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AWARD NUMBER: W81XWH-16-1-0503

TITLE: A Closed-Loop Neural Prosthesis for Restoration of Function after Traumatic Brain Injury

PRINCIPAL INVESTIGATOR: Pedram Mohseni, PhD

CONTRACTING ORGANIZATION: Case Western Reserve University

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Significant progress has been made in developing activity-dependent stimulation (ADS) microdevices for use in both rodent and non-human primate (NHP) models of traumatic brain injury (TBI). Specifically, microdevices have been successfully assembled, benchtop tested for functionality, and deployed in a rodent model of TBI to determine the optimal time window for delivery of the therapy and time course of persistence of the ensuing therapeutic effects. Our results revealed that ADS treatment could be delayed up to 3 weeks after injury, while still improving the motor performance. Moreover, our results showed no drop in motor performance eight weeks after ADS treatment ended in rats that started to receive the therapy 1 week after injury.

Moreover, two generations of the NHP microdevice were developed, which were fully functional electrically at the benchtop level, but have required additional work related to reliable, hermetic packaging/assembly approaches to ensure their long-term functionality during neurobiological experiments *in vivo*. Our work on this critical front is still ongoing.

15. SUBJECT TERMS

Activity-dependent stimulation; Implantable microsystem; Neuroplasticity; Rehabilitation, Traumatic brain injury

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	UU	15	**19b. TELEPHONE NUMBER** *(include area code)*

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The goal of this project is to use an implantable brain-machine-brain interface (BMBI) to facilitate functional reorganization in spared cortico-cortical connections and enhance behavioral recovery after traumatic brain injury (TBI) in both rodent and non-human primate (NHP) models, which will remarkably advance the neurorehabilitation field at the level of functional neurons and networks.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Activity-dependent stimulation; Implantable microsystem; Neuroplasticity; Rehabilitation; Traumatic brain injury

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Major Task 1: Develop functional microdevices for rodent studies for Aim 1 – Completed
Major Task 2: Conduct preclinical efficacy study for optimal time window in ambulatory rats using rodent microdevice – Completed
Major Task 3: Develop functional microdevices for rodent studies in Aim 2 – Completed
Major Task 4: Conduct preclinical efficacy study for persistence of therapeutic effects in ambulatory rats using rodent microdevice – Completed
Major Task 5: Develop functional microdevices for non-human primate studies – Currently underway
Major Task 6: Conduct preclinical efficacy study in ambulatory non-human primates – Currently underway

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

In Year 3, the CWRU team worked on **Major Task 1:** *Develop functional microdevices for rodent studies in Aim 1*, **Major Task 3:** *Develop functional microdevices for rodent studies in Aim 2*, and **Major Task 5:** *Develop functional microdevices for non-human primate [NHP] studies* in Aim 3.

Subtask 2 – Major Task 1 & **Subtask 1 – Major Task 3**: *Microdevice assembly and testing*.

All issues with the re-design and deployment of rodent microdevices were satisfactorily addressed by the CWRU team by the end of Year 2. Therefore, in Year 3, the CWRU team continued to assemble and deliver to the KUMC team new rodent microdevices as requested by them in support of **Major Tasks 2** and **4**, which allowed a successful completion of our experimental protocols with rodents. The neurobiological results are reported below in the KUMC portion of the report.

Subtask 1: *Microdevice assembly and testing* (Major Task 5)

Significant progress was made in the assembly and testing of the NHP microdevices as well. Specifically, we finalized the design of the rigid-flex substrate for the NHP microdevice and fabricated our Gen-0 microdevice that included both the head-mounted and backpack portions. Benchtop electronic testing was initially performed to establish the baseline microdevice functionality at CWRU. Our very first neurobiological experiments on an NHP subject were then performed at KUMC using this Gen-0 microdevice. While we were able to verify the feasibility of our surgical procedures, including the integration of the microelectrode-microdevice within the 3D-printed, skull-affixed, plastic chamber, the experiments were ultimately unsuccessful. Two unforeseen challenges prevented successful operation of the Gen-0 NHP microdevice. First, the subcutaneous cable connecting together the backpack and head-mounted portions of the microdevice was soldered at one end to the head-mounted microdevice inside the 3D-printed, skull-affixed chamber. The epoxy that was used to protect the solder joint expanded in volume over time and displaced a critical component on the rigid-flex substrate that ultimately resulted in premature battery drainage. Second, excessive amount of moisture accumulated inside the skull-affixed chamber that ultimately shorted out the electrical components of the rigid-flex substrate, causing microdevice operation failure after several hours of implantation. To mitigate these issues, modifications were made to the design and construct of our Gen-0 NHP microdevice to address the cable connection issue between the head-mounted and backpack portions and obviate the need for soldering and subsequent use of epoxy via using a microconnector. Additionally, medical-grade epoxy materials were identified for encapsulation of the entire rigid-flex substrate so that it can withstand any moisture accumulation inside the skull-affixed chamber. The resulting Gen-1 NHP microdevice was prototyped and again electrically bench-tested at CWRU. Our second round of neurobiological experiments on an NHP subject at KUMC using the Gen–1 microdevice revealed the persistent presence of similar humidity-related issues as before. Specifically, the microdevice power terminals were found to have a moderate level of aqueous metal-ion corrosion, which indicated a degree of moisture penetration of the previously applied epoxy as well as the presence of highly reactive ionic compounds. Starting from first principles, a number of improvements to the previous microdevice encapsulation procedure based on *manual* epoxy application were identified and will be pursued in Year 4.

In Year 3, the KUMC team worked on **Major Task 2:** *Conduct preclinical efficacy study for optimal time window in ambulatory rats using rodent microdevice*, **Major Task 4:** *Conduct preclinical efficacy study for persistence of therapeutic effects in ambulatory rats using rodent microdevice*, and **Major Task 6:** *Conduct preclinical efficacy study in ambulatory non-human primates*.

Subtask 2 – Major Task 2: *Conduct ambulatory experiments for optimal time window (Aim 1)*

Twelve rats successfully completed the experimental protocol, with the data shown in **Fig. 1**. Results indicate a significant effect of group on behavioral task performance ($F = 11.5$ ($F3, 218$); $p < 0.0001$). All treatment groups were significantly different from the non-stimulation control group upon completion of the ADS treatment. Moreover, Week 1 animals had significantly higher performance scores at the end of ADS treatment compared to Week 3 animals. For all treatment groups, there was no significant drop in behavioral performance between the final day of ADS treatment and one week post-treatment ($p > 0.05$). In summary, ADS treatment can be delayed up to 3 weeks after injury, while still improving the motor performance.

Subtask 2 – Major Task 4: *Conduct ambulatory experiments for persistence of therapeutic effects (Aim 2)*

Five rats successfully completed the experimental protocol, with the data shown in **Fig. 2**. Behavior was assessed weekly for an additional eight weeks following ADS treatment in the Week 1 group to assess the persistence of therapeutic effects on motor performance. Results showed no drop in motor performance eight weeks after ADS treatment ended ($p > 0.05$).

Subtask 2 – Major Task 6: *Conduct ambulatory experiments in non-human primates (Aim 3)*

Neurobiological experiments were performed on NHP subjects in collaboration with the CWRU team to assess the overall functionality of the NHP microdevices *in vivo*. Our findings and lessons learned from two rounds of such experiments are described above in the CWRU portion of the report.

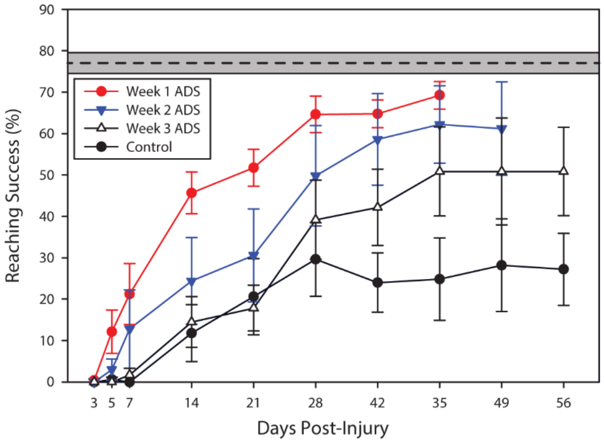

Figure 1: *Performance of rats on a skilled reaching task following a TBI to M1. ADS was initiated at three time points relative to time of injury (Week 1, red; Week 2, blue; Week 3, white; Control, black) and continued for 4 weeks in each treatment group. Control animals did not receive any stimulation. The average pre-injury baseline behavioral success rate of all animals in the study is indicated by the dotted line with a 95% confidence interval in gray.*

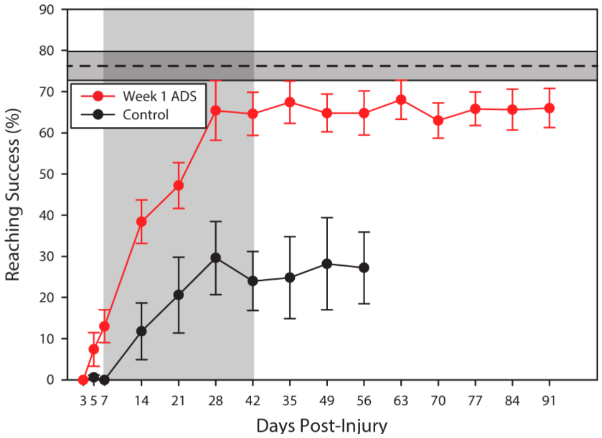

Figure 2: *Performance of Week 1 (red) and Control (black) animals on a skilled reaching task. ADS was applied for 4 weeks starting on Day 7 after the behavioral assessment in the Week 1 animals. Control animals did not receive any stimulation. Light gray block indicates the treatment window. The average pre-injury baseline behavioral success rate of Week 1 and Control animals is indicated by the dotted line with a 95% confidence interval in gray.*

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Four electrical engineering graduate students at CWRU continued their training on a wide range of salient topics, including the development of a wireless link based on a Bluetooth Low Energy (BLE) module for neural interface microdevices, design of implantable microsystems for biopotential recording, and methods of powering/communicating with implantable microsystems. All four students also had professional development opportunities by attending the IEEE Biomedical Circuits and Systems (BioCAS) conference in October 2018.

One postdoctoral fellow at KUMC continued her training on experimental testing of neural interface microdevices, as well as on performing behavioral training, surgical procedures, and post-operative behavioral assessment and analysis.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Results were presented at the IEEE Biomedical Circuits and Systems (BioCAS) conference that took place in Cleveland, OH in October 2018. PI Mohseni served as the General co-Chair of the conference. Results were disseminated in the form of a poster presentation and live demonstration of a functional prototype microdevice.

N. H. Vitale, M. Azin, and P. Mohseni, "A Bluetooth Low Energy (BLE)-enabled wireless link for bidirectional communications with a neural microsystem," in *Proc. IEEE Biomedical Circuits and Systems Conf. (BioCAS)*, pp. 371-374, Cleveland, OH, October 17-19, 2018 **(Selected for presentation in *Live Demonstrations* session)**.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next reporting period, we will continue to assemble and deliver to the KUMC team additional rodent microdevices in support of Major Tasks 2 and 4, if needed. We also plan to assess the effects of elevated humidity found during animal testing on the NHP microdevice and develop more effective hermetic packaging/assembly techniques to mitigate such effects. Such efforts will be critical to ultimately develop long-term-functional NHP microdevices in support of Major Task 6.

Furthermore, we will dedicate significant effort toward neurobiological data analyses resulting from the completion of rodent studies outlined in Major Tasks 2 and 4 with our neurobiology collaborators at KUMC.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are

significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Two unforeseen challenges prevented successful operation of the Gen-0 NHP microdevice in our very first neurobiological experiments at KUMC in Q2. First, the subcutaneous cable connecting together the backpack and head-mounted portions of the microdevice was soldered at one end to the head-mounted microdevice inside the 3D-printed, skull-affixed chamber. The epoxy that was used to protect the solder joint expanded in volume over time and displaced a critical component on the rigid-flex substrate that ultimately resulted in premature battery drainage. Second, excessive amount of moisture accumulated inside the skull-affixed chamber that ultimately shorted out the electrical components of the rigid-flex substrate, causing microdevice operation failure after several hours of implantation.

To mitigate these issues, our efforts focused on modifying the design and construct of the head-mounted portion of the NHP microdevice so that the subcutaneous cable can be connected via a microconnector, obviating a need for soldering and subsequent use of epoxy. We also focused on identifying medical-grade epoxy materials for encapsulation of the entire rigid-flex substrate to protect it against moisture accumulation inside the plastic chamber. This effort in turn necessitated establishing an experimental setup in the CWRU laboratory, for the first time, for accelerated testing of the longevity of various epoxy materials as a function of changes in temperature and moisture content.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

In light of the fact that ACURO approval was received in August 2017, which was almost one year after the start date of the award performance period, we required additional time to complete the proposed specific aims with no additional funds being requested. Hence, we successfully obtained approval for a no-cost extension of the performance period until August 31, 2020.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution *committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

Significant changes in use or care of human subjects

Not applicable.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nicholas H. Vitale
M.S. Thesis Defense: August 7, 2019
Graduation Date: January 2020
Thesis Title: A Bluetooth Low Energy-Enabled Neural Microsystem for Activity-Dependent Intracortical Microstimulation in Non-Human Primates
Current Position: Doctoral Student, Dept of Electrical Engineering, Stanford University

publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

N. H. Vitale, M. Azin, and P. Mohseni, "A Bluetooth Low Energy (BLE)-enabled wireless link for bidirectional communications with a neural microsystem," in *Proc. IEEE Biomedical Circuits and Systems Conf. (BioCAS)*, pp. 371-374, Cleveland, OH, October 17-19, 2018 **(Selected for presentation in *Live Demonstrations* session)**.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the

understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Pedram Mohseni
Project Role: PD/PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-2849-4677
Nearest person month worked: 1.9
Contribution to Project: Dr. Mohseni oversaw the project progress related to the development of microdevices at CWRU, and maintained communications with the collaborating team at KUMC.

Name: Randolph Nudo
Project Role: Subaward PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-4674-0907
Nearest person month worked: 0.9
Contribution to Project: Dr. Nudo oversaw the project progress related to the neurobiological studies at KUMC, and maintained communications with the collaborating team at CWRU.

Name: Nicholas Vitale
Project Role: Graduate Student at CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: 12
Contribution to Project: Mr. Vitale has performed work in the area of bidirectional wireless links for the microdevices based on a Bluetooth low energy (BLE) module.

Name: Meysam Azin
Project Role: Independent Contractor for CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: 4
Contribution to Project: Dr. Azin performed work in the area of algorithms and coding as well as verification of experimental setup reliability and stability.

Name: Reza Erfani
Project Role: Graduate Student at CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Mr. Erfani has performed work in the area of wireless powering of biomedical implants.

Name: Fatemeh Marefat
Project Role: Graduate Student at CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Ms. Marefat has performed work in the area of integrated circuit development for multichannel biopotential recording.

Name: Hossein Zamani
Project Role: Graduate Student at CWRU
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Mr. Zamani has performed work in the area of neural signal processing for online data compression.

Name: David Guggenmos
Project Role: Senior Investigator at KUMC
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Dr. Guggenmos coordinated the work at KUMC, including performing implantation procedures, troubleshooting neurophysiological equipment, and assisting in analysis and interpretation of acquired data.

Name: Heather Hudson
Project Role: Post-Doctoral Fellow at KUMC
Researcher Identifier (e.g. ORCID ID): -
Nearest person month worked: -
Contribution to Project: Dr. Hudson performed the behavioral training, assisted on surgical procedures, and performed post-operative behavioral assessment and analysis.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc, available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other*

Organization Name: University of Kansas Medical Center
Location of Organization: Kansas City, KS, USA
Partner's contribution to the project: Collaboration

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

A Bluetooth Low Energy (BLE)-enabled Wireless Link for Bidirectional Communications with a Neural Microsystem

Nicholas H. Vitale, Meysam Azin, and Pedram Mohseni

Electrical Engineering and Computer Science Dept, Case Western Reserve University, Cleveland, OH, USA
{pedram.mohseni@case.edu}

***Abstract*—This paper reports on the design and implementation of a Bluetooth low energy (BLE)-enabled wireless link for bidirectional communications between a user base station (UBS) and a neural microsystem. The microsystem comprises a previously developed application-specific integrated circuit (ASIC) for activity-dependent intracortical microstimulation (ICMS), and the BLE link is dedicated to remote programming of the ICMS ASIC as well as to remote monitoring of several parameters such as the average stimulus rate, electrode site impedance, or power supply level. A prototype system is developed that incorporates the ICMS ASIC, SAMB11 BLE module, and peripheral electronics for supply management and ASIC monitoring, as well as a BLE user interface custom developed in C#. The end-to-end functionality of the BLE-enabled wireless link is experimentally demonstrated in representative benchtop tests in which several ASIC parameters are successfully programmed from the UBS over a distance of > 3.5m. The prototype system consumes ~618µW from a 3.6V, 1.6Ah, lithium-ion battery and is estimated to feature a lifetime of > 8 months for continuous operation, making it suitable for longitudinal studies with the ICMS ASIC in a non-human primate model.**

***Index Terms*–Activity-dependent stimulation, Bluetooth low energy, brain-machine interface, intracortical microstimulation, neural microsystem, wireless communications.**

I. INTRODUCTION

Activity-dependent stimulation is an emerging approach in neural interfacing for creating artificial connections in the nervous system that can be used to re-establish lost sensory-motor communication channels in the cortex [1], or to regulate the neurochemical levels in the brain [2]. Specifically, in the electrical paradigm, such approaches have been employed to induce functional reorganization by driving Hebbian plasticity-based mechanisms in an injured nervous system [1], [3].

We have previously developed an application-specific integrated circuit (ASIC) for activity-dependent intracortical microstimulation (ICMS) that was capable of performing spike-triggered ICMS in the brain of an ambulatory rat [4], [5]. In longitudinal studies over the span of one month, the ICMS ASIC was successfully shown to facilitate rapid and significant recovery of the motor function in a skilled reach task involving rodent models of focal traumatic brain injury (TBI) in the caudal forelimb area (equivalent to the primary motor cortex) [1].

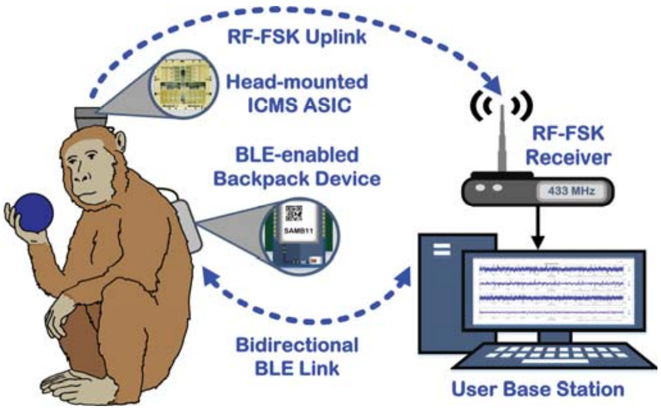

Fig. 1. Illustration of an experimental setup involving a non-human primate equipped with BLE-enabled backpack device for bidirectional wireless communications b/w head-mounted neural microsystem and user base station.

The next step in the evolution of this approach is to demonstrate the efficacy of activity-dependent stimulation in driving motor function recovery in a non-human primate model of TBI. However, such an effort is currently hindered by the lack of a bidirectional wireless communication link between the ICMS ASIC and a user base station (UBS). Specifically, while the ICMS ASIC does incorporate a radio-frequency frequency-shift-keyed (RF-FSK) transmitter operating at ~433MHz for wirelessly transmitting the neural activity on a selected channel to the UBS via the uplink [5], programming various ASIC parameters or temporarily monitoring the ASIC operation can only be done via a wired link from the UBS.

While this strategy was feasible in rodent experiments [1], [4], due to the ease of accessing the head-mounted system for connecting the wired link on a temporary basis, this approach would not work well in experiments with non-human primates in which the head-mounted system is typically enclosed within a skull-affixed primate chamber, making it impractical to use a wired link for programming the ICMS ASIC or monitoring its function during longitudinal studies, except sporadically for simultaneous multichannel monitoring of neural activity from the ICMS ASIC to assess recording quality.

In this work, we address this limitation by developing a low-power, bidirectional, wireless communication link between the head-mounted ICMS ASIC and the UBS using Bluetooth low energy (BLE), an emerging technology for biomedical applications [6]. Figure 1 illustrates an experimental setup involving a non-human primate equipped with the ICMS ASIC as part of a head-mounted device enclosed within a primate chamber, as well as a backpack device that contains a BLE module for bidirectional wireless communications with the UBS.

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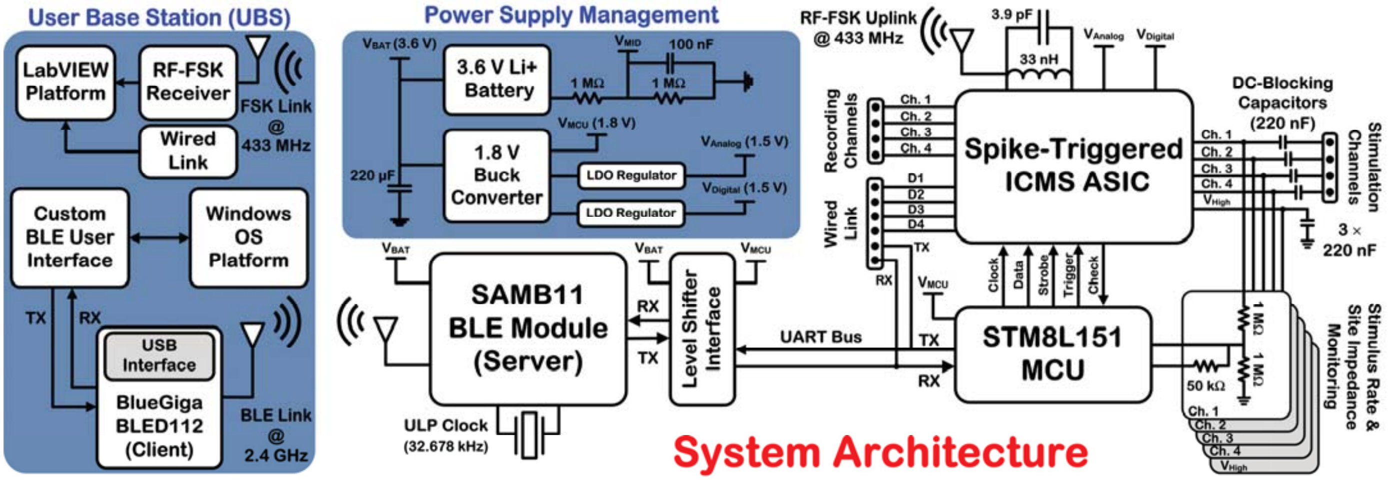

Fig. 2. System architecture for the implementation of a BLE-enabled, bidirectional, wireless communication link between the ICMS ASIC and the user base station.

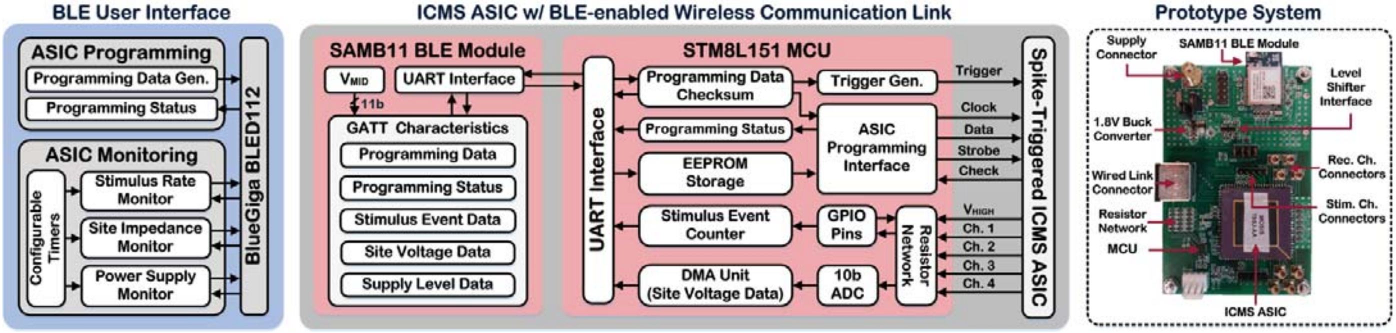

Fig. 3. **Left –** Illustration of the communication flow between the custom BLE user interface in the user base station and the ICMS ASIC. **Right –** Photograph of the system prototype, incorporating the ICMS ASIC, SAMB11 BLE module, and all requisite peripheral hardware.

II. BLE-ENABLED WIRELESS LINK DESIGN

A. *System Architecture*

Figure 2 depicts the system architecture for the implementation of the BLE-enabled, bidirectional, wireless communication link with the ICMS ASIC. The system can be partitioned into three separate sub-systems, namely, a UBS, a BLE module (SAMB11, *Atmel*) and power supply management electronics that are housed in the backpack device, and the ICMS ASIC and a microcontroller unit (MCU, STM8L151G6U6, *STMicroelectronics*) that are housed in the head-mounted device.

The UBS hosts a BLE user interface that is custom developed in C# for a Windows-based operating system (OS). This interface serves as a client-side console through which the user can initiate various BLE tasks for bidirectional communications with the ASIC using a universal serial bus BLE dongle (BlueGiga BLED112, *Silicon Labs*). Moreover, the UBS houses a LabVIEW-based platform that can receive and process neural signals recorded on one channel of the ASIC through the RF-FSK uplink at ~433MHz that is integrated onto the ASIC. If neural signals from all four channels of the ASIC are to be monitored simultaneously, a custom, wired, serial link can be utilized to communicate between the ASIC and the LabVIEW platform of the UBS on a temporary and sporadic basis.

The backpack device contains the BLE module, which serves as an intermediary data server between the UBS and the ASIC. Various tasks that require communications with the ASIC are commanded by the SAMB11 BLE module to the MCU via a universal asynchronous receiver-transmitter (UART) bus after bidirectional level shifting between 3.6V and 1.8V. The backpack device also contains the power supply management electronics, including a lithium-ion battery that directly powers the BLE module and a 1.8V buck converter that powers the low-power MCU. The buck converter also powers two low-drop-out (LDO) regulators that generate the 1.5V analog and digital supplies of the ASIC. Finally, a resistive voltage divider generates a reference voltage, V_{MID}, which is used for power supply level monitoring via the SAMB11 BLE module.

Finally, the head-mounted device contains the ICMS ASIC, low-power MCU, and the two LDOs for generating the ASIC power supplies. Utilizing the bidirectional nature of the BLE link, the system is designed to feature stimulus rate and site impedance monitoring for reporting back to the UBS upon user demand. Specifically, a resistive network is connected to each stimulation channel of the ASIC (and to its "high" voltage output of 5V) to attenuate the stimulus signal and meet the voltage level requirements of the general-purpose input-output (GPIO) pins of the MCU for stimulus rate monitoring, as well as the input level requirements of an analog-to-digital converter (ADC) integrated onto the MCU for site impedance monitoring.

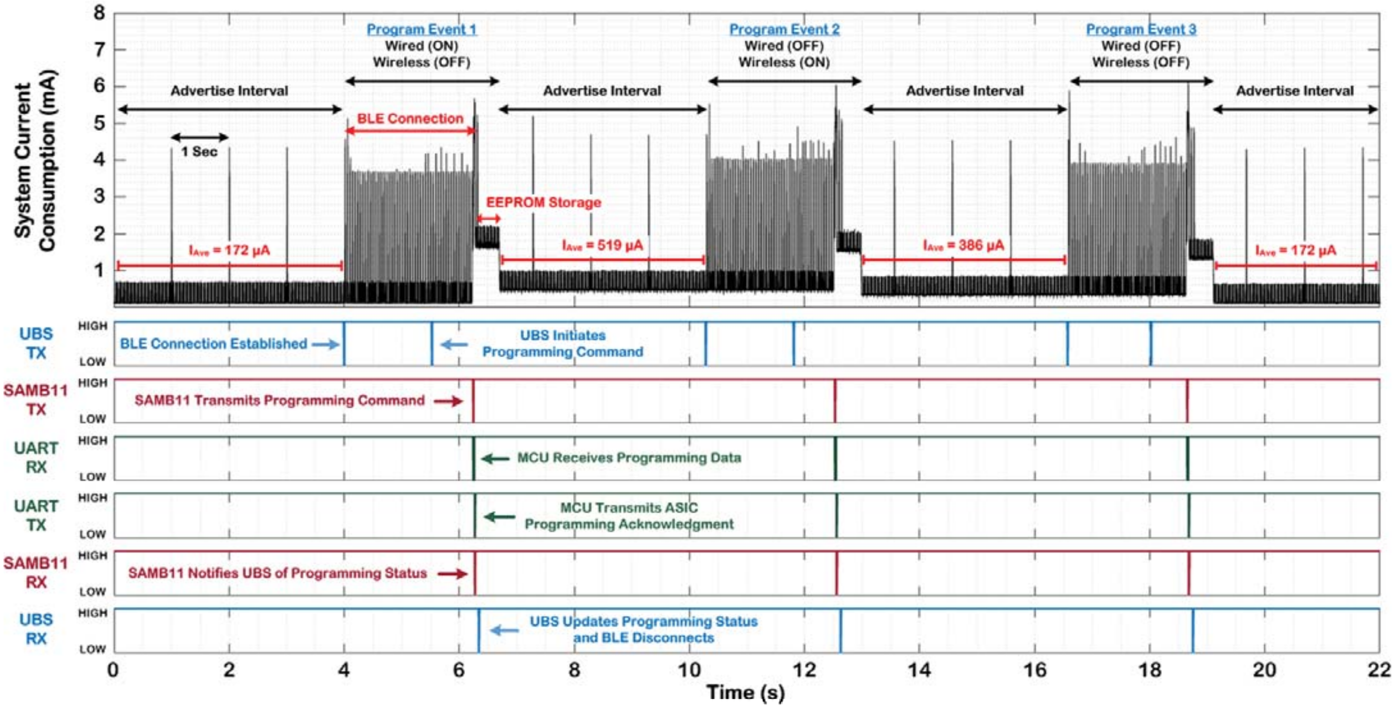

Fig. 4. Measured signals in various phases of system operation during BLE-enabled wireless ASIC programming from the user base station, resulting in successful toggling of ASIC operation between the wired and RF-FSK wireless modes, as reflected in the measured instantaneous system current consumption.

B. *Communication Flow*

Figure 3 illustrates the communication flow between the BLE user interface of the UBS and the ICMS ASIC for both programming and monitoring purposes. For all operations, the data received by the SAMB11 BLE module are stored within custom generic-attribute (GATT) characteristics. For ASIC programming purposes, 95 bytes of data are generated on the UBS and transmitted to the BLE module, containing the settings for the analog and digital blocks of the ASIC (92 bytes), as well as the setting for the source of stimulus trigger (3 bytes). The trigger source can be derived either in an activity-dependent manner from the ASIC itself (closed-loop) or via a *Trigger* signal from the MCU (open-loop). A simple checksum routine is preformed when the programming data are received by the MCU. If valid, the MCU will configure the trigger source and program the ASIC via the programming interface comprised of *Clock*, *Data*, and *Strobe* signals. In return, the ASIC sends back to the MCU an acknowledgment via a *Check* signal as the programming status, which is subsequently transmitted to the BLE module for notifying the UBS. If programming is successful, the MCU will save the programming data to its EEPROM for ASIC boot-up programming. Otherwise, the UBS is notified of the failure, and the MCU will skip over the EEPROM routine.

For ASIC monitoring purposes, the UBS receives information such as the average stimulus rate, electrode site impedance, and power supply level. These monitors can be set to execute on command or poll periodically by utilizing configurable timers located on the UBS. Specifically, the average stimulus rate per channel is monitored by counting the number of stimulation events within a pre-specified time window tracked by the UBS timers. The electrode site impedance is monitored by recording the corresponding site voltage waveform (and that of the "high" voltage output of the ASIC) using the 10b ADC of the MCU and transmitting the information to the UBS via the BLE module. A custom script on the UBS next analyzes the waveforms to evaluate the level of the site impedance. Finally, the supply level is monitored by averaging 256 samples of V_{MID} that are digitized with the 11b ADC of the BLE module and transmitting the results back to the UBS. Custom alerts can be created on the UBS to notify the user when supply level reaches a pre-specified critical value.

III. MEASUREMENT RESULTS

To verify the functionality of the BLE-enabled wireless link in remote programming the ASIC functions from the UBS, representative benchtop tests were performed in which the ASIC was initially configured in its normal operating mode for stimulating on all four channels at a stimulus rate of ~33Hz and current level of ~40μA. Additionally, the wired and RF-FSK wireless links of the ASIC were disabled under the normal operating mode.

In our first experiment, programming data were compiled on and commanded from the UBS to remotely turn ON/OFF the wired and wireless links of the ASIC via the BLE module. Figure 4 shows the measured signals in various phases of the system operation that are time-synchronized with the measured instantaneous system current (in mA).

Prior to the first programming event, the wired and wireless links of the ASIC were disabled, as stated previously, and the BLE module was configured to advertise its identification information once every second. This can be clearly seen in Fig. 4 by the three large current peaks of ~4.4mA occurring once every second. The measured average system current prior to the first programming event was ~172µA in which the SAMB11 BLE module consumed 13.2µA during advertising and idle modes, whereas the buck converter and the level shifter consumed 155µA and 3.8µA, respectively.

For the first programming event (i.e., turn ON the ASIC wired link), the UBS first established a BLE connection and then initiated a programming command for the MCU via the BLE module. Once ASIC programming was performed successfully, an acknowledgment signal was sent by the MCU to the BLE module for relaying back to the UBS upon which the BLE connection was severed. As seen in Fig. 4, within the duration of this programming event (~2.68 sec), the system consumed an average of 764µA, 42.9% of which was due to the BLE module. Ultimately, upon the termination of this programming event, the measured average system current increased from the previous baseline of ~172µA to a new higher level of ~519µA, indicating successful engagement of the ASIC's wired link.

Next, for the second programming event, the ASIC wired and wireless links were turned OFF and ON, respectively. As seen in Fig. 4, the same sequence of events repeated shortly after t = 10 sec, which ultimately decreased the measured average system current by 133µA to ~386µA. A final programming event turned OFF both wired and wireless links of the ASIC, returning the average system current to the baseline level of ~172µA.

In our second experiment, the BLE-enabled wireless link was used to remotely change the stimulus current level of the ASIC from the UBS. As seen in Fig. 5, from the time that the UBS initiated the programming command, it took < 0.8 sec to successfully update the programming status back at the UBS, although it should be noted that the ASIC stimulus current changed (from a maximum level of 94µA to 46µA) almost instantaneously once the MCU received and validated the programming data from the UBS. Collectively, these tests established the overall functionality and fast response time of the BLE-enabled wireless link for remote ASIC programming.

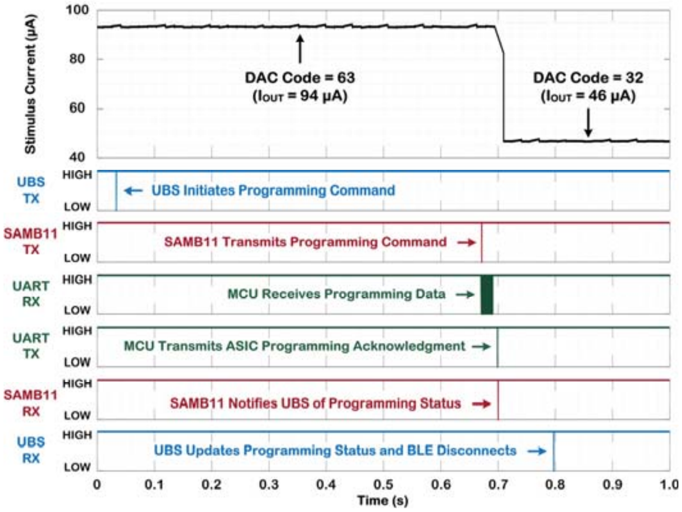

Fig. 5. Measured signals in various phases of system operation during BLE-enabled wireless ASIC programming from the user base station, resulting in successful re-programming of the ASIC stimulus current from maximum level of ~94µA to ~46µA.

TABLE I
SUMMARY OF POWER BREAKDOWN

Subsystem	Building Block	Power (µW)	%
Backpack Device	Level Shifter Interface	13.7	2.2
	SAMB11 BLE Module	47.5	7.7
	3.6V-to-1.8V Buck Converter Loss	127.9	20.7
Head-Mounted Device	MCU	24.1	3.9
	ASIC (Digital)	94.1	15.2
	1.5V LDO Loss (Digital Supply)	38.2	6.2
	ASIC (Analog)	233.7	37.8
	1.5V LDO Loss (Analog Supply)	39.0	6.3
Total System Power Consumption		**618.2**	**100**

Table I tabulates the power breakdown of the prototype system with a 3.6V, 1.6Ah, lithium-ion battery (LTC16M-S4, *Eagle-Picher*). The system consumed a total of 618.2µW during its normal operation mode, with the ASIC and the two LDOs consuming 405µW while the BLE module and the MCU consumed 71.6µW. The system lifetime for continuous operation in its normal mode was estimated to be > 8 months based on our battery lifetime tests, although this estimate is subject to change based on the rate of use of the wired/wireless links of the ASIC and the level of the output stimulus current. It should also be noted that the BLE transmission range in all aforementioned experiments was ~3.6 meters (i.e., 12 ft).

IV. CONCLUSION

This paper reported on the design and implementation of a bidirectional wireless communication link between a user base station and a neural microsystem using low-power BLE technology. A prototype system was developed that incorporated a SAMB11 BLE module, an activity-dependent ICMS ASIC, and peripheral electronics for supply management and ASIC monitoring. The system was successfully used to remotely program several ASIC parameters from the user base station over a distance of > 3.5m, while consuming ~618µW from a 3.6V, 1.6Ah, lithium-ion battery.

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