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Review

# Non-invasive imaging of nerve regeneration

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ABSTRACT

The need for non-invasive imaging of peripheral nerves that can reliably assess extent of nerve fiber degeneration and regeneration is increasingly realized. Availability of such a technology has several immediate clinical and preclinical applications. Diffusion tensor imaging (DTI) is an emerging magnetic resonance based technology that is particularly suited for imaging nerve fiber tracts. This review highlights immediate clinical and preclinical uses of non-invasive imaging of peripheral nerve regeneration and DTI as a potential technology that can fulfill these clinical and research needs.



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## Introduction

The morbidity and health costs associated with neuropathic conditions are enormous because diseases of the peripheral nerves are among the commonest neurological disorders. It is estimated that 2.5% of the general population and 8% of those above age 55 have some form of neuropathic disorder (England and Asbury, 2004; Martyn and Hughes, 1997). The advances in non-invasive imaging technology have significantly improved diagnosis and management of various neurological diseases with most visible impact in the areas of stroke and multiple sclerosis. Magnetic resonance imaging (MRI) of the peripheral nerve (MRI neurography) is already in clinical use and it is most helpful in defining the anatomy of the nerves and in establishing continuity or discontinuity of the injured nerves in patients with traumatic nerve injuries (Filler et al., 2004). In the context of available and evolving imaging technologies an emerging question is: whether there is a role for non-invasive imaging of nerve regeneration in clinical and preclinical settings, and if so, what are those needs and which imaging technologies can potentially fulfill these needs? In the clinical arena there is an immediate need for reliable measures to assess peripheral nerve regeneration in patients with traumatic nerve injuries. Another immediate and major clinical and preclinical need for non-invasive measurement of nerve regeneration is in the area of therapeutics aiming to enhance nerve regeneration/repair. For these applications, the technology with most promise and immediate availability, for clinical and preclinical use, is diffusion tensor imaging

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(DTI), an MR imaging technique, based on the movements of water molecules within biological tissues, particularly suitable for imaging nerve fiber tracts. This review outlines the clinical and preclinical needs to assess peripheral nerve regeneration and discusses DTI as a potential technology that can fulfill these needs.

## Immediate clinical and preclinical needs

### *Traumatic nerve injuries*

Civilian and combat trauma to limbs often results in serious injuries to the peripheral nerves that cause significant morbidity. Advances in trauma management including availability of dedicated centers have significantly reduced mortality, however, patients with severe and multiple injuries are left with significant disability and morbidity due to peripheral nerve injuries. It is estimated that up to 5% of all admissions to level I trauma centers have a peripheral nerve injury (Noble et al., 1998). In general, injuries to the upper extremity are more common than those to the lower extremity, accounting for two thirds of all peripheral nerve injuries (Noble et al., 1998). A significant proportion of nerve injuries leave the nerves in continuity and reliable predictors for recovery/regeneration in this group are not available (Midha and Kline, 1998). A conservative approach can save the patient a needless surgery but it requires following the patient for many months to 1–2 years for regeneration/recovery to occur. The major caveat of this approach is that "a window of opportunity" to repair the nerve can be missed or lost. Currently, non-invasive techniques that allow early assessment of regeneration in nerve lesions in continuity are not available in clinical practice (Stanisz et al., 2001).

Proximo-distal regeneration of severed axons is the most important mechanism of recovery for most severe nerve injuries. The crucial issues in the medical/surgical management of nerve injuries include: a) whether or not segments of nerve adjacent to injury are in physical continuity; b) extent of Wallerian-like degeneration in the nerve segment distal to the injury site; c) initiation of regeneration in injured axons proximal and across the injury site; and d) regeneration of injured axons in distal segment. Nerve discontinuity is often established during surgical exploration of patients with traumatic nerve injuries or MR neurography can identify this, thus confirming the need for surgical repair. However, majority of injuries do not disrupt the continuity of injured nerve (Sunderland Grades I–IV) (Noble et al., 1998). In Sunderland grades II–IV injuries, a fundamental dilemma is, whether or not the nerve needs repair and, if so, what is the appropriate time of repair and/or graft procedures? A substantial body of opinion indicates that after periods of 12–18 months (after nerve injury/transection) recovery of function following nerve repair is likely to be poor. The complete basis of this poor recovery after late repair is not well understood but most experts in the field would agree (also supported by experimental data) that decrease in neuronal capacity to regenerate, denervation-associated changes in the endoneurium (particularly Schwann cells) in the distal denervated segment of the injured nerve, and atrophic changes in denervated targets especially muscles all contribute to this poor recovery (Fu and Gordon, 1995a, 1995b; Hoke, 2006). Protocols/algorithms about whether or not to operate at specific intervals after nerve injury are not widely/strictly followed largely due to lack of reliable non-invasive measures to assess ongoing regeneration of injured nerve fibers into the distal segment of the injured nerves (pathway).

In clinical practice, nerve conductions and EMG studies are most commonly used for the assessment of nerve injuries. This clinical tool is useful for confirming bedside localization of the site of nerve injuries and is very effective in distinguishing between neurapraxia (Sunderland Grade I) and axonotmesis (Sunderland Grade II). However, electrodiagnostic testing is limited by its complete dependence on target innervation and virtual inability to provide information about regeneration in the pathway distal to the site of injury particularly when evoked sensory and motor responses are not elicited or in complete nerve injuries. Furthermore, electrodiagnostic testing is highly dependent on operative and interpretative skills of the electromyographer with wide variations between different centers. Sometime "Tinel's" sign is used as a surrogate marker to determine the leading edge of the regenerating nerves, but this subjective test is a very inaccurate bedside tool. Nerve biopsies although very sensitive and specific for detection of nerve repair, are not feasible particularly for injuries in continuity because this procedure permanently sacrifices a set of nerve fibers and this technique cannot be used serially.

### *Experimental therapeutics to enhance nerve regeneration/repair*

The principal goal for researchers in this area is to devise strategies to enhance short and long distance nerve regeneration in various peripheral nerve disorders. Based on the current understanding of peripheral neurobiology it is increasingly realized that different interventions targeting specific elements of nerve repair such as growth state of neurons, axonal elongation in the nerve, and axonal reconnectivity with targets might be necessary to enhance successful regeneration. A fundamental issue for the evaluation of stage specific interventions to enhance nerve regeneration is the ability to follow growth state of the neuron and associated axonal elongation/regeneration in the nerve (pathway) prior to its reconnectivity with targets. Lack of non-invasive measures that can assess the growth state of neuron by monitoring regeneration in the nerve/pathway is a major hindrance in achieving this primary goal. Lack of reliable outcome measures that can monitor axon regeneration in the nerve/pathway has been considered as a contributor to the failure of several previous clinical trials (including those with neurotrophic factors) aimed at enhancing nerve regeneration in neuropathic conditions (Boulton, 2007). Availability of a technique that is based on the integrity of nerve fibers in nerve trunks and potential for detection and quantification of the extent of axon degeneration along the nerve tracts can facilitate patient recruitment and randomization process in the trials by inclusion of patients with spatially similar degeneration along the nerves in different treatment arms. Besides monitoring the efficacy of novel drugs in polyneuropathies non-invasive imaging of nerve regeneration can be used for examining the regeneration through existing or newer nerve conduits used for nerve repairs, which are anticipated to incorporate nanotechnology, gene/protein delivery, and stem cells and will go through studies for clinical use (Chew et al., 2007; Schlosshauer et al., 2006; Schlosshauer et al., 2003).

Use of animal models of nerve regeneration is an essential/indispensable step prior to advancing to clinical studies. Initial strategies for enhancing nerve regeneration will almost certainly be developed and tested in rodent models of nerve regeneration. Mouse models are particularly attractive because of the availability of transgenic strains, which allow investigation of the roles of specific genes and molecules in nerve regeneration. Moreover, technologies developed in mouse models are usually easily transferable/adaptable for application to larger animals and humans. Although morphological studies can provide definitive and quantitative measurement of regeneration in experimental animals, however, these studies are very labor intensive, cannot be used serially, and unsuitable for high throughput screening studies in animals.

## Potential technologies

Development of validated non-invasive outcome measures that can quantitate axonal regeneration in the nerve/pathway and indirectly assess the growth state of the neuron and applied serially to patients and animals would address some of the clinical and