Published in final edited form as:

Am J Phys Med Rehabil. 2014 November ; 93(11 0 3): S145–S154. doi:10.1097/PHM.
0000000000000128.

Robotics, Stem Cells and Brain Computer Interfaces in Rehabilitation and Recovery from Stroke; Updates and Advances

Michael L Boninger, M.D.^{1,2}, Lawrence R. Wechsler, M.D.³, and Joel Stein, M.D.^{4,5}

¹ Department of Physical Medicine and Rehabilitation, University of Pittsburgh School of Medicine, Pittsburgh PA.

² Human Engineering Research Laboratory, VA Pittsburgh Health Care System, Pittsburgh PA.

³ Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh PA.

⁴ Department of Rehabilitation and Regenerative Medicine, Columbia University College of Physicians and Surgeons, New York, NY

⁵ Division of Rehabilitation Medicine, Weill Cornell Medical College, New York, NY

Abstract

Objective—To describe the current state and latest advances in robotics, stem cells, and brain computer interfaces in rehabilitation and recovery for stroke.

Design—The authors of this summary recently reviewed this work as part of a national presentation. The paper represents the information included in each area.

Results—Each area has seen great advances and challenges as products move to market and experiments are ongoing.

Conclusion—Robotics, stem cells, and brain computer interfaces all have tremendous potential to reduce disability and lead to better outcomes for patients with stroke. Continued research and investment will be needed as the field moves forward. With this investment, the potential for recovery of function is likely substantial

Keywords

Stroke; Stem Cells; Robotics; Rehabilitation; Brain Computer Interfaces

INTRODUCTION

Stroke is the fourth leading cause of death in the U.S. and effects nearly 800,000 individuals yearly.¹ Despite recent advances in stroke prevention and acute therapy, there are over 6 million stroke survivors living with disability due to stroke.¹ Since the 1980s, progress in

Corresponding author: Michael L. Boninger, M.D. 3471 5th Ave Suite 201 Pittsburgh, PA 15213 (412) 648-6979 (ph) (412) 492-6610 (fax) boninger@upmc.edu.

None of the authors report any conflicts of interest.

stroke treatment has focused on prevention and acute therapy. Only recently has attention turned toward applying robotics, stem cells and brain computer interfaces to foster brain repair and recovery.

Robotics

The development of robotic devices for rehabilitation purposes has grown steadily over the last decade, but the overall impact on rehabilitation care delivery remains modest. The potential applications of robots in stroke rehabilitation may be classified in various ways. We classify them as follows:

- Exercise training devices for neurological disorders
- Wearable powered braces for daily use
- Range of motion/strength training devices for musculoskeletal disorders
- ADL assistance
- Social/Telepresence robots

In this paper, we will focus on the use of robots as exercise training devices in this paper, as this is the best studied rehabilitation application of these devices, and also the most relevant to regenerative medicine.

Cell Based Therapy

Cell therapy is one approach to brain repair that is safe and effective in animal models of stroke. Stem cells migrate to the site of injury, survive and differentiate. Cell therapy is attractive because of the multiple potential mechanisms for benefit in brain repair. Stem cells may differentiate into multiple cell types including neurons, astrocytes and endothelial cells promoting both neurogenesis and angiogenesis. Secretion of growth factors, interleukins or cytokines may enhance the local environment and promote axon growth or synaptogenesis. Suppression of immune responses to brain injury could also reduce the extent of infarction and improve outcomes. Some cell types are capable of integrating with the local environment possibly directly influencing brain function.

Brain Computer Interfaces

Brain computer interface (BCI) generally refer to directly accessing brain activity as a means to obtain control signal for control of devices, or potentially to tap into neuroplasticity. Restoration of upper limb function is a top priority for individuals with stroke. Although initial work has not generally focused on stroke, BCI research has also focused on recovery of upper limb function. Sophisticated, motorized prostheses are being developed^{2,3} that enable natural upper limb movement and have advanced sensing capabilities. These Motorized prostheses can provide function comparable to that of an intact limb, but a high degree-of-freedom control interface is needed. Recent work has shown great success in achieving motor control in two subjects with paralysis.

In this paper we will review that success and discuss the implications of all three approaches for individuals with sequela from stroke. In each area we review the conceptual basis for use

of the therapy and barriers to broader clinical adoption. Finally we discuss how these three separate areas could work in concert to achieve maximum clinical improvement.

ROBOTIC REHABILITATION AT THE CROSSROADS

While exercise training robots may be useful in a variety of disorders (e.g. cerebral palsy, traumatic brain injury, spinal cord injury), treatment of hemiparesis after stroke is the most widely studied application.⁴ The reasons for this focus on stroke include the large number of people affected, the well-documented behavioral benefits and cortical plasticity that occurs in response to exercise training post-stroke, and the relatively focal deficits that commonly leave stroke survivors capable and motivated to participate in robotic therapy.

Why use robots to deliver exercise therapy for stroke rehabilitation? Several arguments in their favor have been advanced. Among the most important is the potential for labor-saving allowing greater therapeutic productivity for therapists. Currently, most exercise therapy is delivered one-on-one by skilled practitioners (chiefly physical and occupational therapists) at considerable cost. Developing devices that would allow delivery of the same amount of therapy with fewer staff, or, greater amounts of therapy with the same personnel resources provides potential economic and clinical benefits. While the optimal amount of therapeutic exercise post-stroke remains unknown, many stroke rehabilitation clinicians and researchers believe that few stroke patients receive sufficient therapy presently to achieve optimal motor outcomes.

There are important economic barriers to achieving the productivity advantages that robots offer. The commercially available robots are expensive, with some costing several hundred thousand dollars. At the same time, these devices remain under rapid evolution, and the useful life of any specific device is likely to be relatively short. Moreover, many of these devices (especially the workstation devices) consume a substantial amount of space – an expensive resource that is often in short supply.

Robotic devices remain highly specialized, and are limited in their ability to truly substitute for human therapy. For example, no currently available robot can assist patient with learning dressing tasks, or with bathroom transfers. Thus robots tend to be used to supplement, rather than substitute for, conventional therapy. While adding robotic exercise to conventional therapy this may be desirable therapeutically, the incremental costs are currently not reimbursable by insurance.

Robot-assisted therapy currently lacks specific reimbursement codes in the United States, and is generally billed as standard PT or OT. This adds the equipment costs of the robots to the cost of providing PT or OT without providing any incremental revenue. This also contributes to the inability to substitute for conventional therapy, as robotic therapy that is not directly overseen by a therapist is not billable under existing rules.

Overcoming these economic barriers is challenging, but there are several strategies that might be employed. One is to reduce the cost of robots through economies of scale so that the costs associated with their adoption are relatively minor in the overall process of rehabilitation. Another would be to move robotic therapy into the home environment, where

patients require less supervision. This approach requires devices that are easier to use, and also development of less expensive devices. An alternative would be to develop robotic gyms, where one therapist supervises multiple individuals.⁵ However, alterations to the payment system are needed to make this strategy economically advantageous.

Another putative advantage of robots is their ability to deliver a well-defined and reproducible form of exercise therapy. Human therapists vary from person-to-person and from session-to-session in the specific activities that constitute exercise therapy. This lack of standardized therapy makes it difficult to precisely compare different therapy techniques. In contrast, robots deliver exercise therapy based on their programming that varies only based on the patient's performance and as dictated by their algorithms. In principle, this ability to precisely control the therapy delivered by a robot should allow reliable studies to compare different treatment algorithms and optimize motor retraining. In practice, the small effect sizes seen for *all* motor therapies (both robotic and non-robotic) in patients with chronically hemiparetic stroke makes comparisons of different treatment algorithms challenging, unless large patient populations are studied.

Many robots can incorporate virtual reality or gaming scenarios to make exercises more interesting for the patient and to maintain a high level of patient motivation. While existing commercial devices have not yet fully leveraged this approach, incorporation of more sophisticated and enjoyable games appears inevitable.

One potentially alluring aspect of rehabilitation robotics is more effective therapy than conventional human delivered rehabilitation. The potential to deliver a more effective treatment algorithm has been hampered by our limited understanding of the optimal form, dosage, and timing of exercise therapy. The ability of robots to deliver greater numbers of repetitions than human therapists with greater consistency is appealing, but robotic therapies have not yet proven to be more effective than dose-matched human delivered treatment.⁶

Given that most available robotic devices are workstation devices that simulate functional tasks rather than allowing performance of actual tasks, it is important to explore the impact of interaction with actual objects in functional context on motor outcomes. The treatment algorithms currently embedded in robots lack the same degree of feedback and adjustment as a skilled human therapist. While robots can be programmed to provide motivating stimuli, they lack the nuanced ability of a human therapist to detect the user's emotional state, motivation, and effort, and adjust therapeutic strategies accordingly.

Many robotic devices contain built-in measurement capabilities, providing an automated means of measuring various aspects of patient movement abilities.⁷ These measures have been demonstrated to be sensitive to change in patients undergoing robot-aided rehabilitation,⁸ and to correlate with clinical measures.^{8,9} While utility as a research tool is well-established, it is not yet clear what role these measures might play in monitoring progress during routine clinical rehabilitative care.

While each robot has a distinct design, there are common themes that allow classification of exercise robots into several broad categories. These include:

Workstation – End Effector Robots

These devices are designed to be used in a therapeutic environment (e.g. gym), and the user interacts with the device in this defined area. The primary means of exerting force on the user is through a single point of contact, typically at the distal part of the limb.

Workstation – Exoskeletal

Workstation robots can also be of exoskeletal design, where the device provides forces at multiple locations along the limb (see figure 1).

Wearable Exoskeletal

Wearable exoskeletal robots are, in essence, powered orthoses (see figure 2). These have the potential advantage of allowing interaction in varied environments and in a variety of activities. Conversely, unlike workstation robots, wearable robots do not generally incorporate virtual reality/gaming. Safety considerations can be complex for wearable devices, because of the less predictable and controlled environment, and the risk of falls while using the device. An important aspect of wearable exoskeletal devices is that they can be used for exercise training purposes, and/or as wearable powered braces for daily use. The use of such devices as powered braces to substitute for weak or paralyzed muscles is notably important for spinal cord injury, but applicable to a number of other neurological conditions as well.

CELL THERAPY

Cell Types

A variety of cell types have been used for cell therapy and each has advantages and disadvantages (see table 1). Neural stem cells include embryonic, fetal and adult cells according to the source. These cells generate multiple cell types that may be beneficial in repairing ischemic injury when there is loss of brain parenchyma. Neural stem cells are easily expanded in cell culture allowing production of sufficient numbers for clinical applications. Embryonic stem cells may be more prone to tumor formation than cells of more committed lineage and both embryonic and fetal derived cells are associated with ethical concerns.

Immortalized cells are transformed by an oncogene or isolated from primitive tumors. They avoid the issues surrounding fetal and embryonic tissue yet, like those cells, are easily expanded in cell culture. Because they must undergo some degree of differentiation prior to transplantation to prevent tumor formation, the cell types produced are more limited. Even with differentiation there is concern about tumor formation given the origin of these cells.

Mesenchymal stem cells (MSCs) are most commonly used at present for cell therapy. These cells may be derived from bone marrow, adipose tissue, umbilical cord blood and dental pulp. They can be isolated from one or more donors then expanded for clinical use (allogeneic) or isolated from a single patient then given back to the same patient after sufficient expansion (autologous). MSCs only transiently survive when implanted in the brain or infused intravenously and thus the likely mechanism by which these cells improve

neurological function is a paracrine function with secretion of growth factors and other substances. Considerable preclinical data show improvement on a variety of functional tests and enhancement of neurogenesis, synaptogenesis and angiogenesis. MSCs also alter the immune response after stroke possibly reducing the contribution of early inflammation to brain injury and impairment of recovery.

The mechanism of action for each cell type may differ depending on the time after stroke onset. In the first 24 hours after stroke neuroprotection is likely most important to prevent further cell loss and apoptosis in penumbral areas. In the early post stroke period, possibly up to one month after stroke, there is active remodeling of the brain and promoting angiogenesis, neurogenesis and synapse formation may be desirable targets. Later, repair of established scar tissue might require scaffolds and multiple cell types capable of forming functioning new connections.

The optimal route of administration may also vary across cell types. Intravenous infusion of cells is most convenient and universally applicable. Cells must pass through the lungs and larger stem cells may clump in passage through the small pulmonary arterioles causing pulmonary and systemic symptoms. Intravenous infusion also distributes cells to other organs besides the brain. Intra-arterial infusion bypasses the lungs but also could potentially occlude small brain vessels and must traverse the blood brain barrier to reach the brain. Direct intraparenchymal injection assures that cells will reach the site of injury. Complications of stereotactic cell delivery are rare but include parenchymal hemorrhage, subdural hematoma, seizures or infection.

Clinical Trials of Cell Therapy for Stroke

In 2000, Kondziolka et al published the first safety and feasibility trial of cell therapy for stroke.¹⁰ Patients 6 months to 6 years after stroke onset were treated by stereotactic infusion of immortalized cells into the basal ganglia. The NT2N cells were isolated from a teratocarcinoma and maintained in cell culture. After treatment with retinoic acid, these cells consistently differentiated into post mitotic neurons that when implanted in animal models of stroke formed synapses and axons resulting in improved performance on functional tests. In the first clinical study 12 patients were treated with 2 or 6 million cells 7-55 months after stroke. One patient suffered a seizure likely related to the stereotactic procedure and another suffered an unrelated brainstem stroke 6 months after treatment. Two patients died during follow-up, one from an MI and another due to pneumonia. In a subsequent Phase II study of 14 patients there were no complications directly related to the infused cells.¹¹ A seizure in one patient and an asymptomatic subdural was attributed to the stereotactic procedure. Improvement compared to baseline was observed in some clinical measures including the Stroke Impact Scale and Action Research Arm Test but the significance of these changes in this small group of patients is uncertain. One patient died from a myocardial infarct 27 months after cell implantation. In this patient, neuropathological studies showed evidence of surviving transplanted neurons in the area of the graft indicating that transplanted cells can survive at least 2 years after treatment¹² (see figure 3).

In the past few years several additional trials of cell therapy have been published.¹³⁻¹⁷ Most used autologous MSCs infused either intravenously or in one case, intra-arterially for MCA

territory strokes. All are relative small studies including 6-16 patients receiving cell infusions. Time from stroke onset varies from 5-9 days to 3-12 months after stroke. These studies all found adequate safety without any cell related complications. Conclusions regarding efficacy are hazardous with such small numbers of patients but in most studies no significant clinical changes were observed. In one study there was an increased rate of change of NIHSS after cell infusions¹⁴ and another found a trend toward improved outcomes after 3.5 years.¹⁵

BRAIN COMPUTER INTERFACES

In discussing BCI, understanding a few concepts are key. One concept is degree of freedom (DOF) of control. One DOF allows for control of a point moving back and forth along a line in space. Two DOF, or 2D, allows for movement along a plane, similar to controlling a computer cursor with a mouse. Three DOF allows for reaching in 3D space. Additional DOF allow for additional levels of control needed to perform complex tasks. A second concept is related to where the BCI signals are recorded. The least invasive source of BCI signals is electroencephalography (EEG). Unfortunately, because the electrical activity of the brain is filter by bone and soft tissue, EEG only allows limited DOF control. We will therefor focus on two other methods of recording data. Electrocorticography (ECoG) records signals from the surface of the brain, thus recording from populations of neurons. Finally microelectrode arrays (MEA) penetrate into the brain a short distance and record from individual neurons.

Below we describe techniques involved and results from two studies at the University of Pittsburgh that demonstrated high DOF control in subject with paralysis at the level of the spinal cord. After presenting this information we discuss the potential relation to stroke.

Motor Mapping for BCI Planning

Because electrode placement is important to success, we complete functional magnetic resonance imaging (fMRI) to map motor-related cortical activity as part of the presurgical planning.^{18,19} The first subject participated in our ECoG BCI study and had C4 complete SCI. The second subject participated in our MEA BCI study and had an multiple sclerosis variant that resulted in complete motor loss below the level of the neck, but intact sensation. During fMRI we used a simple block design paradigm where subjects imagined performing single-joint movements along with a video. Participants imagined performing repeated joint movements to mimic the movement of a 1st person video of the same task. The goal of this mapping was to identify which areas of the motor cortex were active during attempted arm and hand movements to help direct the surgical placement of recording electrodes.

ECoG BCI and Somatotopy in the Sensorimotor Cortex

In our ECoG study¹⁹ signals were recorded with a high-density 32-electrode grid over the hand and arm area of the left sensorimotor cortex. ECoG signals demonstrated modulation when the participant observed and simultaneously imagined right hand and arm movement even though the participant was unable to generate overt movements. The most prominent modulation patterns were an increase in power for the gamma and high-gamma bands and a decrease in power for the sensorimotor rhythm (10-30Hz), both tightly coupled in time with

movement. Attempted movements of hand and elbow elicited distinct cortical activity patterns, with the centers of activation being lateral for attempted hand movement and medial for attempted elbow movement on the ECoG grid.

Based on the different cortical activation patterns for different imagined movements, the participant was able to volitionally modulate sensorimotor cortical activity to achieve high-fidelity real-time BCI control of 2D and 3D cursor movement. The subject reported that imagining specific movements, such moving a videogame joystick, was more effective than just thinking about “moving his thumb”. That motivated us to study the effect of goal-directed tasks for covert brain mapping. Using imagined movement to drive the computer cursor, the subject achieved a success rate of 87% over 176 trials in the last 2D cursor control session. By the end of training, the participant achieved an 80% success rate for 3D cursor control. On Day 27, the participant controlled 3D movement of a prosthetic arm successfully to hit physical targets and “high-five” members of the research team. The subjects commented that this was the first time that he reached out to another individual in seven years. This not only demonstrates the potential utility of an ECoG BCI based on somatotopic organization, but also that BCI control can be translated to different end effectors.

Intracortical MEA BCI

In order to perform activities of daily living, one needs to be able to position the hand in space, orient the palm, and grasp an object. Non-human primate studies have shown that intracortical MEAs can capture natural movement-related information that can enable these movements.^{20,21} Our research group demonstrated that a person with tetraplegia was able to rapidly achieve control of a state-of-the-art motorized prosthetic limb (MPL, Johns Hopkins University, Applied Physics Laboratory).³ Two MEAs were implanted in motor cortex based on pre-surgical functional mapping. The neural decoder, which translate the brain activity into movement commands for the arm was trained while the subject observed motion of the sophisticated multiple degree of freedom prosthetic arm (MPL under automatic computer control. After 13 weeks of training, robust 7D (3D translation, 3D orientation, 1D grasping) movements were performed routinely. These movements included reaching and grasping tasks, similar to many activities of daily living, which were carried out with coordination, skill, and speed approaching that of an able-bodied person. This BCI allowed the study participant to perform a wide variety of tasks including shaking hands, stacking cones, and eating (Figure 4).

Sensation

Ultimately, the goal is to restore function to the entire upper limb. The loss of proprioception and tactile cues will make it more challenging for people to take advantage of neuroprosthetic technology designed to restore movement such as FES, as well as external assistive technology like exoskeletons and robotic manipulators. Proprioception is generally considered to be crucially involved in the learning and control of motor action and loss of proprioception can have a significant effect on a person's ability to move without visual input.^{22,23} Tactile feedback will be required to allow participants to manipulate compliant or fragile objects, to operate the BCI with limited or obscured vision, and to feel the sensation

of performing a movement like a handshake. Motorized prosthetics, as shown in Figure 2, are equipped with sensors that detect tactile and proprioceptive information. It may be possible to transmit this information to the BCI user through stimulation of the nervous system.

The Dorsal Root Ganglion – an Ideal Target

The dorsal root ganglion (DRG) has many advantages as a site for recording neural signals and stimulating, when appropriate.²⁴⁻²⁷ While there are many alternative sites to consider, the DRG (and adjacent dorsal roots) are the only structures where PA neurons can be accessed in isolation from other neurons or fiber tracts. Since the majority of PA neurons from an entire limb are grouped into ~2-4 adjacent DRG, they provide a compact target for accessing the complete set of PA neurons for the limb. Experiments have been performed to record simultaneously from large numbers of neurons in DRG and S1 during passive movement of the hindlimb. Modulated activity of a single DRG neuron and a single S1 neuron during passive movement demonstrate firing rates for both neurons that covary strongly with ankle joint angle, demonstrating that these neurons may encode proprioceptive information for the ankle.

Applications of BCI in Stroke

There are a number of possible applications of BCI in the population with stroke.²⁸ First and, most desirable, would be to use BCI as a means to maximize neuroplasticity during the recovery phase. BCI can provide a high level of biofeedback and could be used, through both stimulation and demonstration of recording to train different areas of the brain to compensate for function compromised by the initial stroke. This would require a temporary implantation and therefore potential complications related to long-term neural recording would be avoided.

If functional recovery could not be achieved via neuroplasticity, another option would be direct control of the effected limb using a long-term implant. The BCI signal and decoder could be to simulate the patient's own muscles using functional electrical stimulation. Alternatively the BCI could control an exoskeleton or a robotic arm as pictured in figure 2. The BCI signal could come from an unimpaired portion of the impacted hemisphere. Alternatively, the BCI signal could be derived from the hemisphere ipsilateral to the impacted arm. Recent work has shown that bilateral control can be obtained from a single hemisphere. These findings also indicate that ipsilateral control could be obtained from the intact hemisphere. Finally, BCI could be used in conjunction with the stem cells and robotic techniques described earlier in this document. This possibility is described in the following section.

INTERSECTIONS

While exciting possibilities for patients exist with each of the three modalities discussed, the best chance for success likely exist by combining these interventions. One can envision a future where a patient who has neurologic deficit related to a stroke is initially treated with stem cells. The stem cells reduce inflammation and seed the infarcted area with the cell

types needed for repair. At the same time as the surgery is done to inject the stem cells BCI electrode is implanted. The BCI electrode's purpose is two fold, record signals from existing cells that can be used to provide biofeedback, thus maximizing neuroplasticity. In addition, once the stem cells are ready they can be given a trigger toward appropriate differentiation and to make connections by the signal provided by the BCI implant. During this entire process the patient will be undergoing robotic rehabilitation, which will maximize neuroplasticity and then provide the training need to increase the utility of the stem cells. The robotics is also documenting progress at a fine level so that plateaus in gains are noted and investigated. As this imaginary future illustrates the modalities are complementary, which in the end might offer our patients the best recovery.

BARRIERS

Each of the approaches discussed above face considerable barriers to clinical translation. A common barrier for all is the cost of research and treatment. Cutting edge approaches, such as those discussed, require considerable research investment. In each area research has been ongoing for years, yet only in the robotics realm has there been any penetration into more routine clinical practice and a business model that appears profitable. Interestingly, what has driven the use of robotics is likely marketing related and less to do with proven outcomes. In the United States providing robotic therapy does not allow for extra billing, but may differentiate one institution from another and therefore attract patients. In the stem cell and BCI related areas the hurdles are higher for translation as the intervention is invasive and will have an absolute requirement for a reimbursement model to be successful. The authors strongly feel that investment in all three areas will lead to better outcomes for individuals with stroke and many other disorders.

CONCLUSIONS

Robots provide a method for providing well-defined, reproducible therapeutic exercise in a potentially labor-saving fashion. Advantages of robots compared with dose-matched human therapy for the delivery of exercise therapy remain intriguing, but still unproven. Despite the promise of robots to deliver exercise therapy, utilization of these devices in clinical centers remains relatively low. There are a number of important barriers to broader adoption that need to overcome to expand robotic use, with perhaps the most important ones being economic. Further advances in robotic technology, coupled with new delivery and reimbursement models, may be needed to fully overcome these barriers.

Our current understanding of the potential mechanism by which cell therapy improves outcome after stroke is limited. It is likely stem cells have multiple mechanisms of action and further research is necessary to define the optimal route of administration, timing of treatment and number of cells for each cell type. Chronic stroke presents additional challenges. Innovative solutions will be needed involving scaffolds to allow multiple differentiated cell types to replace or repair irreversibly injured brain tissue.²⁹ Endogenous neural stem cells reside in the subventricular zone and are capable of migrating to the site of brain injury. However, the contribution of these cells to brain repair appears to be limited. As our knowledge of epigenetics evolves, it may be possible to enhance this process through

modification of the microenvironment and targeted differentiation and integration.³⁰ We are now in the earliest stages of cell therapy and the promise of this therapeutic approach appears bright.

Finally in the BCI area, tremendous breakthroughs have occurred related to achieving control with multiple degrees of freedom. However, before this work translates to the clinical setting work needs to be done to improve the long term viability of implants. In addition, integrating sensory information into the motor control must be achieved to obtain the highest degree of freedom, such as would be need to operate a dexterous hand. Further study is needed to achieve these goals and to fully understand the possible interactions between BCI and recovery from stroke.

Advances in each area is likely to profoundly change the way we treat patients with stroke in the future and the use of all three modalities likely holds the most promise.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: A report from the american heart association. *Circulation*. 2013 epub ahead of print.
2. Resnik L. Research update: VA study to optimize DEKA arm. *J Rehabil Res Dev*. 2010; 47:ix-x. [PubMed: 20665342]
3. Johannes MS, Bigelow JD, Burck JM, Harshbarger SD, Kozlowski MV, van Doren T. An overview of the development process for the modular prosthetic limb. *Johns Hopkins APL Tech Digest*. 2011; 30:207-16.
4. Lo AC. Clinical designs of recent robot rehabilitation trials. *Am J Phys Med Rehabil*. 2012; 91(11 Suppl 3):S204-16. [PubMed: 23080037]
5. Krebs, HI.; Volpe, BT.; Lynch, D.; Hogan, N. Stroke rehabilitation: an argument in favor of a robotic gym.. *Proceedings of the 9th International Conference on Rehabilitation Robotics*; Chicago, IL. New York: IEEE. 2005 Jun 28-Jul 1; 2005.
6. Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med*. 2010; 362:1772-83. [PubMed: 20400552]
7. DePietro L, Krebs HI, Volpe, et al. Learning, not adaptation, characterizes stroke motor recovery: evidence from kinematic changes induced by robot-assisted therapy in trained and untrained task in the same workspace. *IEEE Trans Neural Syst Rehabil Eng*. 2012; 20:48-57. [PubMed: 22186963]
8. Mazzoleni S, Sale P, Tiboni M, Franceschini M, Carrozza MC, Posteraro F. Upper limb robot-assisted therapy in chronic and subacute stroke patients: a kinematic analysis. *Am J Phys Med Rehabil*. 2013; 92(10 Suppl 1):e26-37. [PubMed: 24052027]
9. Rohafza M, Fluet GG, Qiu Q, Adamovich S. Correlations between statistical models of robotically collected kinematics and clinical measures of upper extremity function. *Conf Proc IEEE Eng Med Biol Soc*. 2012:4120-3. [PubMed: 23366834]
10. Kondziolka D, Wechsler L, Goldstein S, et al. Transplantation of cultured human neuronal cells for patients with stroke. *Neurology*. 2000; 55:565-9. [PubMed: 10953194]
11. Kondziolka D, Steinberg GK, Wechsler L, et al. Neurotransplantation for patients with subcortical motor stroke: A phase 2 randomized trial. *J Neurosurg*. 2005; 103:38-45. [PubMed: 16121971]
12. Nelson PT, Kondziolka D, Wechsler L, et al. Clonal human (hnt) neuron grafts for stroke therapy: neuropathology in a patient 27 months after implantation. *Am J Pathol*. 2002; 160:1201-6. [PubMed: 11943704]
13. Bhasin A, Srivastava MV, Kumaran SS, et al. Autologous mesenchymal stem cells in chronic stroke. *Cerebrovasc Dis Extra*. 2011; 1:93-104. [PubMed: 22566987]
14. Honmou O, Houkin K, Matsunaga T, et al. Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. *Brain*. 2011; 134:1790-1807. [PubMed: 21493695]

15. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells*. 2010; 28:1099–106. [PubMed: 20506226]
16. Moniche F, Gonzalez A, Gonzalez-Marcos JR, et al. Intra-arterial bone marrow mononuclear cells in ischemic stroke: a pilot clinical trial. *Stroke*. 2012; 43:2242–4. [PubMed: 22764211]
17. Savitz SI, Misra V, Kasam M, et al. Intravenous autologous bone marrow mononuclear cells for ischemic stroke. *Ann Neurol*. 2011; 70:59–69. [PubMed: 21786299]
18. Collinger JL, Wodlinger B, Downey JE, et al. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet*. 2013; 381:557–64. [PubMed: 23253623]
19. Wang W, Collinger JL, Degenhart AD, et al. An electrocorticographic brain interface in an individual with tetraplegia. *PLoS One*. 2013; 8:e55344. [PubMed: 23405137]
20. Moran DW, Schwartz AB. Motor cortical representation of speed and direction during reaching. *J Neurophysiol*. 1999; 82:2676–92. [PubMed: 10561437]
21. Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB. Cortical control of a prosthetic arm for self-feeding. *Nature*. 2008; 453:1098–101. [PubMed: 18509337]
22. Sainburg RL, Ghilardi MF, Poizner H, Ghez C. Control of limb dynamics in normal subjects and patients without proprioception. *J Neurophysiol*. 1995; 73:820–35. [PubMed: 7760137]
23. Sainburg RL, Poizner H, Ghez C. Loss of proprioception produces deficits in interjoint coordination. *J Neurophysiol*. 1993; 70:2136–47. [PubMed: 8294975]
24. Stein RB, Weber DJ, Aoyagi Y, et al. Coding of position by simultaneously recorded sensory neurones in the cat dorsal root ganglion. *J Physiol*. 2004; 560(Pt 3):883–96. [PubMed: 15331686]
25. Gaunt RA, Hokanson JA, Weber DJ. Microstimulation of primary afferent neurons in the L7 dorsal root ganglia using multielectrode arrays in anesthetized cats: thresholds and recruitment properties. *J Neural Eng*. 2009; 6:055009. [PubMed: 19721181]
26. Weber DJ, Stein RB, Everaert DG, Prochazka A. Limb-state feedback from ensembles of simultaneously recorded dorsal root ganglion neurons. *J Neural Eng*. 2007; 4:S168–80. [PubMed: 17873416]
27. Bruns TM, Wagenaar JB, Bauman MJ, Gaunt RA, Weber DJ. Real-time control of hind limb functional electrical stimulation using feedback from dorsal root ganglia recordings. *J Neural Eng*. 2013; 10:026020. [PubMed: 23503062]
28. Silvoni S, Ramos-Murguialday A, Cavinato M, et al. Brain-Computer Interface in Stroke: a Review of Progress. *Clin EEG Neurosci*. 2011; 42:245–52. [PubMed: 22208122]
29. Dihn M, Hartung HP, Seitz RJ. Restoring neuronal function after stroke by cell replacement: anatomic and functional considerations. *Stroke*. 2011; 42:2342–50. [PubMed: 21737804]
30. Qureshi IA, Mehler MF. The emerging role of epigenetics in stroke: III. Neural stem cell biology and regenerative medicine. *Arch Neurol*. 2011; 68:294–302. [PubMed: 21403016]

Figure 1.
Example of an exoskeletal-design workstation robot

Figure 2.
Example of a wearable exoskeleton robot

Figure 3.

Neuropathological findings in area of transplant (left) demonstrating surviving human neurons (C and D) after 27 months. FISH probes (right) identify these cells as transplanted LBS cells that are triploid for chromosome 21 (D and F) and diploid for chromosome 13 (C and E).

Figure 4. Using an intracortical BCI, a person with tetraplegia was able to use the MPL to shake hands (left), stack cones (center), and feed herself (right).

Table 1

Cell types for cell therapy of stroke

Cell type	Source	Mechanism	Delivery
Neural stem cells	Embryo Fetus Adult	Neurogenesis Angiogenesis Paracrine	Intraparenchymal
Immortalized stem cells	Primitive tumors Transformed by oncogene	Neurogenesis Angiogenesis Paracrine	Intraparenchymal Intra-arterial
Mesenchymal stem cells	Bone marrow Adipose tissue Umbilical cord Dental pulp	Paracrine Immune suppression	Intravenous Intra-arterial Intra-parenchymal
Endogenous neural progenitor cells	Subventricular zone Hippocampus White matter	Neurogenesis	Humoral mobilization BDNF EGF Statins EPO