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Contacts: Emily Ortman, (202) 962-4090
Anne Nicholas, (202) 962-4060

Potential Treatments Emerging for Chronic Spinal Cord Injuries

Techniques overcome scar tissue, generate new nerves, use brain-machine interface to restore motion

WASHINGTON, DC — Research findings suggest possible new approaches to treat chronic spinal cord injuries, which have long been considered untreatable. Scientists report successful efforts to overcome or circumvent seemingly irreparable and long-standing damage at the site of the original injury using a variety of methods, from implantation of early-stage brain cells to brain-machine interface, in which technology allows the brain to communicate directly with an external device such as a motorized wheelchair. These results have the potential to impact millions of people worldwide who suffer from motor deficits caused by spinal cord damage.

The research was presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Worldwide, roughly 250,000 new spinal cord injuries occur each year, and they often cause paralysis below the level of the injury. This increases a person's risk of secondary medical conditions, such as urinary tract infections, respiratory complications, and clinical depression, which affects about one-fourth of those injured.

Presently, there is no cure for spinal cord injury and conventional treatment is limited to physical therapy. Most treatment strategies under development target recently injured patients rather than patients with long-standing disability.

Today's new findings show that:

- More than a year after spinal cord injury, injection of a bacterial enzyme that breaks down scar tissue can improve lung function (Philippa Warren, 523.10, see attached summary).
- Long after the initial injury, early-stage nerve cells transplanted into the site of a paralyzing spinal cord injury in rats generate new nerve cells capable of making long-range connections (Ken Kadoya, PhD, 523.28, see attached summary).
- A high-bandwidth brain-machine interface is able to translate brain signals into instructions that allow monkeys to operate a motorized wheelchair (Miguel Nicolelis, MD, 444.02, see attached summary).
- Paraplegic patients can operate a supportive "exoskeleton" that allows them to walk through the use of an advanced brain-machine interface (Miguel Nicolelis, MD, 636.15, see attached summary).

"Today's findings illustrate the ways that research can harness neuroscience, medicine, and engineering in an effort to overcome the damage caused by spinal cord injuries," said moderator Oswald Steward, PhD, of the University of California, Irvine, an expert in the molecular repair processes in the central nervous system. "New treatments on the horizon promise to be more effective than traditional rehabilitation practices."

This research was supported by national funding agencies such as the National Institutes of Health as well as other private and philanthropic organizations. Find out more about spinal cord injury and recovery at *BrainFacts.org*.

Related Neuroscience 2014 Presentation:
Special Lecture: The Brain is Needed to Cure Spinal Cord Injury
Monday, Nov. 17, 11:30 a.m.–12:40 p.m., Hall D, WCC

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Abstract 523.10 Summary

Lead Author: Philippa Warren, PhD (216) 778-8966
Case Western Reserve University pmw45@case.edu
Cleveland

Researchers Restore Respiratory Function After Paralysis From Spinal Cord Injury

In animal model, technique used to improve breathing more than a year after original injury

A single injection of a bacterial enzyme restored respiratory function in an animal model up to 1.5 years after paralysis caused by spinal cord injury, according to a new research study. The enzyme chondroitinase acts by breaking down scar tissue, which is a known obstacle to spinal cord repair. The findings were presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our research advocates new hope for the repair of paralyzed respiratory muscle activity, even long after the initial spinal cord injury, allowing huge improvements to a patient's ability to breathe," said lead author Philippa Warren, PhD, of Case Western Reserve University in Cleveland. "These findings could lead to treatments that ease the suffering and improve quality of life for the many injured people who depend on artificial ventilation to survive."

Loss of respiratory function is the main cause of death among people paralyzed by high spinal cord injuries. Furthermore, reliance on artificial methods to maintain breathing compromises the quality of life for many survivors. Most previous research has focused on restoring respiratory function immediately following injury to the spinal cord. There has been little investigation into restoring the breathing of people who continue to suffer respiratory difficulties for years after the injury, which is the majority of patients.

Warren and her colleagues showed that a single injection of the bacterial enzyme chondroitinase in an area of the spinal cord dense with respiratory nerves (but not the area of trauma itself) enabled recovery of diaphragm muscle and nerve activity in two-thirds of animals studied.

Furthermore, the study found that combining chondroitinase treatment with respiratory rehabilitation therapy led to normal respiratory function in two out of three cases. The physical rehabilitation involved exposing animals to lower-oxygen environments for short periods of time, encouraging them to take larger and quicker breaths. This provides a trigger for respiratory nerves to fire and thus strengthen the system.

However, the researchers also reported that some erratic muscle activity emerged as a side effect of the combined treatment, indicating that substantial research is required before this combination of techniques could be applied in a clinical setting.

The research was supported with funds from the International Spinal Research Trust, the Craig H. Neilsen Foundation, MetroHealth Medical Center, and the National Institutes of Health.

Scientific Presentation: Tuesday, Nov. 18, 9–10 a.m., Halls A-C

523.10, Extensive recovery of respiratory motor function at chronic and super-chronic time points following cervical spinal cord injury
***P. M. WARREN**[1], P. M. MACFARLANE[2], J. SILVER[3], W. J. ALILAIN[1]; [1]Dept. of Neurosci., Metrohealth Med. Centre, Case Western Reserve Univ. Sch. of Med., Cleveland, OH; [2]Dept. of Paediatrics, [3]Dept. of Neurosci., Case Western Reserve Univ., Cleveland, OH

TECHNICAL ABSTRACT: Treatments to restore respiratory function following chronic cervical spinal cord injury (SCI) have not been extensively studied. We provide evidence that a pharmacological agent and rehabilitative training may provide the key for recovery of diaphragm activity following chronic trauma. The ablation of respiratory function is caused by disruption of motoneuron pathways, formation of the chondroitin sulphate proteoglycan (CSPG) rich astroglial scar, and a reduction in interneuron, motoneuron and synaptic density.

Following acute cervical SCI, CSPG breakdown by application of chrondroitiase ABC (ChABC) can restore functional diaphragm activity while intermittent hypoxia (IH) training increases respiratory drive and synaptic strength. We now provide evidence for the recovery of robust functional respiratory motor activity at both chronic (3 month) and super-chronic (1.5 year) time points following LC2H through a combination of IH training and ChABC. We used diaphragmatic electromyography (diaEMG) and phrenic nerve recordings to demonstrate that a single application of ChABC (0.005U) can recover extensive respiratory motor function following chronic and super-chronic SCI. Control treated animals showed no endogenous recovery of diaphragm function. While having limited effect upon diaEMG patterns, IH training alone was shown to enhance maximal phrenic nerve activity. However, the combined treatment of IH and ChABC was shown to substantially enhance diaEMG and maximal phrenic nerve activity beyond that demonstrated by either group alone.

Interestingly, in a subpopulation of animals the muscle activity in this combination group can become unstructured, degrading patterned activity on the lesioned side. This tonic/chaotic activity is governed by a serotonergic (5-HT) mechanism and suggests considerable remodeling of spinal cord circuitry below the level of the lesion at chronic stages. Indeed, ChABC- and IH-treated animals which recover normal breathing patterns following treatment can be made chaotic by giving exogenous 5-HT, while those that are already chaotic can be normalized by blocking certain 5-HT receptors. These data demonstrate the significant restoration of diaphragm function and nerve activity at chronic and super-chronic time points following cervical SCI due to matrix modification, induction of plasticity and facilitation of drive. Yet, the potential emergence of chaos is indicative of the complications inherent in repairing the chronically injured spinal cord and suggests the need for tight mechanistic and environmental control.

Abstract 523.28 Summary

Lead Author: Ken Kadoya, MD, PhD (858) 822-2140
University of California, San Diego kkadoya@ucsd.edu
La Jolla, Calif.

Scientists Use Developing Nerve Cells to Generate New Nerves Long After Spinal Cord Injury

Transplanted cells mature into new nerve cells and sprout new connections in rat model

New animal research indicates that transplanting nerve cells early in their development into the site of a spinal cord injury long after the time of the injury can generate new nerves. The findings have implications for a new potential treatment for reversing paralysis caused by spinal cord injury. The research was presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"The regeneration of nerves during the chronic stage of spinal cord injury has been a formidable challenge," said lead author Ken Kadoya of the University of California, San Diego. "Our study provides evidence that transplanted early-stage nerve cells can overcome the limitations of the chronically injured environment, grow robustly, and make new connections."

In healthy people, neurons form a kind of wiring network that connects through their extensions called axons. But adult axons generally cannot regenerate or reconnect to neurons beyond the site of injury. One obstacle to such repair is the environment around the injury site, which is often clogged with scar tissue and other biological debris.

The researchers worked with a rat model to transplant a type of stem cell, called neural progenitor cells, into injury sites either two weeks after the injury (subacute stage) or six months after the injury (chronic stage). In both cases, the transplanted rat neural progenitor cells developed normally and generated new neurons. The new neurons extended axons for long distances down the spinal cord and connected with neurons below the injury. Animal studies are underway to determine whether functional recovery can result from this treatment.

The researchers are now testing whether early-stage human neural cells have the same capacity to grow and develop neurons as do rat progenitor cells.

Research was supported with funds from the Veterans Administration, National Institute of Biomedical Imaging and Bioengineering, and the Adelson Medical Research Foundation.

Scientific Presentation: Tuesday, Nov. 18, 11 a.m.–noon, Halls A-C.

523.28, Neural progenitor cells overcome extrinsic inhibitors and extend axons in chronically injured spinal cord
***K. KADOYA**[1], K. NGUYEN[1], M. TUSZYNSKI[1,2]; [1]Neurosciences, UCSD, LA JOLLA, CA; [2]VAMC, La Jolla, CA

TECHNICAL ABSTRACT: The environment of a chronic stage of spinal cord injury (SCI) is more refractory to adult axonal growth, at least due to additional obstacles, including myelin debris and developed scar formation at lesion sites consisting of reactive astrocytes and chondroitin sulfate glycosaminoglycans (CSPGs). At the previous SFN meeting, we reported a great axonal extension from 6 months delayed NPC grafts (chronic) placed in T3 complete transection sites. But there was a significant reduction in their number of axons, compared to two weeks delayed NPC grafts (subacute) placed in the same lesion. Because the size of the graft/lesion; the presence of fibrous tissue separating the graft; and the extent of atrophy of the host spinal cord were different, the undiluted effect of chronically injured spinal cord on axonal growth from NPCs remains to be clarified. To ask this question, in the present study, GFP expressing NPCs were grafted into sites of rat C4 dorsal column injury at a time point two weeks (subacute) or six months (chronic) after the initial injury. Six weeks later, lesion sites were filled with mature neurons and glia without fibrous tissue, and there was no difference of graft/lesion size in both groups. GFP-labeled, graft-derived axons emerged from the lesion site in high numbers and extended over long distances of up to 2cm. Of note, there was no significant difference in the number of emerging GFP axons in host white matter when quantified 3mm caudal and rostral to grafts. In both grafted groups, GFAP and CSPG expression around the lesion site was attenuated compared to control lesioned, non-grafted groups. In another group of subjects, we examined whether degenerating white matter in chronic SCI inhibits NPC-derived axon outgrowth. Lesions were placed in the C5 dorsal columns, and GFP expressing NPCs were micro-grafted subacutely or chronically into dorsal column sensory tract at the C4 level, where axons were undergoing Wallerian degeneration after injury. While much myelin debris was present from one to six weeks after the injury, much of the debris was cleared by six months. When examined six weeks later, extending axons from NPCs in this degenerating tract were in equal numbers in both groups at a point 3 mm rostral to grafts, indicating that NPCs can extend axons robustly in degenerating white matter at the both of chronic and subacute stage of SCI. Collectively, these findings indicate that NPCs exhibit a remarkable ability to extend axons over chronic scar formation around injury site and through degenerating white matter.

Abstract 444.02 Summary

Senior Author: Miguel Nicolelis, MD (919) 684-4580
Duke University nicoleli@neuro.duke.edu
Durham, N.C.

Monkeys Steer Motorized Wheelchair Using Brain-Machine Interface

Advanced technology taps directly into brain, translates brain signals into motor commands

Scientists have developed a brain-machine interface that allows rhesus monkeys to control the movement of a motorized wheelchair. The work demonstrates that wireless recordings from large numbers of brain cells can enable highly accurate and versatile navigation of a wheelchair. The findings were presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Millions of people suffer from disabilities that require them to use a wheelchair," said senior author Miguel Nicolelis of Duke University in Durham, N.C. "Brain-machine interfaces can overcome the limitations of paralysis by connecting intact brain areas directly with assistive devices."

In patients with spinal cord injury, although the connection between the brain and the spinal cord is severed, brain motor function is unharmed. The brain-machine interface bypasses the severed connections. Instead, it records brain activity, extracts motor commands from these recordings, and establishes direct control over the wheelchair, restoring mobility. Previous use of noninvasive brain recordings had limited success because of their limited bandwidth.

To overcome this obstacle, the researchers implanted two rhesus monkeys with electrode recording arrays that connected to several different areas of the cortex, the brain's outermost layer. The researchers used a specially developed portable wireless recording system to extract up to 512 channels of brain signals and transmit them to the controller, which converted them into steering command signals: forward, backward, speed, and turns. The monkeys learned to steer their chairs, which were mounted on the base of a human motorized wheelchair, in order to reach grapes set out in an open area.

Research was supported with funds from the National Institute of Mental Health.

Scientific Presentation: Monday, Nov. 17, 2–3 p.m., Halls A-C.

444.02, Wheelchair navigation with wirelessly recorded cortical ensembles
*P.-H. TSENG[1,2], S. RAJANGAM[1,2], A. YIN[3,2], G. LEHEW[1,2], D. SCHWARZ[1,2], M. LEBEDEV[1,2], **M. A. L. NICOLELIS**[1,2,3,4,5]; [1]Neurobio., [2]Ctr. for Neuroengineering, [3]Biomed. Engin., Duke Univ., Durham, NC; [4]Edmond and Lily Safra Intl. Inst. of Neurosci. of Natal, Natal, Brazil; [5]Ecole Polytechnique Federale De Lausanne, Lausanne, Switzerland

TECHNICAL ABSTRACT: Controlling a wheelchair through a brain-machine interface is a significant step as a neuroprosthetic application. Up to now, only noninvasive recordings have been used for wheelchair control, but these suffer from limited bandwidth. Here we show for the first time that invasive, wireless recordings from large ensembles of cortical neurons can enable highly accurate and versatile navigation of a wheelchair. Two rhesus monkeys were chronically implanted with multielectrode recording arrays in multiple cortical areas. We used our recently developed wireless recording system to sample from hundreds of cortical neurons simultaneously. We challenged the monkeys to drive their chairs, mounted on the base of a human motorized wheelchair, by using their cortical ensembles from the primary motor cortex, the supplemental motor area, and the primary somatosensory cortex. Multiple Wiener filters decoded the monkeys' cortical activity into the navigational signals: forward or backward velocity and turns. Both monkeys successfully acquired the ability to independently steer the wheel chair towards a grape reward in an open area using their cortical activity. They learned to achieve this task with multiple car starting positions and orientations. The monkeys learned the task within a short span of time and developed efficient control of the car. This learning was accompanied by adaptive changes in cortical modulations to the wheelchair movements. We suggest that such neuronal adaptations underlie an incorporation of the wheelchair in cortical representation of the body schema.

Abstract 636.15 Summary

Senior Author: Miguel Nicolelis, MD (919) 684-4580
Duke University nicoleli@neuro.duke.edu
Durham, N.C.

Patients With Paralysis Walk Using Robotic 'Exoskeleton' and Brain-Machine Interface

Patient's brains control wearable prosthetic suit

Eight patients living with paralysis have learned to operate a robotic "exoskeleton" using a brain-machine interface (BMI). The exoskeleton supports the weight of the person inside and is powered by hydraulics and operated by a BMI. Each study participant was able to control walking and kicking in the exoskeleton, according to the findings presented today at Neuroscience 2014, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"One study participant delivered the inaugural kick of the 2014 FIFA World Cup, demonstrating the system's reliability," said senior author Miguel Nicolelis of Duke University in Durham, N.C. "Our results indicate that BMI-based control of an exoskeleton could become a rehabilitation tool for severely paralyzed individuals."

A BMI extracts and translates motor commands from functional brain areas and sends them to machines that execute the desired movement. To conduct the study, neuroscientists, engineers, and clinicians working with the Walk Again Project designed a wearable robotic exoskeleton. A cap of electrodes on the user's head captures activity from multiple sensorimotor areas of the subject's cortex, the brain's outermost layer. A computer mounted on the back of the exoskeleton interprets the brain activity and displays a visual representation of that activity on a LED display in the user's helmet. Based on this display, the user selects movements for the mechanical exoskeleton to perform. Over six months, the researchers conducted 1,152 hours of training for eight individuals living with spinal cord injury.

The system allows the patient to dictate movements such as walking and kicking, while permitting the exoskeleton to manage other motions, like specific joint adjustments. In this way, the users were able to indicate the action that they wanted to perform, while the exoskeleton system ensured its safe execution.

Research was supported through a grant from the Brazilian Government Federal Agency: Financiadora de Estudos e Projetos (FINEP), and the Alberto Santos Dumont Association for Research Support (AASDAP).

Scientific Presentation: Tuesday, Nov. 18, 3–4 p.m., Halls A-C.

636.15, The Walk Again Project: Brain-controlled exoskeleton locomotion
*A. LIN[1], D. SCHWARZ[2,3], R. SELLAOUTI[6], S. SHOKUR[1], R. C. MOIOLI[1], F. L. BRASIL[1], K. R. FAST[1], N. A. PERETTI[1], A. TAKIGAMI[7,8], S. GALLO[9], K. LYONS[10], P. MITTENDORFER[12], M. LEBEDEV[2,3], S. JOSHI[11], G. CHENG[12,13], E. MORYA[1], A. RUDOLPH[14], **M. NICOLELIS**[1,2,3,4,5]; [1]Edmond and Lily Safra Intl. Inst. of Neurosci. of Natal, Natal, Brazil; [2]Dept. of Neurobio., [3]Ctr. for Neuroengineering, [4]Dept. of Biomed. Engin., [5]Dept. of Psychology and Neurosci., Duke Univ., Durham, NC; [6]BiA France, Conflans Sainte Honorine, France; [7]Associação Alberto Santos Dumont para Apoio à Pesquisa, São Paulo, Brazil; [8]Faculdade de Medicina, Univ. de São Paulo, São Paulo, Brazil; [9]École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [11]Dept. of Mechanical and Aerospace Engin., [10]Univ. of California Davis, Davis; [12]Inst. for Cognitive Systems, [13]Electrical Engin. and Information Technol., Tech. Univ. Munich (TUM), Munich, Germany; [14]Colorado State Univ., Fort Collins, CO

TECHNICAL ABSTRACT: As part of the Walk Again Project, a state-of-the-art robotic exoskeleton was designed to enable patients with spinal cord injury (SCI) to perform lower-limb locomotion via brain activity. Hydraulic generators were used to control 15 degrees of freedom (DOF) of the exoskeleton. Real-time trajectory corrections were calculated from data gathered by gyroscopes, strain gauges, force-torque, and pressure sensors positioned along the exoskeleton's limbs, giving it the ability to pivot laterally to stabilize its center of mass. At the interface of the subject's body and exoskeleton, multi-modal sensors were placed to monitor interaction with the exoskeleton. To enable brain-controlled locomotion, movements were discretized into higher level control states. A small computing unit was utilized to 1) receive biosignals from subjects, 2) interpret them as state transitions for the exoskeleton, 3) provide visual and tactile feedback, and 4) monitor user interaction with the exoskeleton. The control system and exoskeleton functioned without the need of an external operator. Sixteen EEG and two EMG channels served as the inputs for discrete state control. EEG during motor imagery tasks was classified by linear discriminant analysis (LDA), using features extracted by common spatial pattern (CSP). The resulting classifier was visualized by the subject via a custom display. Muscle contractions detected by EMG were used to confirm the classifier and initialize state transitions. The transition was sent to the exoskeleton controller, which performed the indicated mechanical trajectory with aforementioned online corrections. Participants received tactile feedback along their inner forearms synchronized with the exoskeleton walk phase. The subject's interaction with the exoskeleton was compared for both static and dynamic walking. A total of eight SCI patients were trained using this control strategy. Results indicate that BMI-based control of an exoskeleton can become a feasible rehabilitation tool for severely paralyzed patients.
Acknowledgments: The authors thank Alberto Santos Dumont Association for Research Support (AASDAP) and the 156 people involved in this project.