4-27-2011

Brain Plasticity Influencing Phantom Limb and Prosthetics

Heather Scott
University of South Florida

Brain Plasticity Influencing Phantom Limb and Prosthetics

Heather Scott

A Thesis Submitted in Partial Fulfillment of the

Requirements for the Degree of

Bachelor of Science in Biology

The Honors College of the University of South Florida

April 27, 2011

Thesis Committee: Ralph E. Leighty, Ph.D.

Gordon A. Fox, Ph.D.

Brain Plasticity Influencing Phantom Limb and Prosthetics

The relationship between brain and behavior represents an important area of research. The complexity of the brain, however, poses significant challenges to investigators, while at the same time offers great promise for new discoveries. By selecting a specific structure or function of the brain, we may begin to explore the neural basis of behavior and cognition, and examine potential therapies for treating neurological disorders. For example, phantom limb syndrome is a mysterious medical condition in which individuals continue to perceive the presence of a missing body part -- typically a limb or limb segment -- for some time following its loss through amputation (e.g., combat-related injury). In this thesis, I intend to examine phantom limb phenomena and relate these findings to furthering prosthetic research and rehabilitative therapy.

Phantom Limb

Many amputees experience a bizarre and seemingly unreal sensation called phantom limb syndrome or, in some cases, even phantom pain (11). These sensations occur because the brain continues to relay motor signals to the missing limb or digit, but does not receive sensory feedback. The individual afflicted by this unusual sensation will perceive movement as if their limb still exists, but will visually recognize that the limb is, in fact, absent (11). The amputee is not delusional; the brain is simply unable to interpret the conflicting sensory information.

The internal representation of the body maintained in the brain is created by feedback mechanisms of the muscle and skin sensory afferents. This representation persists over time and helps us determine our body position in relation to the surrounding environment (3). Thus, it requires time and experience to adjust to the loss of a limb because the brain still retains the stored representation image of an intact body. In addition to the sensory representation of the body in the cortex, there is a second internal representation of the body in the motor cortex of the brain which is responsible for controlling the muscles of movement. Like the representation created from sensory information, this motor cortex representation is organized like a geographic map -- each region of the body is mapped onto a specific location of the cortical surface. This cortical map is commonly referred to as the Penfield homunculus (1).

The sensory and motor cortical representations of the body are established and refined during development and maturation of the individual. In infancy, multiple neural projections within different layers of the brain and between the brain and muscles begin to form, and throughout development some of these nerve pathways will strengthen while others will weaken or disappear. The persistence of neural pathways is dependent upon experience -- pathways that are more active are more likely to be retained. Hence, the structure of connections between the cortex and the body is shaped by experience, and reflects the activity patterns of the individual. In addition, the relative size of the cortical map region associated with a body part depends upon the innervation density of that body part; larger cortical regions are associated with body parts having extensive neural innervation. The largest regions, for instance, are associated with the fingers and lips, reflecting an individual's constant handling of objects, writing, and talking.

The brain is a dynamic organ and the network of neural connections changes in response to experience. This capacity for self-modification based on activity is called "brain plasticity." Because the cortical regions associated with a missing limb are no longer receiving sensory information from the limb, nor sending coherent motor signals to the limb, the cortical area will slowly become absorbed by neighboring cortical areas, gradually becoming associated with different body structures. As the function of the cortical region shifts away from the missing limb, the sensation of the phantom limb is gradually lost (10). This natural plasticity of the brain allows the cortex to modify itself, and is how neuroscientist V.S. Ramachandran was able to map one patient's phantom hand representation onto his face- and his upper arm-associated cortical areas.

A study conducted by Pons, Preston, and Garraghty (6), on deafferentation in adult primates, has determined that the removal of a limb will result in altered cortical maps through mechanisms of brain plasticity. They were able to map the phantom limbs corresponding deafferentated area of the brain onto the face and using electrodes saw the cortical map nerves did not change. By directly stimulating the face they were able to view the missing limb's associated cortical region of the brain receive signals as if the limb still remained (6). They theorized that the face nerves either already existed as passive nerves in the deafferentated area of the cortical map or the face nerves grew into the deafferentated area of the cortex (6).

Penfield and Boldrey describe the loss of perception of the phantom limb as systematic, beginning with the proximal parts and progressing toward the distal parts (2). This is because the proximal parts have lower innervation density (that is, fewer sensory nerves per unit area) and less sensory acuity. A phantom upper arm will fade faster than phantom fingers, therefore, because the upper arm representation in the cortex is comparatively smaller than the finger-associated region. Gradually, the phantom limb will recede into the residual limb until there are only phantom digits remaining at the residual limb, because the digits have a relatively larger cortical area and require more time for perception to fade (2). This process can be hastened by the use of the "mirror box," a simple device that is able to "trick" the mind into detecting a previously-present limb.

Phantom Limb Pain and the Mirror Box

The brain receives extensive environmental sensory information from visual signals, thus making the mirror box the most efficient means, currently, to help relieve phantom limbs and pain. By placing before a patient a cardboard box fitted inside with a vertical mirror, the patient will see their amputated limb seemingly reappear due to the reflection of their remaining limb (1). The time needed for the phantom to fade varies from person to person based on age, amount of time spent with mirror box, and personality type. With continued practice, the brain will adjust the body representation map because while the patient can "see" the amputated limb's image, he doesn't receiving any sensory signal from the image. This conflicting feedback presumably causes the brain to "deny" the existence of the phantom limb, promoting the rewiring of sensory and motor cortical connections.

Patients who have never been able to move a frozen phantom limb will remarkably gain control over it merely by viewing the reflection. Over a period of a few weeks, Ramachandran's patient, Philip, was able to force his phantom limb that had persisted for ten years to fade away (1). A phantom limb does not always result in phantom pain, but when pain occurs, alleviating the pain associated with a nonexistent source presents a medical challenge. Phantom pain tends to linger due to the constant feedback of the residual limb nerve pain to the brain. This pain is caused by irritation of the nerve clumps of scar tissue (2). Often, the removal of this scar tissue will relieve the pain, but in some cases the pain may return, or even worse -- for reasons which remain unclear. The use of the mirror box hastens the disappearance of the phantom limb and, thus, may hasten the loss of the pain (1). In the next section, I present an outline of an experiment to examine whether a phantom limb could help or hinder the use of a prosthetic.

Prosthetics

Inventors are currently trying to create unique prosthetics for animals for performing complex actions which can then be applied to human patients. Prosthetics are produced in many different designs, for both functional and cosmetic purposes. In addition, there are prosthetics that can sense the movement of muscles attached to it through the use of electrodes. Dr. Todd Kuiken, a researcher from the Rehabilitation Institute of Chicago, has recently developed a prosthetic that can sense and feel objects by transplanting sensory and motor nerves to his chest from his amputated hand (4). This will help make movements with fingers more delicate, but it only transfers information from the hand prosthetic to the chest and vice versa (4). This research suggests that it may be possible to use electrodes on the cortical area of the brain associated with the amputated limb to further enhance sensory input. This type of instrument would be able to communicate sensation from the prosthetic device to the brain much like a real limb. However, this method would involve extensive surgery to attach electrodes onto the motor cortex, which may be too risky for many patients. Another consideration is the delay between the amputation and the surgery. For instance, how soon following the amputation would the electrodes need to be implanted to assure successful cortical control over the new prosthetic? And, does this timing affect functional dexterity and fine control over the amputated limb? Clearly, these are questions which invite experimental investigation.

Experimental Proposal

Early experiments might be performed on chimpanzees because their limbs are the most closely related to humans'. Research conducted at Duke University Medical Center has already demonstrated that a monkey can learn to control a mechanical robotic arm through the use of computer analysis of brain activity measured from implanted electrodes (5). The proposed experiment would also involve a direct connection between the brain and the prosthetic, without reliance on computer-mediated communication as in the Duke studies. A performance comparison between chimpanzees having intact limbs and animals receiving the brain-prosthetic treatment would identify patterns of functional recovery, as well as evaluate the effect of delayed surgical intervention, as discussed in the previous section. The results of this early experiment would determine the next stages of the study leading, perhaps, to clinical trials involving human amputees.

Another question that could be addressed by the experiment concerns whether the perception of a phantom limb helps or hinders the prosthetic connected to the brain. Current research suggests that phantom limbs help "fill-in" the prosthetics (1). It is possible, therefore, that through mechanisms of brain plasticity and functional reorganization, prosthetic use may actually accelerate the disappearance of the phantom limb. The fading of the limb would result from the brain sending motor impulses to the prosthetic and receiving visual feedback, confirming the execution of movements. Just as with the mirror box, this process could create a type of illusion, effectively "tricking" the brain into perceiving movement of the missing limb in the absence of limb-associated sensory signals -- only visual cues. Moreover, experimental prosthetics research involving the use of animal subjects could lead to enhancements of existing human prosthetics.

Animal Prosthetics

Kevin Carroll is a leading prosthetic designer who has developed a prosthetic tail for a dolphin named Winter. It took over a year to construct and refine the tail prosthetic, while training the dolphin to use the artificial tail for locomotion. His work on the project began with an idea to create a prosthetic strong enough to withstand the forces generated during movement, flexible enough to yield for water movements, and soft enough to avoid damaging the residual fin stump. The resulting prosthetic fin was constructed from a silicon-based gel that suctions onto the stump and does not irritate the skin. This new silicon-based gel has already been tested on an Iraq veteran's prosthetic legs (8), and additional clinical studies are underway. Additionally, veterinarians have used prosthetic devices for treating domestic animals with missing or lost limbs, significantly restoring independent mobility and improving overall physical health through activity.

Prosthetics and the Brain's Body Representation

Experimental studies of real-time brain function during tool use (3) suggests that a tool can be integrated into the body representation of the motor cortex through constant use of the tool. The brain effectively extends the perception of body image to include the tool because it is receiving visual and sensory information from the tool (3, 9). This further suggests that because a prosthetic is essentially a tool, it should also become rapidly integrated into the body perception. Hence, if a prosthetic is introduced after the phantom limb disappears, it may still be possible to integrate the prosthetic into the body representation of the cortex. However, the use of a tool allows it to be temporarily made part of the body representation since it will be perceived by visual and tactile sensations (3, 9). The experiment proposed previously may help determine whether phantom limbs would aid the prosthetic integration into the body representation better than only the residual limb. The downside is this temporary perception will eventually return to the original body representation (9).

Intensive practice with the prosthetic may cause a more durable change to the body representation, thus permitting integration of the artificial prosthetic as if it were a natural limb. Studies have shown that if a child undergoes limb amputation at three years of age or younger, they will not experience phantom limb syndrome (3). This suggests that body representation requires experience to develop rather than only sensory input.

One of the ways to obtain additional information about how the brain responds to amputation is to map the changes on a non-human primate's brain using appropriate neuroimaging and electrophysiologic measurement techniques. First, a recording of a normal intact primate's brain would provide baseline measurements and behavioral observations for later comparison, and reveal patterns of activity associated with limb movement or other performed actions. Next, similar recordings would be made following surgical amputation of a limb, to observe immediate changes in brain activation patterns, as well as patterns of neural activity during the performance of specific movements or actions. Abnormal behavior, either through movements or expressed by other means (e.g., vocalization), may suggest phenomena reminiscent of human phantom limb or phantom pain perception (13). Over time, we expect the recordings to show changes associated with sensorimotor recovery and accommodation. Neuroimaging-based evidence of brain plasticity could be correlated with behavioral evidence of functional recovery. In addition, researchers might observe transitional patterns of electrophysiologic measures associated with functional recovery. We may predict that, if a patient's brain scan

can reveal areas that are active during perceived the movements of a phantom limb, we could compare the human's brain activation pattern to those of the primate's, and interpret similar patterns as evidence of phantom limb syndrome in non-human primates. Similarly, we could record the amputee-primate's brain activity before and after exposure to (and training with) a mirror box to further evaluate the therapeutic benefits of the mirror box.

<u>History of Phantom Limb/Pain</u>

Phantom pain syndrome was first described as an illusion or a mental illness (11). Many patients would keep this condition hidden at the risk of being labeled insane, since it seemed fanatical to claim to detect a limb that no longer existed (10). For example Dr. S. Mitchell in 1866 published the first account of phantom limb as a short story of a Civil War soldier unknowingly having both legs amputated. The soldier asked a nurse to scratch his itchy calf, which she replied that he had no leg to scratch. Dr. Mitchell published the story to test how the scientific community would react to the idea of phantom limbs(11). Before studies were conducted on amputees, some of the treatments involved severing the nerves in the stump or surgically lesioning the nerve roots at the spinal cord leading to the residual limb (2). Another drastic method of trying to dissipate the pain was to continue amputation up the remaining limb. These methods were highly ineffective, often leaving patients grotesquely disfigured and functionally compromised. Scientists understood at the time that nerves in the body could grow and change, but thought the brain was in continued stasis throughout a human's life. The theories that were proposed to explain phantom limbs suggested that neuromas would form, nerves would regenerate, or psychological stress attributed to the traumatic event caused phantom limb/pain to occur (10).

Current theory focuses on brain plasticity and self-organizational processes, that is, that the brain effectively re-wires itself as a consequence of losing sensory input from the missing limb (10). These new pathways of nerves are then triggered by the sensory input from other locations on the body causing the sensation of the phantom limb to exist (10). The motor cortex is informed of sensory inputs by the somatosensory cortex (11). When these signals are lost, the somatosensory cortex relays the information to the motor cortex which develops the map of the body. The map is rewired due to the brain plasticity. resulting in the perception of phantom limbs (7).

Congenital Amputees

An obvious exception to the notion of phantom limbs acquired through amputation of existing limbs is the finding that phantom limb syndrome can occur in humans who are born without limbs (1). Such individuals have never received sensory signals to reinforce the idea of a body image in the brain. This phantom limb may be the cause of passive wiring occurring in the brain, as a fetus, that supports the limb's possible existence. Comparison of neuroimaging and/or electrophysiologic measures between individuals having congenital vs. acquired amputation may provide clues to differences in neural organization, processing, and functional accommodation. One theory for explaining the phantom limb phenomenon in congenital amputees involves the role of a basic network of nerve pathways throughout the brain which connect to remote body regions (1).

As discussed earlier, during development, neural pathways are selectively strengthened through limb movement and sensory reception, causing other pathways to weaken or disappear. It is possible that nerve pathways which normally would weaken are somehow retained in a congenital amputee, eventually resulting in a phantom limb (1). Taken together, these observations and findings suggest that phantom limb/pain is distinctly different from a shock reaction following the loss of an important part of the body. Indeed, phantom limb/pain syndrome represents a fundamental alteration in brain structure and function.

Physical Therapy for Amputees

Current prosthetic technologies under investigation for direct implantation in the brain include the artificial cochlea and the virtual eye. The main difference between these prosthetics and limb replacement is that the communication between the cochlea and the brain, as well as between the photoreceptors of the eye and the brain, is unidirectional: These sensory organs transduce physical stimuli into electrical signals and transmit these signals to the brain; there is no motor output from the brain to either the cochlea or photoreceptive region of the eye. By contrast, limb replacement prosthetics require bidirectional communication: Sensory signals conveyed to the brain and motor signals conveyed to the prosthetic, with continuous feedback correction. To perform as functional replacements for natural limbs, such prosthetics would need to be highly advanced and use computer circuits for signal processing. Additionally, human patients fitted with prosthetics require extensive therapy and training to learn to use the prosthetic.

I interviewed physical therapists at the local Veterans Affairs Physical Therapy Clinic (12) to learn more about physical evaluation, treatment options, and therapeutic protocols related to amputation and prosthetics. Both therapists are musculoskeletal specialists focusing on lower-extremity therapy. Dr. Julie Martin described new rehabilitation techniques for helping stroke victims to relearn use of their affected limb. Studies have shown that most victims of limb loss will compensate with movements of other parts, so an effective therapeutic strategy is to restrict the usable limb (12), forcing the individual to relearn control over the impaired limb. Indeed, therapy typically begins the day following surgery on a residual limb. With training and practice, the patient gradually reacquires proper movement of the affected limb, through the process of rewiring the brain to accept and strengthen the signals associated with that limb. Both therapists stated that the capacity to recover optimal functionality and strength in the limb is largely determined by the patient's psychological state of mind, background, culture, and current support system of family and friends (12).

Psychological factors also influence the extent of recovery and the duration of therapy. Both therapists also informed me that during a period of twenty years' experience they have never observed a patient reporting a phantom limb without an associated phantom pain (12). The presence of pain associated with a phantom limb has been widely reported (e.g., 2, 7, 10). Moreover, the severity and extent of pain experienced by patients varies significantly. For instance, an individual who is prone to anxiety prior to the amputation tends to report a greater amount of pain in the phantom limb, compared to an individual who is more relaxed (2).

Types of Therapies

Certain social and psychological qualities are associated with improved therapeutic outcomes. For example, patients having a good social support system and an optimistic attitude tend to recover faster. These individuals are more likely to continue therapy after leaving the clinic and to practice more often with a prosthetic, if they receive one (12). As an adjunct to physical therapies, counseling and psychiatric therapies may be helpful in many cases. For instance, recovering combat veterans with a negative image of their new life circumstances will tend not to receive a prosthetic from the military due to their lack of interest (12). Doctors use a combination of anti-inflammatory medicine, pain medicine, counseling, and physical therapy to help patients overcome the emotional and physical trauma of limb amputation. However, because the recovery of the patient is dependent upon many factors, there is no single, standardized approach to help them adjust to their situation (12); certain therapies will work better for some patients than others, and trial-and-error is sometimes the only means for determining what will work best.

The physical therapists informed me that one of the best forms of reducing pain is through proprioceptive stimulation, with early touch of the residual limb. They also use the mirror box technique to help reduce pain, just as Ramachandran described in his studies (1). The bilateral visual representation helps the patient imagine the position of the limb in space, especially if the limb is kept in a specific position. For lower-extremity limbs, the physical therapists encourage the patient to practice sitting, standing, walking, and running (12), to help develop strength and balance, joint control, and endurance, under different conditions (carpeted vs. smooth floor, for example). The main objective of these exercises is to provide enough repetitive motion for the patient to relearn how to move under their new circumstances. The therapies are intended to make life easier for the patients either with or without the use of a prosthetic. Counseling is also a major part of the treatment process, to encourage and maintain patient compliance and practice efforts (12). Finally, therapy is an ongoing process -- patients learn to help themselves.

Conclusions

Phantom limb and phantom pain syndromes are mysterious neurological phenomena, once considered psychological anomalies or exaggerated reactions to wartime trauma, are now recognized as natural consequences of the brain's plasticity and recovery process following sensorimotor loss. Contemporary rehabilitative medicine treats amputees with a broad range of therapies -- including psychological and physical -- to address both structural and functional difficulty related to the loss of a limb. Moreover, the insights provided by experimental neurophysiological research and neuroimaging studies in both animal models of amputation and human patients continue to guide development of therapies.

Today, as global conflicts continue to produce combat-injured veterans, the need to understand and address neurological syndromes becomes even more immediate. Finally, the experiments I proposed in this thesis -- directly connecting external artificial prosthetics with the cortex of the brain -- suggest that our understanding of phantom limb phenomena can be used for practical, therapeutic purposes. Indeed, such advanced prosthetics, in theory, could ultimately be crafted into durable, protective exoskeletal armor for fighting wars, or into delicate, precision sensorimotor prosthetics for playing the violin.

Acknowledgements

I would like to thank Dr. Leighty for his inspiring input and constant feedback, Dr. Fox for helping me complete and design the thesis, Amanda Paez for her help with editing, my mom and dad for teaching me to work under pressure, and the Honors College for giving me the opportunity to publish a thesis.

References

1. Ramachandran, V.S., and S. Blakeslee (1998). *Phantoms in the Brain: Probing the Mysteries of the Human Mind*. HarperCollins Publishers.

2. Sternback, R. (1968) *Pain: A Psychophysiological Analysis*. Academic Press.

3. Maravita, A. (2006). From "Body in the Brain" to "Body in Space," in: *Human Body Perception from the Inside Out*. G. Knoblich, I. Thornton, M. Grosjean, and M. Shiffrar (eds.). Oxford University.

4. Singer, E. (2007). Prosthetic limbs that can feel. *Technology Review,* 4. Accessed online in January 2011 at URL: http://www.technologyreview.com/biotech/19759/.

5 "Monkeys Consciously Control a Robot Arm Using Only Brain Signals" (2003). *Biotech Week*, 144.

6. Pons, T.P., Preston, E., and A.K. Garraghty (1991). Massive cortical reorganization after sensory deafferentation in adult Macaques. *Science*, **252**, 1857-1860.

7. Qi, H.-X., Jain, N., Collins, C., Lyon, D., and J. Kaas. (2010). Functional organization of motor cortex of adult macaque monkeys is altered by sensory loss in infancy. *Proceedings of the National Academy of Sciences USA*, **107**, 3192-3197.

8. Yahalom, T. (2007). "Dolphin and Iraq veteran share wonder of prosthetics." *USA Today*, **Science**.

9. Holmes, N., and C. Spence (2006). "Beyond the Body Schema," in: *Human Body Perception From the Inside Out.* G. Knoblich, I. Thornton, M. Grosjean, and M. Shiffrar. Oxford University Press.

10. Will, B.E., Schmitt, P. and J.C. Dalrymple-Alford. (1985). *Brain Plasticity, Learning, and Memory.* Plenum Press.

11. Melzack, R. (1992). Phantom limbs. *Scientific American*. 120-126.

12. Veterans' Affairs Physical Therapy Clinic, Tampa, Florida. Personal communication with Dr. Clark Hersey, Physical Therapist Orthopedic, and Dr. Julie Martin, Physical Therapist, on February 10, 2011.

13. Vaccarino, A.L., and R. Melzack. (1991). The role of the cingulum bundle in self-mutiliation following peripheral neurectomy in the rat. Experimental Neurology, 111,131-134.