REVIEW ARTICLE

# Functional imaging in neurosciences

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## Abstract

Recent advances in functional imaging of the brain have enabled a better understanding of the brain functions in health and disease. Amongst various functional imaging techniques, functional magnetic resonance imaging (fMRI) has been more rigorously employed in both clinical practice and in the research arena. This review will discuss the principles and techniques of fMRI, its role in understanding the pathophysiology of brain injury and finally, its clinical application in diagnosing neurological conditions and prognostication of outcome in patients with neurological disorders.

**Key words:** Brain injury, functional magnetic resonance imaging, functional imaging, neurosciences, trauma

## INTRODUCTION

Imaging of the brain forms an essential component of diagnosis and clinical management of neurological disorders. Till a few years ago, brain imaging was largely restricted to structural (anatomical) imaging. With recent advances in neuroimaging technology, functional (physiological) brain imaging has been increasingly adopted for supplementing diagnostic information and also for better understanding of the neurobiological processes in the pathological brain. The most commonly utilised functional imaging techniques include magnetic resonance spectroscopy (MRS), single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).[1] SPECT is used to measure cerebral perfusion, MRS to assess brain metabolism, PET to evaluate both perfusion and cerebral metabolism and fMRI for examining the brain connectivity or networks. Further, fMRI also identifies the areas of the brain responsible for various functions such as language, sensory and motor function. These imaging modalities provide information on the severity of the injury, provide insight into their pathophysiology and facilitate prediction of outcome following brain injury. This review will focus on fMRI in neurosciences including clinical applications in traumatic brain injury (TBI), epilepsy, stroke, Parkinson's disease (PD), etc.

A literature search was made in PubMed database with search terms 'functional imaging', 'fMRI', 'neurosciences', 'TBI', 'stroke', 'neurosurgery', 'neurology', 'spinal cord injury (SCI)' and 'pain'. Only human studies were considered including original articles and review articles. For simplicity and clarity, the topic is discussed under following subheadings:

- Functional imaging; principles and techniques
- Understanding the functional changes in pathological brain
- Clinical application of functional imaging in neurological disorders
- Utility in predicting outcome following neurological injury.

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## FUNCTIONAL MAGNETIC RESONANCE IMAGING: PRINCIPLES AND TECHNIQUES

Functional magnetic resonance imaging technique of imaging the brain is based on the blood-oxygenation-level-dependent (BOLD) signal. This signal is due to the magnetic field inhomogeneities arising from different magnetic properties of oxy- and deoxy-haemoglobin in the blood. Brain activity initiates metabolic events causing an increase in blood volume (assuming normal flow-metabolism coupling) and a resultant reduction of the deoxy-haemoglobin content of the activated tissue. These changes cause increases in the BOLD signal.[2]

There are mainly two types of fMRI techniques: Task-based and task-independent or resting-state (rs). In task-based fMRI, the patient performs a task (cognitive, motor) or is presented with stimuli (auditory or visual) alternatively with a rest period (no task or stimuli). In the most commonly used task-based fMRI experiment, a block design, stimuli are presented in discrete epochs and the BOLD signal during the stimulus period ("on") is compared to signal during a rest period ("off"). Activation maps depicting differences between signals at rest and during the task are then derived. One of the commonly used statistical approaches for quantifying these differences is general linear modelling.[3]

Even at rest, different areas of the brain interact with each other in the low-frequency range (<0.1 Hz). Rs-fMRI allows examination of this brain's intrinsic resting-state networks (RSN). Default mode network (DMN), salience network, thalamocortical networks and executive control network are some of the identified RSN. DMN, the most extensively studied RSN, consists of posterior cingulate cortex (PCC), precuneus (pC), medial prefrontal cortex and inferior parietal lobule[4] [Figure 1]. Statistical analyses of rs-fMRI either consist of seed voxel correlation or multivariate approaches like independent component analyses (ICA). A seed-voxel analysis uses one or more pre-defined regions of interest ('seeds') and identifies voxels showing the correlation of fMRI signal time-courses with the respective seed region. ICA, on the other hand, delineates spatially independent patterns of coherent signals. Both these approaches facilitate identification of functional connectivity (FC) between areas with similar functional purposes and known anatomical locations.[2] Rs-fMRI can image patients with various neurological impairments without their active involvement and study multiple networks simultaneously and hence may be more informative in patients with severe brain injury.

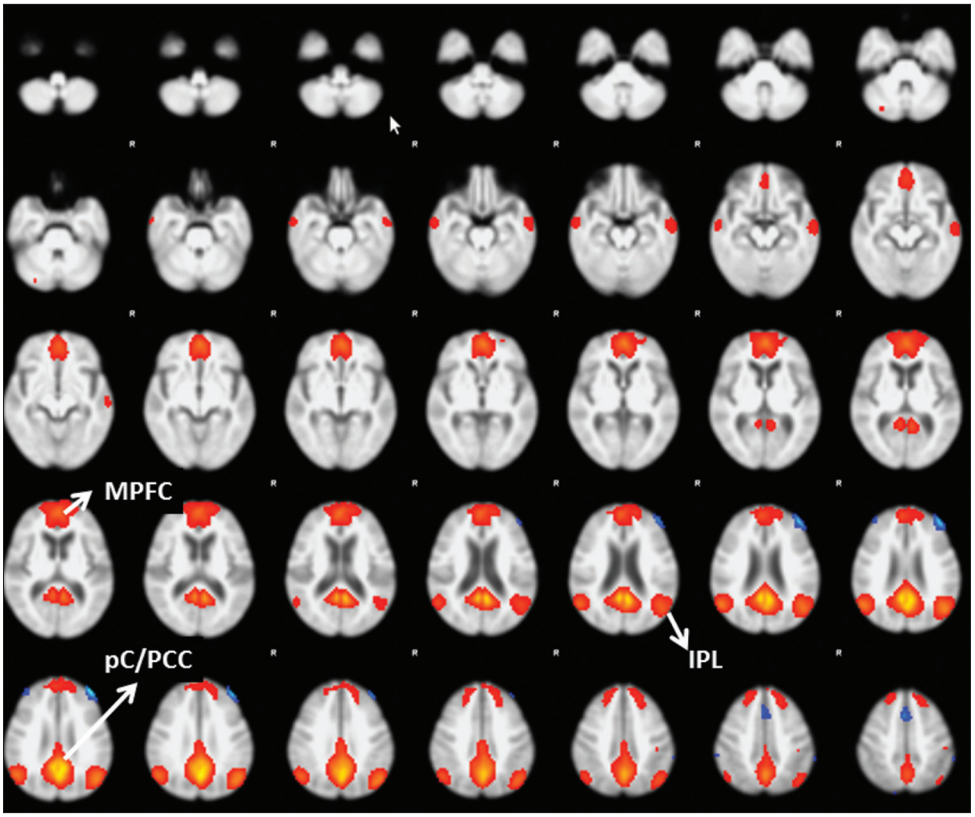


**Figure 1:** The default mode network in healthy volunteers demonstrating its constituents; posterior cingulate cortex (PCC), precuneus (pC), medial prefrontal cortex (MPFC) and inferior parietal lobule (IPL)

## UNDERSTANDING PATHOPHYSIOLOGY IN NEUROLOGICAL INJURY

The brain is functionally organised into a set of widely distributed networks. Therefore, although structural damage may be focal following a neurological insult, remote dysfunction can occur in regions connected to the area of lesion. The fMRI has been increasingly used to understand both related and remote pathophysiological changes in the injured brain. Since task based technique is difficult in brain injured patients, passive tasks or rs-fMRI based methods are generally employed.

Traumatic brain injury often results in various degrees of functional impairments that restrict recovery. The underlying pathophysiology of these impairments is uncertain, which limits clinical assessment and management. These patients show abnormalities in information processing and attention when compared with age-matched controls. Furthermore, though some patients may be able to perform the tasks accurately, the response is slow and variable. In a rs-fMRI based study in patients with TBI and controls, brain regions activated by the task were similar between the groups, but TBI patients showed greater deactivation within the DMN, in keeping with an increased cognitive load. Patients with the highest FC had the least cognitive impairment. Lower DMN FC was seen in those patients with more evidence of diffuse axonal injury (DAI) within the adjacent corpus callosum.[5]

Following TBI, abnormal brain activation patterns detected by fMRI correlated with a broad range of neurocognitive and functional deficits. Apart from being explored as a prognostic biomarker, fMRI has also been used to elucidate the mechanisms involved in neuroplasticity as has been demonstrated by recruitment of additional neuro-anatomic networks during recovery that were not previously associated with a particular function.[6] FC has also been shown to correlate with the structural injury of white matter pathways as measured by diffusion tensor imaging.[7,8]

Attention impairments in TBI patients are associated with an increase in DMN activation, particularly within the pC and PCC. FC between pC with the rest of the DMN can predict the occurrence of impairments of attention. DAI after TBI produces cognitive impairment by disconnecting nodes in distributed brain networks.[8]

An earlier study has shown that an increased amplitude low-frequency fluctuations detected on fMRI corresponds to better cognitive performance in chronic TBI. The loss of structural connectivity produced by damage to the cingulum tract has been explained as a cause for the compensatory increases in FC within the frontal node of the DMN. This knowledge is likely to contribute to the improved clinical management and rehabilitation programmes.[9]

Disturbances in the brain connectivity after stroke are shown to occur not only in the vicinity of the lesion but also between remote regions in the affected and unaffected hemisphere. Activation of premotor areas and contralesional primary motor cortex (M1) is a consistent finding following stroke.[2] In another study, stroke patients showed a significant decrease in brain activity in parietal and basal ganglia (BG) networks and widespread increase in brain activity in the remaining ones when compared with healthy controls.[10]

Connectivity information may be utilised as a neuroimaging biomarker for the early diagnosis of PD. Inferior orbito-frontal area plays a crucial role in non-motor dysfunctions. The contralateral inferior parietal area is shown to positively correlate with the severity of motor symptoms in patients with PD.[11]

Compared to control subjects, patients with SCI show increased FC between the M1 and other motor areas such as the supplementary motor area (SMA) and BG on rs-fMRI. A decreased connectivity between the primary somatosensory cortex (S1) and secondary somatosensory cortex (S2) is also found in SCI.[12,13] In addition, increased FC within motor network negatively correlates with the total American Spinal Cord Injury Association motor score during the early stages of SCI.[13]

## APPLICATIONS IN CLINICAL SETTINGS

Functional magnetic resonance imaging has several applications in neurosurgical and neurological patients. Functional imaging techniques provide greater insights into residual cognitive function than bedside examination or conventional neuroimaging in patients with neurological problems. In addition, fMRI can identify patients who might benefit from therapeutic interventions aimed at restoring consciousness and other neurological functions.

In neurosurgical patients, functioning cortex within or adjacent to tumour margins can be demonstrated, which may translate into partial or complete preservation of clinical function at surgery. This becomes all the more important when morphologic landmarks are no longer identifiable on anatomic images. This pre-operative workup may obviate the need for conducting awake neurosurgery and on some occasions, may even help to reassess the indication for surgery.[14-16] Pre-operative fMRI can help identify eloquent areas involved in motor and language functions and help predict the occurrence, clinical presentation and even the duration of the post-operative neurological deficit. This information facilitates better and well-informed communication with

the patients and prepares for the post-operative course and care. The fMRI may also identify the epileptic foci and reinforce the information obtained from the conventional tools like electroencephalogram and help determine the relationship between epileptic foci and eloquent areas of the brain before surgery. Speech-activated fMRI can assess hemispheric dominance without the need for invasive WADA test.

Anaesthetic drugs affect the brain connectivity both in heath and disease. The fMRI is being increasingly used to understand the anaesthetic drug targets and explore mechanisms of reversible loss of consciousness following anaesthesia in healthy volunteers.[17,18] Recently, attempts have been made to evaluate whether anaesthetics alter functional brain networks in neurological patients like in those with chronic pain differently than that is seen in healthy volunteers. In an unpublished study, propofol sedation resulted in generalised decrease in the integration within large-scale brain networks as compared to awake state [Figure 2] while increased strength of FC between PCC and thalamus was observed in patients with chronic back pain (unpublished data).

In neurological patients, fMRI may help in determining prognosis of recovery after brain injury, assess effect of interventions such as medications and rehabilitation in patients with stroke and movement disorders and identify patients at risk of developing Alzheimer or PD at an early stage before morphological changes occur and clinical manifestations are obvious.[19,20]

Coma has to be accurately diagnosed to stratify prognosis and inform the family and also for ethical, social and economic considerations. Hence, differentiating minimally conscious state (MCS) from the vegetative state (VS) is important. Currently, it is extremely difficult clinically and with conventional diagnostic tools to accurately predict a patient who is likely to improve and who will not, after severe TBI or other forms of brain injury. The fMRI has helped in differentiating different components of disorders of consciousness (DOC).[3] Cortico-cortical FC has been shown to be more efficient in MCS compared to VS patients.[21] In patients with DOC, a task-based fMRI (auditory or visual stimuli) could be used to detect signs of consciousness, not found during a thorough neurological examination.[22]

## FUNCTIONAL IMAGING IN ASSESSING RECOVERY AND PREDICTING OUTCOME AFTER BRAIN INJURY

Recovery of conscious awareness and cognitive function following severe brain injury can be unpredictable and prolonged. Furthermore, a significant dissociation between motor response and consciousness recovery is not uncommon following severe brain injury. Recovery following injury and its prediction will depend on the

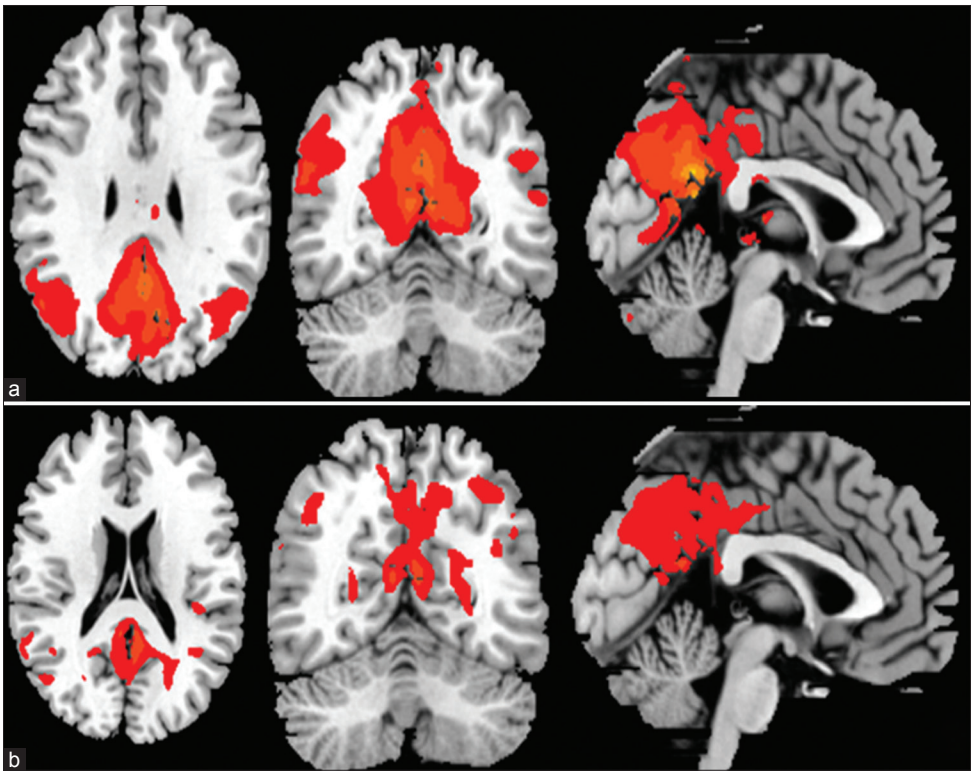


**Figure 2:** Functional connectivity at pre-propofol sedation state (a) and post-propofol sedation state (b) overlaid on the T1-weighted structural image (axial, coronal and sagittal sections [left – right] of brain) in patients with chronic back pain

accurate interpretation of the DOC. Differentiating brain death and consciousness are easy but separating coma, VS, MCS and locked-in state might be clinically difficult. Functional neuroimaging techniques are increasingly applied to identify brain activity and improve prognostic accuracy in patients recovering from coma given the limitations of computed tomography, MRI and clinical assessment in predicting outcomes following severe brain injury in patients with DOC. Correlation between fMRI data and 6 months behavioural outcomes suggest that acute fMRI may provide good prognostic utility.[23]

The pattern of the restoration of FC may serve as a biomarker for clinical recovery after brain injury. In a study, involving 13 patients who survived stroke, Bajaj *et al.*, studied how brain interactions are affected following stroke and how the functional organisation is regained from rehabilitative treatment as patients begin to recover motor behaviours. They observed that motor scores were higher and correlated with FC measures when stroke survivors underwent both mental practice and physical therapy.[24]

The degree of functional recovery after stroke has been shown to be associated with the extent of preservation or restoration of ipsilesional corticospinal tracts in combination with reinstatement of interhemispheric neuronal signal synchronisation and normalisation of small-world cortical network organisation following stroke in rats.[25] Patients with good cognitive recovery following stroke showed increased activity in the DMN and fronto-temporal network when compared with patients with poor cognitive recovery in a rs-fMRI based study.[10]

Long-term cognitive impairment after TBI occurs due to disruption of networks within the brain that supports cognition. The assessment of brain network function after TBI provides insights into the pathophysiology of cognitive dysfunction and the mechanisms involved in recovery. These advances are likely to provide the basis for a more detailed understanding of rehabilitation and guide the development of targeted individualised therapy after TBI. The effects of drugs that augment rehabilitation like methylphenidate are currently being studied in the context of their effect on network function after TBI.[26]

The network resilience/vulnerability to interictal epileptiform discharges, as evidenced by magnitude changes in the network topography, was studied in children with medically intractable epilepsy using fMRI. The authors observed that the resilience of network topologies to interictal discharges is associated with stronger RSN connectivity and vulnerability to interictal discharges is associated with worse neurocognitive outcomes.[27]

## OTHER POTENTIAL ROLES OF FUNCTIONAL IMAGING

During development from childhood and adulthood, simultaneous with cognitive maturation, there is progressively increased functional activation in task-relevant lateral and medial frontal, striatal and parieto-temporal brain regions, which mediate these control functions. This is accompanied by greater functional inter-regional connectivity in the fronto-striatal and fronto-parieto-temporal networks.[28]

The ability to functionally image the brain in health and disease has enabled us to study the effect of therapeutic drugs on the activity and organisation of the brain networks and assess how the brain reacts to their administration. This translational ability of fMRI using brain networks to evaluate therapeutic interventions on the disease process can serve as biomarkers in novel drug development as well.[29]

## LIMITATIONS

Until large multi-centric studies demonstrate more consistent findings, the accuracy of functional imaging in detecting evidence of consciousness in patients with DOC after neurological insults will remain unknown, despite its increasing use in the diagnostic and prognostic protocols. Methodological considerations affecting fMRI data interpretation such as movement, sedation and slow cognitive processing remain to be addressed. Statistical tools for analysing the fMRI data are also not completely validated till date. Until these issues are resolved, its routine use in the clinical setup will remain uncertain.

## CONCLUSIONS

Functional imaging of the brain can provide information about the functional integrity of neural networks that are critical to consciousness and brain functions. Despite significant developments, its day to day clinical utility in patients with neurological disorders remains uncertain. However, further refinements, validation across various populations and standardisation of image acquisition and analysis, will improve the accuracy of diagnosis and prognostication, facilitate development and testing of novel therapeutic interventions and help families and physicians make more informed decisions regarding goals of care in these patients.

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### Conflicts of interest
There are no conflicts of interest.

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