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SCIENCE DIRECT
Experimental Neurology 198 (2006) 479 – 482
Experimental Neurology
www.elsevier.com/locate/yexnr

In vivo three-dimensional reconstruction of human median nerves by diffusion tensor imaging

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Received 30 September 2005; accepted 15 December 2005
Available online 7 February 2006

Abstract

The in vivo assessment of axonal projections of the peripheral nervous system has been severely limited by the lack of noninvasive techniques. We examined whether MR diffusion tensor imaging with fiber tracking of the human median nerve is feasible. The median nerve was examined with a 3-T MRI scanner in wrists of three healthy volunteers and the wrist of a patient after median nerve repair. In vivo three-dimensional (3D) reconstruction of axonal projections of the median nerve could be achieved in healthy volunteers with intact median nerves and a patient with a transected median nerve using diffusion tensor imaging combined with fiber tracking. The median nerve could be visualized and correlated well to the expected location on T1-weighted images in the patient and all volunteers. The transected median nerve in the patient could be detected up to the site of repair one month postoperatively, whereas the nerve could not be detected more distally immediately after repair. Two months postoperatively, it could clearly be tracked more distally, indicating nerve regeneration. Diffusion tensor imaging can detect the median nerve in healthy individuals as well as up to the lesion site in a patient with a complete transection of the median nerve.

Keywords: MRI; DTI; Fiber tracking; Peripheral nerve; Median nerve; Nerve regeneration

Introduction

The effects of proton diffusion in NMR and MRI have been known for over 45 years, but clinical usefulness remained unestablished and somewhat speculative for a long time (Moseley et al., 1991). In vivo 3D reconstructions of axonal projections became feasible with a recently designed fiber reconstruction algorithm combined with rapid high-resolution diffusion tensor MR imaging (DTI) (Xue et al., 1999).

DTI with fiber tracking is a new technique used in the evaluation of the central nervous system. Fiber tracking relies on diffusion of water molecules around a nerve fiber. Diffusion can be defined as the displacement of molecules in a liquid or gas as a result of thermal excitation (Brownian motion). Diffusion is less restricted in the direction of a nerve fiber (possibly due to the layers of myelin) than in the direction perpendicular to the fiber. The diffusion of water molecules can be measured in vivo with DTI. By using special fiber-tracking software, it is possible to visualize neural tracts using the DTI data (Stieltjes et al., 2001).

DTI is likely to be the most sensitive imaging modality for the detection of early nerve dysfunction in the central nervous system. Since 2002, DTI has successfully been applied clinically and has been used to visualize white matter in the central nervous system. In patients with multiple sclerosis, the volume of the spinal cord has been measured (Clark et al., 2004; Filippi and Grossman, 2002). DTI has also been used to define tissue at risk and to monitor recovery after cerebrovascular accidents (Dijkhuizen and Nicolay, 2003; Rother, 2001; Toi et al., 2003). DTI has been used extensively to image white matter tracts in the central nervous system (Wakana et al., 2004).

In June 2004, Skorpil et al. demonstrated for the first time that a peripheral nerve (the sciatic nerve in 3 healthy volunteers) can be imaged in vivo by using DTI with fiber tracking (Skorpil et al., 2004). Their findings were reproduced by Hiltunen et al.

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doi:10.1016/j.expneurol.2005.12.014

who suggested the use of this technique for monitoring regeneration of the nerve (Hiltunen et al., 2005). To our knowledge, the technique has not been described in scientific journals to image the median nerve in patients with a peripheral nerve lesion. Peripheral nerve imaging can be valuable in determining prognosis and follow-up; it can be extremely important in determining whether surgery is indicated after injury, e.g., loss of nerve function after trauma. T2-weighted MRI is currently a common technique to provide information about nerve anatomy. Besides this, it is capable of providing information about nerve compression, inflammation, trauma, or neuropathies (Grant et al., 2002; Britz et al., 1996; Filler and Maravilla, 2004). However, it cannot discriminate between a nerve containing living axon fibers and one that does not (as may be the case in a nerve transplant or distal to a nerve repair site).

The objectives of this study are to determine whether noninvasive diffusion tensor imaging can be used to track the human median nerve and whether complete transection and repair would show up as in inability to track fibers distal to the lesion site.

Materials and methods

Subjects

Healthy wrists of three volunteers and one wrist of a patient with an isolated unilateral median nerve lesion were examined. The healthy volunteers consisted of two males aged 27 and 31 and one female aged 30. They did not use any form of medication and had no previous operations or history of neurological disorders.

The patient, 23 years old, sustained a glass injury of his right forearm. He had an isolated unilateral median nerve lesion just proximal from the distal wrist crease. The patient did not use any medication. He had no previous operations or any history of

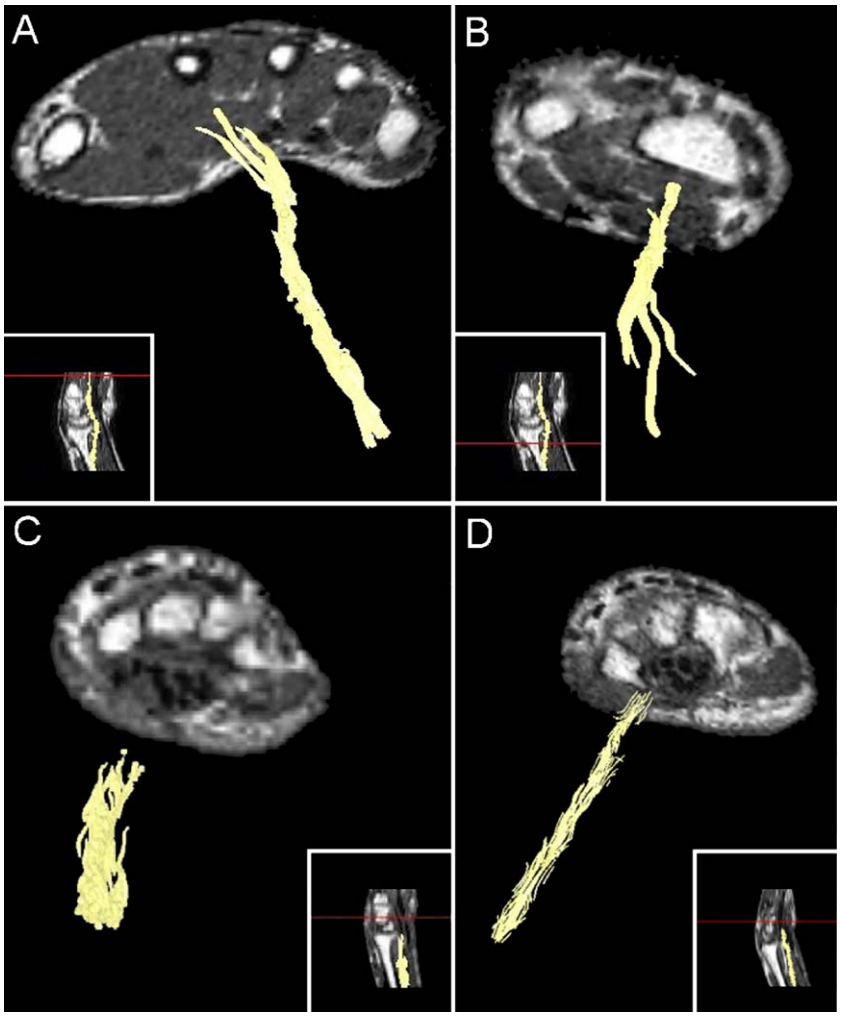

Fig. 1. Diffusion tensor images (A) in black and white, a view from proximal to distal on a T1-weighted slice through the metacarpals. The exact anatomical location of the slice can be seen in the inset (red line). Bottom is proximal, and top is distal. Perpendicular to this slice is a 3D over-projection of the fiber obtained by fiber tracking (yellow structure). (B) The same right wrist as in panel A but now a distal to proximal view on a slice through the distal radius and ulna. (C) One month postoperatively images of the patient with the right median nerve lesion. The T1-weighted slice is through the carpus, seen from proximal. The inset also shows where the fiber tracking of the median nerve stops. (D) The same patient, 2 months postoperatively. The fiber can be tracked more distal than 1 month earlier.

neurological disorders. He underwent fascicular nerve repair 1 month before the first DTI examination. A second scan was made 2 months postoperatively.

The median nerves of the volunteers and the patient were examined with MR diffusion tensor imaging with fiber tracking using a 3-T MR scanner with a 6-channel head coil. The fiber-tracking images were laid over T1-weighted images.

MRI/DTI data acquisition

The study was performed on a 3-T Philips Intera scanner (Philips Medical Systems, Best, The Netherlands) using the standard 6-channel SENSE head coil. Each subject lay prone with their arm above their head. The wrist was positioned in the center of the coil using cushions. DTI was performed using spin echo planar imaging (SE EPI) (TR = 4.6 s; TE = 90 ms; FA = 90°) with 35 transversal slices of 4 mm thickness with no gap between the slices. A rectangular FOV of 140 × 140 mm^2 with a scanning matrix of 96 × 76 with a SENSE factor of 3 and reconstructed at 128 × 128 resulted in an in-plane resolution of 1.09 × 1.09 mm^2. Diffusion weighting with a *b* value of 1000 s/mm^2 was applied in 32 encoding directions. To increase SNR, each encoding direction was acquired three times, and the average of these three acquisitions was used in the data analysis. In addition to the diffusion-weighted images, a single reference image without diffusion weighting ($b = 0$ s/mm^2) was acquired. Total scan time was 7 min, 36 s. For anatomical reference, a T1-weighted turbo spin echo image (TR = 500 ms; TE = 21 ms; FA = 90°; TSE factor = 3) with the same FOV and the same number of slices as the DTI scan but with an in-plane resolution of 0.27 × 0.27 mm^2 was acquired.

Fiber tracking

Fiber tracking was performed with the IDL-based (Research Systems Inc., Boulder, CO, USA) PRIDE-tool provided by Philips. This tool is based on the work of Mori et al. (1999) and Xue et al. (1999). The tool can automatically reconstruct fibers starting from a user provided seed point. Seed points were selected on the basis of the T1-weighted scan in the region of median nerve proximal and distal to the lesion site. The datasets of all four subjects were analyzed in an identical way (i.e., using the same settings of tunable parameters in the tool).

Results

In all healthy wrists, a bundle of fibers was identified from the most proximal slice till the most distal slice: from 5 cm proximal to 5 cm distal to the distal radioulnar joint. The location of the fibers correlated to the median nerve. We even noticed distal branching of the nerve (Figs. 1A, B).

In the first scan (1 month postoperatively) of the patient, the median nerve could be tracked from the most proximal slice up to the site of the lesion (Fig. 1C), whereas the nerve could not be detected more distally immediately after repair. In the inset can be seen that the nerve could be tracked as far as the distal radioulnar joint. In the second scan (Fig. 1D), 1 month later, it could clearly be tracked further than this point. Clinically, nerve function had not improved at that moment.

Discussion

This study shows that it is now possible to visualize intact median nerves in human forearms in vivo by employing a fiber-tracking algorithm on DTI data. We also showed that this technique is sensitive to visualizing living and regenerating nerve fibers. It does not visualize a nerve distally of a lesion after nerve repair, which contains living Schwann cells and connective tissue, but no axons. Because it is not entirely clear whether the anisotropy imaged in neural tissue is due to the existence of axons per se, loss of the anisotropy signal does not undoubtedly proof a lack of axons. However, distal to the nerve repair site the technique used showed no signal at a moment where no viable fascicles are expected distal to the lesion site.

Using a T1-weighted MRI as background greatly facilitated orienting the anatomical location of the fibers and confirmed our hypothesis that we were dealing with the median nerve. Being even more critical whether other structures than nerves (such as a flexor tendon or vessel) would be sensible to our technique, we tried fiber tracking on many other locations in the neighborhood of the median nerve. This resulted in no other longitudinal fibers.

Recently, Skorpil et al. discussed the interest of visualizing smaller peripheral nerves than the sciatic nerve by using the DTI(Skorpil et al., 2004). In our study, it was possible to detect smaller peripheral nerves than the sciatic nerve. DTI can be performed within several minutes with the 3-T MRI scanner in our institution. The software is accidentally able to track fibers in other tissues, but these were never longer than a few millimeters and had a very small caliber. This could be due to noise, artifacts or coincidental anisotropic properties of the tissues. In the nerve repair patient, we extensively searched for fibers distally from the lesion but we were unable to find these.

Currently, one of the major drawbacks of this technique is its spatial resolution. Although exact specifications are still unknown, we know that a minimal nerve caliber is essential in order to be tracked by the software. Hopefully, this can be improved in the future by higher resolution scans, a better signal to noise ratio, stronger gradients and better software. We think that images of higher resolution will be available as dedicated coils (i.e., wrist coil) and higher-field-strength magnets become available.

Knowing that this technique is capable of visualizing living nerve fibers might offer us the opportunity to follow nerve regeneration in vivo especially after trauma. Although clinical examination and EMG may give some clues regarding the progression of nerve regeneration, DTI and fiber tracking offer the opportunity to track the progression of nerve regeneration itself after nerve injury and repair. This can be of importance in

nerve entrapment syndromes, diagnostics of peripheral nerve derived soft tissue tumors, nerve lesions after trauma (i.e., uncertain peripheral nerve transections, brachial plexus lesions).

Another example for the near future can be the exact timing of muscle transplantation after a cross-face nerve transplant in-patients with facial paralysis. In the first stage of these operations, the patients receive an autologous nerve transplant sutured to a healthy facial nerve branch. This nerve is tunneled through the upper lip to the paralyzed side. After nerve regeneration through the nerve graft to the paralyzed side, muscle transplantation can be performed. Currently, the clinical Tinel's sign is used to identify the regenerating axons through the graft. When the nerve reinnervation reaches the contralateral side of the nerve graft, Tinel's sign can also be found there. When this happens, a second procedure is planned. In this procedure, the regenerating nerve is anastomosed to a microvascularly transplanted muscle (e.g., gracilis muscle). Sometimes the Tinel's sign, however, is absent. In those cases, it is difficult to know whether regenerating axons are present in the autograft or not. This is a dilemma for the plastic surgeon: can the secondary operation be performed or is reoperation necessary? In such a situation, it would be of inestimable value being able to visualize the extent of the regeneration of the nerve.

T2-weighted neurography is currently able to show nerve pathology, however, this technique has not been used in human peripheral nerves to visualize how far regenerating fibers have grown. We think that DTI combined with fiber-tracking software may be able to do so. Another advantage of DTI is that curves in the nerve can be easily followed, without making labor-intensive maximum intensity projections.

In conclusion, we showed that in vivo three-dimensional (3D) reconstruction of axonal projections of the median nerve can be achieved in healthy volunteers with intact median nerves and a patient with a transected unilateral median nerve up to the transection site using DTI combined with fiber tracking and correlated to T1-weighted images.

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