will henceforth call threshold). In our analysis, we used $\alpha = 0.999$ to avoid false positives.

If $C(\omega)$ was statistically significant, we calculated phase spectrum $\phi(\omega)$ (Halliday et al., 1995) as follows: $\phi(\omega) = arg\{\bar{S}_{EEG,HbD}(\omega)\}$. The explicit expression that relates phase spectrum and frequency can be written as $\phi(\omega) = \delta\omega + c$, where δ is the delay between EEG and HbD.

2.3. Stochastic model

We considered the following stochastic model to test the assumption that the NVC can be quantified by transforming the EEG and HbD signals into a DTF. We assumed the sample rate to be 1000 Hz and simulated two Gaussian-distributed white noise sequences, (x, y) for 40 min to model EEG and HbD, respectively. In almost all HIE infants, we observed FRPs in the EEG and introduced