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Quantitative STIR of Muscle for Monitoring Nerve Regeneration

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Purpose: To assess whether short tau inversion recovery (STIR) MRI sequences can provide a tool for monitoring peripheral nerve regeneration, by comparing signal intensity changes in reinnervated muscle over time, and to determine potential clinical time points for monitoring.
Materials and Methods: For this prospective study, 29 patients with complete traumatic transection of the ulnar or median nerves in the forearm were followed up to 45 months postsurgery. Standardized 1.5 Tesla STIR-MRI scans of hand muscles were obtained at fixed time intervals. Muscle signal intensities were measured semi-quantitatively and correlated to functional outcome.
Results: For the patients with good function recovery, mean signal intensity ratios of 1.179 $\pm$ 0.039, 1.304 $\pm$ 0.180, 1.154 $\pm$ 0.121, 1.105 $\pm$ 0.046 and 1.038 $\pm$ 0.047 were found at 1-, 3-, 6-, 9-, and 12-month follow-up, respectively. In the group with poor function recovery, ratios of 1.240 $\pm$ 0.069, 1.374 $\pm$ 0.144, 1.407 $\pm$ 0.127, 1.386 $\pm$ 0.128 and 1.316 $\pm$ 0.116 were found. Comparing the groups showed significant differences from 6 months onward ($P < 0.001$), with normalizing signal intensities in the group with good function recovery and sustained elevated signal intensity in the group with poor function recovery.
Conclusion: MRI of muscle can be used as a tool for monitoring motor nerve regeneration, by comparing STIR muscle signal intensities over time. A decrease in signal intensity ratio of 50% (as compared to the initial increase) seems to predict good function recovery. Long-term follow-up shows that STIR MRI can be used for at least 15 months after nerve transection to differentiate between denervated and (re)innervated muscles.

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In patients with traumatic peripheral nerve transection and subsequent surgical repair, it is important to monitor the nerve regeneration process, to ensure that sprouting axons bridge the gap and to determine whether sufficient axons reach the end organs. Even after technically correct surgical nerve repair, functional recovery often is suboptimal.[1–8] If nerve regeneration fails, a surgical re-intervention may be attempted, by resecting the scar and performing a secondary nerve repair.[9] Chances of success of such a reoperation are best in the first 6 months after initial trauma,[3,7,10–15] due to deterioration of the distal nerve stump[3,10,13,15–19] and fatty degeneration of the denervated muscle.[20–23] Therefore, early monitoring of the regenerating nerve is of utmost importance.

Besides clinical tests, the current method of choice for early monitoring nerve regeneration is needle electromyography (EMG).[24–27] However, EMG has several disadvantages, as it is time-consuming, temperature dependent, invasive, and painful.[28–30] Moreover, the results can be difficult to interpret.

Therefore, new validated biomarkers are needed to predict successful outcome. MRI is promising in this respect, as previous research has shown that short tau inversion recovery (STIR) and T2-weighted sequences can be

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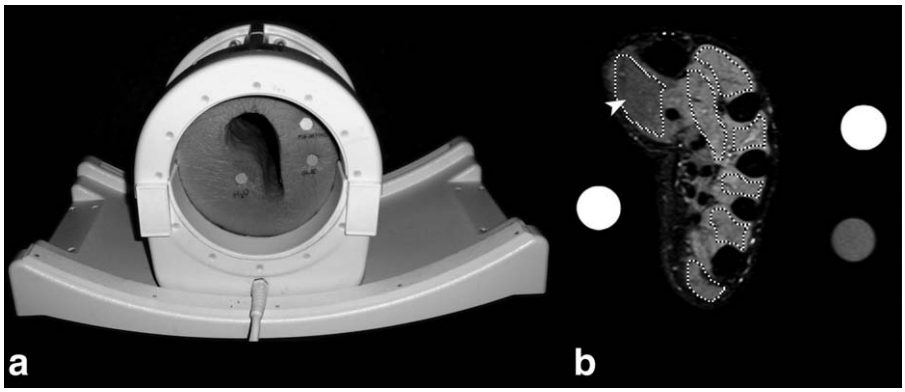

FIGURE 1: Coil setup and drawing protocol. a: Knee coil and wrist cushion, with the three embedded calibration tubes. b: STIR-MRI image of a patient with transection of the ulnar nerve, showing midhand contours for the thenar, the adductor pollicis muscle, the four interosseous muscles and the hypothenar muscles. Note the normal signal intensity of the thenar (white arrowhead), which is innervated by the median nerve, and the increased signal intensity of the other muscles, innervated by the ulnar nerve.

used to differentiate denervated from reinnervated muscles, by comparing muscle signal intensities of unaffected and affected muscles, and comparing signal intensities over time.[31–37] However, it remains unclear whether STIR-sequences can be used to predict successful outcome. In the decision to re-operate, a surgeon has to identify nerve regeneration to all denervated muscles. In all aforementioned studies, only a few selected sample regions of interest (ROIs) were measured. As not all muscles may recover, using just a few ROIs may not be representative for the whole nerve. Therefore, for this study, a more elaborate measuring method was used, assessing signal intensities of all intrinsic hand muscles throughout all scan slices, in patients with complete nerve transection and subsequent nerve repair of median and/or ulnar nerves in the forearm, thus providing a more representative insight into the regenerating nerve. Patients were followed for the first 12 months after nerve injury, and mean muscle signal intensities were correlated to functional outcome.

Furthermore, little is known about the long-term STIR signal intensity changes after nerve transection. As fatty infiltration takes place in denervated muscle, it is to be expected that STIR signal intensities will gradually drop over time. Therefore, it is not clear whether STIR signal intensity differences can be used to differentiate between denervated and (re)innervated muscles beyond 1 year posttrauma.

The purpose of this study was, therefore, to assess whether STIR MRI sequences can provide a tool for monitoring peripheral nerve regeneration, by comparing signal intensity changes in reinnervated muscle over time, and to determine in which period after surgical nerve repair STIR can be used for monitoring nerve regeneration.

Materials and Methods

Study Design

For this prospective study a total of 33 consecutive patients (31 male, 2 female) with complete transection of the ulnar or median nerves in the forearm were recruited at the department of Plastic and Reconstructive and Hand Surgery over a period of 4 years. Of these 33 patients, 4 were lost to follow-up (1 patient died of unrelated causes, 3 patients changed their address without notice). Inclusion criteria were a surgically confirmed complete nerve transection between the elbow and wrist crease, age over 12 years, and absence of contraindications for MRI. All patients underwent nerve repair within 48 hours after trauma. Diagnosis was based on findings during surgical exploration: 13 patients had a median nerve transection, 10 patients had an ulnar nerve transection, and 6 patients had a transection of both nerves. Mean age of the patients was 31.0 years (males 30.9; females 32.2), with an age range of 14–76 years.

The 29 remaining patients were followed during the first year posttrauma by obtaining standardized STIR MRI scans of the affected midhand at 1, 3, 6, 9, and 12 months postsurgery. In a randomly selected subgroup of 10 patients with one nerve transection (4 with good and 6 with poor function recovery), additional scans were obtained in the subsequent years, up to 45 months after trauma, to assess long-term signal intensity changes. At 12 months, hand function tests were performed. Signal intensities in denervated and nondenervated intrinsic hand muscles were measured over time and correlated to functional outcome. This study was approved by the institutional review board and written informed consent was obtained from all patients and as well from both parents for minors.

Acquisition Technique

STIR images of the affected hand were obtained at 1, 3, 6, 9, and 12 months after nerve repair. All scans were acquired using a standard clinical 1.5 Tesla (T) MRI scanner (Gyroscan Intera Powertrak 6000, Philips Medical Systems, Best, The Netherlands), using a Philips Intera 20 cm quadrature nonphased array knee coil. In all examinations a STIR turbo spin-echo sequence was used (repetition time [TR] 1693 ms, inversion time [TI] 170 ms, echo time [TE] 15 ms, a turbo spin echo [TSE] factor of 5, number of averages 2, a 256 × 256 matrix, field of view [FOV] 16 cm, slice thickness 3 mm, interslice gap 0.3 mm, and a scan time of 4 min).[31,32,34,38] No other sequences were used to minimize acquisition time. The patient's hand was positioned in the center of the

knee coil by using a custom made wrist cushion, which also contained three sealed calibration tubes, filled with standard Philips calibration fluid (aqueous copper sulfate solution), olive oil and liquid paraffin, respectively (Fig. 1a). These fluids were chosen because of their inert nature, their signal characteristics and ample availability. With the imaging parameters used, these substances result in signal intensities that are far apart, while still being close enough to the signal intensities measured in muscle tissue. Also, using these calibration tubes simplified postprocessing, by forcing the automatic transmitter adjustments in all examinations to be in the same range. The tubes were sealed and the contents were left unchanged throughout the duration of the entire study.

In all patients, 23 transverse slices of the midhand were acquired parallel to the plane through the first and fifth metacarpophalangeal joints and the middle of the second metacarpal bone with the thumb placed in neutral position. All acquired images were stored in 16-bit DICOM format for further processing.

Postprocessing

To compensate for location-dependent signal variation, all patient scans were corrected with scans obtained in a homogeneous phantom, using a standardized protocol.[39,40] For this purpose, a phantom exactly fitting the knee coil and containing standard Philips calibration fluid, was scanned at eleven different left-to-right positions in the MRI-bore, using the same acquisition parameters as used for our patients, as it is known that left–right positioning of the RF coil influences image intensity significantly.[39,41] These phantom scans were used to correct the patient scans for B_1-field nonuniformity in three directions.

Image intensity nonuniformity correction was performed by dividing a patient scan by the nearest phantom scan. This was done automatically with in-house developed dedicated analysis software, written in C (Visual C/C++ 6, Microsoft Corporation, Redmond, Washington, USA).

Finally, from the signal intensities measured in the calibration tubes, per examination a calibration factor was calculated, which in turn was used to linearly scale all image intensities relative to the background.

Signal Intensity Measurements

To measure the nonuniformity corrected signal intensities in the intrinsic hand muscles, contours were drawn using in-house developed dedicated analysis software and a drawing tablet (Graphire, Wacom Company, Saitama, Japan). In all 23 slices of the midhand, the intrinsic hand muscles were identified visually and contours drawn manually. Not all boundaries between individual muscles could be defined unambiguously in the MRI images, therefore, some groups of muscles were combined. This proved necessary for the median nerve innervated thenar muscles (the opponens pollicis muscle, the abductor pollicis brevis muscle, and the superficial head of the flexor pollicis brevis muscle), and for the ulnar nerve innervated (dorsal and palmar) interosseous muscles and hypothenar muscles (the abductor digiti minimi brevis, the flexor digiti minimi brevis, and the opponens digiti minimi muscles).

Due to limitations in spatial resolution, the lumbrical muscles and the deep head of the flexor pollicis brevis muscle were not considered. Contours were drawn approximately 1 mm within the muscle boundary, to minimize partial volume effects, while avoiding inclusion of intramuscular blood vessels (Fig. 1b). On average, 84 ROIs per patient scan were defined, to obtain a representative overview of the regenerating nerve, which is 42 times more data than with the commonly used standard two ROIs. Per muscle, the mean signal intensity was computed, by averaging all voxels within the obtained regions of interest of all 23 slices. Subsequently, the mean signal intensity per nerve was computed by averaging the corresponding muscle means (the thenar muscles for the median nerve and the adductor pollicis, interosseous and hypothenar muscles for the ulnar nerve). For the patients with one transected nerve (median or ulnar), a signal intensity ratio for the denervated muscle group was calculated, by dividing the mean signal intensity ratio of the denervated muscle group by that of the unaffected muscle group. For the patients with transection of both median and ulnar nerves (for whom no normal reference muscle is present), signal intensities were calculated by dividing the signal intensities of the denervated muscle groups by the mean signal intensity of normal muscle found in the group of patients with only one affected nerve. To assess intra-observer variability, in 15 examinations all ROIs were drawn twice.

Hand Function Tests

In all patients, 12 months after nerve transection and subsequent repair, hand function was assessed by grading muscle strength according to the Medical Research Council (MRC) scale.[42] This scale distinguishes six grades of muscle contraction: 0 = no contraction; 1 = flicker or trace of contraction; 2 = active movement, with gravity eliminated; 3 = active movement, against gravity; 4 = active movement, against gravity and resistance; 5 = normal power. The mean strength of all affected muscles was calculated and patients were divided into two groups: a group with good function recovery, defined as a mean MRC score of 4 and higher, and a group with poor function recovery, defined as a mean score below 4. For this study, the cutoff point at MRC grade 4 was chosen, as this defines muscle strength against resistance, which is considered to be the minimum requirement for practical use.[6,43,44] In all patients, hand function was assessed before muscle signal intensities were measured.

Statistical Analysis

After ensuring normal distribution of the data by applying the Shapiro-Wilk test, the measured muscle signal intensities in the groups with poor function recovery and good function recovery were compared at the five different time intervals using the analysis of variance (ANOVA) test. Analysis of variance was also used for comparing in-group measurements at different time intervals. For all statistical analysis, SPSS 14.0 for Windows (SPSS Inc., Chicago, IL) was used.

Results

In all remaining 29 patients, hand function tests were performed after 1 year. Of the 23 patients with transection of a single nerve, 7 showed good functional recovery and 16 did not. One of the 6 patients with transection of both median and ulnar nerves, showed good functional recovery of both nerves, and in the others good recovery was limited to one

TABLE 1. Mean Signal Intensity of Denervated Muscle Relative to Non-denervated Muscle in Patients with Median or Ulnar Nerve Repair

		Months after nerve transection				
		1	**3**	**6**	**9**	**12**
Poor function recovery (n = 16)	No. of examinations	6	13	13	12	12
	Mean relative signal intensity[a]	1.240 ± 0.069	1.374 ± 0.144	1.407 ± 0.127	1.386 ± 0.128	1.316 ± 0.116
Good function recovery (n = 7)	No. of examinations	4	5	6	7	6
	Mean relative signal intensity[a]	1.179 ± 0.039	1.304 ± 0.180	1.154 ± 0.121	1.105 ± 0.046	1.038 ± 0.047
Group comparison	ANOVA, *P* values	0.154	0.632	< 0.001	<0.001	<0.001

[a]Data are mean ± standard deviation.

nerve only. In total, 6 of 16 ulnar nerves (38%), and 8 of 19 median nerves (42%) showed good recovery.

Mean age of patients with poor and good function recovery was 32.7 and 33.0 years, respectively, mean distance to wrist crease 8.8 and 7.7 cm, respectively. A total of 115 scans were made in these 29 patients, which is on average 4 examinations per patient.

In the group with poor function recovery, denervated muscle signal intensity ratios were found of 1.240 ± 0.051 (standard deviation), 1.374 ± 0.076, 1.407 ± 0.066, 1.386 ± 0.053, and 1.316 ± 0.067 at, respectively, 1, 3, 6, 9, and 12 months after surgery. For the group with good function recovery, at these time intervals signal intensity ratios of, respectively, 1.179 ± 0.038, 1.304 ± 0.144, 1.154 ± 0.090, 1.105 ± 0.034, and 1.038 ± 0.035 were found (Table 1). Comparing the groups with poor and good function recovery, showed significant differences at 6, 9, and 12 months ($P < 0.001$), whereas no differences were found at 1 and 3 months (Table 1; Fig. 2).

When comparing signal intensity ratios between different time intervals (Table 2), the group with poor function recovery showed significant differences between 1-month follow-up and 6-month follow-up ($P = 0.005$) and between 1-month and 9-month follow-up ($P = 0.014$); no significant differences were found between measurements at 3, 6, 9, and 12 months. However, the group with good function recovery showed significant differences between measurements at 9-month follow-up and at both 1- and 3-month follow-up ($P = 0.025$ and $P = 0.016$, respectively). Also, at 12-month follow-up, all measurements were significantly lower than those obtained at previous time intervals ($P < 0.037$).

The results of long-term follow-up in the subgroup of 10 patients are shown in Figure 3. The highest signal intensity ratio measured was 1.69. The lowest maximum signal intensity ratio found in a patient was 1.16. In the group with poor function recovery, no significant difference was found between the measurements at 12 months and 15 months ($P = 0.82$). Therefore, mean muscle signal intensity in this group remains elevated at least 15 months after nerve repair; thereafter signal intensity ratios seem to show a rapid decrease (Fig. 3).

In Figure 4, the muscle signal intensities of the patients with both ulnar and median nerve transections are shown, as compared to the mean value of normal muscle found in the patients with a single nerve transection. Measurements at the first month show an overall higher signal than in the patients with one nerve transection, varying from 1.25 to 1.89, on average 1.46. In this figure, also a patient with severe fatty muscle degeneration is demonstrated.

In Figure 5, sequential scans of two patients with an ulnar nerve lesion are demonstrated, one with good recovery (Fig. 5a) and one with poor recovery (Fig. 5b). It can be

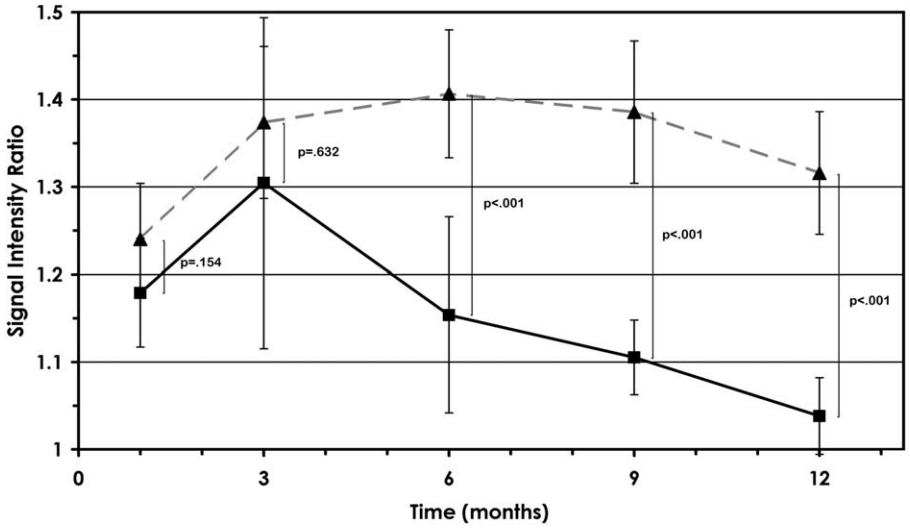

FIGURE 2: Good versus poor function recovery. Mean signal intensity ratios of denervated muscle for the groups with good function recovery (squares) and poor recovery (triangles). After 6 months follow-up, the groups show significant differences ($P < 0.001$). Signal intensities are significantly different from 6 months onward.

seen that in the patient with good recovery, muscle signal intensity normalizes at the ulnar side first, as is also reflected by the signal intensity measurements (Fig. 5b). This is to be expected, because the ulnar nerve enters the hand at the hypothenar side. In the patient with poor recovery, muscle signal intensities remain elevated during the year following surgical nerve repair. Intra-observer variability for the signal intensity ratio measurements in the 15 examinations was 0.019 (SD).

Discussion

In patients with traumatic nerve transection and subsequent surgical repair, it is extremely important to monitor whether sprouting axons from the proximal nerve stump grow into the distal stump toward the end organs. If this reinnervation process fails, re-operation may be attempted. As needle-electromyography, the gold standard for early monitoring motor nerve regeneration, has several aforementioned disadvantages, new monitoring methods are needed.

MRI could be a viable candidate in providing noninvasive, detailed anatomic information about the nerve regeneration process.[31,33,34,36,37,45,46] For very early monitoring, MR-neurography and MR-tractography could be used to determine whether sprouting axons have bridged the gap between the proximal and distal nerve stumps.[45,47–56] However, the mere presence of axons in the distal stump does not guarantee successful functional outcome, as growing axons could take a wrong turn toward the sensory end organs instead of the intrinsic hand muscles. Therefore, monitoring the target muscles is necessary as well.

It is known that STIR-MRI can be used to diagnose motor denervation,[32,33,38,57–64] as denervated muscles

TABLE 2. Comparison of Mean Muscle Signal Intensities at Different Time Intervals (ANOVA, *P* Values[a])

		Months after trauma			
		3	**6**	**9**	**12**
Poor function recovery group	1	0.081	**0.005**	**0.014**	0.135
	3	-	0.536	0.833	0.270
	6	-	-	0.678	0.065
	9	-	-	-	0.168
Good function recovery group	1	0.216	0.699	**0.025**	**0.001**
	3	-	0.100	**0.016**	**0.003**
	6	-	-	0.342	**0.037**
	9	-	-	-	**0.020**

[a]Significant differences are shown in bold.

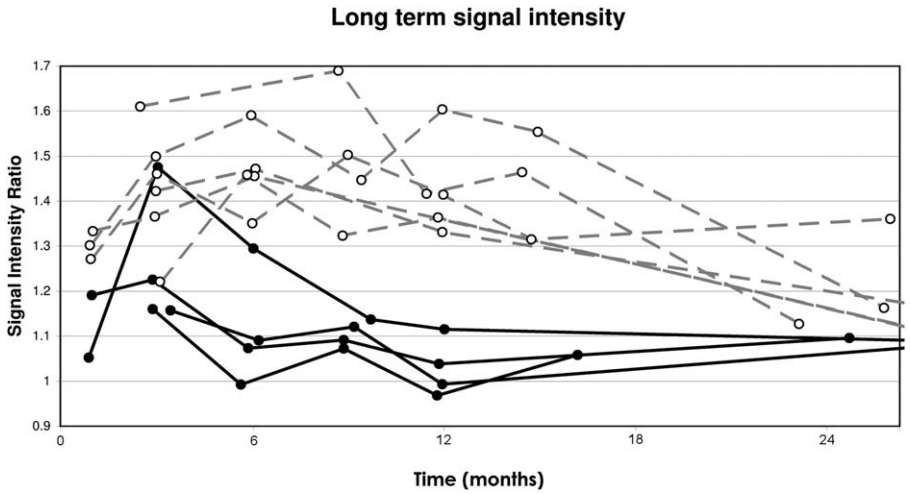

FIGURE 3: Long-term follow-up. Signal intensities in the ten patients that had additional scans beyond 1 year, to assess long-term signal intensity changes. The measurements in patients with good function recovery show sustained low signal intensities after one year (closed circles). In the patients with poor function recovery (open circles), signal intensities are elevated at least 15 months and drop afterward.

display higher signal intensities than normal muscle, due to various histochemical changes, including increases in the proportions of extracellular fluid and capillary bed.[20,32,33,35,46,59,64] The present study shows that MRI, apart from diagnosis, can also be used for monitoring nerve regeneration, as muscle signal intensity ratios between the groups with poor and good functional recovery differ significantly ($P < 0.001$) after 6 months (Fig. 2). Therefore, it seems that STIR-MRI can provide useful additional information to standard needle electromyography. For example, one of our patients reported to have no signs of functional recovery at 6 months after nerve repair, while at that time the measured muscle intensities had almost completely returned to normal. Later on, the patient reported that hand function had started to return 3 weeks after this scan with complete recovery within 7 weeks after the scan. This observation may indicate that normalization of MRI signal intensity precedes hand function recovery.

In the group with poor function recovery, the mean signal intensity ratios of denervated muscles at 3 and 6 months were 1.37 and 1.40, meaning approximately 40% signal intensity increase as compared to normal muscle, whereas in the group with good function recovery, mean signal intensity ratios at 3 and 6 months were 1.30 and 1.15, respectively, meaning 30% and 15% higher signal intensity when compared with normal muscle. Therefore, our data suggest that a 50% decrease in signal intensity (relative to the initial increase) may predict a positive functional outcome. However, more research is needed to investigate whether this can be applied to individual cases.

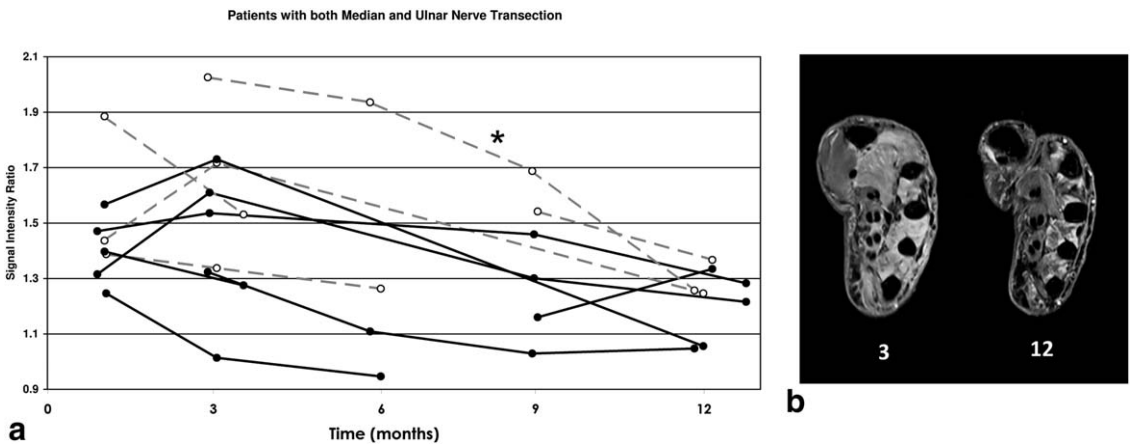

FIGURE 4: a: Measurements in the patients with both median and ulnar nerve transections, divided in groups with poor recovery (open circles) and good recovery (closed circles). It can be seen that measurements at month one are high, due to the presence of wound edema. Also, a remarkable signal drop is seen in a patient with poor recovery of the ulnar nerve (asterisk). b: Scans of this patient at 3 and 12 months show that this was caused by an early and extensive form of fatty infiltration, as can be seen in the interosseous muscles.

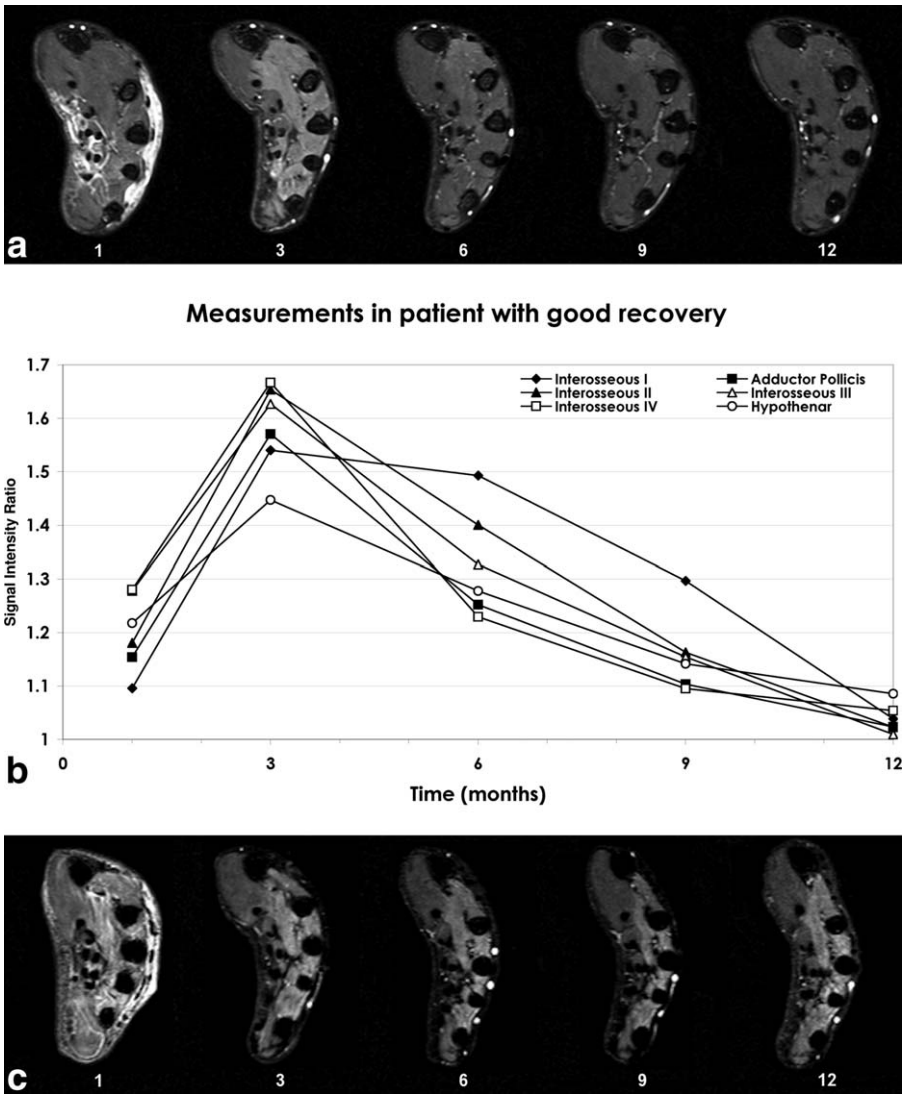

FIGURE 5: a: Standardized, signal corrected STIR-MRI scans in a patient with full function recovery after ulnar nerve repair, at 1-, 3-, 6-, 9-, and 12-months follow-up. Notice the distinct swelling and subcutaneous edema at 1 month, while at 3 months signal intensities of the denervated adductor pollicis, interosseous and hypothenar muscles are markedly increased compared with the thenar muscle. It can be seen that signal intensities of the hypothenar and interosseous muscles at the ulnar side normalize at 6 months, with remaining high signal intensities in the first and second interosseous and adductor pollicis muscles. At 9 months, the first interosseous muscle still shows slight signal intensity increase, while at 12 months, all signal intensities returned to normal. b: Measurements in the same patient, of the separate muscles, clearly showing that the hypothenar and interosseous muscles IV and III recover before interosseous muscles I and II, thus visualizing the regeneration process from the ulnar side toward the radial side. c: Images of a patient with poor recovery of the ulnar nerve for comparison. Signal intensity remains elevated during the year following surgical nerve repair.

From our results it can be seen, that signal intensities in the group with poor function recovery show a tendency to decrease between 6 and 12 months, but these differences are not significant, whereas the signal intensities measured in the group with good function recovery show significant decrease at 9 and 12 months, compared with month 3. Signal intensity in the group with poor recovery remains elevated for at least 15 months. Thereafter, signal intensity drops toward normal. This is likely caused by atrophy and increasing fatty degeneration in the muscle. It seems that before 15 months, STIR-MRI can be used to distinguish between re-innervation and denervation.

In several prior studies, investigating MR-imaging in patients with denervation, a small number of ROIs is defined to determine signal intensity ratios.[31,33,36,37,46] Typically, one contour is drawn per muscle group. For our study, a more elaborate measuring method was used, by measuring all voxels of all muscles in all slices, and finally computing a mean signal intensity per nerve. In comparison with a previous study,[36] in which only two ROIs were measured, this method shows higher significance of the differences between the groups with poor and good recovery.

In the present study, only 14 of 35 repaired nerves showed good function recovery after 1 year. This may seem

a poor result, but this is consistent with outcomes reported in literature,[8,44,65–67] inadvertently illustrating the importance of finding new methods to improve nerve regeneration. For this study, in all patients hand function was assessed at twelve months. Although most nerve regeneration occurs within 1 year in this type of injury, it is known that regeneration may slightly improve up to 3 years after nerve repair.[6] Therefore, final outcome could be somewhat better. Also, for this study, a mean MRC grade below 4 was classified as poor recovery. However, this does not necessarily reflect the clinical point of view. For instance, if in case of an ulnar nerve transection the hypothenar, the adductor pollicis muscle, the first and second interosseous muscles all recover to MRC grade 5, while the third interosseous muscle remains at strength 0 and the fourth interosseous muscle recovers to strength 3, outcome will be classified as poor recovery, as the mean MRC grade will be 3.83. However, from a clinical point of view this patient shows good function recovery, as functions of his index finger, thumb and fifth finger are (almost) intact. Therefore, to be used for clinical decision making, especially the decision to re-operate, a better algorithm may be needed, as in the current setup all ulnar nerve innervated muscles are assigned equal clinical importance. Nonetheless, at present there is no unambiguous algorithm to weigh muscle importance, and simple mean values were used for both hand function grading and signal intensity measurements.

The measurements in patients with transection of both ulnar and median nerves, show remarkably higher signal intensity at month one. This may be caused by wound edema, as previous research showed that this, on average at one month postsurgery, accounts for a signal intensity increase of 18%.[40] Especially in the case of more extensive injury, it is to be expected that the amount of wound edema also increases. It can be seen that the curves show a less distinct pattern as seen in the patients with single nerve injury. This may reflect that, in these patients, measurements are compared with a fixed value, whereas in the patients with a single nerve lesion, the signal intensities are compared with a local reference muscle, reducing the influence of interindividual variations and field inhomogenities. Scanning the unaffected hand as a reference could be a solution; however, due to spatial constraints of the used knee coil, for this study, the contralateral hand was not considered. In one patient with poor recovery, a substantial signal drop was caused by an early and severe form of fatty infiltration. Although we did not observe such comprehensive fatty infiltration in other patients, this shows that the images need to be carefully reviewed as signal intensity can be influenced by other factors than muscle edema.

In theory, missing values could influence the mean values for the different time intervals. However, as on average 4 scans per patient were acquired, it seems unlikely that any missing values would result in a significantly different outcome. Also, the signal intensity in the group with poor recovery shows an overall tendency to remain elevated, while in the group with good recovery, signal intensity distinctly returns to normal.

Another possible limitation of the present study may be the different rate of regeneration of nerve fibers in different patients. On average, both median and ulnar nerves regenerate at a rate of approximately 1 mm/day.[68–71] However, with aging, this rate may change.[72–76] As mean age in the groups with good and poor function recovery was similar (33.0 and 32.7 years, respectively), it does not seem likely that this factor will significantly influence our results. Nonetheless, small inter-individual differences in axon growth rate likely do exist.

Another factor that may influence our results is the site of nerve injury. Obviously, axons in proximal nerve transections have to regenerate over longer distances than distal transections to reach the target muscles. In the groups with good and poor recovery, mean distances of the nerve lesions to the wrist crease were 7.7 cm (range, 0–25 cm) and 8.8 cm (range, 0–27 cm), respectively. Therefore, as axons grow approximately 1 mm/day, in the group with good function recovery axons are expected to reach the end organs 11 days before those in the group with poor recovery. As intensities are measured every 3 months, we expect the influence of this bias to be rather small. Similarly, the different intrinsic hand muscles have different distances to the wrist crease, and the ulnar nerve innervated intrinsic hand muscles on average will be reached later than the thenar muscles innervated by the median nerve. Unfortunately, as the nerves themselves are not visible at 1.5T, the distances and, therefore, exact influence cannot be measured in the current setup. However, as in both groups with poor and good recovery the ratio ulnar:median is about equal, it is to be expected that both groups are affected equally by this bias.

Finally, the presence of anatomic variants, like the Martin-Gruber and Marinacci anastomosis, in which muscles can have double innervation,[77,78] could theoretically bias our results. In these patients, muscle function remains intact, when one of the two supplying nerves is transected. It is to be expected that this would result in no (or a smaller) signal intensity increase. However, in all patients with ulnar nerve transection, similar increased signal intensities of the hypothenar, interosseous muscles, and adductor pollicis muscles were observed and in all patients with median nerve transection, increased signal of the thenar muscles was observed. Therefore, the presence of such an anastomosis seems unlikely in our cohort. In three patients, we encountered another anatomic variant, however, in which the deep head of the flexor pollicis brevis muscle was innervated by the median nerve. Because this muscle was not considered in the present study, this did not affect outcome.

In conclusion, STIR MRI sequences can be used to differentiate between denervated and reinnervated muscles, by comparing signal intensities over time, as signal intensity of re-innervated muscle returns to normal, while signal intensity of denervated muscle remains elevated for at least 15 months after nerve repair. A signal decrease of 50% (relative to the initial increase) seems to predict good function recovery. Therefore, STIR MRI changes may be used as a biomarker for muscle denervation/reinnervation.

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