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Functional Brain Imaging Using Non-Invasive Non-Ionizing Methods: Towards Multimodal and Multiscale Imaging

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1. Introduction

Current and future trends in functional neuroimaging focus on the combination and synchronous application of imaging modalities by integrating more than one measures of brain function, e.g., hemodynamic and electrophysiological (EEG and fMRI). These multi-modal approaches aim at achieving sufficient temporal and spatial resolution in order to localize neural activity and identify the functional connectivity between different brain regions, hypothesizing that the multi-modal information represents the same neural networks (Laufs et al., 2008).

In parallel, besides the impressive recent advancements in neuroimaging research, arguably even more outstanding advances have been reported in molecular medicine and genetics research. In this context, current and future trends in medical research aim at bridging biomolecular information and neural function through studies in anatomic and functional biomedical imaging, focusing on methods to discover novel markers influencing specific traits in psychiatric and neurological diseases. The new field of imaging genetics uses neuroimaging methods to assess the impact of genetic variance on the human brain. Ideally, several imaging methods are implemented in combination to achieve an optimal characterization of structural and functional parameters. The latter are statistically related to the genotype, resulting in a form of a genetic association study. Such procedures acting as a mediator between genetic polymorphisms and psychiatric disease risk may shed light on the relevant underlying neural processes (Hariri et al. 2006). Although this approach is still relatively novel, the emerging literature and initial results hold great promise that it may contribute to the understanding of the pathophysiology of complex psychiatric and neurological disorders. Importantly, the future trends in neuroimaging envision imaging of the chemical functions of the organ cells and even realtime images of the genes and proteins at work within cells. These will convey sophisticated fingerprints of disease processes and better assessment of the effectiveness of curative procedures. Overall, it is evident that profiling of the molecular changes in disease will also expand the scope of body imaging.

In this scientific and technological milieu, the widely-acknowledged "THz gap" makes this region of the electromagnetic spectrum a scientific frontier, with critical questions in physics, chemistry, biology, and medicine that need answers. All molecules (biological,

organic, inorganic, etc) have vibrational and rotational spectra that lie in the Terahertz frequency range with signatures resulting from intra- and inter-molecular interactions. Terahertz technology is considered a viable option for medical imaging (Siegel, 2004), since many biological and chemical substances exhibit signatures in this spectral region. Opportunities for imaging modality development in the Terahertz spectrum range, offers the possibility of understanding complex reactions in which the chemical state of the sample under study changes as time evolves. Nevertheless, despite recent advances, this part of the electromagnetic spectrum, remains unexplored and challenging with respect to medical applications (Siegel, 2004; Sherwin et al., 2004).

The next big challenge in the field of medical imaging and especially neuroimaging is the wide application of functional imaging methods in clinical practice, which will add significant knowledge towards a more holistic comprehension of the mechanisms of neurological and psychiatric diseases. The identification of effective therapeutic strategies, which will have a dramatic impact on the lives of millions of people, as neuropsychiatric disorders (e.g., mood disorders, stroke, epilepsy) are among the most common diseases, will then be the most valuable consequence.

Taking into consideration the aforementioned, the present chapter will focus on the following topics:

a. short review of state-of-the-art of non-invasive, non-ionizing functional neuroimaging techniques,
b. current and future trends in multimodal neuroimaging comprising concurrent measurements during activation of specified brain areas in-vivo via non-invasive and non-ionizing methodologies,
c. current and future trends in neuroimaging genetics with emphasis on the potential identification of new brain biomarkers related to brain functionality both in health and disease through Terahertz biomolecule imaging (ex-vivo) and the newly developed optogenetics method.

2. State-of-the-art of non-ionizing functional brain imaging techniques

The main current common methods for functional neuroimaging are functional magnetic resonance imaging (fMRI), multichannel electroencephalography (EEG), magnetoencephalography (MEG) and near infrared spectroscopic imaging (NIRSI) or functional near infrared spectroscopy (fNIRS). fMRI and fNIRS can measure localized changes in cerebral blood flow related to neural activity. Two other methods which are not actually 3D imaging modalities, but both contain information that, after appropriate post-processing, may result in three-dimensional brain maps of the recorded data, are EEG and MEG.

Local voltage fluctuations or changes in blood flow and volume, are referred to as activations. These activations are monitored and recorded with the various neuroimaging techniques when a subject performs a particular task and it is suggested that local brain activations may be involved in the underlying neural processes which mediate behavior. For instance, in tasks with visual stimulation, extensive activation of the occipital lobe is typically observed. This is explained by the fact that this rear part of the brain receives signals from the retina and is considered to be associated with visual perception.

Different methods present different advantages for research fact that resulted in the design and development of experimental studies that currently focus on a combined concurrent

implementation of the various modalities. Several research groups, for example, have reported results of data elicited using synchronous EEG recordings and fMRI during event-related experimental procedures or fNIR and EEG recordings for instance, aiming at achieving sufficient temporal and spatial resolution to clarify the functional connectivity of neural processes, provided that the methodology combinations represent the same neural networks. Before, presenting the current and future trends of the multimodal configurations of the abovementioned techniques, a brief overview of the current state-of-the-art attributes of each methodology is given in the following sections.

2.1 Recent advances in Magnetic Resonance Imaging techniques

Magnetic Resonance Imaging (MRI) is a well known structural imaging modality that is being used in clinical practice to distinguish tumors, inflammatory lesions, and other pathologies from the normal brain anatomy while it has also been proven useful for the diagnosis of demyelinating disorders. Recently, special advanced techniques of magnetic resonance tomography such as diffusion weighted imaging (DWI), functional magnetic resonance (fMRI) and spectroscopy gave new insights to the acquired images, providing also information about the function and chemical metabolites of the brain. Various MRI techniques, also without the use of contrast agents may present venous or arterial angiograms.

More specifically, diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) and tractography methods constitute an original microarchitectural approach based on water molecule diffusion nearly set to be introduced into clinical practice (Cotten et. Al, 2009). Importantly, the acquisition of diffusion-weighted MRI (DW-MRI) data is multidimensional. Multiple three-dimensional volumes with different diffusion-sensitization scanning parameters are provided by the modality. Following, implementation of appropriate post-processing procedures result in the reconstruction of the features of the three-dimensional diffusion profile of water molecule in each voxel. Depending on the chosen processing technique, different features of the diffusion scatter pattern at voxel level can be estimated.

In this context, many approaches are being proposed for the processing of a set of DW-MRI volumes with diffusion tensor imaging (DTI) being the most popular. Many quantitative measures can be calculated from the diffusion tensor (Pierpaoli et al., 1996) that can be used for in between-subject comparisons, as well as in within-subject follow-up studies.

In parallel, tractography is currently the only tool that allows in an entirely non-invasive manner and in-vivo the reconstruction of white matter anatomical paths. The simplest tractography approaches generate, in a deterministic way, curves that are tangent to the vector field of DTI principal eigenvectors (Basser et al., 2000; Mori et al., 1999). More advanced methods, consider the uncertainty associated with these vectors to produce distributions of curves in a probabilistic framework (Behrens et al., 2003; Parker et al., 2003). Latest approaches utilize frameworks that allow incorporation of information from different MRI modalities to study brain anatomical connectivity that will also allow observations of functional connectivity as well by revealing the way activation of one part of the brain affects and is related to other areas (Sotiropoulos et al., 2010).

Functional magnetic resonance imaging (fMRI) measures the hemodynamic response related to neural activity in the brain, in other words the hemodynamic correlates of neural activity (Cui et al., 2011). It measures the blood oxygen level-dependent (BOLD) response that results from local concentration changes in paramagnetic deoxy-hemoglobin (deoxy-

Hb) (Ogawa et al., 1990a), first discovered the 90s (Ogawa et al., 1990b; Ogawa et al., 1992; Kwong et al., 1992) and is the most common functional magnetic resonance imaging technique. Due mainly to the relatively high spatial resolution provided by this technique fMRI has rapidly become the gold standard for in vivo imaging of human brain activity, (Cui et al., 2011). The main current clinical application of fMRI is presurgical mapping of speech and motor brain areas as well as epilepsy foci (Stippich et al., 2007).
Recently, during rest conditions, functional imaging studies have shown that multiple cortical brain regions are functionally linked forming the so called resting-state networks (Raichle et al., 2001; Greicius et al., 2003; Raichle and Snyder, 2007) and fMRI is suitable to study this functional connectivity of the human brain (Damoiseaux et al., 2006). This finding led to the hypothesis that these regions constitute a network supporting a default mode of brain function. The suggested high level of functional connectivity within resting-state networks implies the existence of direct neuroanatomical connections between the respective functionally linked brain regions to facilitate the ongoing interregional neuronal communication. White matter tracts are the structural highways of our brain, enabling information to travel quickly from one brain region to another (van den Heuvel et al., 2009).
Both functional and diffusion MR images are acquired with fast imaging protocols. The most commonly used fast imaging protocol is echo planar imaging (EPI), which allows the acquisition of an image within a time window of a few milliseconds (Mansfield, 1984; Turner et al., 1990). It should be noted that EPI images suffer from low signal-to-noise-ratio (SNR) a parameter that should be considered when designing experiments.

2.2 Optical methods

The part of the electromagnetic spectrum with wavelengths from approximately 650nm to 950nm, is known as near-infrared (NIR) light and has been described as an "optical window" into biological tissue since it is weakly absorbed by tissue. Due to this property, light of these wavelengths may be detected after having penetrated tissue at a depth of a few centimeters. NIR light eventually interacts with biological tissue and therefore, also, with the human brain tissues. Based on the absorption of different wavelengths of light as it passes through the head, optical methods, such as near infrared spectroscopy (NIRS), have been developed to provide another non-invasive measure of local brain activation (Villringer et al., 1995; Strangman et al., 2002).
Oxyhemoglobin (HbO2) and deoxyhemoglobin (HbR)are the two principal chromophores that are absorbed in the NIR wavelength range and thus constitute two biologically relevant markers for brain activity (Strangman et al., 2002). In other words, near-infrared spectroscopy can provide information on concentrations of oxy-and deoxy-hemoglobin in cortical areas of the brain related to the activation of the brain regions in question. Significant differences in the absorption spectra at near-infrared wavelengths have been observed for other tissue chromophores as well, such as cytochrome oxidase during acquisition of simultaneous data from several wavelengths.
The detection of such hemodynamic markers, as also noted in previous sections, is considered as an indirect measure of brain function. Interestingly, it has been suggested that diffuse optical techniques may simultaneously provide both indirect and even direct measures of neuronal activity monitoring. In this context, supporting data exist to imply that diffuse optical methods may detect cell swelling taking place 50–200 milliseconds after neuronal firing. Although, the spatial interrelations between such signals and hemodynamic

ones remain subject to investigation, they could be feasibly recorded by sufficiently high-speed and sensitive detectors (Strangman et al., 2002).

Hence, by measuring the changes in the intensity of diffusely transmitted near-infrared light across a brain tissue volume, in non-invasive manner from sensors placed on the human skull, it is possible to gain well-localized information about haemoglobin oxygenation, cytochrome-c-oxidase redox state, and two types of changes in light scattering reflecting either membrane potential (fast signal) or cell swelling (slow signal) during local brain activation (Strangman et al., 2002). Advantages of the optical methods include biochemical specificity, a temporal resolution in the millisecond range, the potential of measuring intracellular and intravascular events simultaneously and the portability of the devices enabling bedside examinations (Villringer and Chance, 1997).

Based on the above mentioned, it becomes reasonably evident that near-infrared (NIR) imaging techniques have become an increasingly popular research means to study brain activity (Cooper et al., 2009) non-invasively using harmeless non-ionizing radiation (Gibson et al 2005, Hillman 2007). To date fNIRS has been successfully applied in several fields providing interesting and meaningful brain activation related data (Cui et al., 2011). NIRS has been used to investigate and add useful knowledge to the understanding of the physiological mechanisms of the BOLD response (Toronov et al., 2003; Hoge et al., 2005; Kleinschmidt et al., 1996; Schroeter et al., 2006; Emir et al., 2008; Malonek et al., 1997; Huppert et al., 2006, 2007, 2009). After early studies employing single-site near-infrared spectroscopy, first near-infrared imaging devices are being applied successfully for low-resolution functional brain imaging (Strangman et al., 2002; Villringer and Chance, 1997). NIRS is a very portable technique (Atsumori et al., 2009) and has been proposed as a useful technology for non-invasive brain–computer interfaces (Power et al., 2010; Coyle et al., 2004, 2007; Sitaram et al., 2007; Utsugi et al., 2008). NIRS has been used to study brain activity in both event-related tasks and resting states (Boecker et al., 2007; Herrmann et al., 2005; White et al., 2009; Honda et al., 2010; Zhang et al., 2010; Lu et al., 2010). It has been also proposed as useful alternate in experimental paradigms which are difficult to perform in the MRI scanner, such as face-to-face communication (Suda et al., 2010) or driving (Tomioka et al., 2009).

The applications of NIR techniques which improve spatial information by affording two-dimensional imaging of changes in both oxyhaemoglobin (HbO2) and de-oxyhaemoglobin (HHb) during stimuli driven experiments, include optical topography (OT) (Obrig and Villringer 2003; Cooper et al., 2009). This methodology has been broadly used to study the functional activation of the motor (Franceschini et al 2003, Maki et al 1996) and visual (Zeff et al 2007) cortices as well as in experimental procedure investigating language processing and development (Pe˜na et al 2003; see Cooper et al., 2009 for more details).

NIRS instrumentation is a flexible and portable technology and can be made unobtrusive, low-cost, low-power, even robust to motion artifacts (e.g., Totaro et al 1998) or technology enabling such artifacts to be successfully tackled (Izzetoglu et al., 2005; Izzetoglu et al., 2010). It is supported by three main categories of systems, each presenting advantages and drawbacks: time domain, frequency domain and continuous wave systems (Strangman et al., 2002).

Continuous wave fNIRS systems (CW) apply light to tissue with invariable amplitude and measure the attenuation of the amplitude of the incident light (Hoshi, 2003; Izzetoglu et al., 2004; Obrig & Villringer, 2003; Irani et al., 2007). Although it is evident that CW systems

provide less information than time or frequency domain systems, they also have several benefits that are important for certain applications: they can be manufactured using light emitting diodes (LEDs) and not necessarily using lasers, thus increasing safety with respect to their possible negative effects on vision (e.g. possible negative effect on eye retinas); their total cost can be significantly lower than time and frequency domain systems, enabling deployment of these systems in clinical settings; minimization of dimensions of these systems is also feasible proving them practical solutions for use in educational or clinical settings (Irani et al., 2007). Laser-based time-resolved or frequency domain systems, on the other hand, provide information on both phase and amplitude, and their use is compulsory experimental setups where more precise quantification of fNIRS signals is crucial to ensure robustness of results taking advantage of the added spatial specificity of time domain instruments and the ability to separate absorption and scattering effects (see Hoshi, 2003; Izzetoglu et al., 2004; Obrig & Villringer, 2003; Irani et al., 2007 for more discussion of these system differences). In general, the selection of the fNIR system architecture is determined by the spatial resolution and sensitivity requirements of the brain area activation related research question (Strangman et al., 2002). For investigations of cortical activation and especially when referenced to an external topographic system (e.g., the international 10/20 system), diffuse optical methods seem to provide opportunities and capabilities unavailable with any other brain functional imaging existing technology (Strangman et al., 2002).

2.3 EEG and MEG

Electroencephalography (EEG) and magnetoencephalography (MEG) are well known widely practiced brain monitoring techniques on the scalp surface of the electromagnetic effects of activation of groups of neurons, but without actually being directly three-dimensional imaging techniques. Nevertheless, they are briefly presented in this chapter, focusing on their main operational principles and on a short overview of the inverse problem solution approaches which result in the 3D mapping of EEG and MEG recording, mainly due to the following: measuring electromagnetic field distributions allows localization of cognitive processing (Haufe et al., 2011); EEG and MEG are used in conjunction with functional imaging modalities in most multimodal emerging settings; based on the aforementioned and taking also into account that both noninvasive localization methodologies can be applied without restriction (as opposed to invasive measurements), it is evident that they are highly significant for neuroscience research and medical diagnosis.

The main advantage of the EEG methodology, besides being entirely harmless, is the high temporal resolution opposed though to the relatively low spatial resolution achieved. The typically low EEG spatial resolution is due to the presence of a multilayered tissue interface, such as the skull, the cerebrospinal fluid and other cortex tissue layers between the electrode and the source of brain activation that is being measured (Cooper et al., 2009). Based on the aforementioned it is obviously derived that the scalp maps, namely the activation pattern distributions, of the corresponding cognitive processes elicited via the EEG/MEG measurement analysis, only afford an estimation of the actual underlying sources (Haufe et al., 2011). These spatial maps are derived by the inverse problem solution, which because of its ill-posedness imposes significant restrictions on the way the inverse solution is derived (Darvas et al., 2004). In other words, this inverse problem is ill-defined since any measurement can be equally well justified by infinitely different source distributions (Haufe et al., 2011).

Various approaches have been developed and discussed in order to evaluate inverse problem procedures and to assess the statistical significance of the subsequent results (for a review on this subject, see Darvas et al., 2004; Haufe et al., 2011). It should be noted though that recent developments in this field include the following: (i) independent components analysis has been relevantly recently considered as a useful means of separating physiological and other noise processes from brain activation, and possibly for also revealing distinct dissociated components of neural activation; (ii) time–frequency analysis application to single trial data has been proven useful to the identification of underlying communication mechanisms between neuronal clusters; (iii) the development of multimodal concurrent data acquisition methodologies reveal the potential of combining the high temporal resolution of electrophysiological data with the higher spatial resolution of hemodynamic effects (e.g. Dale et al., 2000; Darvas et al., 2004).
Magnetoencephalography measures the other component of electromagnetism, the magnetic field outside the head induced by current flow within the brain generated directly by neural current generators (Darvas et al., 2004). These primary currents are activated during an event-related study and are used in solving the inverse problem since they are localized to brain activated areas. Recently, MEG and EEG are mostly considered as complementary modalities and MEG based experiments routinely include concurrent multichannel EEG recording (Darvas et al., 2004).

2.4 Focused Microwave Radiometry

Active imaging is very important in the context of clinical practice and has proven its indisputable contribution to medical diagnosis. Nevertheless, constant research efforts are pursued in order to minimize radiation exposure during medical imaging (e.g., CT, PET) since the number of repetitive scans a person may undergo during a specified period of time in order to ensure patient safety is limited. Considering the above, as well as the wide variety of potentially harmful agents that coexist in contemporary everyday life, entirely passive, non-invasive and painless assessment of brain function in living subjects constitutes a wishful perspective and scientific vision.
Under this rationale, the functional imaging perspective of a novel passive microwave imaging device is being investigated during the past 7 years (Karanasiou et al., 2004, 2008; Karathanasis et al., 2010; Gouzouasis et al., 2010). Microwave radiometry is an important scientific research and application area of microwave sensing because it provides a passive sensing technique for detecting naturally emitted electromagnetic radiation. This technique has been used in biomedical applications mainly for monitoring the temperature distribution in depth inside the human body. The proposed system (Microwave Radiometry Imaging System, MiRaIS), is able to provide real-time temperature and/or conductivity variation measurements. The functional imaging perspective of this system is based on the fact that both local temperature and conductivity variations in the brain have been associated with brain activation.
More specifically, it has been suggested that knowledge of thermal patterns inside the brain may provide useful information about brain activity. Under normal, quiet, resting conditions intrabrain heat production is balanced by heat dissipation from the brain, while under several physiological conditions temperature balance modifications occur and brain temperatures either increase above (hyperthermia) or decrease below (hypothermia) their average resting-state values. Experiments have reported for instance, increase by 1–2 C

during the transition from sleep to wakefulness (Abrams and Hammel, 1964; Delgado and Hanai, 1966), in response to various stressful, emotionally arousing, and even simple environmental stimuli (Abrams and Hammel, 1964; Delgado and Hanai, 1966; Moser et al., 1993; Yablonskiy et al., 2000; Kiyatkin 2005; Kiyatkin, 2007). Brain temperature balance may also be affected by pharmacological drugs, which influence brain metabolism and consequently alter heat dissipation to the external environment (Kiyatkin, 2007). Thus, brain temperatures fluctuations that naturally take place may cause significant functional consequences given that most physical and chemical processes that determine neuronal activity are dependent by temperature (Kiyatkin, 2007). Thus, It has been suggested that brain temperature fluctuations reflect neural activation (Kiyatkin et al. 2002). Even empirical data obtained with fMRI suggest that increases in regional cerebral blood flow during functional stimulation can cause local changes in brain temperature and subsequent local changes in oxygen metabolism (Yablonskiy et al. 2000). Nevertheless, brain temperature changes in humans remains generally unknown because of lack of actual direct experimental studies (Kiyatkin, 2007).

In addition, another parameter that has been suggested to change during functional neuronal activity is the electrical conductivity of the brain. It has been hypothesized that an increase of regional cerebral blood volume (rCBV) due to neuronal activity will lead to the decrease of cortical impedance (increase of conductivity) because blood has lower impedance than the surrounding cortex (Geddes and Baker, 1967). During functional activity, there is a predominant impedance decrease as a result of an increase in blood volume. During epilepsy and ischemia, it has also been reported that impedance increases due to cell swelling because this reduces the size of the conductive extra-cellular space (Andrew and MacVicar, 1994). Since brain activation produces changes in regional cerebral blood flow (rCBF), it will also produce conductivity changes in the same direction. These (increased usually) blood-flow changes are associated to increased rCBV. Also, reproducible impedance changes of approximately 0.5% have been measured in humans during visual, or motor activity, using 3-D electrical impedance tomography (EIT) (Tidswell et al., 2001).

As stated above, the MiRaIS system measures temperature and/or conductivity fluctuations at low microwave frequencies. Following the aforementioned rationale, if brain activation related temperature and/or conductivity variation measurements changes can be measured with the proposed method, then it could be used to image brain activity in an entirely passive and non-invasive manner that it is completely harmless and can be repeated as often as necessary without any risk even for sensitive populations. The operation principal of the proposed system is based on the use of an ellipsoidal beamformer providing the necessary focusing on the brain areas of interest. Its main advantage is that it operates in an entirely passive and non – invasive manner. In order to use a diagnostic and device such as the proposed one, it is of great importance to achieve imaging of any arbitrary area inside the human head, placed on the ellipsoid's focal point where maximum peak of radiation is achieved. Previous theoretical results have shown the system's ability to focus on specific areas of human head models with varying depths and positions with respect to the ellipsoidal focal point (Karanasiou et al., 2004; 2008). Also, in an effort to improve the system's focusing properties several configurations using dielectric matching layers on the air – model interface or as filling material inside the ellipsoid chamber were tested both theoretically and experimentally showing promising results for the reduction of the scattering effects on the interface under consideration (Karathanasis et al., 2010; Gouzouasis et al., 2010). Both spatial resolution and detection depth provided by the system have been

estimated through detailed theoretical analysis and validation experimental procedures using phantoms and animals (e.g. Karanasiou et al., 2004, 2008; Karathanasis et al., 2010; Gouzouasis et al., 2010). In the range 1.3–3.5 GHz, imaging of the head model areas placed at the ellipsoid's focus is feasible with a variety of detection depths (ranging from 2 to 4.5 cm) and spatial resolution (ranging from less than 1 cm to over 3 cm), depending on the frequency used. The system's temperature resolution ranges from 0.5 ◦C to less than 1 ◦C in phantom and small animal experiments.
Importantly, the system has been used in human experiments in order to explore the possibility of passively measuring brain activation changes that are possibly attributed to local conductivity and/or temperature changes. The results indicate the potential value of using focused microwave radiometry to identify brain activations possibly involved or affected in operations induced by particular psychophysiological tasks (Karanasiou et al. 2004).

3. State-of-the-art and beyond of multimodal neuroimaging

After having reviewed all basic operation principles and attributes of the functional brain imaging methodologies, it is concluded that MEG and EEG differ from fMRI and fNIR, not only in the physiological processes that are measured but also in the properties of the inverse problem solutions that result in the functional images (Darvas et al., 2004).
Thus, in summary, on one hand MEG and EEG signals directly record neuronal activation at the millisecond scale at which they occur whereas fMRI and fNIR measure neuronal activation indirectly through hemodynamic changes detection at the order of 1s. In addition, it is still under investigation whether these neuronal and hemodynamic changes refer to the same brain activated areas. Regarding the solution of the inverse problem of MEG and EEG it is illposed affording estimation solutions based on the imposed constraints and methodologies used whereas fMRI directly provides images of the activated areas. Finally, fNIR is a less expensive and more easily administered than the gold standard fMRI, having also better temporal resolution and providing larger content information (both oxygenated and deoxygenated haemoglobin data). Nevertheless, it is a not a clinically implemented technology yet with inferior spatial resolution and decreased signal-to-noise ratio compared to fMRI (Cooper et al., 2011).
Since each of the non-ionizing non-invasive functional brain imaging techniques has different characteristics as described in the preceding section, in order to acquire the most valuable complementary data in terms of quality and quantity, benefiting from the advantages of the various techniques, combination of two or more techniques is expected (Shibasaki, 2008). The so-called multimodal approach may be achieved either by post-measurement combination and fusion of data or via simultaneous use of hemodynamic and electrophysiological techniques in order to reveal the multifactorial interplay of the underlying mechanisms during brain activation (Shibasaki, 2008).
In this chapter only the latter will be presented whereas the first category holds the disadvantage of uncontrolled background since it is not possible to guarantee the exact same experimental conditions between different measurement sessions (Honda et al., 1998; Shibasaki, 2008).

3.1 Simultaneous fMRI-EEG

Simultaneous fMRI and EEG is the most widely implemented multimodal human brain mapping technique which aims at combining high time and spatial resolution in a signle

modality, affording research of functional cortical activity and neurovascular coupling. Due to technological progress, technical obstacles are constantly superimposed and concurrent fMRI-EEG studies are increasingly and successfully performed in a variety of recent studies (e.g. Horwitz and Poeppel, 2002; Sammer et al., 2005; Otte and Halsband, 2006; Stern, 2006; Horovitz et al., 2008; Shibasaki, 2008; Ritter and Villringer 2006, Mulert et al 2004; Cooper et al., 2009) including cognitive processing, epileptic and seizure activity in children and adults (Gotman, 2008; Vulliemoz et al., 2010; Cooper et al., 2011) and neurovascular coupling (e.g. Kruggel et al 2000, Goldman et al 2002, Gotman et al 2006; Cooper et al., 2010).

The main artefacts that occur in simultaneous fMRI and EEG recordings rise from the interference of the scanner gradients with the EEG and many artefact elimination methods have been developed to manage this drawback (e.g. Ritter et al., 2007). Other artefacts rise from human physiological activity such as electrocardiographic artefacts and relevant removal methods have also been implemented successfully (Nakamura and Shibasaki, 1987; Nakamura et al., 1990; Shibasaki, 2008).

Currently, simultaneous recording of EEG in the MR scanning room is usually pursued in clinical practice for the presurgical evaluation of partial epilepsy patients (Jager et al., 2002; Stern, 2006). In research, EEG and fMRI paradigms are increasingly developed to study the underlying mechanisms of functional processing in a non-invasive manner combining high time resolution neuronal activation measurements with high spatial resolution hemodynamic response imaging (Shibasaki, 2008).

3.2 Simultaneous EEG-fNIR

The complementary information that is acquired by simultaneously measuring electrophysiological and cerebral blood volume changes, besides the combined fMRI-EEG settings, it has also recently been exploited by simultaneous EEG and NIR spectroscopy (Rovati et al 2007, Roche-Labarbe et al 2007; Cooper et al., 2009).

fNIR and other optical methods such as diffuse optical imaging presents several advantages compared to fMRI which have been exploited in recent studies involving neonatals and infants (Cooper et al.,2011, Telkemeyer et al., 2011; Ancora et al., 2009). They are portable, compatible with EEG and relatively insensitive to movement artifacts and therefore suitable to be used on neonatals and infants. Recently, two studies of concurrent assessment of vascular based imaging and electrophysiological responses of neonatal seizure (Cooper et al., 2011) and infant language acquisition (Telkemeyer et al., 2011) have been carried out with combined EEG and fNIR. Other studies of the simultaneous inegrated use of the two methodologies include the measurement of workload states (Hirshfield et al., 2009), mental stress (Ishii et al., 2008), during epileptic discharges (Machado et al., 2011), in auditory sensory gating (Ehlis et al., 2009).

3.3 Simultaneous MEG-fNIR

Besides the combination of EEG with fNIR, recently simultaneous MEG with fNIR measurements are being performed to once more investigate the neurovascular coupling of activated brain areas. After the first feasibility study using nonselective NIRS and DC-MEG recordings (Mackert et al., 2004, Mackert et al., 2008), several studies with simultaneous MEG and fNIR measurements have been realized (e.g. Sander et al., 2007; Mackert et al., 2008; Ou et al., 2009). Recently, during a standard motor task time-resolved multichannel NIRS (trNIRS) has been combined with DC-MEG to analyze simultaneously and

quantitatively hemodynamic and neuronal changes in activated brain areas (Mackert et al., 2008).
In another recent study (Ou et al., 2009), by simultaneous implementation of diffuse optical imaging (DOI) and magnetoencephalography (MEG) neurovascular coupling is once more investigated. Interestingly, an event-related and not a block design of the experimental paradigm has been followed to achieve evaluation of the contribution of single neural components to the hemodynamic responses, enabling direct comparison of the elicited results with the significant number of neurovascular coupling findings in animals using invasive recordings (Ou et al., 2009).

3.4 Simultaneous fMRI-fNIRs

Several research efforts of the simultaneous implementation of the fMRI and NIRS methodologies have been reported over the last two decades (Kleinschmidt et al., 1996; Punwani et al., 1998; Toronov et al., 2001; Mehagnoul-Schipper et al., 2002; Strangman et al., 2002; MacIntosh et al., 2003; Huppert et al., 2006; Zhang et al., 2006). These studies provide convincing evidence regarding the effective correlation and combination of the two methodologies towards a more practical implementation (Toyoda et al., 2008). Combined fMRI and NIR methods have also been widely used in animal studies (Zhang et al., 2006).
The main constraint imposed by the integration of the two modalities and actually occurs every time during any experimental design in the MR chamber, is the fact that the use of only non-magnetic material is allowed. In the case of combined fMRI-EEG measurements, research and technological progress have resulted in the construction of MRI-compatible EEG devices, many of which currently exist commercially. Similarly, the optical probe must be designed and constructed to be fully MRI-compatible without causing any MR image distortion. Also, the final setup must afford accurate co-registration of optical and MR images in order to achieve an efficient integration of the two imaging techniques (Zhang et al., 2006). The high spatial resolution is accomplished through structural MR imaging where all optical and functional MR data are co-registered. This procedure also forms the basis of the inverse problem solution and the possibility to superimpose all data on the Talairach space for group studies (Zhang et al., 2006).

3.5 Simultaneous recordings using more than two modalities

As shown in previous sections, current and future trends in functional human brain mapping focus research on implementing multimodal approaches in order to acquire the largest possible set of measurements of correlates of neural activity in a single experimental procedure. It has been shown that there is a strong correlation between mass neuronal activity and localized changes in blood flow and volume and this is the reason why methodologies that measure electrophysiological responses are combined with techniques the measure hemodynamic changes in the multimodal approaches in question. Interestingly, each of these modalities through the so-called steady state measurements reveal brain areas that are functionally and structurally correlated and thus, provide new insights into brain function (Gore et al., 2006). Attempts to integrate more than two modalities are also pursued by combing simultaneous fMRI, NIR and ERP measurements (Gore et al., 2006).
In this context, besides electrophysiological and hemodynamic measurements, feasibility of integrating additional measures, such as non-invasive local temperature and conductivity measurements could also be investigated. Magnetic Resonance Spectroscopy (MRS) can

measure temperature noninvasively (e.g. Corbett et al., 1997). It is a well-established technique that uses an MRI scanner to detect certain naturally occurring brain metabolites. By interpreting the relative frequencies of a reference metabolite (N-acetyl aspartate; NAA) and water, it is possible to estimate tissue temperature with precision of approximately +0.5°C (Harris et al., 2008). Microwave Radiometry with the additional advantage of being completely passive maybe used for estimating temperature and/or conductivity changes non-invasively in the brain.

Taking all of the above into consideration, research efforts focus on integrating MiRaIs with EEG and fNIR (Karanasiou et al., 2009). A customized head cap for simultaneous mounting of EEG electrodes and the proposed fNIR system according to the 10-20 system that is also MiRaIS-compatible and appropriate post-processing software tools, focusing on fNIR/EEG image reconstruction are being developed. Therefore, the resulting multi-modal measurements will comprise electrical activity (EEG), blood flow (fNIR), as well as temperature and conductivity variations (MiRaIS) in activated cortical areas.

4. State-of-the-art and beyond of neuroimaging genetics: THz imaging and optogenetics

Besides multimodal functional imaging and the indisputable advances in this field, current and future trends in neuroscience research aim at bridging neural function and biomolecular information and studying microscopic processes at the molecule level. This scope is pursued through studies both in anatomic and functional biomedical imaging, integrating the rapidly advancing research fields of medical imaging/neuroimaging and molecular medicine/genetics. In this context, research has emphasized new methods for discovering novel markers that may have an influence on specific features in psychiatric and neurological diseases, expecting to also take advantage of next-generation imaging technologies that will potentially afford the monitoring of the chemical processes of the cells within the organs and produce real-time images of biomolecules, such as genes and proteins functioning within cells.

In this scientific and technological milieu, the widely acknowledged 'THz gap', including the complete frequency range from 100 GHz up to 30 THz, makes this region of the electromagnetic spectrum a scientific frontier holding great promise not only for identifying and classifying biomolecules, but also for understanding the underlying molecular dynamics. All molecules (biological, organic, inorganic, etc) have inherent vibrational and rotational spectra that lie in the terahertz frequency regime with spectral signatures resulting from intra- and inter-molecular interactions. Specific proteins for instance, absorb certain characteristic t-ray frequencies leading to a distinct terahertz 'fingerprint' for each biomolecule; sensors that can detect this absorption may reveal the identity of the protein. To this end, THz technology can serve as a viable option for medical imaging envisaging the expansion of current knowledge on biomolecular information and its correlation with neural function.

The THz "gap" became the subject of research for the past 8 years approximately and its application in biomedicine is considered very promising (Bakopoulos et al., 2009). Considerable effort has been invested in the development of applications of the THz frequency regime (0.1–5 THz) for the detection and characterization of biological material focusing on their interaction with THz radiation (e.g. Siegel, 2004; Woolard et al., 2005) as well as for the detection of cancer by developing novel THz imaging systems (Woodward et

al., 2005; Wahaia et al., 2010). Nevertheless, THz waves is a state-of-the-art research field exhibiting constant technological progress and as such the interaction of biological materials with THz radiation is not completely known and still under investigation: the THz response of biological samples is considerably affected by the specific radiation properties, the experimental configuration as well as the sample preparation and measurement procedures.
THz technology may add significant knowledge to the understanding of brain function in health and disease by providing biochemical profiling of various neurotransmitters in various conditions. Recent findings support the abovementioned claims; a novel study on the use of terahertz (THz) spectroscopy to distinguish between healthy and diseased snap-frozen tissue samples obtained from three regions of the human brain has been recently reported (Png et al., 2009). The research team based their work on the fact that as protein structures have been successfully marked using THz radiation, the group vibrational modes of protein plaques could be also probed in the THz frequency range. With this view, they used tissue samples with Alzheimer's disease; the latter were neuropathologically diagnosed to comprise abnormal high quantity of protein plaques consistent with the disease in question. Results showed that a rough classification between healthy and diseased tissue was accomplished based on their THz absorption spectra, which could be attributed to pathological changes in the diseased tissue (Png et al., 2009).
Recently, a few more studies have been reported towards the same research direction (Abbas et al., 2009; Treviño-Palacios et al., 2010). A new approach including the development of integrated THz circuits for the detection of biochemical events was implemented to the detection of nitric oxide synthase (NOS) activity (Abbas et al., 2009). The authors designed and fabricated a BioMEMS (Biological MicroElectro-Mechanical System) compatible with microfluidic circulation and electromagnetic propagation which they successfully used to detect NOS activity ex vivo. Real-time THz spectroscopy was used to detect biomolecule processes associated with neurodegenerative phenomena (Abbas et al., 2009). Another group, classify healthy and cancerous tissue using the non-ionizing water absorption to terahertz radiation. This seems to be a somewhat complementary reciprocal classification methodology since one of main drawbacks that THz radiation is not being currently widely considered for in-vivo body imaging is the large absorption by body water content (Treviño-Palacios et al., 2010).
In parallel, in the broader field of genetic imaging, the use of a novel combination of fMRI with a recently developed state-of-the-art technique called optogenetics (Boyden et al., 2005), holds great promise to reveal direct evidence that the fMRI signal is a compelling measure of brain activity. Moreover, combining functional imaging with a technique that controls subpopulations of neurons using light, will result in the enhancement of the basis of neuroscience research and lead new ways to understanding the mechanisms and treatment of brain injury and disease (Lee et al., 2010). The researchers support that the new functional genetic imaging technique, the integrated optogenetics and BOLD-fMRI (ofMRI) will enable the observation of the big picture of the causal connectivity of neurons in specific brain regions without of course suggesting that absence of a BOLD signal would prove the absence of such connectivity. ofMRI aims at further probing and defining the causal generation of BOLD signals and most importantly at enabling the causal connectivity mapping of cells which are genetically and anatomically- by circuit topology -defined (Lee et al., 2010). Nevertheless, this approach being significantly novel and recent is also followed by reservations and some doubts; the validity of the technique itself as well as the interpretation of the fMRI data is still being questioned and under constant debate (Logothetis 2010).

5. Conclusion

Functional neuroimaging has had a huge impact in cognitive neurosciences and in our understanding of the healthy human brain. The next big challenge in this field is the wide application of functional imaging methods in a clinical context, which will help us understand the mechanisms of neurological and psychiatric diseases and to identify effective therapeutic strategies, which will have a dramatic impact in the lives of millions of people, as neuropsychiatric disorders (e.g., mood disorders, stroke, epilepsy) are among the most common diseases.

More precise assessment of the underlying biophysics of the measured signals and especially of their interrelations will be extremely important for the better understanding of the healthy and diseased brain. The proposed unprecedented concurrent assessment of multiple biophysical correlates of neural activation (blood flow, volume and oxygenation, conductivity and temperature) will allow detailed correlation studies that will further elucidate the nature of brain activation measurement and the neurovascular coupling.

The current decade may be remembered in the future for the progress of neuroscience beyond the level of basic and clinical, into a field of innovative and challenging research applications. The development of new tools and methodologies and pursuing integrated approaches focus on revealing not only the underlying mechanisms of the measured neural correlates of local brain activation but also on leading the way to the global mapping of their interrelations, connectivity and causal activation.

Functional brain imaging research in conjunction with the rapidly expanding knowledge in genetics, offers not only the promise of dramatic cures and amelioration of mental health, but also a profound understanding of the brain's functionality.

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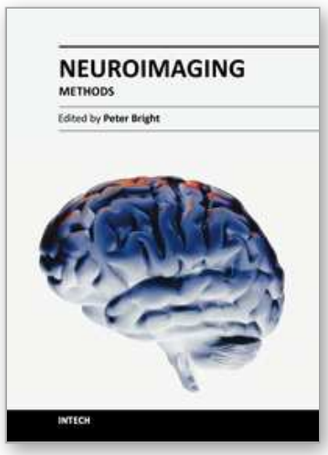

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Neuroimaging methodologies continue to develop at a remarkable rate, providing ever more sophisticated techniques for investigating brain structure and function. The scope of this book is not to provide a comprehensive overview of methods and applications but to provide a 'snapshot' of current approaches using well established and newly emerging techniques. Taken together, these chapters provide a broad sense of how the limits of what is achievable with neuroimaging methods are being stretched.

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