

# Combined T2 and IDEAL MRI Permit Identification of Nerve Injury Prior to Distal Muscle Inflammation and Atrophy, and Nerve Repair Prior to Muscle Regrowth

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**Introduction:** Neurodegeneration is largely a consequence of aging, injury, or disease (eg., amyotrophic lateral sclerosis). Severe neurodegeneration is associated with muscle atrophy, impaired functional capacity, and in some cases, death. In this study, our goals were three-fold: 1) Employ MRI to gain a better understanding of the relationship between nerve injury/repair and associated muscle atrophy/regrowth; 2) Compare T2-RARE and post-contrast T1 (with Gd-P) for direct nerve imaging; and 3) Determine whether MRI findings are directly related to nerve injury rather than from the surgery itself.

**Methods:** All methods were approved and performed according to NIBR IACUC guidelines. MRI experiments were performed using a 7.0T/30cm Bruker Biospec and a 38mm Tx/Rx volume coil. This study was split into two Phases. For Phase 1, N=10 C57BL6 mice were subjected to sciatic nerve injury, with the contralateral non-surgical leg serving as control. Over a period of 3 months, leg muscles were compared for IDEAL MRI volumetric and T2 changes. For Phase 2, N=8 C57BL6 mice were randomized to sciatic nerve injury (N=2), sham surgery (N=4), and naive (no surgical manipulation; N=4). Over a period of 2 months, direct nerve imaging was performed. A single-dose of Gd-P contrast was administered to N=1 nerve crush animal and N=1 naive on Day 2 to compare the sensitivity (CNR) of standard T2 and post-contrast T1 for visualization of the sciatic nerve. Leg muscles were compared for volumetric and T2 changes similar to Phase 1. Imaging sequences included the following: IDEAL MRI: FLASH-based sequence (IDEAL Water-Fat Separation), TR/TE=9.7/2.8ms, NA=1, 3.5cm isotropic FOV, matrix=170x170x64; Standard T2: MSME sequence, TR=2500ms, TE=10.75 → 96.73 (9 echoes), NA=1, FOV=4cmx4cm, matrix=256x256, slice=1mm. T2-RARE: RareFactor=4, TR/TE=2000/30ms, NA=4, FOV=3cmx3cm, matrix=256x256, slice=1.5mm; Post-contrast T1: RAREVTR, TR/TE=1500/15ms, NA=1, FOV=3cmx3cm, matrix=256x256, slice=1.5mm. Values are reported as mean (SD). Statistical analyses were performed using linear mixed models and post-hoc testing using Fisher's LSD. P-values with P<0.05 were considered significant.

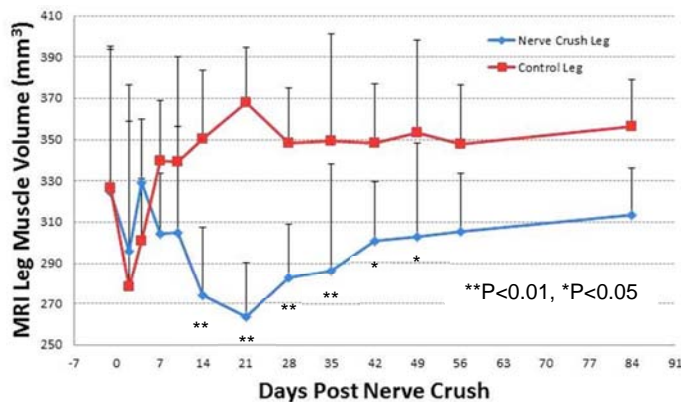


Fig.1. MRI of Leg Muscle Volume. Maximum atrophy was observed Week 3 [260 mm<sup>3</sup> (30) versus 370 (40), -30%]. Regrowth plateaued Week 6 but remained incomplete through Week 12 (-14%).

**Results:** Nerve injury at the site of crush was observed on Day 2, prior to a distal T2 increase in leg muscle on Day 4, and muscle atrophy at Week 3 (Figs.1-2). Nerve Injury and distal T2 increase were related to the nerve crush and not the surgery itself (N.S. differences between Sham and Naive). Nerve Injury was more readily observed on T2-RARE (CNR=10, 15 post Gd-P) versus T1 (CNR=4, 6 post Gd-P), as evidenced by greater CNR. Nerve repair occurred by Week 3 (resolution of T2-RARE abnormalities), prior to partial recovery of T2 in distal leg muscle and muscle regrowth at Weeks 4-6. These findings are consistent with functional measurements in a separate cohort, where sciatic nerve stimulated evoked muscle force, was not observed prior to Week 3 (Fig.3).

**Conclusions:** Combined T2 and IDEAL MRI permit non-invasive identification of nerve injury prior to distal muscle inflammation and atrophy, and nerve repair prior to muscle regrowth<sup>1</sup>. This is with high sensitivity and reliability, *without* contrast agent<sup>2</sup>. These findings provide selection of key time points for target identification and profiling of nerve injury/repair and muscle atrophy/regrowth.

## References:

- Hantai *et al.* Proc Natl Acad Sci. 87 :2926-2930 (1990)
- Bendszus *et al.* Ann Neurol. 57 :388-395 (2005)

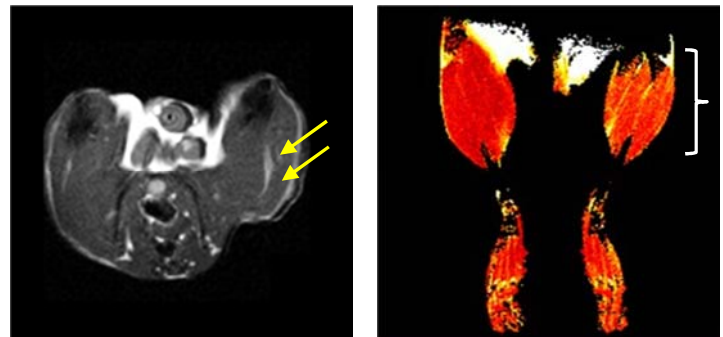


Fig.2. MRI of Nerve Injury. Left – Direct T2 imaging of the Nerve. Right – T2 mapping of the Entire Leg. T2-RARE identified nerve swelling and hyperintensity on Day 2 (left, arrows), prior to a T2 increase in distal leg muscle on Day 4 (right, bracket) [41ms (1) versus 32ms (1), +27%, p<0.01]. Nerve injury observed on T2-RARE resolved by Week 3. The T2 increase in distal leg muscle only partially recovered by Week 12 (+9%).

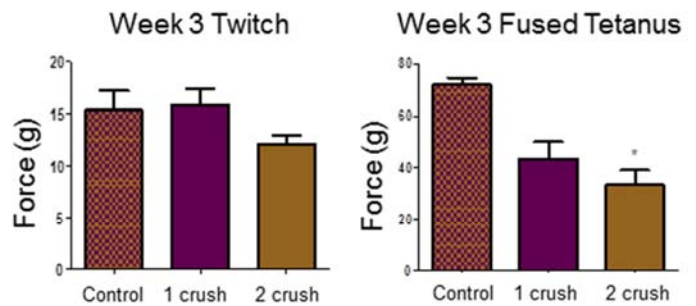


Fig.3. Evoked Muscle Strength. Left – Twitch. Right – Fused Tetanus. No differences were observed for muscle twitch (single, 15 sec), or nerve crush (double, 15 sec x 2), while control vs. two crush tetanus was significant at Week 3.