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AN APPLICATION OF FUNCTIONAL MAGNETIC RESONANCE IN MEDICINE: OPTIMIZATION OF fMRI AND rsfMRI STUDIES*

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Novel functional magnetic resonance techniques based on variation of the blood-oxygenated-level-dependent (BOLD) signal during the performance of a task or in response to a stimulus (fMRI) as well as at the rest (rsfMRI) are compared. These techniques play a significant role in the investigation of functional architecture of the brain. There is a good overlap between the areas of fMRI activation elicited by motor, language, visual or other task studies and the corresponding rsfMRI networks (RSNs). Progress in statistical approaches for processing is presented particularly for rsfMRI data. Both fMRI techniques as completely non-invasive can be successfully used in medical diagnostics and neurosurgery. In recent years, research has focused on the rsfMRI technique since it represents a promising and cost-effective alternative to task-based fMRI for scientific needs as well as for medical applications.

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1. Introduction

Using microscope investigation, Brodmann divided the brain's core into 47 areas that are in various ways involved in life processes [1]. The brain inattentively monitors and manages the work of our body, analyses visual, auditory, sensory, taste stimuli from the outside world and plays a fundamental role in the cognitive and creative processes. Different methods are used to study the mechanisms of brain activity: electroencephalography (EEG), event-related potentials (ERPs), position-emission tomography (PET), functional near-infrared spectroscopy (NIRS) as well as functional magnetic resonance imaging (fMRI). The fMRI method is based on the changes in blood

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oxygenation observed in specific MRI signal, the so-called BOLD (blood-oxygenation-level-dependent) due to the performed task or as a response to a stimulus, revealing activation in certain areas of the brain. The importance of the BOLD contrast in MRI was first recognized by Ogawa *et al.* [2]. In recent years there has been an increase in interest in application of the fMRI technique at rest termed rsfMRI. Rest state fMRI measures spontaneous low-frequency fluctuations in the BOLD signal to investigate functional architecture of the brain [3]. The advantage of rsfMRI is the possibility of studding neurological impaired patients and children, who may be adequately compliant for task-based fMRI.

In addition, functional magnetic resonance spectroscopy (fMRS) can give a direct insight into cellular processes occurring during brain activation. The functional ^{13}C MRS is particularly suited for measuring important neurophysiological fluxes *in vivo* in real time to assess metabolic activity [4]. ^{13}C MRS has been crucial in recognizing that the awake, non-stimulated (resting) human brain is highly active using 70%–80% of its energy for glucose oxidation to support signaling within brain cortex which is suggested to be necessary for retaining consciousness [5]. All these MRI tools have allowed to study the properties of the living brain and contribute essentially to current understanding of brain functional organization. It has been proven that RSNs networks could be registered in humans throughout sleep.

This paper is focused on comparison of fMRI and rsfMRI contributions in neurology knowledge. Various methods for analysing functional magnetic resonance data are presented as well as potential clinical application of both fMRI techniques are discussed on the basis of literature and our own works.

2. rsfMRI versus task fMRI: Biophysical bases

Figure 1 shows the comparison of time courses of signal between task-based fMRI and no task fMRI. One can see that in a task-based fMRI, time course of MRI signal from voxel correlates well with the task unlike the low frequency fluctuations at rest. This phenomenon is connected with the need of oxygen consumption during neural activity. When neurons in a brain area become active, they need oxygen and extra oxygen-containing blood gets pumped to that area changing the degree of intercellular oxidation blood flow as well as its magnetic properties (HbO_2 — diamagnetic/Hb — paramagnetic) in varying vascular volume. Due to these effects, the BOLD signal increases in response to a stimulus according to block design (Fig. 1 (a)), revealing that certain areas of the brain are activated. Nevertheless, low-frequency fluctuations which do not correlate with the task can demonstrate the existence of synchronous spontaneous fluctuations (Fig. 1 (b)). The presence of spatially coherent activity in the BOLD signal at rest was first reported by Biswal *et al.* in 1995 for sensorimotor areas [3]. The basics of biophysical resting brain activity were subjects of landmark works by Raichle and his co-workers [5, 6]. Primarily, functional connections were defined as the presence of a high temporal coherence in the signals between spatially distinct areas that allowed for identification of neural resting state networks, the so-called RSNs.

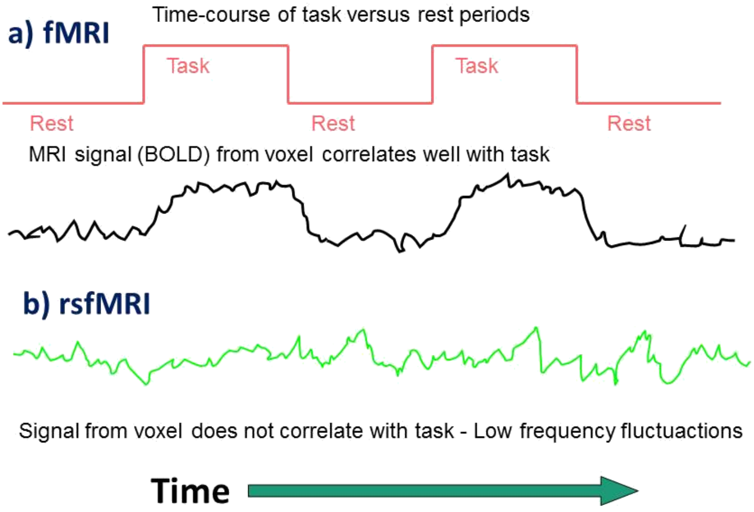

Fig. 1. Time-courses of BOLD signal in fMRI and rsfMRI.

Various RSNs can be constituted. However, the most fundamental RSN is DMN (default mode of neural network) which presents consistent regions of the active brain at rest that decrease their activity when cognitive tasks are performed [5, 7, 8]. The resting-state brain organization includes the RSNs such as sensorimotor, visual, auditory, language, attention or fronto-parietal control network, basal ganglia network, executive network, precuneus network, *etc.*

3. Brain connectivity analysis methods

Functional connectivity is the study of the interaction between two different brain regions and reveals the coherence in the activity between cerebral areas under task or in the resting state. The functional and anatomic images are usually carried out using parametric mapping (SPM) packet in MATLAB (MathWorks, Inc. enviromment), which is still being modified. However, inferring resting state connectivity patterns from functional magnetic resonance imaging data is a challenging task for any analytic technique, therefore, after pre-processing different approaches are proposed such as Seed Correlation Analysis (SCA) [3, 9] independent component analysis (ICA) [10], and others such as graph theory analyses, clustering algorithm, multivariate pattern classification or time varying functional methods described in [11, 12]. However, SCA and ICA seem to be the most popular approaches and have been applied in numerous studies. They give similar results in healthy subjects although they differ in their estimation methods.

The SCA method needs a selection of a "seed" or region of interest (ROI) and then finds the linear correlation of the average BOLD time courses of this ROI with each of all the other voxels in the brain for yielding a seed-based FC map. ICA requires no explicit temporal model, but considers the relationships between all voxels simultaneously to spatially identify distinct RSNs using a blind source separation method (BSS). The ICA method decomposes a two-dimensional (time x voxels) data matrix into a set of time-courses and distinct associated spatial maps. There are two ICA packets: single-subject ICA and group ICA for application depending on clinical needs.

In most conducted analyses, it is usually assumed that functional communication (FC) is static across the whole fMRI examination while fluctuations of rsfMRI can be highly variable at a very fast time-scale. The study of the temporal reconfigurations of FC occurring within rsfMRI session was defined as Time-Varying Functional Connectivity (TVC) [13, 14]. Recently, TVC as a novel approach was in detail described by Valsasina *et al.* [12]. The application of the Time-Varying FC technique to neurological and psychiatric diseases was also presented. The results obtained with temporal reconfigurations of FC occurring within rsfMRI sessions provide significant information on intrinsic brain functional organization, both in healthy and pathological conditions that complement data produced by classical static FC approaches. However, characterization of rapid fluctuations of rsfMRI requires high temporal resolution to acquire fMRI data and further improvement of TVC pre- and post-processing approaches is recommended.

While FC measures the signal among remote brain areas, the regional spontaneous activity can be examined by several metrics such as the regional homogeneity (REHo) [15], the amplitude of low-frequency fluctuation (ALFF) [15, 16] or the fractional ALFF (fALFF) fALFF is defined as the power within the low-frequency range (0.01–0.1 Hz) divided by the total power in the whole, entire detectable frequency range [17, 18]. There are also works focused on the detection of the high frequency > 0.1 Hz (HF) correlation in resting state fMRI suggesting that HF connectivity in the human brain may be obtained with high-speed fMRI, however, the detection sensitivity depends on the network studied, data acquisition and analysis method [19].

4. Examples of optimizing of SCA and group-ICA in rsfMRI studies

It is known that results of rsfMRI studies depend on arbitrary choice of parameters used in FC analyses, hence the need of their optimization. In this part, a focus is given on two approaches; SCA using the amplitude of ALFF and ICA using fractional ALF.

Seed-Correlation Analysis based on bivariate connectivity relationships in DPARSF toolbox was used for MRI data from 20 healthy volunteers. Details of the experimental were described in [20]. The best results of FC imaging of DMN, Auditory, Sensimotor, Visual networks were achieved for ALFF 0.01–0.08, spherical ROIs with the 8-mm radius and Gaussian kernel 8 mm at FWHM. A similar analysis was performed for cerebellum and its main results are presented in Fig. 2. The highest values of functional connectivity were found in pairs of ROIs; 8_9 (within Med cerebellum), 5_3 (within Lat cerebellum), 4_10 (Lat cerebellum and Med cerebellum) for smoothing = 8 mm and ROI's radius = 8 mm. The dominating effect of ALFF (0.01–0.08) on FC correlations in cerebellum was also confirmed. It is noteworthy that the same parameters were distinguished in all the studied areas.

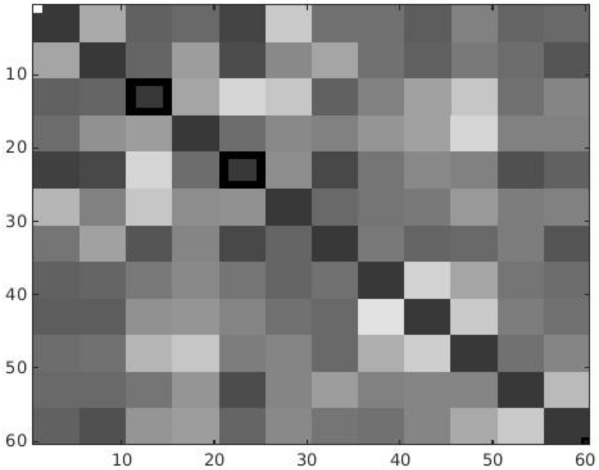

Fig. 2. Functional connectivity (FC) matrix for cerebellum. FC calculated among ROI pairs, taking into consideration each ROI with another one. Parameters: $r = 8$ mm, smooth $= 8$ mm, ALFF: 0.01–0.08 Hz.

In ICA practical challenges are questions: which model should be used (How many components should be estimated)? Which components of feature identification should be used in analysis (*e.g.* peak activity in Gray Matter and components ICs dominated by low frequency below 0.10 Hz)?

Figure 3 displays representative time courses and spatial maps features of IC 21 component obtained in the high model order ICA75 (75 components) with Infomax algorithm using Toolbox (GIFT) for rsfmRI data from 20 healthy participants. Only components with the well formatted shape of fALFF peak fALFF related to level of coherent activity and the sufficiently high intensity of RSN spatial maps related to the connectivity and degree of coactivation with a network may be categorized as RSN according to the guidelines formulated in the paper by Allen *et al.* [18].

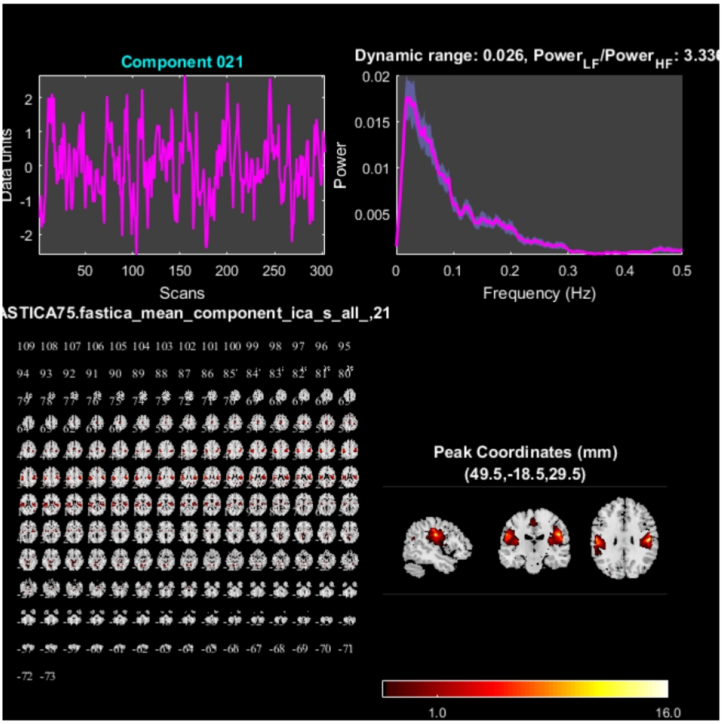

Fig. 3. Spectral features and spatial maps for component IC21 (Right Cerebrum, Parietal Lobe, Postcentral Gyrus, Gray Matter, Brodmann area 2) obtained in group ICA75 for 20 healthy subjects.

An influence of the number of independent components (ICs) on results was considered, among others, by us [21] using group ICA taking into account ICs = 20, 40, 60, 80, 100 in healthy patients and those with multiple sclerosis for the sensorimotor, cerebellum and visual areas (in preparing). It was found that number of components categorized as RSNs increased with high order model ICA for healthy group, probably due to better correspondence of the yielding refined components corresponding to known anatomical and functional segmentation [22].

A comparison of obtained results in healthy group with those reported by Allen [18] indicates a difference in number of components categorized as RSNs, some modifications to the coordinates of some RSNs, probably due to a different number of subjects as well as the ICA packet used. This suggests the need for standardization of research methodology, especially for clinical practice.

5. Clinical application

Many papers have reported potential application of functional magnetic resonance imaging in clinical practice in neurological and psychiatric diseases prognosis as well as in neurosergury. One of the main problems of fMRI when interpreting the results derived from active paradigms in impaired people is to define if and how much they are influenced by intersubject variability in task performance. In contradistinction, imaging of the rest state does not require the performance of paradigms since no-task fMRI is easier to be acquired and standardized and may be more effective in identification of abnormalities characteristic for many different diseases than task-based fMRI. Therefore, recently resting state fMRI has been mainly taken into consideration providing many interesting insights on RSNs in the healthy brain and in multiple disease states. Clinical applications of resting state fMRI at an early stage of development were collected in several review papers [9, 11, 23, 24] and references within. Identification of patients with Alzheimer disease and those with mild cognitive impairment from control were reported. Pattern classification of rsfMRI can be applied in diagnosis of consciousness disorder including major depressive disorder and schizophrenia. The ability of rsfMRI to assist in diagnosis of autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder was indicated. Advanced research using intrinsic functional connectivity variance and state-specific under connectivity allowed to improve the sensitivity in classifying ASD from healthy groups and distinguishing states inside autism spectrum disorder conditions [25]. The potential utility of RSN characteristics in paediatric populations was also noted.

A number of rsfMRI studies have been conducted to find biomarkers for multiple sclerosis (MS) often affecting young people; see overviews by [7, 23, 24, 26]. MS is characterized by multiple lesions in the white matter however the damage of the grey matter also occurs. (Brain atrophy is seen in both WM and GM *e.g.* [27]). All this leads to FC alternations within and between brain networks. Cognitive dysfunction and physical disability (motor, visual, sensitive) can be reflected in various rsfMRI patterns what was confirmed by different analysis techniques (SCA, ICA, graph theory analysis). For example, our rsfMRS studies using ICA in GIFT toolbox [21] showed a drop in the number of independent components with simultaneously marked lower values of fALFF in stable MS patients compared to the healthy group (*e.g.* 9 *versus* 21 in ICA75). Moreover, the number of RSNs in MS conditions disappeared in the highest ICA models.

RSNs abnormalities have been found in almost MS phenotypes and have been considered as biomarkers of disease severity though results are not always concordant and further studies are needed [24]. Recently, a new TVC approach used in MS patients indicated that the abnormal TVC properties of sensorimotor, DMN and salience networks can be associated with more severe structural MRI damage as well as severe physical and cognitive disability [12].

Similar conclusions could be drawn from the application of time-varing FC techniques to other neurological and psychiatric diseases such as: Alzheimer's disease and Parkinson's disease as well as bipolar disorder, schizophrenia, depression, epilepsy and autism spectrum disorders summarized in the overview by Valasa *et al.* [12]. It seems probable that the clinical symptoms associated with these diseases may not only depend on the damage to the specific brain regions but be also due to delayed or abnormal communication between brain areas.

Other applications of rsfMRI were also developed in the last decade. New insigths into the functional connectivity between the hippocampus and other brain regions were found [28]. Cortically-based functional networks were studied to assess early human cortical development [29].

A similarity between altered functional connectivity of the DMN resulting from glucose loading in young, healthy participants and patients with Alzeimer's disease was reported [30]. The reduction of neural activity in the precuneus/posterior cingulate cortex (PC/PCC) which is the functional core of the DMN was observed. Gupta *et al.* [31] focused on quantifying the alternations in BOLD signal by using ReHo, ALFF and fALFF measures in patients with vitamin B12 deficiency which disorders brain networks associated with cognitive functions (DMN, fronto-parietal and cingulo-opercular networks). Moreover, the rsfMRI testing indicated partial recovery after vitamin B12 replacement therapy. Noteworthy is a multivariate analytic approach using a group-independent component analysis for 603 healthy adolescents and adults performed by Allen *et al.* [18] to establish a baseline for investigations of brain networks in health and disease. Moreover, it was reported by Mak [32] that RS FC strength in healthy subjects is associated with RS fluctuations being strongest in adulthood and lowest in childhood and elderly age. This fact should be taken into account in clinical studies.

6. Neurosurgery

Surgical intervention in brain structures with tumour or the other neurological lesion carries a high risk for induced post-operative neurological deficits. For preoperative patients resection of brain tumour aims to remove as much of the changed tissue as possible while preserving essential brain functions simultaneously. Functional magnetic resonance studies are especially important if the tumour is adjacent to or includes the Brodmann areas related to the quality of patient' life, that is speech, motor or vision cortex, what was also presented by us [33, 34]. However, analysis with the SPM should be carried out with a great care since the results of these investigations can be influenced by parameters used in statistical approaches as demonstrated in papers by Karpiel *et al.* [33, 34]. However, fMRI study is relatively much time-consuming and requires prepared stimuli together with hardware unlike rsfMRI. In addition, resting state activity can be registered in propofol-anesthetized patients with tumors that is especially important in oncolocical neurosurgery [35]. The role of resting-state functional connectivity in presurgical investigations has considerably increased in the last years [36–38] although fMRI is still used in neurosurgery. A variable concordance of the ventral somatomotor network at the single-subject level between resting-state and task-based fMRI was reported.

The new intraoperative use of rsfMRI (so-called irsfMRI) during brain surgery was presented by Roger *et al.* [39]. Correlations between irsfMRI results and the clinical outcomes for the sensorimotor networks with lesions in/or directly adjacent to the central and/or pyramidal tracks in preoperative patients were shown. Moreover, it was suggested that postoperative neurological deterioration may be predicted by implementing irsfMRI within iMRI surgery. The multiple advantages of rsfMRI have initiated works on automatic extraction of rsfMRI networks for neurosurgical practice *e.g.* [40]. However, software tools aimed at facilitating the derivation of rsfMRI networks for neurosurgery require clinically streamlined tools for quality control, preprocessing, and statistical analysis of rsfMRI and fMRI.

This brief overview of the applications of fMRI studies does not exhaust their possible uses in medicine.

7. Summary

Booth task-based fMRI and rsfMRI as completely non-invasive methods provide interesting insights into fundamental properties of brain functionality and mechanisms of its reorganization throughout the human life in healthy and pathological conditions. The results obtained with these techniques complement each other, what is emphasized in many works. Findings of functional magnetic resonance studies point out their potential application in medicine to increase the diagnostic value of different neurological and psychiatric diseases. Investigations are focused on finding biomarkers of some diseases (*e.g.* MS, Alzheimer, ASD, and *etc.*) but these findings require further studies and validation in clinical trials. fMRI and rsfMRI are the proper tools to assist with pre, intra- and preoperative diagnostics. In order to facilitate the use of fMRI/rsfMRI in neurosurgery, various toolboxes are proposed to make the obtaining results from complex, statistical analyses as well as programs for visual mapping of FC easier in a doctor-friendly form. In comparison with task-based fMRI, rsfMRI offers advantages such as: reduction of image acquisition time due to the possibility of detecting multiple networks from one data set, no need for specific hardware and software for delivery of the task-related stimuli and no need for dedicated personnel for evaluating patients' cognitive status; generally cost-effective. Further investigations — theoretical and experimental — are required to determine a processing strategy that efficiently prepares data for analysis, and a statistical approach that identifies important effects in a manner that is both robust and reproducible.

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