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Potential Clinical Applications for Spinal Functional MRI

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Abstract

Functional MRI (fMRI) of the spinal cord is a noninvasive technique for obtaining information regarding spinal cord neuronal function. This article provides a brief overview of recent developments in spinal cord fMRI and outlines potential applications, as well as the limitations that must be overcome, for using spinal fMRI in the clinic. This technique is currently used for research purposes, but significant potential exists for spinal fMRI to become an important clinical tool.

Introduction

Functional MRI (fMRI) of neuronal function in the brain is a recent addition to the world of diagnostic imaging. This application has quickly become a commonly used tool in medical and research fields for imaging brain activity since first shown successful by Ogawa et al. [1]. fMRI of the spinal cord (spinal fMRI) is a noninvasive tool that can be used to investigate neuronal activity and reveal important information regarding spinal cord function. The application of fMRI to the spinal cord requires specific modification to the conventional brain fMRI methodology, but the theory of conventional brain fMRI applies. Further work is required before the method is optimal for clinical purposes. This article briefly reviews the recent developments in spinal cord fMRI and discusses the feasibility and potential applications of using spinal fMRI in the clinic.

Discussion

Spinal fMRI reveals neuronal function indirectly by changes in blood flow and blood oxygen levels occurring near metabolically active gray matter. Dependent on scanning parameters, the signal change arises in part from the blood oxygen level–dependent contrast, based on the metabolic activity that occurs in active neuronal tissues [1], and in part from the signal enhancement from extravascular water protons (SEEP) contrast, resulting from an increase in water content in the active neural tissues [2,3•]. This mechanism is hypothesized to be related to neuronal swelling and/or glial cells shown to arise at sites of neuronal activity. Also, increased blood flow to active tissues has been shown to be accompanied by increased intravascular pressure and increased production of extra-cellular fluid at sites of neuronal activity. The net effect is a local increase in water content near active neural tissues, causing a higher magnetic resonance signal intensity. Thus, spinal fMRI detects neuronal activity in spinal cord gray matter, which allows for mapping of spinal cord responses to sensory and motor stimulation.

The application of fMRI to the spinal cord is a logical extension of its use in the brain but has been slow to develop because of the many challenges with the method. These challenges, as well as the steps taken to address them, are discussed in the following text.

Despite the challenges, several groups are investigating spinal fMRI. Works published have shown promising results, with positive emphasis that difficulties with obtaining fMRI of the spinal cord can be overcome [4–8]. Using fMRI to investigate spinal cord activity is ideal because the spinal cord, contained within the vertebral column, is otherwise assessable only by physical examination techniques or by invasive measures.

Development of the spinal fMRI method has been growing steadily since first described as feasible by Yoshizawa et al. in 1996 [9]. In the past decade, more work has been published concerning spinal fMRI, in both human subjects [4–6,9–13,14••,15–24] and animal studies [25–30]. The relatively small number of publications in this area likely reflects the difficulty in acquiring functional images of the spinal cord. However, the available literature has shown spinal fMRI to be a reliable tool for assessing spinal cord neuronal function, and it is currently used for research purposes. Studies thus far have suggested that clinical use of spinal fMRI is conceivable.

Spinal fMRI research has focused on imaging of the cervical and lumbar spinal cord during sensory and motor stimulation of the hands [4,5,11], sensory stimulation of the lower leg [12], and during a motor task of the lower leg [17]. Evidence that signal changes observed are related to neuronal activity is provided by the correspondence between the patterns of activity and established neuroanatomy. In an early study involving a motor task and sensory stimulation of the hand, spinal fMRI proved reliable in displaying laterality and spread of activity in the spinal cord [4]. Subsequent spinal fMRI studies have shown that stimulation of specific dermatomes maps to the corresponding spinal cord segments [11], and different types of sensory stimulation have mapped to the analogous gray matter regions [12]. Mackey et al. [6] demonstrated the ability to image dorsal horn activation to thermal nociceptive stimuli, with a resolution adequate to differentiate superficial and deep dorsal horn structures. Appropriate somatotopic representation of activation in the cervical spinal cord to thermal and cold stimuli was achieved. Signal intensity changes in the lumbar cord have been observed to depend on the temperature of cold stimulation and have shown marked differences between innocuous and noxious cold stimulation [12]. The signal intensity changes recorded at a temperature of 29° C averaged 2.6%, increased slightly to 3.2% at 15° C, but increased dramatically to 7% at 10° C, a temperature reported to be uncomfortable to painful by volunteers. Another study similarly showed that the magnitude of signal intensity changes in the spinal cord is dependent on the strength of the stimulus [15]. Results indicated that spinal fMRI was capable of detecting reliable neuronal response to an isometric motor task of the hand, and the magnitude of signal change is proportional to the force applied by the muscle.

In the clinical arena, spinal fMRI has been applied to the study of injured spinal cords. The lumbar spinal cord was imaged during noxious thermal stimulation of the L4 dermatome of complete and incomplete spinal cord-injured volunteers [12,13]. Signal intensity changes for the injured groups were of similar magnitude and had a similar time course pattern as those of the healthy group. However, the areas of activity in gray matter were altered. Spinal fMRI was also used to detect neuronal activity elicited by passive and active lower limb movement tasks in regions caudal to the injury site in volunteers with spinal cord injury [31]. Activity was detected in all volunteers regardless of the extent of injury. During both active and passive participation, activity was seen caudal to the injury site, although the number of active voxels detected with passive movement was less than with the active movement task. Therefore, spinal fMRI is able to detect a neuronal response in the spinal cord caudal to the injury site during both active and passive lower limb movement tasks, and in response to a noxious stimulus, even when subjects could not feel the stimulus. Thus, spinal fMRI is useful for revealing areas of impaired and preserved activity in spinal cord-injured patients.

Potential Clinical Applications

Currently, the American Spinal Injury Association (ASIA) [32] assessment scale is the standard for classifying spinal cord injuries. This involves a battery of light touch and pin prick examinations to assess where a patient has preserved sensory perception. To determine preserved motor function, the patient's ability to move specific key muscle groups is assessed. This physical examination technique reveals information regarding spinal cord function but does not reveal information about the condition of the spinal cord caudal to an injury site. Further information regarding the condition of the spinal cord caudal to the level of injury must be obtained by invasive measures or deduced from reflex actions.

Electrophysiological techniques such as somatosensory-evoked potential, H-reflex, or stretch reflexes are capable of assessing residual function after a spinal cord injury. The utility of these techniques is limited by the incomplete scope of information obtained with each measure, such that a combination of measures is required to determine residual function. For example, somatosensory-evoked potentials examine conduction along large areas of the body, and the results can be affected by peripheral damage, nerve root damage, or spinal cord damage without revealing where along the pathway the damage has occurred. Similarly, an increase in reflexes denotes an upper motor neuron disorder but will not reveal the degree of damage, or whether the damage is complete or incomplete. Although these methods are useful for many research applications, they require specific equipment and are time-consuming. Therefore, these methods are not in routine clinical use. Thus, the ability of spinal fMRI to detect neuronal activity below the injury site in spinal cord-injured patients is of considerable value for those assessing an injury, planning a treatment strategy, or monitoring recovery of function during and after treatment.

Although spinal fMRI is not yet ready for routine clinical use in examining spinal cord injuries, it is certainly fit for use in assessing recovery of function strategies. As discussed, the ability of other measures such as somatosensory-evoked potentials or H-reflex that are able to assess residual function caudal to injury is limited because they reveal the effect but not the location of damage along a conduction pathway. In addition, these methods are invasive. The ASIA assessment scale, although routinely used to assess and classify injuries and residual function, lacks sensitivity for neuronal change. Spinal fMRI will become more useful as intervention strategies develop, because it can detect differences in neuronal activity pre- and post-treatment. Spinal fMRI could become an important tool for assessing the efficacy of interventions. Currently, the ASIA assessment scale is used to follow progress in research interventions, and this, as mentioned, is unable to detect neuronal changes. Similarly, spinal fMRI could serve in assessing pharmacologic treatment effects on spinal cord and nerve root function. Likewise, spasticity drug trials also could greatly benefit, again because presently there are few noninvasive measures available to objectively see changes in neuronal activity. This noninvasive technique is able to show where functional activity occurs in response to a stimulus, regardless of a patient's ability to feel the stimulus—a feature that the ASIA assessment scale lacks. Therefore, in the case of spinal cord injury, the neuronal activity in the spinal cord both above and below the injury site can be monitored after initial injury for prognosis and recovery-of-function strategy decisions, as well as throughout rehabilitation and in response to pharmacologic treatment. A protocol can be developed such that a standard battery of tests may be conducted to assess ascending, descending, and reflex activity.

fMRI has been used to investigate nociceptive processing and central sensitization in the brain to better understand pain. However, the spinal cord and brain stem are also critical centers for nociceptive processing before sending signals to the brain and are sites for significant functional abnormalities in chronic pain states. Chronic neuropathic pain is known to lead to central nervous system changes. Spinal fMRI can be used to study the

structural and functional correlates of pain and advance our understanding of mechanisms of nociceptive processing, central sensitization, and chronic neuropathic pain. In addition, the neural mechanisms underlying attentional modulation of pain are not known, but data suggest the involvement of multiple levels of the central nervous system, including the dorsal horn of the spinal cord. Dorsal horn involvement has yet to be shown in functional neuroimaging studies. Future research using functional neuroimaging in this area is warranted and is likely to have a significant impact on therapeutic interventions. Combined imaging of the spinal cord, brain stem, and brain will provide information regarding the neuronal activity of the entire central neural axis, advancing scientific knowledge on how clinical chronic pain states are generated and maintained. The ability to image the spinal cord to the brain, as well as descending modulatory pathways back to the spinal cord, will enable investigation of plasticity changes associated with chronic pain conditions and provide opportunity to evaluate changes in both the disease state and the response to peripherally and centrally acting treatments. With spinal fMRI, objective means of assessing neural function in patients with chronic pain will thus be available. Spinal fMRI could be useful in identifying the pathogenesis of many chronic pain conditions, whereas presently this is not understood. Spinal fMRI could expose the neuronal abnormalities underlying several pain conditions such as irritable bowel syndrome, chronic lower back pain, or fibromyalgia. It is possible that central sensitization is involved in many chronic pain conditions, and great potential exists for spinal fMRI to reveal the underlying initiation or maintenance of this state.

Although still under debate, cervicogenic headache, as well as many head and neck pain conditions, is thought to involve, in part, a dysfunction in processing information at the convergence of the upper cervical roots on the trigeminal nucleus caudalis. Its cause, symptoms, and best course of treatment are unknown, and spinal fMRI with combined brainstem fMRI could elucidate the underlying cause of this disorder and provide insight into the best treatment for this painful condition. Spinal fMRI also could be of use in the investigation of migraine. Recent work has revealed that migraine sufferers are at increased risk for subclinical lesions [33], that functional cortical changes occur in patients with migraine, and that these changes might be secondary to the extent of subcortical structural damage [34]. It would be beneficial to understand whether migraine correlates to central nervous system lesions and long-term functional deficits. This could be accomplished by determining the frequency of occurrence of lesions in migraine sufferers and assessing whether these lesions have long-term functional consequences, a task for which spinal fMRI would be well-suited. An enhanced understanding of the pathology of migraine may assist in the development of relief strategies.

Although anatomical spinal MRI is used to detect a number of specifically spinal cord-related conditions such as a Chiari malformation, a defect causing Brown-Sequard syndrome, or hydromyelia, a functional image of these conditions would be useful for monitoring the effects of lesion or structural abnormality on physiologic response and subsequent alterations in neuronal function. It might help differentiate a neurodegenerative disorder such as tabes dorsalis, which involves a breakdown of sensory fibers but has symptoms that include weakness, loss of proprioception, and decreased coordination and reflexes, in addition to the sensory disturbances and pain. The ability of spinal fMRI to capture the activity of dorsal column neurons will aid in the diagnosis, prognosis, and monitoring of disease states such as this. As with many conditions, symptoms may not occur immediately after the initial insult but may appear gradually over time, resulting in a situation in which it may not be immediately clear where to begin investigation. When it is difficult to identify the cause of symptoms, spinal fMRI could indicate areas of abnormal neuronal function or identify the point at which the breakdown is occurring. For example, spinal fMRI could determine whether it is an upper motor neuron disorder, a lower motor

neuron disorder, or both, as in amyotrophic lateral sclerosis. Whether neurons are firing normally but the breakdown is at the neuromuscular junction or with the muscle fibers themselves, as in muscular dystrophies, could similarly be determined. MRI is used to locate lesion sites in multiple sclerosis, but use of spinal fMRI would aid in tracking disease progression and prognosis. Functional characterization of disease could be carried out with spinal fMRI. In cases of transverse myelitis, inflammation of a spinal cord segment occurs, which can cause myelin damage, thereby impairing nerve conduction and interfering with neuronal communication. The benefit of functional imaging for these types of conditions is clear.

Presurgical mapping localizes function in cortical tissue near areas intended for surgery or resection. Functional and anatomically distinct regions of cortex vary between different people. The use of fMRI can identify areas associated with specific functions, so that these areas may be targeted or avoided during resection. This method is a less invasive alternative to electrophysiological cortical mapping commonly used for obtaining this type of information. Functional imaging of the spinal cord could be useful for diagnosis and prognosis of nerve decompression surgery. For example, in patients with cervical or lumbar radiculopathy, it is often unclear which nerve root is irritated or injured. Noxious stimulation of the affected region with simultaneous spinal fMRI would help localize the specific region affected. In another example, for diabetic neuropathy, the relief of pressure on a trunk is achieved by the excision of the constricting band or the widening of the bony canal to alleviate pain symptoms. With diabetic neuropathy, it is not always clear based on patient reports which spinal nerves are implicated, as often a number of nerves are involved in creating the symptomatology. Similarly, the draining of problematic Tarlov cysts, which can produce altered sensation and impaired motor abilities, could be aided in this way. It would be important to identify and treat any cysts that compress nerve roots, as untreated cysts may cause permanent neurologic damage. The surgical intervention for syringomyelia, with the sensory, motor, and autonomic disturbances that can result, could likewise be assisted in this fashion. In some cases of intractable pain conditions, the severing of spinal nerve roots is possible to provide relief, and again this is a situation in which identifying an individual's distribution of neuronal activity would be of great value. With spinal fMRI, it could be possible to better identify the specific nerves involved in particular symptoms, as well as desired retained behaviors, therefore improving surgery planning and decreasing surgical risk.

The ability of spinal fMRI to detect changes in neuronal function in the absence of overtly physical manifestations could be valuable for patients undergoing recovery of function, rehabilitation, or pharmacologic treatment. Aside from physiologic information obtained by the clinician, patients could benefit psychologically. In the initial stages of a treatment strategy, it may be discouraging to patients when signs of improvement are not yet detectable. In the absence of measurable physical improvements, the "proof" of improvement in neuronal activity (increases or decreases in conduction, condition-specific) could provide the encouragement and motivation to continue with rehabilitation strategies. Alternately, spinal fMRI could reveal a strategy to be ineffective and accelerate the search for alternate strategies.

What Will It Take to Get There?

The technical limitations of spinal fMRI must be addressed and improved for it to be useful clinically. The need for greater signal-to-noise ratio in spinal cord functional imaging is an issue. Future spinal fMRI studies will likely benefit from noise reduction of cardiac origin. Modeling the time course of non-neuronal-related activity should reduce or eliminate noise caused by cardiac-driven motion. Increased use of the 3 Tesla magnet will help increase

signal and sensitivity to magnetic susceptibility, because the different tissue types are in close proximity within the spinal canal. More work is needed to resolve this issue. Identification and elimination of errors (falsely activated pixels) is required. Addressing these issues will improve the reliability and sensitivity of spinal fMRI, resulting in an imaging method sufficient for use on an individual basis. Whereas most studies use grouped analysis for statistical strength, this is clearly unacceptable for clinical purposes. The scanning parameters ideal for contrast in spinal fMRI result in slow imaging acquisition, whereas a faster imaging technique is desirable. Also, at present, fMRI is expensive and requires highly trained personnel for data acquisition and analysis.

Progress has been made in the advancement of spinal fMRI toward clinical use. Obtaining functional images in sagittal orientation allows for activity maps to be displayed in axial, coronal, and sagittal orientation, with improved spatial resolution in the superior/inferior direction [14••]. In addition to demonstrating details of subsegmental organization in the spinal cord, neuroanatomic details such as spinous processes and position of nerve roots, as well as cervical and lumbar enlargements, were identifiable. In addition, results can be normalized and consistent right/left and anterior/posterior dimensions constructed, which facilitates comparison within and across spinal cords. With further development of this method, optimal normalization dimensions can be produced and a spinal cord atlas could be assembled, which may facilitate a standard method of documenting the results. Ideally, a software program would be available for technicians and clinicians to use for simple and quick data analysis. Packaging a standardized spinal fMRI assessment protocol with an efficient and comprehensible analysis program could expedite spinal fMRI into clinical use. Although advances have been made in this area, further work is required before the method is optimal for clinical purposes.

In addition to the technical advances required before spinal fMRI is ready for clinical use, other issues need to be considered. Careful study design is required for spinal fMRI to be effective. The task paradigm should ideally isolate the specific behavior under investigation to the exclusion of other behaviors. This can be especially difficult in the situation of impaired functioning or loss of function. As pointed out by Detre [35], it is difficult to acquire a functional image of an impairment, both because of the difficulty in designing a well-characterized paradigm for examining the particular aspect of the deficit, and because of the difficulty in imaging neural correlates of a behavior the patient cannot properly perform. This is not specific to spinal fMRI but holds true nonetheless.

It is probable that the utility of spinal fMRI will provide supplementary information to that obtained with other tools, rather than replace them. Although spinal fMRI may prove the optimal tool in particular cases, it is more likely that the pairing of spinal fMRI with other tools will be used to provide a more complete picture. For example, combining information from electrophysiology with spinal fMRI could resolve issues with greater temporal and spatial resolution, thus overcoming the limitations of each technique while building on the strengths of both. Diffusion tensor imaging provides structural information regarding orientation of white matter tracts in a noninvasive manner. Anatomic and functional connectivity may be mapped to provide important information regarding neural circuitry, essential information for surgical purposes. Spinal neuronal activity is altered in the absence of descending modulation from supraspinal centers, and thus the effects of resection or stimulation may be detectable at the spinal cord level. Magnetic resonance spectroscopy allows for the investigation of tissue metabolism and biochemistry; combined with fMRI, it can impart insight into spinal cord normal and disease states.

Conclusions

Ultimately, the goal is for spinal fMRI to be a useful and practical clinical tool. The potential for brain fMRI in clinical use is now being appreciated [36,37]. Spinal fMRI was first shown to be feasible one decade ago, and its advance into clinical use, with the resolution of the issues outlined earlier, is promising and imminent.

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