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Review

The current state-of-the-art of spinal cord imaging: Applications

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ABSTRACT

A first-ever spinal cord imaging meeting was sponsored by the International Spinal Research Trust and the Wings for Life Foundation with the aim of identifying the current state-of-the-art of spinal cord imaging, the current greatest challenges, and greatest needs for future development. This meeting was attended by a small group of invited experts spanning all aspects of spinal cord imaging from basic research to clinical practice. The greatest current challenges for spinal cord imaging were identified as arising from the imaging environment itself; difficult imaging environment created by the bone surrounding the spinal canal, physiological motion of the cord and adjacent tissues, and small crosssectional dimensions of the spinal cord, exacerbated by metallic implants often present in injured patients. Challenges were also identified as a result of a lack of "critical mass" of researchers taking on the development of spinal cord imaging, affecting both the rate of progress in the field, and the demand for equipment and software to manufacturers to produce the necessary tools. Here we define the current state-of-the-art of spinal cord imaging, discuss the underlying theory and challenges, and present the evidence for the current and potential power of these methods. In two review papers (part I and part II), we propose that the challenges can be overcome with advances in methods, improving availability and effectiveness of methods, and linking existing researchers to create the necessary scientific and clinical network to advance the rate of progress and impact of the research.

Contents

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Introduction

Our ability to research and understand human spinal cord function, its role in pain processing, the effects of traumatic injury or diseases such as multiple-sclerosis, and our understanding of pain processing, is all significantly hampered by the limited accessibility of the spinal cord. In the part I of our two part series we have described the current state-of-the-art of spinal cord imaging, the current greatest challenges, and the greatest needs for future development in order to support non-invasive human spinal cord research (Stroman et al., 2013). The general assumption is that providing increased sensitivity and specificity of spinal cord imaging in the context of well-defined clinical readouts will be instrumental to improve novel approaches in the diagnostic and treatment of spinal cord diseases. The objectives of this paper are to:

1) describe the current state-of-the-art and capabilities of human spinal cord imaging applications;
2) identify the greatest current needs, from a clinical point of view, that will drive forward future development.

In order to achieve these objectives we provide a general overview of two key techniques employed in clinical research, functional Magnetic Resonance Imaging (fMRI) and Diffusion Tensor Imaging (DTI), and then focus on specific applications of spinal cord imaging on four areas: investigations of cervical spondylotic myelopathy (CSM), spinal cord injury (SCI), pain and multiple-sclerosis (MS). Wherever applicable, reference to quantitative imaging methods other than fMRI and DTI, such as magnetic resonance spectroscopy (MRS) and magnetization transfer (MT) imaging, will also be mentioned. Issues related to spatial resolution, registration of subsequently acquired volumes, partial volume effects with the cerebrospinal fluid (CSF), as well as the lack of a standard common template and the effects of physiological noise are still limiting the adoption of many techniques into the clinical setting, confounding quantitative MRI of the spinal cord to research studies. The overall goal of this work is therefore to foster the development of novel and sensitive means of characterizing neural function and cellular structure in clinical populations that can supplement or surpass current methods for patient assessment, serve as clinical trial endpoints, and be used for monitoring of disease progression and efficacy of therapies.

General overview of fMRI and DTI

fMRI in the human spinal cord: Applications

A growing number of studies (summarized in Table 1) have been carried out to investigate spinal cord function in response to various sensory stimuli and motor tasks and to characterize the effects of traumatic injury and pathology.

Determining the sensitivity and reliability of spinal cord fMRI is a challenging task in that there is no “gold-standard” method that can be used to verify the results obtained in humans (Stroman et al., 2013). Even studies with animal models (Lawrence et al., 2004, 2007; Majcher et al., 2006, 2007; Malisza and Stroman, 2002; Malisza et al., 2003) can provide only limited validation because surgical interventions, anesthetics, and differences in emotional and cognitive factors can all significantly alter neural activity in the spinal cord (Hochman, 2007; Lawrence et al., 2004, 2007; van Eijsden et al., 2009). The reliability of spinal fMRI results must therefore be inferred from consistency across repeated studies, sensitivity to different stimuli or tasks, and correspondence with recorded responses and psychophysical ratings by the participants.

The studies listed in Table 1 have shown active regions in the spinal cord that are consistent across groups of participants, and that correspond with the region of the body being stimulated, or motor task being performed. A high degree of laterality has been demonstrated in comparisons of right-side and left-side motor activity or stimulation of the hand and shoulder (Maieron et al., 2007; Stroman et al., 2012). Although this is very encouraging, the relatively low resolution and consequent partial volume effects need to be considered when studying patients with severe spinal cord atrophy. Spinal fMRI studies in rats have provided further support by showing a correspondence between areas of activity detected with spinal fMRI and cells labeled with c-fos staining stimuli, when a noxious electrical stimulus was applied (Lawrence et al., 2004). This body of results provides strong evidence that signal changes related to neural activity in the spinal cord can indeed be detected with spinal fMRI methods. Several of the studies have further shown that spinal responses vary with the intensity, and modality of the stimulus. Most notably, applying thermal stimuli of between 32 °C and 10 °C to the leg revealed areas of activity in the lumbar spinal cord where signal intensity responses

Table 1
Examples of studies employing spinal cord fMRI:.

Healthy (uninjured) volunteers:	Motor tasks (hand, and leg) (Kornelsen and Stroman, 2004; Maieron et al., 2007; Stroman and Ryner, 2001; Stroman et al., 1999).
	Thermal stimulation (hand, leg) (Stroman, 2009; Stroman and Cahill, 2006; Stroman and Ryner, 2001; Stroman et al., 2001, 2004b, 2011).
	Thermal pain (Brooks et al., 2008, 2012; Cahill and Stroman, 2011; Eippert et al., 2009a, 2009b; Sprenger et al., 2012; Stroman et al., 2001, 2002a,b; Summers et al., 2010).
	Electrical stimulation (Xie et al., 2012).
	Vibration (Lawrence et al., 2008).
	Light touch (Agosta et al., 2009c; Ghazni et al., 2010; Summers et al., 2010).
	Sensitization with capsaicin (Ghazni et al., 2010).
	Event-related fMRI with brief thermal stimulation (Figley and Stroman, 2012).
Patients with carpal tunnel syndrome:	Pressure on affected median nerve (Leitch et al., 2009, 2010).
Patients with spinal cord injuries:	Thermal sensory stimulation (hands, legs) (Stroman et al., 2002c, 2003, 2004a).
	Leg motor tasks (active and passive) (Kornelsen and Stroman, 2007).
Patients with multiple sclerosis:	Thermal sensory stimulation (Agosta et al., 2008b; Valsasina et al., 2010).
	Proprioception (Agosta et al., 2008b; Valsasina et al., 2010).
	Hand motor tasks (Agosta et al., 2008b; Valsasina et al., 2010).

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