User Research

Combining EEG and fMRI signals in both humans and rodents: Advantages and limitations
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Abstract: There exist two prevailing tools to study the mechanisms that lie behind the brain functioning in healthy individuals and patients: the electroencephalogram (EEG) and the functional magnetic resonance imaging (fMRI). For about a decade, physicists and biomedical engineers have struggled to develop compatible devices and methods for the right combination of these two imaging modalities. Recent major efforts by different groups have been on developing a) means to perform EEG–fMRI concurrent recordings in other species, b) forward-generative models that comprise both the physical principles of data genesis and the physiological causal mechanisms, and c) strategies for statistical inference about these models from simultaneously recorded data. Here, I discuss recent achievements by members of my group in Tohoku University, Sendai Japan, which in one way or another dealt with interesting problems related to these emergent research/technological lines.

Introduction:

The human race has strived for centuries searching for the origin of our “thoughts” somewhat expressed as propensities, sentiments, sensations and faculties. Brilliant renaissant philosophers, like Andreas Vesalius (1514–1564) and René Descartes (1596–1650), focused themselves on revealing the brain as the region in our bodies where thoughts emerge from. In a more elaborated theory, the doctrine of phrenology by Austrian physician Franz Joseph Gall (1758–1828), the brain was considered to be composed of many “organs”, each of them responsible for a given mental faculty. By means of brain-damaged patients, Paul Broca confirmed that certain brain regions were involved in specific functions, a hypothesis that was evidenced by many other scientists at the end of the XIX century (e.g. language areas – Carl Wernicke and motor-related areas – John Hughlings Jackson). These preliminary studies gave subsequently rise to the Korbinian Brodmann’s cytoarchitectonic anatomical definitions, which are still used in modern research. However, the problem of “where the thoughts are originated inside our brains?” acquired a second dimension with the discovery of the functional magnetic resonance imaging (fMRI) in 1990 by Seiji Ogawa at AT&T Bell labs (Ogawa et al., 1990). By means of this contemporary noninvasive technique, neuroscientists have been able to determine brain areas involved not only in most mysterious task-demanding states (e.g. love, fears, and social interactions) but also those underlying resting states of alertness and attentiveness. In contrast, for some researchers the question “how are the thoughts generated inside our brains?” seemed to be more relevant. The electroencephalogram (EEG), discovered early by Hans Berger (1873-1941, Berger et al. 1929) has been at all times considered as the recording modality suitable to answer this particular question. In the past, this technique has been crucial to determine the origin of brain rhythms either in resting conditions or during sleep, as well as to study how these rhythms are altered by the presence of external stimulus and intrinsic brain processing.

The neurovascular coupling

The complementary differences in the spatial and temporal resolutions of the EEG and fMRI recordings have early motivated the development of technology to observe simultaneously these two data modalities. Also, asymmetrical approaches have been in parallel proposed to combine EEG and fMRI data from a methodological viewpoint.

However, in order to integrate properly EEG and fMRI data modalities, symmetric biophysical models based on the physiological mechanisms for the neurovascular coupling and the physical principles for the genesis of these two types of data are mandatory. For readers interested in this topic, the following recent reviews are recommendable (Poznanski and Riera, 2006; Valdes et al., 2009; Rosa et al., 2010). Therefore, the determination of the major mechanisms implicated in the communication between the neuronal networks and the surrounding vasculature (i.e. called the neurovascular coupling) has been a high priority subject for my group. Recently, we have revised the most important pathways for communication between these two cellular substrates (Riera and Sumiyoshi, 2011), which may comprise a fast/unspecific phasic signaling direct from specialized neurons and a slow/robust tonic signaling mediated by the astrocytes (Fig. 1). In a first study, we proposed linear autoregressive models to explain both neuronal activities and hemodynamic changes which were related by a static–nonlinear function (Riera et al., 2005). It was our belief that both inhibitory and excitatory postsynaptic activity contribute to the neurovascular coupling. A preliminary model of the phasic pathway (Riera et al., 2006) was used to explain the doses (stimulus: frequency & amplitude) – response curves observed experimentally in the visual cortex of humans (Wang et al., 2006). Thanks to this model, we were able to identify a reinforcement of the internal inhibitions in the primary visual cortex of humans (Vi) when the reversion frequency of the presented checkerboard was increased (Riera et al., 2007). Recently, we have proposed a model for Ca++ signaling in astrocytes (Riera et al., 2011a) and used it to determine major dysfunctions of the astrocytic networks in the early stage of the Alzheimer disease (Riera et al., 2011b). We are using this model to represent the tonic pathway in the neurovascular coupling, as well as to predict the main
signatures that an amyloid-β deposition will imprint in the resting states fMRI signal.

Humans vs. rodents: Advantages and limitations

Simultaneously recorded EEG and fMRI data is broadly used to study higher cognitive processing in humans and also to evaluate/ diagnose patients with a variety of brain pathological conditions. In principle, the technique could be also potentially beneficial in monitoring patient’s responses to drug treatments and psychotherapies. However, there are several limitations related to its use in humans for basic research of both normal and abnormal brain functions. For example, the use of either pharmacological or physiological manipulations is very limited to merely a few (e.g. glucose/lactate administration, inducing either hyper/hypocapnia or hyper/hypo-xia states). Also, the lack of practical methods to monitor crucial physiological parameters (e.g. pO2, pCO2, heart rate, blood pressure, temperature, pH, end-tidal CO2, hematocrit, hemoglobin, metabolites) while humans lie down inside an MRI scanner constitutes another important limitation, which is worsened by the fact that the more invasive the method the better the precision in reading actual values. Important time- dependent effects on fMRI signals have been associated with changes in several of these physiological parameters.

Therefore, we were highly motivated at the end of 2008 in extending this multimodal technique to small laboratory animals, which are very useful in the pharmacological industry. In particular, we found attractive to target the rodents because of the large amount of methods currently developed for systemic (i.e. BBB permeable drugs) and local (i.e. microinjection, drug-delivery probes built on nanotechnological bases) administrations of chemical compounds into the brain. These chemical components are very useful to understand the physiopathology of many brain disorders and traumas. In addition, by means of such technique researchers will be able to get a precise picture of the neurovascular coupling mechanisms through the evaluation of the impact on the EEG and fMRI data of different cocktails of enzyme inhibitors for both the phasic (e.g. nNOS: 7-nitroindazole; COX-2: refecoxib) and tonic (e.g. mGluR5: MPEP; COX-1: SC-560; cPLA2: MAFP; CYP2C11: MS-PPOH) pathways. Further advantages of using rodents are the following: a) the possibility of using higher magnetic field strength, b) the use of muscle relaxant for eliminating movement artifacts, c) the histological validation after in vivo experiments, and d) the existence of pharmacological intervention protocols such as the phMRI. We started this long term project by addressing technological aspects essential for obtaining EEG and fMRI concurrent observations from adult Wistar rats (Sumiyoshi et al., 2011; Dr. Akira Sumiyoshi, PhD dissertation, Tohoku University, 2011). First, we created an EEG mini-cap comprising thirty recording units that were able to produce minimal contamination on the fMRI signals (Fig. 2, top). These recording units were built based on working principles for the amplification of the EEG signal at each location on the scalp (Fig. 2, bottom-left). The details about this EEG mini-cap can be found in our patent (Riera et al., 2010). We evaluated this multimodal technique using a well-known paradigm of forepaw stimulation which produced a localized BOLD signal in the contra-lateral hemisphere and standard ERP responses (Fig. 2, bottom-right)
We believe that the existence of rat models (i.e. transgenic, genetic, knock-out/in) for several brain disorders (e.g. Alzheimer disease, McGill-R-Thy1-APP rats, Leon et al., 2010; epilepsy, Genetic Absence Epilepsy Rats from Strasbourg, GAERS, Danober et al., 1998; Parkinson’s disease, Pelled et al., 2005; stroke, Middle Cerebral Artery Occlusion model, MCAO, Li et al., 2000; autism, Umeda et al., 2010) will give a boost to such new technology, first in the area of basic research and later in the pharmacological industry. In the past, several attempts have been made to combine EEG and fMRI imaging modalities in rodents but in all studies few number of electrodes have been successfully used (Table 1, Sumiyoshi et al., 2011). We are able to provide the EEG mini-cap under a scientific collaboration agreement (Jorge Riera, riera@idac.tohoku.ac.jp).

In vivo T2 MRI template set for Wistar rats

Finally, having T2 MRI individual images facilitates the co-registration of EEG and fMRI data. As a consequence of the presence of the EEG paste, the positions of the recording units are clearly visualized in the T2 MRI images (Fig. 3, A), which is recommendable while creating realistic volume conductor models for the rat’s head. Recently, we created an in vivo rat T2 MRI template set (Fig. 3, B), comprising average images of both intensity and shape, obtained via nonlinear registration (Valdés-Hernández et al., 2011). Also, we have obtained white/gray matter probabilistic segmentations, expanding its use to those applications demanding prior-based tissue segmentation, e.g. SPM voxel-based morphometry. The template and probabilistic segmentations are available by request at the following website (http://www.idac.tohoku.ac.jp/bir/en/db/rb/101028.html).

By the help of such a T2 template, fMRI data obtained from adult Wistar rats can be properly analyzed using the tools available in the Statistical Parametric Mapping software (SPM) package (MATLAB, Functional Imaging Laboratory, UCL).

All electrophysiological recordings in the above mentioned experiments of my group were obtained using a 32 channel MR-compatible BrainAmp system (Brain Products, Munich, Germany). EEG signals were amplified, filtered (0.5 Hz high-pass, and 250 Hz low-pass), digitized (5 kHz sampling rate, 0.5 V resolution) and stored on a hard drive (Software BrainVision Recorder: Brain Products, Munich, Germany).

References

