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Current Role of fMRI in diagnosis of movement disorders

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Abstract

The emergence of functional magnetic resonance techniques for the purpose of brain mapping serves as a valuable tool for understanding both normal physiology and the dysfunction taking place in disorders of the brain. This article provides an overview of fMRI methods and their applications in the study of neurological movement disorders. We then review the current neuroimaging literature regarding Parkinsonisms, Dystonia, Essential Tremor, and Huntington's disease, including discussion of current methodological limitations and future directions for this exciting field.

Keywords

Neuroimaging; fMRI; Parkinson's disease; Tremor; Dystonia

Background: fMRI in Movement Disorders

The emergence of functional magnetic resonance (fMRI) techniques for the purpose of brain mapping has led to an explosion of data on normal brain physiology and the dysfunction that takes place with disease. This article is intended to provide a brief overview of fMRI methods and their applications in the study of neurological movement disorders. Readers should note that, at this time, there are no clinical indications for the use of fMRI-based techniques in the area of neurological movement disorders. We have therefore summarized seminal contributions in the various areas of movement disorder research, while providing the reader with a sketch of what this technology allows now and where this technology may lead.

History of Functional Neuroimaging

Human interest in visualizing the active brain is nothing new. The notion that regional cerebral blood flow could serve as a surrogate marker of underlying neural activity was first demonstrated by the work of Roy and Sherrington in 1890.[1] Early efforts to map neural

activity utilized short-lived radionuclides incorporated into compounds such as glucose and water.[2, 3] These radionuclides could be quantitatively and qualitatively measured with computed tomography, leading to the development of positron emission tomography (PET). [4] The ongoing development of PET tracers has allowed for the virtually limitless ability to study any metabolic pathway, as long as a relevant radiotracer could be synthesized to target the area of interest. The primary limitations associated with PET remain the radiation exposure, albeit limited, extensive infrastructure required for synthesis of the radiopharmaceuticals, and lack of temporal resolution during data collection.

The development of magnetic resonance imaging (MRI) techniques for functional brain mapping is a much more recent development. A wide variety of techniques fall under the category of functional MRI (fMRI), with most techniques utilizing the different magnetic properties of hydrogen atoms (protons) comprising water molecules ubiquitous throughout the body. Despite the lack of targeting probes as seen with PET, MR-based techniques compare favorably due to the relative ubiquity of scanners at various points of care, lower cost of implementation, non-invasiveness, and higher temporal resolution compared with PET. The reader should however consider that no single imaging modality is likely to provide a comprehensive understanding; the use of complementary modalities in serial or parallel is now becoming a standard part of research protocols.

Overview of fMRI Techniques

The technique most commonly used in fMRI studies is based on the principle of blood oxygen level-dependent (BOLD) contrast changes.[5] BOLD-fMRI uses the different magnetic properties of oxygenated and deoxygenated hemoglobin to identify regional blood flow changes in the brain. If we assume a baseline level of neural activity and blood flow, then activation of this neural region will lead to increased oxygen consumption. This increased oxygen demand leads to a brief reduction (100–200 msec) in the concentration of oxy-hemoglobin relative to deoxy-hemoglobin at the vascular bed. This small reduction in oxyhemoglobin is followed by a disproportionately larger compensatory increase in blood flow leading to an increase in oxyhemoglobin and drop in deoxy-hemoglobin that surpasses pre-activation levels. The signal from these blood flow changes is derived from the drop in deoxy-hemoglobin, and leads to an increase BOLD signal within a few seconds that peaks around 4 to 8-seconds before returns to baseline 14–16 seconds after the stimulus onset. (Figure 1)

Echoplanar imaging (EPI) sequences are frequently used for these functional studies since they can rapidly collect multiple two-dimensional slice snapshots after the application of a single gradient radiofrequency pulse. With each slice being acquired in ~50-msec, EPI sequences can collect whole-brain volumes in a standard 2-second repetition time (TR). Multiple volumes are collected during the course of a study.

fMRI Experimental Designs

Based on the area of interest and the hypothesis, three main types of study designs are utilized in fMRI experiments: block, event-related, and slow event-related. Block design paradigms are the most frequently used due to the simplicity, ease of implementation and

sensitivity. This design consists of continuous presentation of a task for at least 20-seconds followed by an alternate condition which is frequently a similar duration rest period. The data collected from a block design experiment allow each task condition to be averaged to improve the signal to noise (SNR) and then a simple ‘contrast’ can be performed to compare the two conditions. The contrast can be as simple as a subtraction of the BOLD responses of one condition from another or, more commonly, parametric statistics are performed at each voxel. (Figure 2)

The prolonged duration required for each condition in a block design experiment, however, has many inherent design limits. For example, the long duration required for each condition limits the ability to study multiple conditions within the time constraints of a standard scanning session. The ability to extract temporal information about the brain responses is also limited due to the prolonged BOLD response. These restrictions among others have led to the use of slow and fast event-related designs. In the case of slow event-related paradigms, the standard experimental blocks are shortened while maintaining the alternating patterns of stimulation. Fast event-related experiments, on the other hand, consist of rapid stimulus periods (as short as 34-msec) occurring repeatedly at varying intervals. All of these experimental designs assume a linearity with the BOLD signal [6], with fast event-related designs being most dependent on this principle. Despite the apparent advantages associated with the faster designs, each sacrifices some SNR (35% drop in SNR for slow-ER vs. Block [7]; 17–25% drop in SNR for fast-ER vs. slow-ER [8]) though this is arguably outweighed by the increased number of trials possible.

fMRI Data Analysis

A detailed summary of the various steps required to process fMRI data is beyond the scope of this review. For those interested in learning more about the various steps in preprocessing and data analysis at the single subject and group level, we would recommend: Saad ZS, et al. Functional Imaging Analysis Contest (FIAC) Analysis According to AFNI and SUMA. *Hum Brain Mapp* 27:417–424, 2006.

Clinical Indications of fMRI to Diagnose Neurological Movement Disorders

The rapid development of fMRI for both clinical and non-clinical applications provides a unique opportunity to use this exciting modality to answer questions of pathophysiology, diagnostic uncertainty, identify mechanisms of therapeutic action as well as monitor effectiveness of therapy, among many other possibilities. Despite the wide array of opportunities for the use of fMRI as a clinical test, no indications are currently available for its use in neurological movement disorders. The following sections will, however, provide an overview of the large volume of work that has taken place in this area, and provide potential directions for future clinical applications.

SUMMARY OF fMRI FINDINGS IN SELECT MOVEMENT DISORDERS

Parkinson disease

Clinical overview of Parkinson disease—Parkinson disease (PD) was first described in 1817 by James Parkinson in “An Essay on the Shaking Palsy.” PD is the second most

common neurodegenerative disorder, after Alzheimer's disease, with a prevalence of 0.6%. The clinical hallmarks of PD include:

- Resting tremor
- Muscle rigidity
- Bradykinesia
- Postural instability

At least two of these aforementioned features are required to make a formal diagnosis, though the symptoms of PD include a diverse range of other motor and non-motor impairments. Many of these impairments are attributed to a loss of dopaminergic cells in the substantia nigra which project from the midbrain to areas such as the putamen and caudate in the striatum. Since the predominant abnormality in PD involves a loss of dopamine production, therapy is targeted at restoring dopamine levels. Dopamine levels can be increased using a wide variety of approaches, including the use of dopamine precursors (levodopa) that are converted to dopamine by the brain, the use of dopamine agonists, or by slowing the breakdown or re-uptake of dopamine at nerve terminals.

The constellation of clinical features combined with evidence of a functional improvement on dopaminergic therapy helps to confirm the diagnosis of primary or idiopathic PD. Idiopathic PD is the most common parkinsonism, accounting for 42 % of cases.[9] There are many varieties of parkinsonisms, however, that present with distinctive combinations of clinical findings and a lack of response to dopaminergic therapy. These dopamine non-responsive disorders are referred to as Parkinson-Plus syndromes and include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). As a group, Parkinson-Plus disorders progress more rapidly than primary or secondary parkinsonisms and have more widespread and severe neurodegeneration. A review of each of these disorders and their similarities or differences is beyond the scope of this review, though we would emphasize that the current best in vivo method for differentiating between primary, secondary and Parkinson-Plus disorders is a clinical examination by an experienced movement disorder neurologist. Furthermore, the distinctive characteristics of these various disorders frequently become evident only after a diagnosis of parkinsonism is made and treatments are found to be ineffective. Such limitations in early diagnosis constrain the ability of the clinician to develop a stratified plan of management based on the particular disease subtype. fMRI studies of Parkinson disease

Early fMRI studies of PD hoped to identify differences between patients and controls in the motor network which could be used as signatures of the disorder. Early work by Tada [10] noted decreased activation in the supplementary motor area during movement in PD versus controls. This finding was confirmed by Sabatini and colleagues [11] who also demonstrated otherwise a common pattern of motor network activation (premotor, motor, parietal cortex, striatum and cerebellum) in both groups, though cortical motor areas showed higher levels of activation in patients than controls. Similar findings were reported using PET [12, 13] and single photon emission computed tomography (SPECT) [14] while others [15, 16] found reduced activation in motor-related cortical areas. These seemingly discrepant findings are

disconcerting in their relative ubiquity in the neuroimaging literature. It should be noted however that these findings emphasize the context-specific performance of the neural networks being studied. In the majority of these neuroimaging studies, efforts were made to ensure that state-related confounds (e.g., differing performance, effort, anxiety) were minimized between the groups being compared. Despite such efforts, it is inevitable that such confounds exist even in patients with mild disease when compared to healthy controls.

The cognitive manifestations of PD have also been studied with fMRI. The findings of these early studies have identified dysfunction in numerous cognitive domains including working memory [17], set-shifting or the ability to alter behavior to dynamically changing circumstances [18], reward processing [19], and semantic sequencing [20]. Such cognitive impairments also have the potential to impact motor performance. This was evident when subjects with PD performed both simple and complex dual tasks during fMRI.[21] The findings suggested that poorer performance of dual tasks related to impairments in attention, performance monitoring, and a limited capacity of such resources. Despite the behavioral basis of these impairments, administration of a dopaminergic agent led to both an enhancement of prefrontal cortex performance, relative to a baseline hypodopaminergic state, and fMRI activation patterns normalized.[22]

The development of a non-invasive measure to distinguish the various parkinsonian subtypes might also serve as a tool to monitor disease progression and the impact of therapy. Work by a number of groups using fMRI as a potential biomarker to differentiate disease subtypes and to monitor progression is ongoing. At this time, no clinical indications are approved for the use of fMRI in a patient suspected of having parkinsonism.

Dystonia

Dystonia is a neurologic movement disorder characterized by sustained muscle contractions that lead to disabling repetitive movements or abnormal postures. Dystonia can begin at any age from childhood through late adulthood. Early onset cases (before the age of 25), referred to as primary dystonia, typically present with a generalized pattern of muscle involvement and can lead to disabling muscular and orthopedic deformities. Patients with a later onset of dystonia typically present with more focal or segmental regions of involvement, with the most common presentation being cervical dystonia. The prevalence of primary generalized dystonia is estimated to be 3.4 per 100,000, while the frequency of focal dystonias is 29.5 per 100,000.[23]

The etiologic mechanisms of dystonia are not known. This is compounded by the fact that no test is currently available for diagnostic confirmation, with exception of a small number of inherited subtypes (e.g. DYT-1 mutation) confirmed by genetic testing. One possible cause of dystonic symptoms involves neurotransmitter changes which lead to an imbalance of dopamine transmission within the basal ganglia.[24, 25] Direct evidence for this comes from dopa-responsive dystonia. Indirect evidence for this hypothesis comes from the development of dystonic symptoms in patients treated with the dopamine precursor levodopa (used to treat Parkinson disease) or following the use of dopamine antagonists frequently used to treat psychosis. Additionally observations of patients with dystonia note difficulty initiating and performing voluntary movements using only the appropriate muscles

required to carry out the action. In such cases, antagonist muscles are simultaneously activated leading to the occurrence of muscular 'co-contraction' and the appearance of dystonic sustained muscular contractions. This observation has led to the hypothesis that normal brain mechanisms leading to the inhibition of surrounding antagonist muscles are impaired in dystonia.

Routine structural imaging of the brain in patients suspected of having dystonia show no consistent abnormalities. Studies using diffusion tensor imaging (DTI) to characterize the architectural integrity of white matter tracts have identified changes in subgyral sensorimotor cortex [26] and the lentiform nucleus [27], with the latter area appearing to normalize four weeks after treatment with botulinum toxin.[28] Voxel-based morphometry (VBM) methods have similarly been useful in identifying subtle changes in the gray matter volumes of subjects with dystonia.[29, 30]

Functional imaging methods such as PET and fMRI have provided additional insights into the neural mechanisms underlying dystonia. Abnormalities in premotor, supplementary motor, and primary motor cortices have been identified during movement in both generalized and focal dystonias. These results are confusing since there was decreased activity of patients relative to controls in one study [31], and increased activity in others.[32, 33] Future studies would likely benefit from the inclusion of behavioral measures such as electromyography during fMRI to allow for better differentiation of task from rest, while matching performance with healthy controls.[34]

Essential tremor

Essential tremor (ET) is a very common movement disorder, seen as early as childhood with increasing incidence with age and affecting up to 14% of people over age 65. ET is most frequently exemplified by rhythmic shaking of the arms, but may also involve the head, tongue, legs, voice and face. ET is recognized as a heritable disorder with apparent Mendelian autosomal dominant transmission, though no disease-causing genes are yet certain. Treatments are based primarily on pharmacological agents, although surgical intervention may be an option in the most disabling cases.

The pathophysiology of ET has only partially been defined. A number of direct and indirect neurophysiological studies have implicated a neuronal network involving the thalamus, the sensorimotor cortex, the inferior olivary nuclei, and cerebellum in the production of ET. This is also supported by an animal model using harmaline, that induces a reversible essential tremor-like state with abnormal tremor-specific oscillations observed in the olivocerebellar pathway.

Studies of ET using fMRI have helped to confirm the neural network involved. Such studies have typically contrasted the brain activations observed during postural or action tremors in ET patients with the brain responses of patients during rest when the tremor resolves, or with healthy controls mimicking tremor. Findings from a number of studies [35, 36] have consistently shown involvement of a widespread motor network associated with tremor, including primary motor cortex, primary sensory cortex, thalamus, globus pallidus, red nucleus, cerebellar hemispheres, and dentate nucleus of the cerebellum. Mimicked tremor by

healthy controls led to a similar network becoming active, though at slightly lower levels than in patients. These findings suggest that tremor is generated through the same neural network that generates voluntary movement. Studies to date, however, have been unable to elucidate the location of the tremor oscillations. Determining whether there are changes in functional connectivity may also help to explain the occurrence of the tremor during posture or action, but not at rest.

Studies in essential tremor give some indication about the difficulties in this sort of work. Studies at rest in the patients seem theoretically fair to compare in the treated and untreated condition, and even to compare with normals, but, of course, tremor is not present in this situation. Studies with voluntary movement and tremor are difficult to compare with normal voluntary movement, even if tremor is mimicked.

Huntington disease

Huntington disease (HD) is a hereditary progressive neurodegenerative disorder with neurological and psychiatric features. The classic signs of HD include the development of chorea (diffuse, involuntary, rapid, irregular, jerky movements), a gradual loss of thought processing and acquired intellectual abilities (dementia). Although symptoms typically become evident during the fourth or fifth decades of life, the age at onset is variable and ranges from early childhood to late adulthood (e.g., 70s or 80s). HD is transmitted has an autosomal dominant inheritance pattern, with disease severity and age of onset correlating with the number of trinucleotide DNA repeats on chromosome 4. The neurodegeneration associated with HD primarily affect the basal ganglia (especially the caudate nucleus) and the cerebral cortex.

The use of fMRI to study HD has primarily focused on two goals: characterizing the neural dysfunction and developing a biomarker for presymptomatic diagnosis. To assess the impact of HD on various neural domains, performance of functional tasks was assessed during fMRI and compared with healthy controls. HD patients were found to have widespread cortical and subcortical increased BOLD responses on maze performance [37] and the Simon effect task [38], especially in motor and visual processing areas. A lack of motor response inhibition also correlates with patterns of impaired activation in the caudate and thalamus. [39] The constellation of fMRI changes in activation and connectivity [40] suggests the neurodegeneration or decreased activation observed in basal ganglia lead to compensatory recruitment (hyperactivation) of accessory motor pathways.[41]

The development of a biomarker to predict the onset of HD in the presymptomatic stage is critical to improvements in disease management. Efforts to develop such a test based on the fMRI patterns previously described have led to a variety of potential measures, though further work is needed to validate these findings before clinical implementation can proceed. It is important to note that the task-related patterns of basal ganglia hypoactivation noted in symptomatic disease are preceded by a period of increased activation in the caudate, thalamus and fronto-temporal cortices [42] which likely signifies local compensation taking place in the setting of early neurodegeneration. Activation of the left dorsal anterior insula during the processing of disgusted facial expressions was also absent in HD.[43] These and numerous other changes on fMRI have been able to identify presymptomatic HD as early as

12 years before the estimated disease onset.[44] Despite these promising results, it should be noted that all studies to date have reported these differences at the group level. Due to the high degree of variability inherent in presymptomatic HD, assessing risk of future disease at the single subject level is not currently possible.

FUTURE DIRECTIONS for fMRI

The utility of fMRI in the field of neurological movement disorders is only at its infancy. The early findings we have summarized thus far have adopted traditional case-control visual comparisons of statistical parametric maps. Furthermore, the vast majority of studies utilized block-design paradigms with alternating periods of rest and tasks with limited ecological validity. Attempts in most studies were made to minimize confounds between patients and controls, though in our view these efforts have only skimmed the surface and may explain many of the differences identified between patients and controls. For example, when we look at the neural correlates of essential tremor, we find no qualitative differences in brain activation identified by fMRI between patients with tremor and subjects simulating tremor. What is most commonly identified is a quantitative difference in activation with unknown clinical or physiologic significance. Such small quantitative differences may even be a consequence of subtle asymmetries in performance between patients and controls. Having identified the potential weaknesses of fMRI-based methods in neurological movement disorders, we would now like to highlight the unique contributions this modality can provide.

The growth of fMRI in clinical research over the past decade has been greatly benefitted by advances in the speed and quality of higher field-strength MRI hardware, as well the wealth of methods developed to more fully characterize the BOLD response. Studies comparing activation maps between patients and controls are now complemented by measures of functional connectivity to characterize the actions of the neural network at large. These developments are being enhanced further with the ability to simultaneously collect both high spatial resolution fMRI-based BOLD-responses and high temporal resolution electroencephalography. More recently, transcranial magnetic stimulation (TMS) performed during fMRI has allowed investigators to understand the impact of a virtual lesion both locally and on the neural network. The use of a combination of MR modalities, such as magnetic resonance spectroscopy (MRS) or diffusion tensor imaging (DTI), helps to provide a comprehensive understanding of the pathologic changes not seen by standard structural MRI sequences.

Newer methods of BOLD-fMRI analysis will also make a significant impact on our understanding of the brain. Older univariate methods of analysis have limited sensitivity since they depend on restricted models of the BOLD response. These sensitivity limits drive the need for longer studies to collect adequate amounts of data, while also increasing the risk of inducing patient fatigue. With more sophisticated statistical methods and the low cost of high-throughput computing, multivariate analyses of fMRI data can now be performed within relatively short periods of time. Model-based analyses are being replaced by ‘artificial intelligence’ or ‘machine learning’ methods which are model independent. These more sophisticated techniques are also providing the statistical power necessary to make

inferences on brain activations collected over just a few seconds of time. Rapid acquisition and interpretation now allows the MRI scanner to provide the participant with near-realtime biofeedback of their brain responses.

The rapid development of functional MRI for clinical and non-clinical applications is underscored by its availability, sensitivity, and non-invasiveness. The use of fMRI to probe brain function in neurological movement disorders is only in its infancy.

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Figure 1.

Predicted BOLD hemodynamic response function (HRF) following a brief stimulus. The HRF demonstrates the three characteristic regions: the initial dip, the rising phase, and the post-stimulus undershoot. The significance of the initial dip has been shown to represent the early increased oxygen consumption and increase in deoxy-hemoglobin, prior to the blood flow response. The rising phase reflects the lagging contribution of the blood flow response and leading to an overcompensation (peak) whereby deoxy-hemoglobin concentrations are even below baseline levels. This drop in deoxy-hemoglobin leads to the increase in signal intensity. The mechanisms behind the post-stimulus undershoot are not well understood and vary by task

Predicted BOLD Response by Study Design

Figure 2.

Overview of fMRI-based paradigm designs. A standard block design demonstrates the expected prolonged BOLD response with a continuous stimulus or task performance, alternating with periods of rest leading to a change from the task-specific BOLD response. Slow event-related designs allow more frequent stimulus presentations while still allowing a complete separation of BOLD response between potentially different stimuli. Fast event-related responses are presented in a random or pseudo-random manner that generates a BOLD response which cannot be easily resolved without analytical tools such as deconvolution to separate the contributions of each respective task over time.