Multi-modality based diagnosis: A Way Forward

Hafeez Ullah Amin*

Centre for Intelligent Signal and Imaging Research, University Technology PETRONAS, 32610 Seri Iskandar, Perak, Malaysia

---

Abstract

The Human brain is our most complex organ and responsible for controlling all bodily functions. The brain is also implicated in many psychiatric disorders and diseases such as Dementia, Depression, Epilepsy, Parkinson, Stroke, Tumour, and so on. Researchers from different fields including Neuroscience, Neurosurgery, Psychiatry, Psychology, Pharmacology, Engineering, and Computing, are continuously working to investigate and develop novel techniques to diagnose and treat the brain's disorders using neuroimaging modalities. Today, many different modalities are currently used such as electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), functional near infrared (fNIR), Magnetoencephalography (MEG), positron emission tomography (PET), and computed tomography (CT). Each technique has its own strengths and limitations and thus is suited to a specific area of study. However, these modalities can be used simultaneously to reduce the limitations of using one technique and enhance the accuracy of disease diagnosis. Multi-modality-based diagnosis will help clinicians to identify both early and accurately those individuals who are at risk of many conditions including brain tumor, tumor recurrence, and Alzheimer's disease.

Keywords: Multimodal approach, treatment, neurofeedback, and neurotherapy.

ARTICLE INFO
RECEIVED November 18
REVIEWED January 19
ACCEPTED February 19

** Corresponding author.*

Email: hafeezullahamin@gmail.com

1. Introduction

The brain is an extremely complex organ, which is responsible for controlling all activities such as sensation, perceptual inference, planning, execution, evaluation, movements and decision making. It consumes approximately 20% of the energy in the entire body (K. Uludağ, 2014). The structure of the brain consists of different types of cells (including pyramidal neurons, interneurons and glia), which relate to each other through biological pathways. Modern neuroimaging techniques probe the structure and functions of the human brain and expose neuro-glial bases of human cognition and behavior in healthy subjects as well its dysfunctions in patients. Every imaging technique has its strength and limitations; hence, a multi-modal approach can give important insights into the brain functions and structure in addition to improving spatiotemporal resolution (including quantification, generalization and normalization) (K. Uludağ,2014).

The multimodality approach combines two or more data sets collected with different imaging techniques with the objective of enhancing our understanding of brain structure and functions. It provides a fusion of different data sets. While there are advantages of a multimodal approach, there are also challenges, including cost, wide knowledge of multiple instrumentations, and data quality of one modality being compromised over another, and so on. In this paper, the existing studies utilizing the multimodal approach for studying the brain in healthy subjects and brain disorders are described.

2. EEG-fMRI

Understanding the neural basis of brain functions needs awareness regarding the spatial and temporal aspects of the underlying mechanisms in information processing in the brain. Electroencephalography (EEG) and Functional Magnetic Resonance Imaging (fMRI) are two non-invasive imaging techniques (V. Menon, 2005). However, neither of these techniques alone can provide spatiotemporal information processing. EEG is a widely used brain imaging modality in research as well as in clinical practice due to its good temporal resolution. The recording of EEG requires electrodes to be placed over the scalp to capture neural activity in terms of electrical voltage potential. The captured signal from the brain region will show a pattern, and this data can be interpreted. However, the diagnosis with EEG technique lacks spatial resolution. The actual cerebral sources of the recorded EEG over the scalp is not known. The solution to this issue is to estimate the sources, but the solution of estimating sources from EEG signals is quite complex (the inverse problem). The existing methods of source localization are either dipole-based, which assumes that sources are localized, or distributed source analysis, which also relies on some assumptions such as smoothness (J. Gotman, 2006). Hence, both the source analyses are based on assumptions, which are difficult to confirm because to know the complete distribution of the intracerebral potential is almost impossible. Therefore, researchers and clinicians have begun diagnoses of brain functions by combining EEG with functional magnetic resonance imaging (fMRI) technique. FMRI measures the changes in the blood oxygen level of the brain with high spatial resolution.

There are a number of studies that have utilized simultaneous EEG-fMRI measures. For example, Hoppstädter and colleagues conducted a simultaneous EEG-fMRI study for recognition memory using event-related potentials (ERPs) in old/new effect (M. Hoppstädter, 2015). Their findings showed that the right dorsolateral prefrontal cortex and right intraparietal sulcus were linked with the amplitude of the frontal old/new effect between 350ms to 550 ms. Gorka et al., also conducted simultaneous EEG-fMRI techniques in their investigation into reward anticipation (S. M. Gorka, 2015). Their results suggested that increased left frontal activity was linked with increased activity in the left anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC). The fusion of EEG and fMRI data is likely to enhance our understanding of brain functions and structure (S. Debener, 2011).

3. PET-MRI

PET and MRI are brain imaging modalities which are well established in clinical practice. Standard MR imaging technique plays an important role in the diagnosis of brain disease, such as brain tumours, due to its capability of capturing anatomic detail of the brain. However, MRI only gives the structural information of the brain and no detail about the tissue and its functioning. Position emission Tomography (PET) is another imaging technique which uses a radioactive substance (tracer) to look for injury or disease in the brain. The PET scan provides information about the brain size, shape and functions (tissues and its working). Catana and colleagues reviewed methodologic enhancement and neurologic applications of PET/MRI data acquisition (C. Catana, 2012). Combined PET and MRI provide the spatial and temporal correlation of the measured changes in the brain, which are impossible with a single modality. With the advent of combined PET/MRI scanners, the relationships of different elements of tumour metabolism can be explored simultaneously.

Moodley and colleagues employed simultaneous PET-MRI to compare patterns of cerebral hypo metabolism and atrophy in six different syndromes of both Alzheimer’s disease (AD) and frontotemporal dementia (FTD) (K. K. Moodley, 2015). Their findings suggested that the concordance of atrophy and hypo metabolism differ significantly across syndromic variants of AD and FTD, reflecting underlying molecular pathologies as well as operational differences employed in the criteria to diagnose these syndromes.

The application of PET/MRI includes, but is not limited to diagnosis of tumour, dementia, stroke injury, cerebrovascular disorders, Parkinson disease and epilepsy. For workflow and protocol design for PET/MRI combined data acquisition, see (F. de Galiza Barbosa, 2015). The combination of MRI with PET improved quantification and tissue characterization as compared to PET/CT imaging. The advantages of simultaneous PET/MRI data include enhancement of diagnostic accuracy and it is likely to have benefits for planning surgery and radiation therapy.

4. EEG-fNTRS

FMRI, EEG and PET are in practice modalities to study the functions of brain in humans. These modalities have improved and enhanced our knowledge of the neural networks that impair emotional and mental processes (C. J. Price,2012), (R. J. Huster, 2012). However, these neuroimaging technologies each have advantages and restrictions. FMRI is non-invasive and has exceptional spatial resolution, but is expensive, exceptionally sensitive to movement artefact, confines the participants into limited positions within the magnet, is difficult to incorporate with other imaging methods [like (EEG)], and also necessitates that participants endure loud noises. PET also requires a limited range of movement and confinement and requires the injection of radioactive substances. These factors make these imaging techniques unsuitable for many applications such as the assessment of children, and the observation of cognitive activities under working stress.

A decade ago, functional near-infrared (fNIR) spectroscopy was introduced as a neuroimaging modality to run functional neuroimaging experiments. fNIR Technology employs wavelengths of light over the entire scalp, to allow the measurement of changes non-invasively at the relative ratios of deoxygenated haemoglobin (Deoxy Hb) and oxygenated haemoglobin (Oxy Hb) from the capillary beds during brain action. This technology allows the layout of mobile, safe, cheap, non-invasive, and more intrusive tracking systems. These attributes make fNIR acceptable for investigation of hemodynamic changes because of emotional and cognitive brain action under many working conditions.

Concurrent recording of fMRI with EEG/MEG is difficult to apply, because of technical limitations; however, NIRS is suited to concurrently recorded EEG measurements (M. E. Pflieger, 2012). The reason is that NIRS uses near-infrared light, and the EEG signals are not contaminated by light as in the case of fMRI-EEG with gradient and ballistocardiogram artefacts (T. Zama, 2015). In addition, the EEG-NIRS recordings are relatively cost effective, portable, and tolerable to participants’ movement, which make it suitable for long-term recording, and it’s easy to use with infants and patients and is suitable for naturalistic human motor control studies.

5. EEG-MEG

Magnetoencephalography (MEG) enables us to assess the continuing brain activity using millisecond time resolution. Considering that 300 detectors dispersed over the head detect the neural activity, it's likely to identify where, with moderate accuracy, the activity is generated in the brain. This makes MEG suited to analysing the human brain as a system of interacting brain regions during the operation of different tasks. The key applications of MEG are in clinical and cognitive neuroscience research and analyses.

MEG technology relies on SQUID. The superconducting quantum interference device (SQUID), which was introduced in the late 1960s, and is a more sensitive detector of magnetic flux. Now whole-head MEG techniques have a high number of SQUIDs (involving 100 to 300) attached to detector coils in a configuration approximating the curvature of the human head. It measured the magnetic field produced by neuronal activity in the brain and records signals in a millisecond time. This high temporal resolution makes the MEG different from fMRI, which records blood flow changes over much longer periods of time. MEG records signals, which may be in response to visual stimulation, or spontaneous brain activity.

Simultaneous EEG-MEG data acquisition improves the accuracy of source localization, because MEG signals are not distorted by concentric heterogeneities in conductivity. Thus, in epileptic activity combined EEG-MEG is recommended to increase reliability of results (Ü. Aydin, 2014).

6. Discussion and Conclusion

The first step for a researcher is to look into the single modality results and derive inferences for diagnosis of a mental condition. However, single modality results may not provide a clear and effective picture of the mental health of an individual. Hence, the use of multimodality may be valuable in situations once the researcher has already exhausted the option of a single modality. In addition, the multimodal approach can provide a better map of neural activities and hence aid not only in diagnosis but also treatment of a mental health condition. Hence, the objective of multimodality wouldn't be to unite information but to supplement the results of single modality. The supplementary information may provide additional biomarkers which allows the clinician to assess the neural condition and assist in the interpretation for intra- and inter-subject variability. In addition, EEG signals can provide information about the drowsiness of the subject and other peripheral information based on the external stimulus (K. Rosenkranz, 2010).

In case of non-repeatable and non-standard experiments, this is particularly important. As an instance, combined EEG--fMRI experiment has found its way to cognitive neuroscience studies (C. S. Herrmann, 2008), in which it is helpful when the subject performance (such as attention, errors, learning and trial-by-trial evaluation processes) must be equivalent and the order effects must be avoided. The existence of a subject performance condition could compensate the expenses of combined EEG-fMRI recording discussed previously and make such experimentation an essential requirement. EEG is typically used as the biomarker in EEG/fMRI research. It will be interesting to look at a change in opposite direction of this multimodality investigation asymmetry. An example of such investigation is presented by De Martino et al. (F. De Martino, 2010), where they utilized multivariate prediction approaches to estimate single-trial EEG using fMRI images of the whole brain. Recent exciting findings of combined use of EEG-fMRI is the modulation of human cortical responses in the behavioural experiments by state of ongoing occipital alpha oscillations (Becker et al., 2011; Scheeringa et al., 2011)

Multimodality methods can serve various purposes including investigation of brain functions and structures based upon the processing of their information. Several functional studies utilized two or more modalities to attain the most effective spatial and temporal resolution. They assumed that the recorded data has exactly identical sensory sources. Nevertheless, the imaging techniques may differ not just in the data acquisition, but the way neuronal activities and structures bring about the image contrasts. This presents, on the one hand, a problem in fusion of multimodality data without a model describing the series of physiological and bodily events leading to the signals. On the other hand, the advantage is that it enables one to receive a perspective on the neuronal processes more comprehensively.

Therefore, it is important to discover the sources of discrepancies in multimodality approaches which can lead to an improved perspective on cognitive processes and structural composition than that of a single modality (K. Uludağ, 2014). To this end, in order to solve the discrepancies, biophysical generative units need to be developed. Multimodal imaging is also helpful if one is simply interested in the outcomes of a single modality as another modality can confirm the interpretation of the data (in case of biomarkers derived from one modality). One example can be of a learning experiment, when variability of mind states can't be avoided. At length, multimodality approach may be utilized to measure parameters that may be used to generalize the outcomes from specific methods and algorithms. Though, use of multimodality, data acquisition and their fusion need to address several challenges, such as additional software applications, setup time, subject discomfort, extra cost etc., and the merits of multimodality approach make it a very useful and an essential tool to explore neuronal processes and structural composition. Besides data acquisition techniques and analysis methods, the number of research studies using multimodality approach will continue to grow, particularly in the application of neurotherapy (neurofeedback) to treat the patients non-invasively and with more precision.

References

C. Catana, A. Drzezga, W.-D. Heiss, and B. R. Rosen, "PET/MRI for neurologic applications," *Journal of Nuclear Medicine,* vol. 53, pp. 1916-1925, 2012.

C. J. Price, "A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading," *Neuroimage,* vol. 62, pp. 816-847, 2012.

C. S. Herrmann and S. Debener, "Simultaneous recording of EEG and BOLD responses: a historical perspective," *International Journal of Psychophysiology,* vol. 67, pp. 161-168, 2008.

F. de Galiza Barbosa, G. von Schulthess, and P. Veit-Haibach, "Workflow in simultaneous PET/MRI," in *Seminars in Nuclear Medicine,* 2015, pp. 332-344.

F. De Martino, G. Valente, A. W. de Borst, F. Esposito, A. Roebroeck, R. Goebel, *et al.*, "Multimodal imaging: an evaluation of univariate and multivariate methods for simultaneous EEG/fMRI," *Magnetic resonance imaging,* vol. 28, pp. 1104-1112, 2010.

J. Gotman, E. Kobayashi, A. P. Bagshaw, C. G. Bénar, and F. Dubeau, "Combining EEG and fMRI: a multimodal tool for epilepsy research," *Journal of Magnetic Resonance Imaging,* vol. 23, pp. 906-920, 2006.

K. Uludağ and A. Roebroeck, "General overview on the merits of multimodal neuroimaging data fusion," *Neuroimage,* vol. 102, pp. 3-10, 2014.

K. K. Moodley, D. Perani, L. Minati, P. Anthony Della Rosa, F. Pennycook, J. C. Dickson, *et al.*, "Simultaneous PET-MRI Studies of the Concordance of Atrophy and Hypometabolism in Syndromic Variants of Alzheimer's Disease and Frontotemporal Dementia: An Extended Case Series," *Journal of Alzheimer's Disease,* vol. 46, pp. 639-653, 2015.

K. Rosenkranz and L. Lemieux, "Present and future of simultaneous EEG-fMRI," *Magnetic Resonance Materials in Physics, Biology and Medicine,* vol. 23, pp. 309-316, 2010

M. Hoppstädter, C. Baeuchl, C. Diener, H. Flor, and P. Meyer, "Simultaneous EEG–fMRI reveals brain networks underlying recognition memory ERP old/new effects," *Neuroimage,* vol. 116, pp. 112-122, 2015.

M. E. Pflieger and R. L. Barbour, "Multimodal Integration of fMRI, EEG, and NIRS," in *Biomedical Optics,* 2012, p. BSu2A. 1.

R. Becker, M. Reinacher, F. Freyer, A. Villringer, and P. Ritter, "How ongoing neuronal oscillations account for evoked fMRI variability," *Journal of Neuroscience,* vol. 31, pp. 11016-11027, 2011.

R. J. Huster, S. Debener, T. Eichele, and C. S. Herrmann, "Methods for simultaneous EEG-fMRI: an introductory review," *Journal of Neuroscience,* vol. 32, pp. 6053-6060, 2012.

R. Scheeringa, A. Mazaheri, I. Bojak, D. G. Norris, and A. Kleinschmidt, "Modulation of visually evoked cortical FMRI responses by phase of ongoing occipital alpha oscillations," *Journal of Neuroscience,* vol. 31, pp. 3813-3820, 2011.

S. M. Gorka, K. L. Phan, and S. A. Shankman, "Convergence of EEG and fMRI measures of reward anticipation," *Biological Psychology,* vol. 112, pp. 12-19, 2015.

S. Debener and M. D. Vos, "The benefits of simultaneous EEG–fMRI for EEG analysis," *Clinical Neurophysiology,* vol. 122, pp. 217-218, 2011.

T. Zama and S. Shimada, "Simultaneous measurement of electroencephalography and near-infrared spectroscopy during voluntary motor preparation," *Scientific Reports,* vol. 5, p. 16438, 2015.

Ü. Aydin, J. Vorwerk, P. Küpper, M. Heers, H. Kugel, A. Galka, *et al.*, "Combining EEG and MEG for the Reconstruction of Epileptic Activity Using a Calibrated Realistic Volume Conductor Model," *PLoS ONE,* vol. 9, p. e93154, 2014

V. Menon and S. Crottaz-Herbette, "Combined EEG and fMRI studies of human brain function," *International Review of Neurobiology,* vol. 66, pp. 291-321, 2005.