MRI Biomarkers of Traumatic Peripheral Nerve Injury and Repair: Validation and Multisite Application

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PUBLIC ABSTRACT

In the military, modern body army allows Soldiers to survive wounds that were previously fatal. This increasing rate of survival means that more Wounded Warriors are living the rest of their lives with injured arms and/or legs as well as amputations to these limbs. In civilians, peripheral nerve injuries in the arms and legs are also very common in the United States. Following these injuries, many people experience lifelong disabilities that necessitate activity and work restrictions along with numerous symptoms, including paralysis, muscle weakness, and chronic pain. Often, these nerve injuries heal poorly, and amputations are sometimes required because of severe nerve, bone, and blood vessel injuries.

For severe nerve injuries, surgery is required to regain function, but many of these surgeries fail. Right now, doctors have limited tools to tell if the nerves are regrowing immediately after surgery. Because nerves grow slowly, this forces physicians and patients to adopt a “wait and watch” approach, which ultimately delays clinical decision-making and increases the likelihood of permanent muscle loss and pain. Given these limitations, new methods that can measure nerve health throughout the recovery process would allow for the earlier identification of failed repairs after surgery, even guiding secondary operations when failures are identified.

This study seeks to develop a magnetic resonance imaging (MRI) strategy to monitor nerve recovery immediately after injury and surgical repair to intervene in situations where nerves are not recovering appropriately. MRI is non-invasive, while current methods (electromyography and nerve conduction studies) are invasive, painful, and offer limited information about the repairs.

This specific method investigated in this project is called diffusion MRI. Our preliminary data in animal models and humans suggest this method can detect failed peripheral nerves surgeries and successful reoperations. The first aim of this project will build upon these preliminary data to validate the ability of diffusion MRI methods to detect failed repairs earlier than existing methods, which will be performed in animals with controlled nerve injuries and repair. The second aim of this project will move diffusion MRI methods toward clinical trial readiness by (i) demonstrating consistency across different institutions and human MRI scanners and (ii) performing a larger, multi-site study to evaluate whether diffusion MRI methods can identify failed repairs earlier than existing methods in humans.

If successful, these studies will provide new tools for monitoring nerve regeneration throughout the recovery process (i.e., prior to clinical signs of recovery), which would improve our ability to restore function after nerve injuries. In addition, these methods will likely be useful in injuries closers to the spinal cord, where the likelihood for recovery is currently poor due to the prolonged time (a year or

more) required to detect failed repairs using current methods. Furthermore, these methods will likely be of clinical value prior to surgery, as current methods often struggle to identify nerves that warrant surgery immediately after the injury.

Longer term, these studies will also provide new measures for future clinical trials. There are numerous emerging surgical methods and regenerative medicine-based solutions that have shown promise in improving outcomes following nerve trauma; however, the studies required to evaluate these methods are currently dependent on subjective clinical assessments that are highly variable and slow to change. An associated clinical trial would, therefore, be lengthy and require large numbers of patients to demonstrate an effect. Given these limitations, the new methods developed herein would be transformative for the success, length, and cost of these future clinical trials. Similarly, the validated protocols herein would be of significant value in animal studies of cutting-edge solutions for peripheral nerve injuries.

In terms of the FY21 PRMRP Topic Areas, this application addresses the Topic Area of peripheral neuropathies. If successful, these MRI biomarkers will allow researchers to evaluate novel regenerative medicine-based solutions for peripheral nerve injury, which is an FY21 PRMRP Area of Encouragement. To ensure success, we have established a unique partnership between (i) a peripheral neurosurgeon with expertise in peripheral nerve repairs and (ii) an engineer with expertise in developing MRI approaches for peripheral nerves.