NeuroImage xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Review

Statistical analysis of fNIRS data: A comprehensive review

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ARTICLE INFO

Article history:
Accepted 7 June 2013
Available online xxxx

Keywords:
fNIRS
t-Test
Correlation analysis
Spectral analysis
GLM
Statistical parameter mapping
Multi-level analysis
Group analysis
Multiple comparison
Data-driven analysis

ABSTRACT

Functional near-infrared spectroscopy (fNIRS) is a non-invasive method to measure brain activities using the changes of optical absorption in the brain through the intact skull. fNIRS has many advantages over other neuroimaging modalities such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), or magnetoencephalography (MEG), since it can directly measure blood oxygenation level changes related to neural activation with high temporal resolution. However, fNIRS signals are highly corrupted by measurement noises and physiology-based systemic interference. Careful statistical analyses are therefore required to extract neuronal activity-related signals from fNIRS data. In this paper, we provide an extensive review of historical developments of statistical analyses of fNIRS signal, which include motion artifact correction, short source-detector separation correction, principal component analysis (PCA)/independent component analysis (ICA), false discovery rate (FDR), serially-correlated errors, as well as inference techniques such as the standard *t*-test, *F*-test, analysis of variance (ANOVA), and statistical parameter mapping (SPM) framework. In addition, to provide a unified view of various existing inference techniques, we explain a linear mixed effect model with restricted maximum likelihood (ReML) variance estimation, and show that most of the existing inference methods for fNIRS analysis can be derived as special cases. Some of the open issues in statistical analysis are also described.

Contents

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http://dx.doi.org/10.1016/j.neuroimage.2013.06.016

Introduction

Functional near-infrared spectroscopy (fNIRS) is a non-invasive method to measure brain activity by measuring the absorption of the near-infrared light between 650 and 950 nm through the intact skull (Villringer and Dirnafl, 1995). As the absorption spectra of oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) are distinct in this region, it is possible to determine the concentration changes of HbO and HbR from diffusely scattered light measurement (Ferrari et al., 2004; Jobsis, 1977; Kleinschmidt et al., 1996; Villringer et al., 1993).

fNIRS has many advantages over other neuroimaging modalities. For example, fNIRS can measure a wide range of functional contrast such as HbO, HbR, and total hemoglobin (HbT). In contrast to blood-oxygenation level-dependent (BOLD) response measured by functional magnetic resonance imaging (fMRI), which is a nonlinear function of oxygen level and cerebral blood flow (Buxton et al., 2004), a direct measurement of oxygen concentration in fNIRS can provide a potential way to unveil the mechanism of complicated neurovascular coupling (Tak et al., 2010, 2011; Yücel et al., 2012). Furthermore, fNIRS has high temporal resolution that allows us to study the temporal behavior of the hemodynamic response to neural activation. Such high temporal resolution is especially useful for functional connectivity analysis which has become increasingly important as a new brain imaging paradigm (Hall et al., 2013; Homae et al., 2011; Kozel et al., 2009; Lloyd-Fox et al., 2010; Medvedev et al., 2011; Mesquita et al., 2010; Niu et al., 2012; Quaresima et al., 2012; Y. Zhang et al., 2010). Other advantages of fNIRS include that it requires only a compact measurement system and is robust to motion artifacts, which allow brain studies during daily working, exercise, and rehabilitation (Arenth et al., 2007; Ferrari et al., 2004; Hoshi, 2003; Irani et al., 2007; Saitou et al., 2000).

However, fNIRS lacks anatomical information, making it difficult to localize the brain area where the fNIRS signal originated (Ferrari et al., 2004; Kleinschmidt et al., 1996; Lloyd-Fox et al., 2010; Villringer et al., 1993). Moreover, fNIRS has poor spatial resolution and limited penetration depth due to the high level of light scattering within tissue (Ferrari et al., 2004; Kleinschmidt et al., 1996; Lloyd-Fox et al., 2010; Villringer et al., 1993). Another important limitation is that the fNIRS signal is corrupted by measurement noise, motion artifacts, and physiological noise arising from cardiac pulsation, respiration, and blood pressure Mayer waves (Boas et al., 2004). Therefore, to improve the sensitivity and spatial specificity of neuronal activity from fNIRS data, careful statistical analysis is required (Ferrari et al., 2004; Koh et al., 2007; Lloyd-Fox et al., 2010; Schroeter et al., 2002; Ye et al., 2009).

In the early ages of fNIRS studies, brain signal detection was usually attempted through visual inspection or simple thresholding with some preprocessing steps (Benaron et al., 2000; Murata et al., 2002). However, such heuristic approaches are prone to error, especially when the noise and interference levels increase, so more rigorous statistical analyses were called for. Hence, various statistical analysis methods such as *t*-test or analysis of variance (ANOVA) have been applied (Germon et al., 1994; Hoshi et al., 2001, 2003; Isobe et al., 2001; Kleinschmidt et al., 1996; Mehagnoul-Schipper et al., 2002; Okamoto et al., 2004; Tsujimoto et al., 2004; Young et al., 2000). These approaches often take average values during the task period as data to avoid any assumption of the exact shape or timing of the time course of changes in HbO and HbR in response to stimuli.

However, such an average sample-based statistical test also has limitations in that it does not utilize the time course of data, which is quite important in fNIRS data. Therefore, many investigators are interested in understanding the fNIRS time course. The well-known and widely used method of regression approach in this regard is the general linear model (GLM) (Friston et al., 2011), which assumes that data can be represented as a linear combination of several sources (regressors). These several sources consist of task-related regressors and non-task related so-called nuisance regressors. Schroeter et al. (2004) were the first to apply the GLM to analyze fNIRS data to overcome the uncertainty of the assumed differential pathlength factor (DPF), and numerous authors have employed GLM analysis for a variety of fNIRS experiments (Abdelnour and Huppert, 2009; Custo et al., 2010; Koh et al., 2007; Minagawa-Kawai et al., 2011; Plichta et al., 2006, 2007; Shimada and Hiraki, 2006; Singh and Dan, 2006; Ye et al., 2009). Another advantage of GLM is that group analysis can be implemented relatively simply using multi-level analysis, as investigated by many authors (Ciftci et al., 2008; Okamoto et al., 2006; Plichta et al., 2006; Singh and Dan, 2006; Ye et al., 2009).

Having reviewed the historical developments of statistical analysis briefly, in this paper we are interested in explaining these tools in more detail in a self-contained manner so that fNIRS practitioners can easily obtain the required information without searching through many papers and textbooks. In particular, rather than describing specific statistical analysis, such as one sample *t*-test, paired *t*-test, ANOVA, GLM, multi-level analysis, etc. with separate contexts, we show that all these methods can be derived from a general mixed model with restricted maximum likelihood (ReML) covariance estimation and hypothesis testing. Even though most of these materials are not novel and can be found in standard statistics textbooks, we believe that such a unified and extensive review can help students understand the existing works in a more organized way and provide them the opportunity to develop their own statistical approaches for their specific problems.

In addition, we also provide an overview of the existing data-driven approaches that have been investigated quite extensively to overcome the limitations of the classical approaches, and in particular for the new research area of functional brain connectivity using fNIRS (Hall et al., 2012; Homae et al., 2011; Kozel et al., 2009; Lloyd-Fox et al., 2010; Medvedev et al., 2011; Mesquita et al., 2010; Niu et al., 2012; Quaresima et al., 2012; Y. Zhang et al., 2010).

While this paper is mainly to review the existing works, there are a few novel contributions. In particular, a complete derivation of group analysis using multi-level analysis is performed using linear mixed effect model, which was not available before and will be included in a

Please cite this article as: Tak, S., Ye, J.C., Statistical analysis of fNIRS data: A comprehensive review, NeuroImage (2013), http://dx.doi.org/10.1016/j.neuroimage.2013.06.016