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14. ABSTRACT

We propose to complete a Phase II Clinical Trial to demonstrate the safety and efficacy of a fully-implanted neuroprosthesis to provide upper extremity function for individuals with cervical spinal cord injury (SCI). This study will utilize the "networked neuroprosthesis" (NNP). The NNP system is completely implanted, including all power, signal processing, stimulus generation, and electrodes. We expect that this advanced system will lead to increased regular use of the neuroprosthesis, with a subsequent positive impact on quality of life. The completion of this study will allow us to proceed to broad dissemination of advanced neuroprosthetic systems for the provision of motor function in SCI and similar diseases.

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1. INTRODUCTION:

We propose to complete a Phase II Clinical Trial to demonstrate the safety and efficacy of a fully-implanted neuroprosthesis to provide upper extremity function for individuals with cervical spinal cord injury (SCI). We have completed a clinical feasibility study of a neuroprosthesis that provides myoelectrically-controlled hand grasp to this population. That device utilized external powering and processing, requiring the subjects to have assistance in donning and doffing the neuroprosthesis. We have now completed the design of a fully-implanted, modular neuroprosthetic system, the "networked neuroprosthesis" (NNP). The NNP system is completely implanted, including all power, signal processing, stimulus generation, and electrodes. This eliminates the requirement of having to wear any external components taped to the skin in order to gain hand function, which has been a requirement of all upper extremity neuroprostheses to date. We expect that these advances will lead to increased regular use of the neuroprosthesis, with a subsequent positive impact on quality of life. We have completed the development of this technology and have established a full supply chain for manufacture of this system. Recent funding from the State of Ohio has been obtained to develop this technology within the required manufacturing practices necessary for a commercial implantable medical device. In conjunction with the development of the technology, we have also developed and implemented a complete marketing strategy that is specifically targeted for implantable devices in SCI, with the NNP hand system as the first product. Thus, we are now fully equipped and prepared to conduct a Phase II clinical trial of this technology to demonstrate safety and efficacy. The completion of this study will allow us to proceed to broad dissemination of advanced neuroprosthetic systems for the provision of motor function in SCI and similar diseases.

2. KEYWORDS:

Neuroprosthesis
Functional Electrical Stimulation
Spinal Cord Injury
Paralysis
Rehabilitation
Upper Extremity
Implantable Medical Device
Tetraplegia

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goal of this proposal was to implement the NNP System with ten cervical level spinal cord injured subjects and evaluate the resulting improvement in upper extremity function. Compare functional abilities with and without the use of the neuroprosthesis. The outcome assessments are designed around two hypotheses regarding the advantages of the NNP:

#**1**. We hypothesize that at least 70% of all subjects will demonstrate improved function compared to their baseline performance in one or more activities (primary outcome measure).

#**2**. We hypothesize that the proportion of subjects demonstrating daily usage (7 days/week) of the NNP System will be significantly higher than the published rate of daily usage for the first generation neuroprosthesis.

Project major tasks and milestones for the entire project, showing percentage of completion as of 9/29/2018, on following page.

Major Task 1: Preparations and Support for Clinical Study	Months	% Completion	Notes
Subtask 1: Prepare Regulatory Documents and Research Protocol			
Coordinate Sites for IRB protocol submission at MHMC and LSVA	1	100%	
Submit screening protocol to IRB at MHMC and LSVA	2	100%	
Assemble response for IDE application to U.S. Food and Drug Administration (FDA)	1-5	100%	
Submit IDE response	5	100%	
Finalize consent form & human subjects protocol	5	100%	
Submit implantation protocol to IRB at MHMC and LSVA	5	100%	
Submit implantation protocol to HRPO	5	100%	
Assemble Clinical Events Committee	6	100%	
Submit amendments, adverse events and protocol deviations as needed	as needed		
Milestone Achieved: Local IRB approval of Screening Protocol at MHMC and LSVA	3	100%	
Milestone Achieved: IDE approval from FDA	7	100%	
Milestone Achieved: Local IRB approval at MHMC and LSVA	6	100%	
Milestone Achieved: HRPO approval for all protocols	7	100%	
Subtask 2: Acquire Networked Neuroprosthesis Systems (NNP)			
First round of purchases and assembly (3 systems)	6	100%	
Second round of purchases and assembly (3 systems)	12	100%	
Milestone Achieved: NNP Systems received and sterilized	7,13,17,21	100%	
Major Task 2: Conduct Clinical Study	Months	% Completion	Notes
Subtask1: Subject Screening			
Begin subject recruitment	6	100%	
Subject Screening	6-30	100%	
Milestone Achieved: 1st participant consented and screened	6	100%	
Milestone Achieved: Study begins	6	100%	
Subtask2: NNP Implantation			
Implant Subject #1	11	100%	[1]
Implant Subject #2	14	100%	[1]
Implant Subject #3	17	100%	
Implant Subject #4	19	100%	
Implant Subject #5	21	100%	[1]
Implant Subject #6	24	50%	[2]
Implant Subject #7	26	50%	[2]
Implant Subject #8	28	50%	[2]
Implant Subject #9	30	50%	[2]
Implant Subject #10	33	0%	
Milestones Achieved: Subjects implanted	11-33	50%	
Subtask3: Subject Assessment			
Complete Outcomes Assessments with Subject #1	15	50%	
Complete Outcomes Assessments with Subject #2	19	30%	
Complete Outcomes Assessments with Subject #3	21	100%	
Complete Outcomes Assessments with Subject #4	23	75%	
Complete Outcomes Assessments with Subject #5	25	25%	
Complete Outcomes Assessments with Subject #6	27	25%	
Complete Outcomes Assessments with Subject #7	29	25%	
Complete Outcomes Assessments with Subject #8	32	25%	
Complete Outcomes Assessments with Subject #9	34	25%	
Complete Outcomes Assessments with Subject #10	36	0%	
Complete Usage Tracking with Subjects	23-36	20%	
Milestones Achieved: Subjects Assessed	36	25%	
Milestone Achieved: Usage Tracking Completed	36	20%	
Major Task 3: Data Analysis and Dissemination	Months		
Subtask 1: Data Analysis			
Perform all analyses according to specifications, share output and finding with all investigators	23-36	100%	
Milestone Achieved: IDE annual report submission	20,32	100%	
Subtask 2: Data Dissemination			
Presentation of results at national meetings	12-36	100%	
Preparation of manuscript #1 - first-in-man upper extremity NNP system case study		50%	
Preparation of manuscript #2 - clinical trial of upper extremity NNP system	35	0%	
Milestone Achieved: Manuscript #1 submitted	18	50%	
Milestone Achieved: Manuscript #2 submitted	18	0%	

Notes: [1]: Subject implantation partially completed under separated funding; assessments completed under SCIRP Award funding.

[2]: Trunk system implant (in addition to hand system implant) - each system can be assessed separately

What was accomplished under these goals?

Accomplishments – Introduction

We review the major accomplishments achieved under SCIRP funding. We first review the **Background and Importance** of the NNP System for grasp and reach and emphasize the key "lessons learned" that led to the features incorporated into the NNP System studied in this proposal. We then review the **Clinical Outcomes** of this study, emphasizing the successes and struggles encountered in this study and present the quantitative and qualitative outcomes of the study. We follow this with a discussion of the **Programmatic Accomplishments** of this study. A key goal of this study was to establish the foundation for commercial distribution of the NNP System for grasp and release. Significant advances were made during the course of this study, but there remain significant future milestones in order to complete this long-term goal, and these are reviewed in this section. Finally, we review the **Technical Accomplishments**. As with the Clinical Outcomes, there are both successes and failures related to the technology. These sections serve to summarize the study accomplishments. The work described was focused on restoration of hand and reaching functions for people with cervical level spinal cord injury. The work represents an interim step between our Early Feasibility Investigational Device Exemption (IDE) experience, and a future Pivotal Clinical Trial, which is necessary for our desired commercialization goals for this technology.

Accomplishments – Background and Importance

For individuals with mid-cervical level spinal cord injury, restoration of hand function is their top priority [Anderson, 2004; Lo, 2016]. The existing alternatives for providing hand function for these individuals are limited. Braces and orthotics, such as the wrist-driven flexor hinge splint, can provide limited grasp function but are often abandoned due to a variety of factors, including poor cosmesis, weak grasp force and limited adaptability [Allen, 1971], and this has not fundamentally changed in over three decades [Knutson et al., 2006]. More commonly, the disabled individual utilizes multiple pieces of adaptive equipment to perform the most common and critical tasks. As a result, the individual is limited in the tasks they can perform independently and limited in the environments in which they can function independently. Not surprisingly, these individuals identify the lack of freedom to be spontaneous as a key limitation of their disability [Kilgore et al., 2001].

Neuroprostheses provide the most promising method for significant gain in hand and arm function for cervical level SCI. Neuroprostheses utilize small electrical currents to activate peripheral motor nerves, resulting in controlled contraction of paralyzed muscles. The fundamental aspects of electrical activation of nerves are well understood and the safe levels of stimulation for long-term use have been established [Chae et al., 1998]. Muscle contractions can be orchestrated to produce coordinated grasp opening and closing; thumb opening, closing and positioning; wrist extension/flexion; forearm pronation; and elbow extension for C5/C6 level SCI individuals. The individual controls the coordinated muscle activity through movement of their voluntary musculature. Neuroprostheses can be coupled with tendon transfers in order to further maximize function [Keith et al., 1996].

The only clinical trial of a motor system neuroprosthesis was the NeuroControl Freehand trial for restoration of hand grasp in SCI, initiated by our team in 1992 [Kilgore et al., 1997; Peckham et al., 2001]. The Freehand neuroprosthesis used an implanted eight channel receiver-stimulator (IRS-8), eight epimysial or intramuscular electrodes, leads, and connectors [Keith et al., 1989]. Electrodes were surgically placed on or in the paralyzed muscles of the forearm and hand, and an inductive link provided the communication and power to the implanted IRS-8 pulse generator. The external components of the neuroprosthesis were an external control unit, a transmitting coil and an external shoulder position transducer. The external control unit performed the signal processing of the control inputs and generated the output signal delivered to the implant. Two grasp patterns were provided for functional activities: lateral pinch and palmar prehension [Kilgore, et al., 1989]. Control of grasp opening and closing was achieved through graded elevation of the user's contralateral shoulder [Johnson and Peckham, 1990]. The Freehand system was transferred to industry (NeuroControl Corp. [NCC]), and was implemented successfully in over 200 patients [Kilgore et al., 1997; Davis et al., 1998; Carroll et al., 2000; Biering-Sorensen et al., 2000; Fromm et al., 2001; Peckham et al., 2001; Taylor et al., 2002]. Premarket approval (PMA) from the FDA was received in 1997 (PMA #P950035), and over 40 sites internationally were trained in its deployment.

Summarizing the results from the Freehand System, the neuroprosthesis produced increased pinch force in every recipient, and there was a significant increase in the ability to manipulate objects of different size and weight [Wuolle et al., 1994; Peckham, et al., 2001]. The independence provided by the neuroprosthesis was directly compared to the maximum independence that could be provided by any other means, e.g. orthotics or tendon transfers. With the neuroprosthesis, 100% of the participants (n= 28) improved in independence in at least one task, and 78% were more independent using the neuroprosthesis in at least three tasks (see Section C for test description details). All participants preferred to use the neuroprosthesis for at least one task and 96% preferred to use the neuroprosthesis for at least three tasks [Peckham et al., 2001]. More than 90% of the participants were satisfied with the neuroprosthesis [Wuolle et al., 1999].

The successful multi-center trial clearly demonstrated the ability of this technology to be implemented outside of the research setting. The strategy of implementation for individual patients was established. Through these efforts, the critical factors necessary to transfer a neuroprosthetic technology have been identified, and we have proven that our designs can be the basis of effective products for the disabled population. For the efforts of our research team in bringing the Freehand product to market, in May 1998, Dr. Peckham was awarded the FDA Commissioner's Special Citation Award for "a career dedicated to restoring movement and independence to those who are paralyzed".

Despite the success of the technology itself in restoring function, in 2001 NeuroControl Corporation discontinued all SCI products, including the Freehand System, in order to pursue the larger stroke market. Attempts to interest other medical device companies in returning the Freehand System to the market were unsuccessful. Yet demand for the system continues from both consumers and clinicians alike. Past Freehand recipients continue to use the device for daily function [Kilgore et al., 2009]. Our team

continues to receive referrals for the Freehand System and field requests for system maintenance on a regular basis. The technology is proven beneficial to the users, but the small market size makes continued commercialization of the technology requires a new strategy to ensure sustainability in the medical marketplace.

Therefore, as an integral part of our foundational work, we have also focused significant effort toward developing a viable and sustainable commercialization strategy (see Programmatic Accomplishments). Our work is a critical interim step towards our larger commercialization goals. If our approach is successful, it will result in a technology translation model that can be used to bring additional products to orphan markets, including other neuroprosthetic systems, such as those for pressure sore prevention, cough assist, trunk assist, standing, walking and bladder/bowel function.

Our proposed work is based on successful foundational work in three key areas. First, we have established the basic safety and effectiveness profile of earlier generation neuroprosthetic systems that restore hand function to people with cervical level spinal cord injury using myoelectric control. Second, we have completed the design, development, and initial human implantation of a new concept in implantable neuroprosthetics, the Networked Neuroprosthetic (NNP) System. This new system has the potential to provide significant functional and technological advances in the use of neuroprosthetics in SCI and other disabilities, and is described below. Third, we have introduced the NNP into early clinical evaluation under an approved IDE, thereby establishing FDA's concurrence that the device is safe to begin use in human clinical studies. Our early clinical experience has identified areas of improvement that will be necessary to address prior to expanding use of the system. We expand on each of these three foundational accomplishments below.

Myoelectrically-controlled Neuroprosthesis for Grasp and Reach. The Implanted Stimulator-Telemeter (IST) System was a second-generation neuroprosthesis built in our laboratory whose fundamental design followed directly from the technical and clinical success of our first-generation design, the Freehand System [Kilgore et al., 2008]. The functional specifications for the second generation neuroprosthesis were developed based on interviews with neuroprosthesis users and clinicians and from our own clinical and technical experience. Three key design principles were identified: 1) elimination of external components whenever possible was extremely desirable, 2) the control method should be as natural as possible and customizable to the specific needs, goals and capabilities of each user, and 3) most users could benefit from additional stimulation channels. We sought to address these issues in the design of the second-generation neuroprosthesis. Although the limitations in battery technology in the early 1990's prevented us from developing a *fully* implanted neuroprosthesis, a key feature of the second-generation system was the introduction of *implanted control signal sensing*. An implanted myoelectric signal (MES) recording neuroprosthesis was developed ["IST-12", Kilgore et al., 2008]. The advantages of MES control include the ease of implantation and the potential to use the same recording electrode design for nearly any active muscle, allowing significant customization of control based on each subject's needs. In addition, we were able to provide two separate channels of myoelectric signal recording, thus enabling the development of more natural and more customizable control functions that were applicable to a greater range of potential users. The technical features of the IST-12 System are described in more detail in our publications [Smith et al., 1987; Smith et al., 1998; Hart et al., 2011].

The significant advantages of myoelectric control for upper extremity neuroprostheses have been demonstrated through a clinical feasibility study initiated in 2003 and summarized here. The IST-12 system has been implanted in ten cervical (American Spinal Injury Association Impairment Scale (AIS) C5 or C6) SCI subjects, including three with systems for restoring movement in both hands, as shown in Figure 1 [Kilgore et al., 2008]. Subjects successfully use the processed myoelectric signal from a wrist extensor for proportional control of grasp opening and closing. Subjects have also demonstrated the ability to generate myoelectric signals from trapezius, platysma, deltoid, and biceps muscles. The use of myoelectric control in neuroprostheses allows considerable flexibility in the control algorithms, enabling them to be tailored to each individual person. The study results showed that every subject improved significantly in pinch force strength and in the ability to manipulate objects. Every subject has demonstrated improvement in at least two activities, with one subject demonstrating improvement in 11 of 12 activities tested and another subject demonstrating improvement in 9 of 9 activities tested. All thirteen arms in the ten subjects showed improved function in eating with a fork and 12/13 showed improvements in writing with a pen. Other tasks in which subjects showed improvement included: office tasks, using a cell phone, getting money out of a wallet, and embroidery. Subjects with bilateral systems are able to perform activities such as using a fork and knife to cut food, using two hands to screw and unscrew a lid on a jar, and brushing hair while blow-drying. Figure 1 is indicative of these results. It should be explicitly noted that no other approach has achieved the performance described above.

Figure 1. Functional activities performed using the IST-12 myoelectrically-controlled neuroprosthesis. From left to right: eating with a fork, holding a pen to write, holding a cup, needle embroidery, holding a tennis racquet. These are all activities that the subjects cannot perform independently without the neuroprosthesis.

In summary, the outcomes of the first and second generation neuroprostheses implemented by the Cleveland FES Center have been universally positive, as shown in Table 1. Across all studies, 98.4% (61/62) of the subjects demonstrated success on the Grasp-Release Test (GRT) [Wuolle, 1994], as defined by improvement in the ability to manipulate at least one additional object using the neuroprosthesis. In Activities of Daily Living (ADL) testing [Peckham et al., 2001], 100% (61/61) of the subjects have demonstrated improvement in the ability to perform activities of daily living. Taken together, the results show that all 62 subjects (100%) demonstrated improvement in either the GRT or ADL tests (or both). These results demonstrate the exceptional efficacy of implanted upper extremity neuroprosthetic systems. The FES Center actively supports a number of implanted neuroprosthesis subjects who have now had daily use of their hand in excess of 15 years [Kilgore et al., 2009]. Adverse events have been few, and include two device infections and one electrode infection over the past 25 years. There is a predicted electrode lead survival rate of 98.9% +/- 0.9% at 20 years [Kilgore et al., 2003].

Table 1.

Outcomes Summary - Upper Extremity Neuroprostheses

System	Subjects (# Unique)[1]	GRT Improvement	ADL Abilities Improvement	ADL Habits[2] Improvement	Improvement in at Least One Functional Test
IRS-8/Freehand	50	49/50	28/28	21/21	50/50
IST-10	3	3/3	3/3[3]	-	3/3
IST-12	9	9/9	9/9[3]	-	9/9
TOTAL	**62**	**61/62**	**40/40**	**21/21**	**62/62**

[1] No subjects counted twice. Two IRS-8 subject upgraded to IST-10 systems and one IRS-8 subject upgraded to an IST-12 system.

[2] The Freehand study used a survey based version of the ADL Abilities test called the ADL Habits (see Peckham et al., 2001 for details).

[3] Includes ADL activities related to both grasp and reach.

Design of the Networked Neuroprosthesis. The IST systems demonstrated significant clinical benefit, but the technology itself was not amenable to technology transfer and commercialization, particularly since the fabrication requires tedious manual steps and the circuitry is based on 20+ year old processes that are no longer available. Thus, in order to enable neuroprosthetic technology to become more broadly available, we fully upgraded and redesigned our implant technology, incorporating many key new features and advantages. This new implanted system, the Networked Neuroprosthesis (NNP), is based on a fundamentally different topology than previous neuroprosthetic systems. It is based on a fully modular approach which permits coordinated control and activation to any region of the body through an implanted network of components. The NNP was conceptualized in response to the clinical needs we identified in our clinical feasibility studies. The specifications for this technology platform were compiled by our team [see Kirsch and Kilgore, 2004], and were based on the features necessary to restore function to individuals with paralysis, including not only spinal cord injury, but other diseases such as stroke, multiple sclerosis and cerebral palsy. Three critical features were identified as priorities: 1) a fully implantable system, including powering, freeing the using from the requirement of donning external components for functional use; 2) a modular system where standard components, such as stimulators, power supplies and sensors, could be utilized without modification; and 3) the capability to stimulate and record from multiple regions of the body. These features of full implantability, modularity and distributed topology are discussed in more detail elsewhere [Peckham & Kilgore, 2013; Kilgore, 2013].

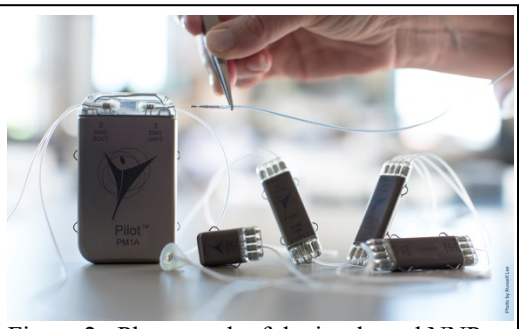


Figure 2. Photograph of the implanted NNP System components. The power module (left) connects through the network cable (held in tweezers) to multiple remote modules (right). The number of remote modules can be expanded as needed to gain the required functions for any particular application. Stimulating and recording electrodes connect to each remote module.

The implanted components of the NNP are a Power Module, a four-channel Pulse Generator Module, a two-channel Biopotential Recording Module, Network Cabling, and Stimulating and Recording Electrodes, as shown in Figure 2. The modules can be connected together as needed for each clinical application, allowing the system to be customized for each subject. Each module contains local processing capabilities in order to minimize the communication rate between modules, and can be programmed through a transcutaneous wireless link. The modules are connected via a network using a single two-conductor lead that distributes power and provides a data communication link between each module, thus simplifying clinical implementation by minimizing lead routing through the body. Network communication utilizes the industrial standard "controller area network" (CAN) protocol. The NNP derives its power from an implanted lithium ion battery that is rechargeable through a single transcutaneous inductive link. Every module also includes additional sensing capabilities, including a 3-axis accelerometer, temperature sensing, and circuit current load.

The design of the NNP eliminates the need for any external components during functional use, resulting in systems that are easy for the users to operate, are robust, are cosmetically acceptable, and are applicable to a broad range of neurological indications. The networked architecture allows the NNP to be applied equally well to modest disabilities using a few components or severe disabilities requiring many components. This novel architecture also facilitates system expansion, technical upgrades, and functional enhancements. The use of implanted power storage, fully implanted sensors, and high performance internal processors frees the user from all external devices during normal operation while also allowing the implementation of much more sophisticated and functional control algorithms. The comparison of the NNP concept with other possible implantable technologies is summarized in Figure 3.

The NNP System is innovative in its fundamental architectural design, yet practical enough to be implemented using technology available today. The key innovation of the NNP concept is that it provides, within a single system, the capacity to implement various configurations of implanted technology, both for stimulation and recording sites, and for addressing multiple body

functions by incorporating additional modules. This is apparent in the upper extremity application, in which the NNP unlocks the potential of advanced sensor-based control systems for use inside the human body. The example configuration that was used in this SCIRP study is diagrammed in Figure 4.

Regulatory Approval to Begin Clinical Evaluation of the NNP. We received full approval by the FDA on September 4, 2015, to begin clinically evaluating the NNP in a small cohort of subjects (N=10) as part of the FDA's Early Feasibility IDE Pilot Program. This approval, along with IRB and HRPO approval, established our ability to initiate the SCIRP study described in this report.

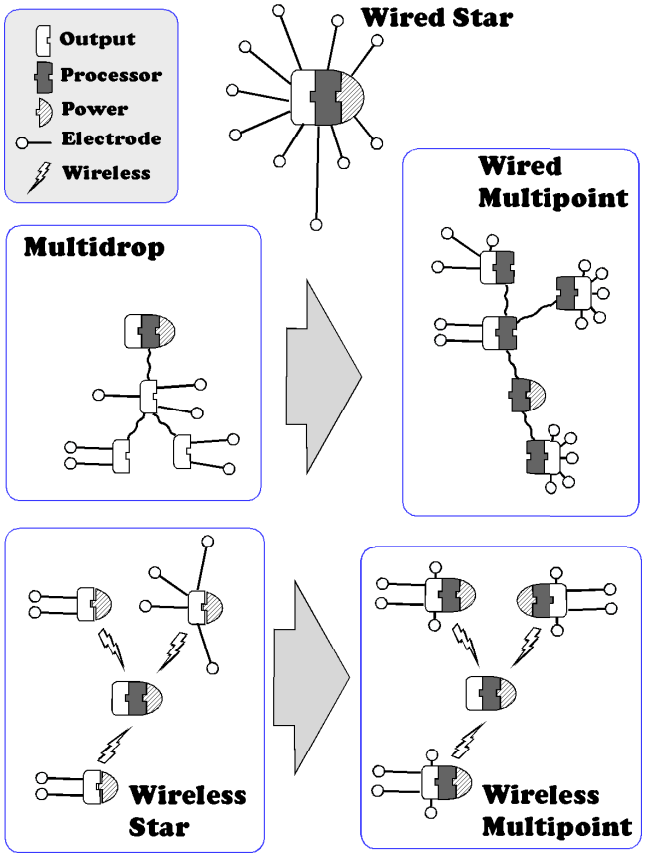


Figure 3. NNP Topology. Implanted motor neuroprosthetic system topologies. Current technologies generally use the wired star, where all of the power, processing and output stages are housed within a single enclosure and all electrodes must be directly connected to that central enclosure. As described in the text, the multidrop configuration is likely to be abandoned for the wired multipoint configuration and the wireless star configuration is likely to be abandoned for the wireless multipoint. The wired multipoint configuration is similar, in principle, to the topology used for standard USB connections.

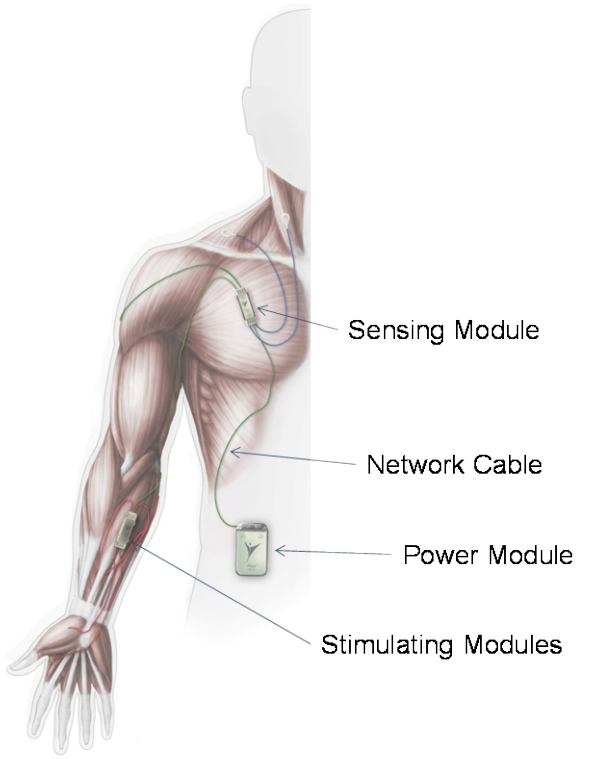


Figure 4. NNP as configured for grasp and release in spinal cord injury.

Accomplishments – Clinical Outcomes – Successes and Struggles

We successfully implanted the Networked Neuroprosthesis (NNP) System in five spinal cord injured subjects. All subject follow-up was performed under the support of SCIRP funding, and the implantation procedure was partially supported under SCIRP funding. Positive functional outcomes were successfully achieved with every subject, although we were unable to complete all assessments with every subject as outlined below. With respect to the two original hypotheses of our project, we successfully demonstrated that "at least 70% of all subjects will demonstrate improved function compared to their baseline performance in one or more activities" (actual success rate was 100%). We were unable to successfully demonstrate our second hypothesis: "the proportion of subjects demonstrating daily usage (7 days/week) of the NNP System will be significantly higher than the published rate of daily usage for the first generation neuroprosthesis." This was due to a variety of medical and technical issues that we have discussed throughout the course of the study (see detailed discussion below). However, during the periods of time in which subjects had full use of their system (i.e. periods without major medical or technical issues), four out of five subjects demonstrated a very high rate of usage. In fact, as we previously reported, one subject demonstrated daily usage for an entire year, which we believe is the first time such a high usage rate has been measured. We conclude that daily usage is likely to approach 7 days/week only after we have resolved the reliability issues of the NNP System.

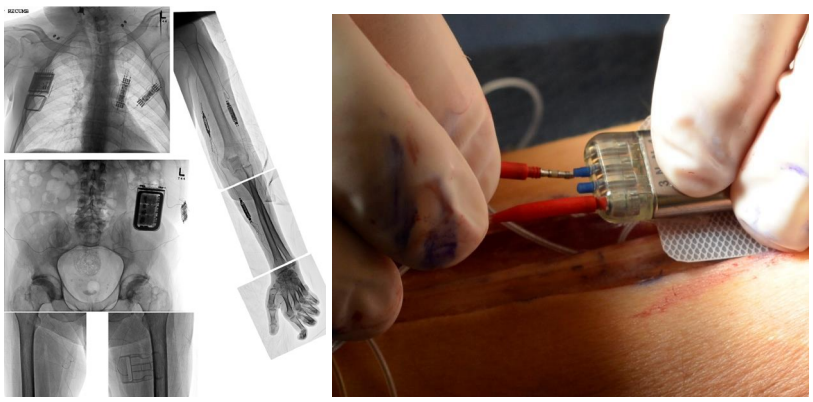


Figure 5. *A) Left side: x-ray of the implanted NNP system for grasp, reach, and postural stability. B) Right side: intraoperative picture showing color-coded connection of a stimulating electrode.*

The first ever human implantation of the NNP System was performed during year 2 of the SCIRP project. The first subject was implanted with a system for grasp, reach, and postural stability. The NNP System included 20 stimulating electrodes, 4 myoelectric signal recording electrodes, 8 3-axis accelerometers, and 11 temperature sensors. All aspects of the system were initially functional and the subject underwent exercise for muscle conditioning. An important aspect of the NNP design is the consideration for practical surgical implantation using standard surgical techniques. Figure 5A shows an x-ray of the complete system, showing the location of each of the modules. Modules are placed near the target muscles for stimulation and recording, and in locations that can be accessed for future surgical servicing (repair/replacement). Figure 5B shows an intraoperative picture of one of the stimulating leads being plugged into the stimulator module in the volar forearm. The first subject demonstrated functional independence ahead of schedule. Figure 6 shows the subject using the NNP hand grasp to hold a fork and stab a blueberry. The subject was unable to hold anything in his hand when the stimulation is off. He was also able to hold a pen and sign his name. Early testing with stimulation of the muscles in his trunk for postural stability (back extensors, hip extensors) demonstrated an increase of 8cm in sagittal reach when the stimulation was on compared to when the stimulation was off. Also, reach above the head and to the side is greatly improved with the addition of trunk stability. Unfortunately, after five months, this subject experienced a Charcot-spine condition in his cervical spine, just below his previous spinal cord injury, and this resulted in a second spinal cord injury (unrelated to the NNP device). This caused extensive denervation of both arms which weakened his grasp and significantly affected the usability of the system. At 18 months post-implantation the subject developed and infection in the Power Module, which had to be removed and rendered the NNP system inoperable.

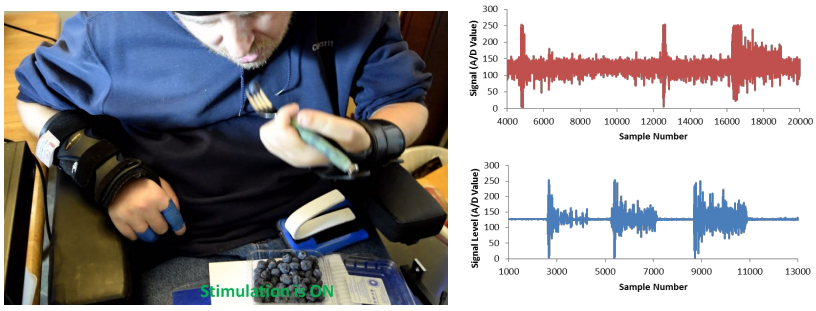


Figure 6. *Left: Subject using the NNP to grasp a fork and stab a blueberry. Right: Myoelectric signals recorded from the NNP during activation of the platysma muscle (top red) and trapezius muscle (bottom blue).*

The NNP System can be customized for the goals and physiology of each subject. The remaining four subjects all received systems that consisted of 24 stimulating electrodes and 2 myoelectric recording electrodes, although the proportion of electrodes devoted to the hand versus trunk function varied. Each subject was programmed with multiple grasp and trunk patterns, as outlined in Figure 7. All subjects received a lateral pinch, which has been demonstrated in the past to be the most common grasp pattern used in daily activities. A palmar grasp was provided to 4/5 subjects, and allows for large hand opening with thumb abduction. This pattern is used to acquire larger objects such as a glass or a book. Three of the five subjects were provided with grasp patterns that were customized to specific activities that they wished to perform, such as holding a sandwich or using a smartphone (pointer grasp).

The primary outcome measure used in this study is the Grasp Release Test, which has been previously validated and accepted by the FDA in previous studies (see Background section). The Grasp and Release Test (GRT) [Wuolle, 1994; Smith et al., 1996; Carroll et al., 2000; Taylor et al., 2002], developed at the Cleveland FES Center, has been utilized by multiple centers to show

improvements in hand function after implantation of a neuroprosthesis and tendon transfers [Peckham 2001]. This pick-and-place test requires the participant to unilaterally acquire, move, and release six objects varying in weight and size. The objects are: 1) a small peg, 2) a wooden cube, 3) a small juice can, 4) a video tape, 5) a paperweight (~1000g) and a simulated fork task (spring-loaded plunger). The number of objects that the participant can successfully manipulate, as well as the number of repetitions achieved in a 30-second trial, are scored. The psychometric properties of the GRT were established by Mulcahey et al. [2004], showing good test-retest reliability with intra-class correlation (ICC) coefficients ranging between 0.87 and 1.00.

The results of the GRT in this SCIRP study are summarized in Figure 8. There are three conditions in which the test is scored. First, prior to any surgical intervention, subjects are scored on the number of objects (out of the maximum six) that they can pick up and move. In most cases, individuals with a C5 level injury, who do not have voluntary wrist extension and therefore do not have a functional tenodesis grasp, cannot pass any of the six objects. As shown in Figure 8, three subjects in this study had a C5 injury and only one subject could pass a single object. Individuals with a C6 level injury have a tenodesis grasp and therefore would

Participant	Prehension Patterns	Postural Patterns
NNP1*	Lateral, Palmar	Sit
NNP2	Lateral	Sit, Side-to-side, Triceps-Pec, Low-Freq Back, Quad Exercise
NNP3	Lateral, Lateral FF, Palmar, Palmar light, Tip, Pointer	Sit, Transfer, Lean Forward, Quad Exercise, Glut Shift
NNP4	Lateral, Lateral FF, Palmar (Exercise)	Sit, Transfer, Lean Forward, Quad Exercise, Glut Shift
NNP5	Lateral, Lateral FF, Palmar, Palmar Light, Intrinsic Plus (Sandwich)	Sitting, Glut Shift, Stand W/C exercise, Quad Exercise, Forward Reach, Dynamic Sit-Up - Right/Left/Forward

Figure 7. Grasp and postural patterns provided to each of the NNP recipients. These patterns are customized based on the functional goals of each recipient and based on their physiology, including the muscles available for stimulation, strength of voluntary musculature, and range of motion available.

Participant	# Objects Passed Before Surgery	# Objects Passed NNP OFF	# Objects Passed NNP ON
NNP1 (C5, 0)	0	0	6
NNP2 (C5, 1)	1	1	*
NNP3 (C6, 2)	2	3	6
NNP4 (C6, 2)	2	*	*
NNP5 (C5, 1) Br-ECRB	0	3	6

Figure 8. Grasp-Release Test (GRT) results of the subject population in the SCIRP study. Three subjects show improvement by 4 to 6 objects between pre-surgery and NNP System capabilities. Two subjects were unable to be tested due to technical issues that prevented full stimulation and control of the hand system.

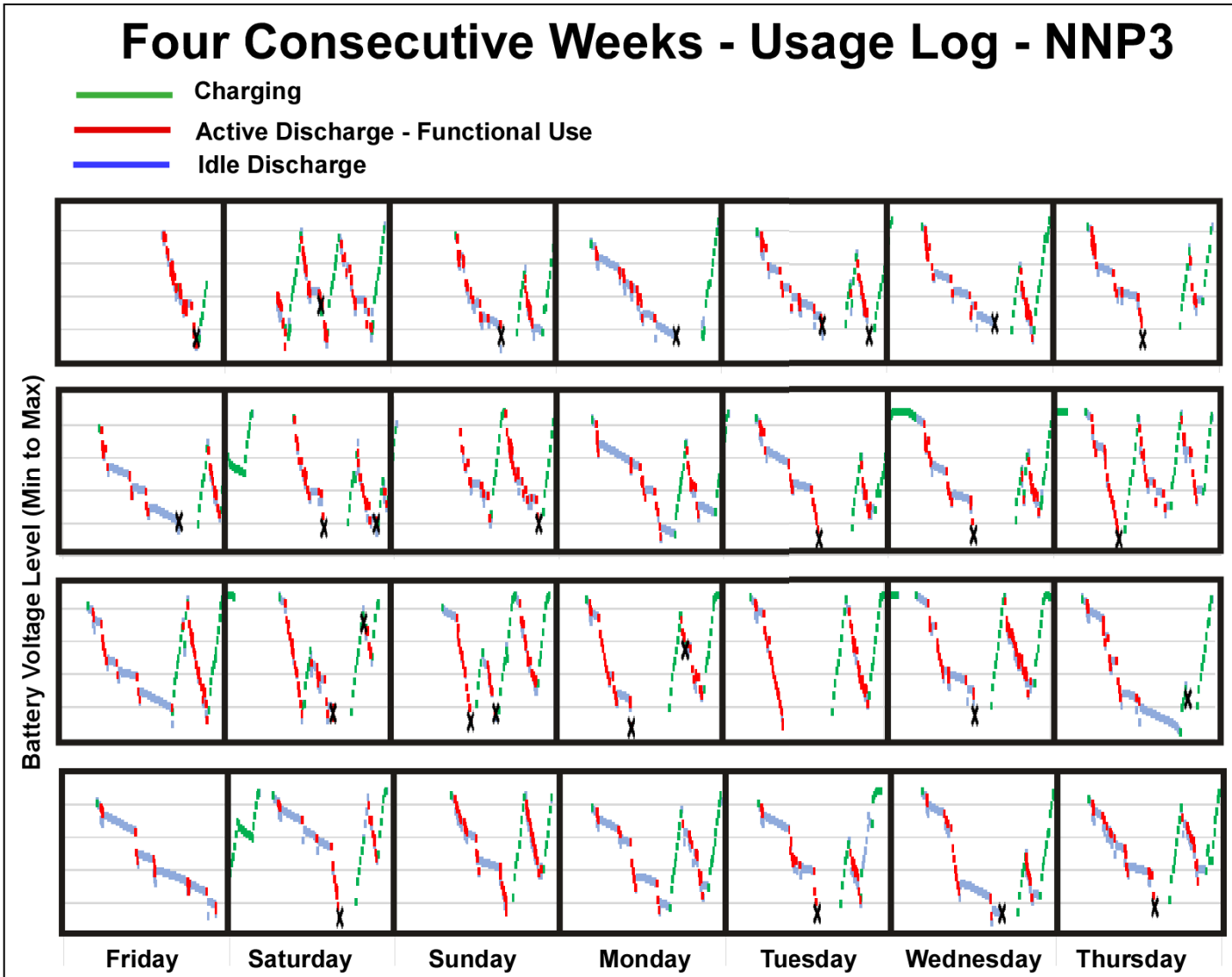
be expected to pass both the peg and cube. Both C6 subjects could achieve this benchmark. Second, the GRT is tested after surgery with the stimulation turned **off** (typically 2-3 months after surgery, which follows the period of immobilization and then muscle conditioning). If the subject had concomitant tendon transfer procedures, they may show increased ability at this stage, even without the stimulation. This is particularly true if the individual gained wrist extension or thumb pinch as a result of the tendon transfers. In our series, two of four subjects improved under this condition. Note, in particular, NNP5 who had the brachioradialis transferred to extensor carpi radialis brevis to provide voluntary wrist extension. This provided the subject with a very effective tenodesis grasp and he was therefore able to pass three objects (compared to zero prior to surgery). Third, the GRT is tested after surgery with the NNP System active and providing stimulated grasp patterns under myoelectric control by the subject. Due to technical issues, we have been able to test three of the five subjects to date, and all three have been able to pass all six objects. This successful result follows the pattern of neuroprosthesis effect previously demonstrated and published, in which 61/62 subjects showed improvement in the GRT (see Table 1).

In addition to the GRT results, subjects were evaluated in their ability to perform daily activities more independently using the stimulation than without the stimulation. Significant success has been achieved with these five subjects. Subjects demonstrated improved functional abilities using the NNP System, such as eating with a fork, picking up finger food, writing, opening doors, taking food out of a refrigerator, holding a glass, improved posture, improved reach, and even improved wheelchair propulsion (see Figure 9). We were not able to achieve the originally proposed cohort of ten subjects due to delays during the project related to manufacture

of the implantable components. These delays were largely resolved by the end of the project period. However we were able to implant nine functional systems in these five subjects, including hand function in four and trunk function in five. Each system was tested independently, and then overall function was tested with the two systems working together. Using this approach, we demonstrated that the combined effect of the two systems on function was significant, and the ability to combine hand function with trunk stability improved function beyond the effect of each system alone.

Figure 9. *Examples of functional tasks accomplished by the subjects in this study. In each of the tasks shown, the subjects demonstrated improved function using the NNP System when compared to their pre-NNP functional status.*

A key aspect of the SCIRP project was the focus is on home usage of the NNP system. During this project we achieved the first implementation of datalogging within the implanted networked neuroprosthesis (NNP) system. We completed the first comprehensive analysis of long term datalogging usage data, with the initial example shown in Figure 10. The data is from Subject NNP3, showing usage rates for a sample four week period (similar data now obtained for out to 12 weeks). This figure illustrates the rich data set that can be obtained from the datalogging capabilities of the NNP System. The data is obtained as a function of battery voltage and system status. The data shows usage in 28/28 days. Every day includes at least one complete charge-discharge cycle, indicating that a full 3-4 hour period of usage occurred every day. On average, usage was approximately 10 hours per day, which indicates an average of more than two complete recharge cycles daily. This is significantly higher than our highest daily usage rate for the previous generation system, where the highest rates were 2-3 hours per day. The additional usage represents the significant benefits of the hand system combined with the trunk system.



Fiugre 10. Example of information obtained from the datalogging function developed in the SCIRP project. Each graph represents a successive day from an entire consecutive 28 day period. The x-axis shows the time during the day (each box is a 24 hour period). The y-axis shows the battery voltage levels, which is one accurate measure of usage. In particular, the charging periods (green dots) show the intentional act of preparing for the next period of use. Surprisingly, this subject typically charges twice a day, which is more frequent than we anticipated and illustrates this subject's desire to have continued use of the NNP System for 12-16 hours per day.

During the SCIRP project period, we expanded our usage monitoring to include monitoring system status parameters. A key parameter is the temperature of the power module (containing the rechargeable battery). As described in Technical Accomplishments section (below), we have developed a water-cooled coil recharge system. Figure 11 shows the temperature of the power module averaged over a two week period of usage (from Subject NNP3). The temperatures indicated are in degrees Celsius. Note that for the vast majority of time, the Power Module is at or just below normal body temperature. Out of a typical day consisting of 20 hours of "on" time, the Power Module is in the temperature range of 38-40°C for only 150 minutes. This has significant implications regarding the potential tolerability of increased heating during recharge, since the typical standard (maximum of 40°C) is based on a 24 hour a day heating, whereas our usage data is showing that the Power Module is only at these slightly elevated temperatures for an order of magnitude lower than that target. Also note that our cooling system is extremely effective in cooling the implanted device as the PM spends about one third

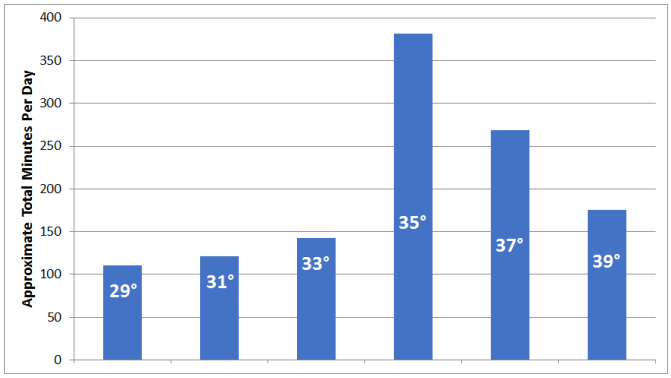


Figure 11. Time spent with the power module at different temperature ranges (values in Celsius). Maximum allowed temperature is 40 deg C, but note that the majority of the time, the power module is actually maintained below body temperature. This shows the effectiveness of the water-cooled recharge coil in maintaining appropriate temperature control.

of the day at temperatures ranging from 28°C to 34°C.

The complete summary of usage patterns for each subject is shown in Figure 12. During the course of the SCIRP project (ending 9/2018) we accumulated 17 months of daily usage. Blue squares show the period of implantation and post-op recovery when the system is not available for use. The numbers in the green squares indicate the cumulative months of daily usage. In fact, for the last three subjects implanted, only technical issues have prevented continuous regular use of the NNP System to date. As the study progresses and we gain experience with the system, we expect that periods of disuse due to technical issues will reduce to very infrequent events (less than a few days per year). We have now accumulated over 2000 charge-recharge cycles during functional use between the most recent three subjects, providing valuable technical experience with the system.

The first two subjects experienced a high degree of both technical and medical issues. The medical issues include: a second, progressive, spinal cord injury; a device infection; and chronic back pain (pre-existing to NNP System implantation). Medical issues are, unfortunately, common in SCI and cannot be prevented. We have modified our inclusion/exclusion criteria to try to identify and exclude subjects who may have a progressive medical condition that would significantly impact their ability to achieve daily use of the NNP System.

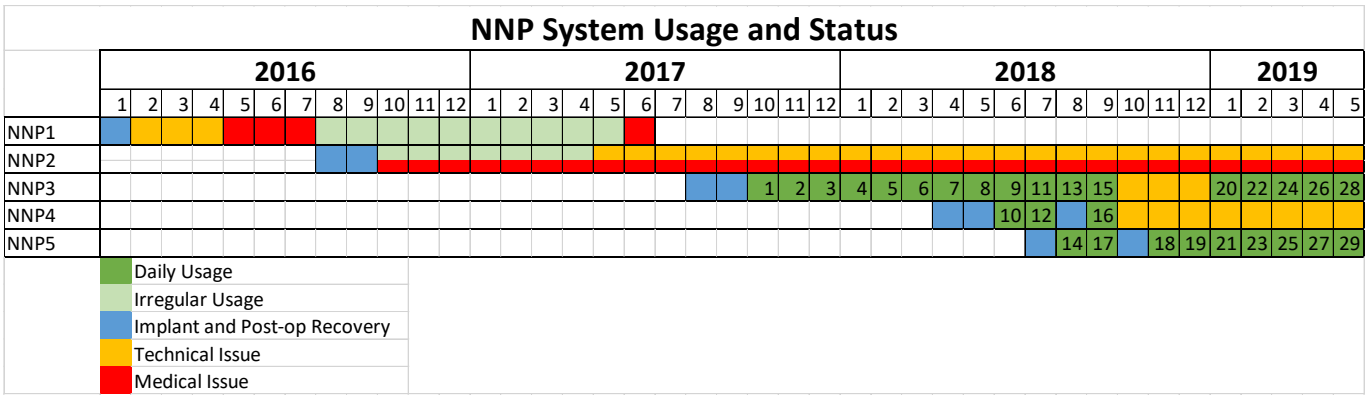


Figure 12. Summary of usage patterns for each subject. We have now accumulated almost 30 months of daily usage among the subjects studied to date. In fact, for the last three subjects implanted, only technical issues have prevented continuous regular use of the NNP System. As the study progresses and we gain experience with the system, we expect that periods of disuse due to technical issues will reduce to very infrequent events (less than a few days per year). The first two subjects experienced a high degree of medical issues, which include: a second, progressive, spinal cord injury; a device infection; and chronic back pain (pre-existing to NNP System implantation). Medical issues are, unfortunately, common in SCI. We have modified our inclusion/exclusion criteria to try to identify and exclude subjects who may have a progressive medical condition that would significantly impact their ability to achieve daily use of the NNP System.

Accomplishments – Programmatic Accomplishments – Successes and Struggles

Significant major accomplishments were achieved during the course of the SCIRP study. These can be summarized as follows:

1. We completed the submission of an Investigational Device Exemption (IDE) to the FDA and received conditional approval to begin the study. We responded to all of the identified conditions and the FDA has now provided unconditional approval to achieve the entire study cohort. This was a major accomplishment and represents the first IDE approval for a battery-powered multi-function neuroprosthesis.
2. IRB protocol for subject screening was obtained quickly, allowing subjects to be screened and prepared for surgery. Throughout the period of the SCIRP study, we have maintained a waiting list of subjects ready for NNP implantation.
3. IRB protocol approval obtained from HRPO.
4. IRB protocol approval obtained from MetroHealth System where the study was conducted.
5. Pre-approval from Centers for Medicare Services to bill for the study-related surgical procedures.
6. Maintained Early Feasibility IDE and IRB approval throughout the study period.

Our numerous interactions with the FDA over the course of the last three years have given us a clear picture of the regulatory requirements for the NNP, particularly around device testing. In addition, we have begun other critical conversations with the agency around our future commercialization plans for the Networked Neuroprosthesis. We have filed formal submissions including two pre-submissions and two IDEs, as noted in Table 2.

Throughout our interactions, we have had numerous positive and fruitful discussions with the FDA review team and with the leadership of the Division of Neurological and Physical Medicine Devices, which oversees products of this type. Our discussions with the FDA around our high-level regulatory strategy culminated in an application to, and acceptance into, the FDA's Expedited Access Pathway in 2016. The Expedited Access Pathway is intended for devices that are innovative, address an unmet clinical need, and are

in patient's best interest. The program offers more systematic attention by an assigned "case manager," as well as access to higher levels of leadership.

Table 2. Prior and Ongoing Submissions to FDA for Networked Neuroprosthesis

Year	Submission Type	Purpose; Outcome
2011	Presubmission	Application to Early Feasibility Pilot Program; Accepted
2011	IDE	Early Feasibility IDE; Disapproved
2014	IDE IDE/Supplements (multiple) IDE/Reports (multiple)	Early Feasibility IDE; Approved Modifications to device, investigational plan; all approved Annual reporting; all accepted
2015	Presubmission Presub/Supplement	High-Level Regulatory Strategy; Introductory Meeting (3/20/15) Application to Expedited Access Program; Accepted

An important emphasis of the SCIRP study was to establish a commercialization pathway for the NNP System for grasp and release. Although we were not able to complete the entire process during the timeframe of the study, we have established significant groundwork for this process. The transition from Feasibility Study to Pivotal Clinical Trial is a formidable hurdle in the development of a new medical device, and involves three major steps: 1) the complete hardening of the technology (i.e. freezing its design, completing device testing on the finished device, and moving manufacturing from "development" to "production"); 2) the transfer of the clinical protocol to multiple sites, where the evidence collected will be sufficient to support a marketing application (the "pivotal clinical trial"); and 3) the approval of a marketing application. Our experience with the formation of and transfer of technology to NeuroControl Corporation in 1994 gives us a framework for anticipating the challenges that this phase poses. Our team experienced being the alpha clinical trial site for that system, serving as the model center for training other sites, creating the original data collection methods and outcome measures, and providing data to support its eventual reimbursement. Under NeuroControl's leadership, but with considerable contribution by members of our current team, the company was successful in bringing two products into the US and European market for SCI applications, one being the Freehand System and the second being the VoCare bladder control system. The Freehand System received PMA approval in 1997 (P950035); the VoCare System, which was licensed from a British manufacturer (Finetech Medical), received Humanitarian Device Exemption (HDE) approval in 1999 (H980005). We subsequently demonstrated that the Freehand system could reduce the overall cost of care for spinal cord injured individuals [Creasey, et al., 2000]. Third party reimbursement was also eventually obtained for the Freehand System [for example, see Cigna Coverage Position Number 0339, Aetna Clinical Policy Bulletin No. 0378, John Deere Health Coverage Update May 2003].

However, while not the direct subject of our SCIRP project, it is important to consider the stages *beyond* the execution of a Pivotal Clinical Trial and eventual market approval, in order to assure that these future stages are set up for success. Again, we can learn from past experience. Despite the clinical success of the Freehand System, and despite having obtained reimbursement for it, in October of 2001, NeuroControl stopped all sales of these devices and focused entirely on development of products for the much larger stroke population. Eventually, *all* of the clinical support for replacement components ended as NeuroControl went out of business in 2005. The Freehand System was a significant clinical success, but a commercial failure. Even *after* NeuroControl ceased sales of the product, Freehand *patients continued to use the device on a regular basis*. Because the Cleveland Functional Electrical Stimulation (FES) Center was the lead site for the original study, many of these users contacted our center, looking for technical support. Through this interaction, we have learned of their extensive reliance on the Freehand technology for their daily functioning.

Our current strategy is a concerted attempt to address past business lessons learned directly from the NeuroControl Freehand experience, while preserving all the positive aspects that the technology provided to patients. Towards this end, we have established a non-profit organization, the Institute for Functional Restoration (IFR) that is based within our academic institution, Case Western Reserve University (CWRU). The mission of the IFR is to restore function to people with spinal cord injury by creating a sustainable business model for neuroprosthetics. The importance of this activity has been recognized by, and has the full support of, the administration of CWRU. By establishing the IFR within the University, we greatly reduce the overhead necessary to establish and maintain all aspects of the organizational structure, such as development (fundraising), technology transfer, and legal.

With guidance from a Business Advisory Council comprised of accomplished medical device company experts, the IFR is the entity driving the current NNP regulatory strategy, establishing critical partnerships with industry, overseeing the conduct of market and economic analyses, and enabling early discussions with reimbursement specialists. If successful, the IFR will serve as a model for similar strategies for deployment of medical technologies to other orphan markets.

The proposed work is an important interim step towards our commercialization goals, but not the final step. Considerable parallel effort will be undertaken to assure that our proposed business model is sound, that the value proposition across multiple stakeholders is well characterized, and that our partnerships with clinical institutions is established. The project will allow us to test and strengthen a number of capabilities that will serve us during the Pivotal Clinical Trial phase and beyond.

Accomplishments – Technical Accomplishments – Successes and Struggles

Throughout the conduct of the SCIRP project, all aspects of maintaining the inventory of implantable technology for the NNP System was a major emphasis and was the primary source of struggles during the project. However, we completed all aspects related to establishing the manufacturing, testing, and sterilization procedure for the NNP System. The system is manufactured at two primary industrial sites: Ardiem Medical, Inc., which manufactures the electrodes, network cabling, and port plugs; and Cirtec Medical, Inc., which manufactures the modules. Key components of the modules, such as the circuit, header, connector springs, and batteries, are manufactured at additional sites and assembled at Cirtec. We have established a complete sterilization protocol with iUVO, our sterilization house (formerly Ethox). They have evaluated all test articles and batch details and have signed off on all aspects of the project. At the close of the SCIRP project we began work with a prospective Manufacturer of Record, Synapse Biomedical, and have now completed an agreement with this company that allows us to acquire complete systems from a single source and should make device acquisition much more streamlined in the future.

There were many aspects of the project conducted during the SCIRP study to design, test, and improve the functioning of the NNP System. These are reviewed in the paragraphs that follow.

Prior to the first implantation, the FDA required complete current leakage testing prior to unconditional approval of the Early Feasibility IDE. These tests were 1) Product Characterization Test (PCT): Damaged Network Cable DC Current, and 2) Design Verification Test (DVT): DC Leakage Current Between Modules. These tests were successfully completed during the first year of the project and the NNP System met all conditions, as follows (in Technical Report Format):

Product Characterization Test (PCT): Damaged Network Cable DC Current

Purpose

To characterize DC current flow caused by a worst-case network disconnect event.

Rationale

The Network Cable delivers power and data to remote modules via a symmetric, <100% duty cycle, 500KHz, square wave signal. This signal, however, is not AC coupled and will deliver net DC current to tissue if left energized.

Setup

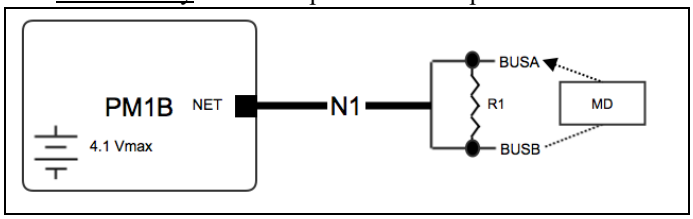
Reference

Measurement setup is derived from ISO 14708-2:2005, Clause 16.2

Materials

Description	MFR	MPN	SN	SW Desc	SW Ver	Note
PM1B	CWRU Cleveland FES Center	PM1B	101	-	317	-
Voltmeter	Agilent	34401A	SG41007482	-	-	400x10^6 ohm Input impedance. Set to measure DC voltage at highest resolution. A minimum of 10 seconds should pass before measurement is recorded.
Resistor, 500 ohm, 1%	-	-	-	-	-	-
4 pole LPF 14708-2	CWRU Cleveland FES Center	XT-8	-	-	-	-

Connectivity – connect power module per schematic:



Connect the voltmeter through the XT-8 4-pole low pass filter to form the Measuring Device (MD). Connect the MD across the terminals of the 500 Ohm resistor.

Results

MEASUREMENT	DESCRIPTION	TRIAL 1	TRIAL 2
Leakage 1	Measure voltage across 500 Ohm resistor	11.065 mV	11.061 mV
	Calculated leakage current	22 µA	22 µA

Conclusion

The network will deliver 22 µA of DC current from a chronic disconnect event. A complete or partial disconnect of any network cable has the potential to expose the subject to unacceptable AC currents. To mitigate this risk, testing is performed

during the surgical procedure to assure adequate connection. Prior to critical steps in the implantation procedure, functional testing is performed on each component in a manner that allows the surgical team to assess full functionality of the unit including its network communication, and to revert to a back-up unit if the test identifies problems. Components are implanted in a distal-to-proximal order, and as each remote module is connected, a functional test is performed using a temporary network connection to confirm network communication prior to embarking on the next stage of implantation. In this way, network communication to distal modules is tested multiple times prior to the final implantation of the Power Module. A final assessment of the complete network is then tested to confirm the lack any intermittent connections that might manifest during gentle movement of the remote modules.

Design Verification Test (DVT): DC Leakage Current Between Modules

Purpose

Measure DC current flow between modules.

Rationale

Running the system on battery power is highly recommended to prevent inadvertent grounding and to provide increased immunity to 60 Hz noise.

References

Limit derived from ISO 14708-1:2000(E) Clause 16

Measurement setup derived from ISO 14708-2:2005 Clause 16.2

Acceptance Criteria

The net DC current (leakage current) of any conductive surface with direct tissue contact must be less than 1 uA.

Materials

Description	MFR	MPN	SN	SW Desc	SW Ver	Note
PM1B	CWRU Cleveland FES Center	PM1B	101	-	317	-
PG4D	CWRU Cleveland FES Center	PG4D	182	-	135	-
PG4D	CWRU Cleveland FES Center	PG4D	183	-	135	-
Voltmeter	Agilent	34401A	SG41007482	-	-	400x10^6 ohm Input impedance. Set to measure DC voltage at highest resolution. A minimum of 10 seconds should pass before measurement is recorded.
10 x Resistor, 500 ohm, 1%	-	-	-	-	-	-
4 pole LPF 14708-2	CWRU Cleveland FES Center	XT-8	-	-	-	-

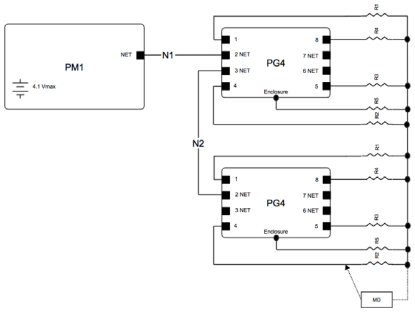
Results

Name	Description	Pass Criteria	Unit	Trial 1	Result
Max Stim	Set stimulus to output to maximum (20 mA,255 µs) on every channel of every module.	-	-	-	-
PG4D182-R1	Measure voltage across R1.	< 500	10^{-6} V	2	PASS
PG4D182-R2	Measure voltage across R2.			4	PASS
PG4D182-R3	Measure voltage across R3.			2	PASS
PG4D182-R4	Measure voltage across R4.			2	PASS
PG4D182-R5	Measure voltage across R5.			7	PASS
PG4D183-R1	Measure voltage across R1.			5	PASS
PG4D183-R2	Measure voltage across R2.			4	PASS
PG4D183-R3	Measure voltage across R3.			2	PASS
PG4D183-R4	Measure voltage across R4.			5	PASS
PG4D183-R5	Measure voltage across R5.			2	PASS

Connectivity Reference

Network Map showing module and network cable arrangement for bench testing.

Network Map



Name	Description
N1-2	Network cable should be: • NNPS Network cable with 25cm maximum length - OR - • 2 conductor copper • 30cm maximum length • twisted pair with a minimum of 1 twist per inch • 26AWG minimum

The successful completion of the DC leakage testing allowed us to obtain IDE approval and commence human testing. With the first human implantation, we identified an issue with the heating of the power module inside the body, as well as heating of the recharge coil. The implanted power supply (the "Power Module") was designed to accommodate module heating during recharge and during functional operation off of the internal battery. Power Module temperature is monitored through four internal thermistors (a fairly unique feature of our system). Our early testing with NNP1 showed that the Power Module heated up faster than our bench testing had predicted. This can be alleviated using a slower recharge rate, but this results in an excessive recharge time (15 or more hours to fully recharge the system). In initial testing with the subject post-implantation, we demonstrated that combining the recharge coil with an ice pack could potentially reduce the total recharge time to three hours or less. Given this promising observation, we proposed to design a water-cooled recharge coil that is practical for daily use by the subject, as diagrammed in Figure 13. We developed this water-cooled recharge coil and submitted the design to the FDA in a Supplement to our IDE. That Supplement was approved and was actively utilized with all five subjects included in the SCIRP study.

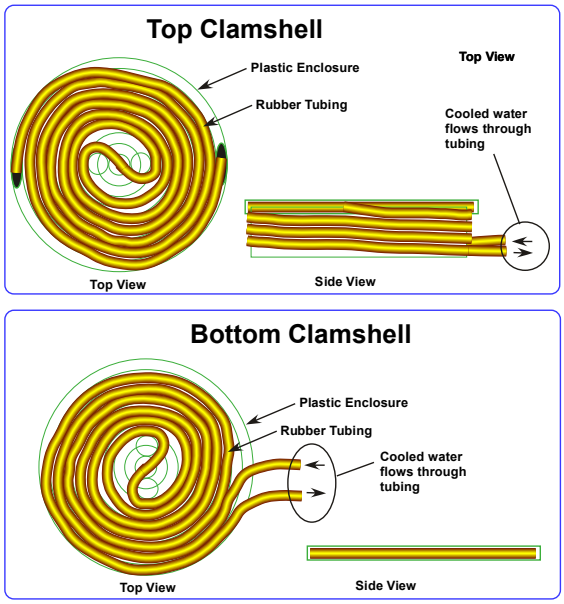


Figure 13. Descriptive figure of the Recharge Coil Enclosure.

Purpose of Coil design. The NNP Active Cooling Enclosure is a plastic, actively water-cooled enclosure for the NNP Recharge Coil. The active cooling maintains skin interface and implanted Power Module at or below the maximum temperature during recharge. The active cooling enclosure also completely encloses the external Recharge Coil so that the Recharge Coil itself does not touch the skin and cannot be touched or directly handled by the User.

Description of Coil Design. The External Recharge Coil safely provides the appropriate time varying magnetic field required to recharge the Power Module. The External Recharge Coil was originally design to be applied directly on the skin over the site of the implanted Power Module. A thermistor is used to measure the temperature of the coil/skin interface. The 3.5 KHz drive level to the Recharge Coil is set in hardware such that the coil temperature at the coil/skin interface cannot exceed 41°C.

As part of the Early Feasibility IDE Study, we identified the External Recharge Coil and the recharging process as areas of examination with each subject to identify the most desirable and practical methods of recharge. We designed an external enclosure that fits around the coil, provides active cooling, and protects against any direct contact with the coil. Using this enclosure, it is now possible to recharge the implanted NNP System in less than three hours, whereas the original design required approximately 15 hours. The Recharge Coil Enclosure consists of two cylindrical clamshells, as shown in Figure 14. The External Recharge Coil fits completely within the clamshells, with only a small opening for the coil cable to exit. The coil cable connects to the Control Tower which is used by each subject for system charging.

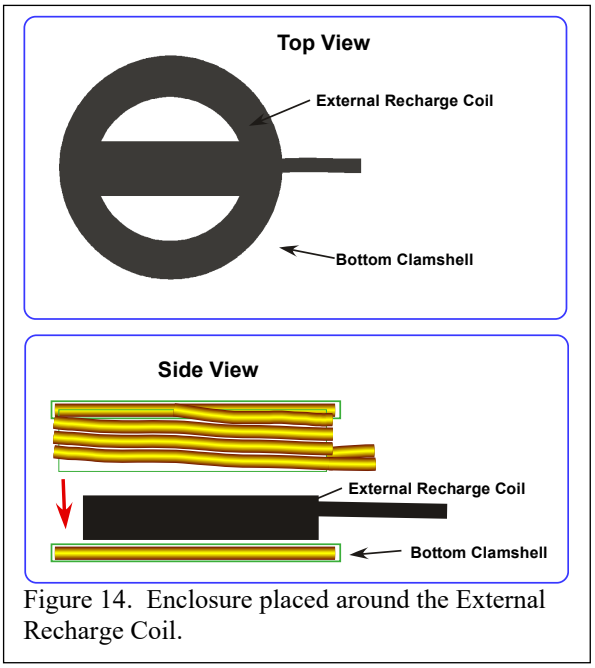


Figure 14. Enclosure placed around the External Recharge Coil.

Each of the two clamshells is a hollow plastic (acetal, nylon, or polycarbonate) enclosure. Within the clamshell is wound a rubber tubing (Tygon A-60-F). Cooled water is pumped through the rubber tubing, providing a cooling effect to the skin and also cooling the external coil itself. Importantly, the cooling maintains the temperature of the outer surface of the Recharge Coil Enclosure below 41°C. The rubber tubing is completely enclosed within the plastic clamshells.

The two halves of the Recharge Coil Enclosure are connected together around the External Recharge Coil and completely enclosed with polyethelyne adhesive tape. The thermistor is placed on the bottom surface of the enclosure, which is in direct contact with the skin. Therefore the thermistor measures the temperature of the skin/enclosure interface. The clamshell is cooled using two Peltier-based cooling pumps (003-07 ThermaZone™ Continuous Thermal Therapy Device). Each pump has a maximum cooling of 4°C and uses distilled water to pump through the tubing within the Recharge Coil Enclosure. The pumps are turned on by the User prior to placing the coil enclosure over the skin. As our testing showed, the cooling effect of these devices while the coil is recharging is typically in the range of 19-23°C (i.e. typically slightly below room temperature).

Results. The Recharge Coil Enclosure was utilized to fully recharge the NNP System in the first subject while in the lab under constant monitoring. The results are shown in Figure 15. The maximum PM temperature was 39.7°C, corresponding to a PM/tissue temperature of 38.7°C. The water-cooled enclosure has the effect of cooling the tissue down to the depth of the PM, as indicated by the steady decrease in PM temperature after ~40 minutes of recharge. The temperature of the skin/enclosure interface was maintained at 19-22°C. This temperature steadily decreased during the 150 recharge period, demonstrating that the cooling pumps are more effective over time. This data was obtained with a 50mA recharge rate per battery, which corresponds to a full recharge from a full discharge in a 3.5 hour period. This allows the subject to recharge in the morning or evenings when he has an aide available to help with positioning of the external coil.

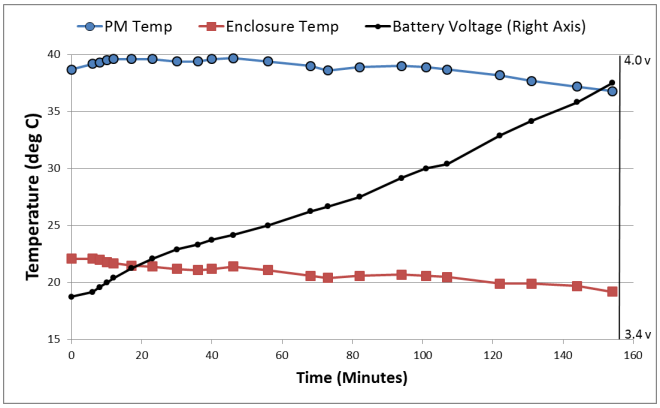


Figure 15. Results of the water-cooled recharge coil compared to the original coil design.

Accomplishments –Summary

In summary, there were significant successes and struggles in this SCIRP project to conduct a clinical trial of the implanted Networked Neuroprosthetic System to provide grasp and release for individuals with cervical spinal cord injury. The key successes were the first-in-man implantation of the NNP System, the successful outcomes for each subject as demonstrated by the GRT and functional testing results, and the successful development of detailed datalogging that can be used to assess daily usage and perform device troubleshooting. The major struggle throughout the project was in maintaining sufficient inventory of the technical components in order to perform surgical implantation. This issue was due to required device testing, to issues of component reliability, and to issues of yield in manufacturing. Component sterilization is an example of these issues. Due to the additional requirements imposed by the FDA, the *average* sterilization process required 14 weeks from start to finish, and the total shelf life of these sterilized components was only 26 weeks. Issues such as these make it very difficult to maintain sufficient device inventory. Despite these issues, we were still able to implant and text five subjects with a total of nine functional systems (four hand systems and five trunk systems). Finally, we encountered significant medical issues with our first two subjects that directly affected each subject's ability to utilize their NNP System, but these issues are to be expected in a cohort of individuals with cervical SCI. Overall, this project provided important groundwork for implementation of the NNP System in SCI and demonstrates the potential of this system to provide function that cannot be achieved through any other means. We are now poised to proceed with our commercialization strategy and make this system available on the medical device market.

What opportunities for training and professional development has the project provided?
"Nothing to Report."

How were the results disseminated to communities of interest?
"Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.
The DoD SCIRP project is now complete. We are now preparing to proceed to a multi-center study of the NNP System for hand function through separate funding.

4. IMPACT:

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What was the impact on the development of the principal discipline(s) of the project?

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project.
We have demonstrated the power of a modular implantable system. Besides the obvious benefits of configurability with respect to multiple clinical applications, we have demonstrated the power of the modular approach to be resistant to component failures.

Specifically, the modular approach provides significant functional redundancy. We have demonstrated that it is possible to surgically implant a modular system that extends essentially throughout the body – from upper thigh, torso, chest, arm, forearm, hand.

What was the impact on other disciplines?
Nothing to report.

What was the impact on technology transfer?
Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Our overall approach remains the same. However, as described throughout the project reports, manufacturing procedures caused delays in the implantation procedure, thus requiring the no-cost extension. We have nearly completed transfer of the manufacturing to a new company that will serve as a general contractor, which should resolve future inventory issues.

Actual or anticipated problems or delays and actions or plans to resolve them
Despite the delays in obtaining inventory of implantable components in a timely manner, we were able to complete the implantation of nine systems in five subjects. However, we were not able to achieve the full cohort of ten within the timeframe originally proposed.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report.

6. PRODUCTS:

Publications, conference papers, and presentations

Ho CH, Triolo RJ, Elias AL, **Kilgore KL**, DiMarco AF, Bogie K, Vette AH, Audu ML, Kobetic R, Chang SR, Chan KM, Dukelow S, Bourbeau DJ, Brose SW, Gustafson KJ, Kiss ZHT, Mushahwar VK. Functional Electrical Stimulation and Spinal Cord Injury. Physical Medicine and Rehabilitation Clinics of North America. 25(3):631-654, 2014.

Peckham PH, **Kilgore KL**, Challenges and opportunities in restoring function after paralysis, IEEE Trans. BME, 60(3):602-609, 2013.

Kilgore KL, "A New Distributed Neuroprosthesis Enables Hand Grasp and Trunk Posture after Cervical Spinal Cord Injury"; American Spinal Injury Association, 2018 Annual Scientific Meeting, Rochester, MN, May 2018.

Kilgore KL, "New Concepts in Networked Implantable Systems"; Neuromodulation: The Science Conference, San Francisco, CA, May, 2016.

Kilgore KL, Bryden AM, Peckham PH, Keith MW, Triolo RJ, DiMarco A, Gustafson KJ, Hoyen HA, Nemunaitis G. Advanced Implantable Neuromodulation Systems. International Microwave Symposium, San Francisco, CA, May 22-26, 2016.

Kilgore KL, Hoyen HA, Keith MW, Triolo RJ, Bryden AM, Lombardo L, Hart RL, Miller M, Nemunaitis GA, Peckham PH. "Implanted network for motor function in cervical SCI", ASIA 2016 Annual Meeting, Philadelphia PA, April, 2016.

Kilgore KL, Bryden AM, Keith MW, Hoyen HA, Nemunaitis GA, Peckham PH, A fully-implanted neuroprosthesis for controlling arm and trunk in cervical SCI. The 4th ISCoS and ASIA Joint Scientific Meeting, Montreal, CA, May 14-16, 2015.

Website(s) or other Internet site(s)
http://restorefunction.org/

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
US Patent No. US 9,108,060 – "Neural Prosthesis"
Inventors: Kevin Kilgore, Hunter Peckham, Tim Crish, Brian Smith

Other Products

- Book Chapters

Brose SW, **Kilgore KL**, Triolo RJ, DiMarco AF, Bourbeau DJ, Nemunaitis G. Functional Electrical Stimulation for Patients with Spinal Cord Injury, In Spinal Cord Medicine (3rd Edition), Kirshblum S, Lin VW, Eds., Springer Publishing, c. 2018.

Jayme S. Knutson, Nathaniel S. Makowski, **Kevin L. Kilgore**, John Chae, Neuromuscular Electrical Stimulation Applications, In Atlas of Orthoses and Assistive Devices (Fifth Edition), https://doi.org/10.1016/B978-0-323-48323-0.00043-3, c. 2018.

Kilgore KL. Introduction and fundamental requirements of neuroprostheses, In KL Kilgore (ed): Implantable Neuroprostheses for Restoring Function, 1st Edition. Woodhead Publishing, Cambridge, UK, c. 2015.

Kilgore KL. Hand grasp and reach in spinal cord injury, In KL Kilgore (ed): Implantable Neuroprostheses for Restoring Function, 1st Edition. Woodhead Publishing, Cambridge, UK, c. 2015.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

PI: P. Hunter Peckham

Others:

Anne Bryden
Brian Smith
Kevin Kilgore
Megan Moynahan
Michael Keith
Harry Hoyen
Greg Nemunaitis
Ron Hart
Antonia Wilson
Alex Campean
Betty Dunger

Provide the name and identify the role the person played in the project.

If information is unchanged from a previous submission, provide the name only and indicate "no change".

As described in the previous annual reports, No change in role, person months, or contribution from the original submission for any of the personnel on the project.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

N/A

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS:

QUAD CHART: In appendix.

9. APPENDICES: Quad Chart

Efficacy Study of a Fully Implanted Neuroprosthesis for Functional Benefit to Individuals with Tetraplegia

SC130252
W81XWH-14-2-0173

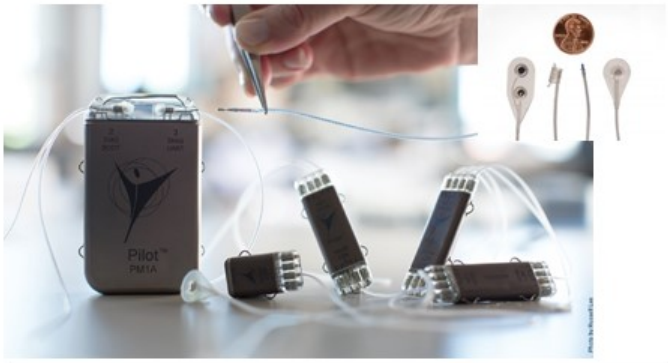
PI: P. Hunter Peckham **Org:** Case Western Reserve University, Cleveland, OH **Award Amount:** $2,363,423

Study/Product Aim(s)

•Task #1 – Implement ten cervical level spinal cord injured subjects and evaluate the resulting improvement in upper extremity function. Compare functional abilities with and without the use of the neuroprosthesis.

Approach

The outcome assessments are designed around two hypotheses regarding the advantages of the Networked Neuroprosthesis (NNP): #1. We hypothesize that at least 70% of all subjects will demonstrate improved function compared to their baseline performance in one or more; and #2. We hypothesize that the proportion of subjects demonstrating daily usage of the NNP System will be significantly higher than the published rate of daily usage for the first generation neuroprosthesis.



Accomplishment: First subjects have been successfully implanted and have demonstrated functional use of the hand and trunk.

Timeline and Cost

Activities PY	1	2	3	
Regulatory and Administrative				
Technology Acquisition				
Implantation of NNP				
Assessment of Outcomes				
Estimated Budget ($K)	**$792**	**$446**	**$262**	**$000**

Updated: Dec. 26, 2018

Goals/Milestones (Example)

PY1 Goal – Complete Regulatory; Acquire first systems, First implant
☑ IDE
☑ Acquire first systems (100% complete)
PY2 Goals – System Implantation and Evaluation
√Acquire technology (100% complete)
√ System Implantation (100% complete)
√ System Evaluation – Functional Assessments
PY3 Goal – System Implantation and Evaluation
√ System Implantation (50%)
√ System Evaluation – Functional Assessments (25%)

Comments/Challenges/Issues/Concerns

- Encountered manufacturing yield issues and slow procedures.
- Delay- initial surgeries – still expect to complete project in 4 years.

Budget Expenditure to Date

Projected Expenditure: $1.2M
Actual Expenditure: $1.2M