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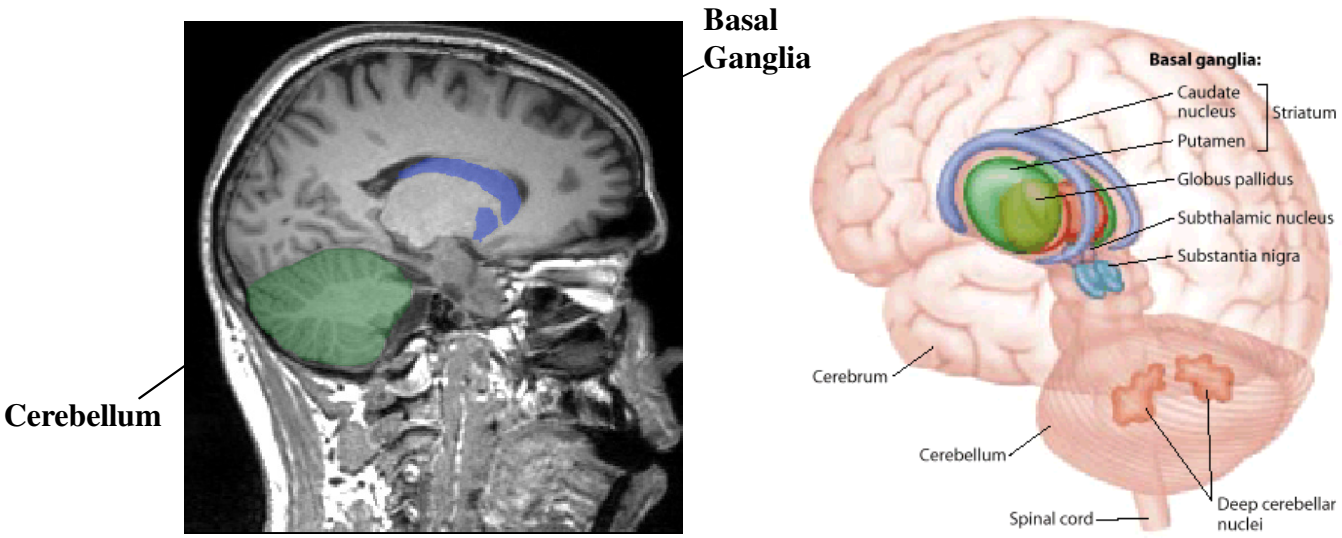
Spring is here! It's the time for new things to hatch, and this holds for the daffodils in our front yard, the recruitment of new graduate students for the fall, and the annual newsletter from our Cognition and Action Lab at UC Berkeley. As always, I like to begin with an overview of our general mission-- this will be a review for many of you so feel free to skip ahead to the report of our newer activities.

The research in our lab focuses on how different types of neurological conditions disrupt skilled movement. Our primary studies explore the functions of what neuroscientists call the "subcortex," the part of the brain that lies under the cerebral cortex, or cerebrum (see the picture). The subcortex is sometimes considered the "ancient" brain, reflecting the fact that the structures that form the subcortex are found in almost all animals, including prehistoric fish, reptiles, birds, as well as mammals. While these animals didn't need to perform complex mental tasks such as balancing checkbooks and driving cars, they did require the neural machinery that allowed them to move about and interact with their environment. Animals that can't control their movements are at a huge disadvantage in the natural world. They can't flee from enemies, nor can they venture out in search of food and mates. So, it is logical that the systems that control movements are deeply embedded in the brain and that there are numerous similarities in the ways that movements are controlled across a range of animals.



We focus on two large structures within the subcortex: the basal ganglia and the cerebellum. If either structure is damaged, a person is likely to have coordination problems. The basal ganglia are the part of the brain that is primarily affected in Parkinson's disease. Many cells in the basal ganglia are dependent on dopamine, one of the chemicals in the brain that allows nerve cells to communicate with each other. Parkinson's disease is caused by a dramatic reduction in the production of dopamine. Cerebellar problems do not result from a loss of a particular brain chemical. Rather, various degenerative disorders, some of which have a known genetic basis, target the cerebellum, resulting in ataxia, or a loss of the fine control of skilled movements. In addition, strokes can affect any part of the brain including the basal ganglia and cerebellum. Those of you who have participated in our

studies for many years know that we are working on several different projects, which might, at times, seem completely unrelated. Nonetheless, there are a number of central themes that guide our work. Most prominent is our goal to understand how the brain produces skilled movements. Note that I talk about how the "brain" produces these actions. Obviously the muscles are also important; you wouldn't be able to walk, talk or type on a computer if the neural signals were unable to activate the muscles. But, to the surprise of many, much of what determines whether a movement is clumsy or skilled has more to do with the brain than the body. Coordinated actions require that we select the appropriate action once we've recognized the environmental conditions. An expert tennis player cannot simply stand fixed in the center of the court and swat at the ball as hard as he can. Rather, much of the expertise involves anticipating where the opponent's shot will land, glancing up to see which part of the court is open, and adjusting the stroke to give the ball just the right spin, speed, and direction. The same holds true for basketball; the professionals can all make shots from just about any place on the court when unguarded in practice. The real challenge is in making that shot when there are nine other—rather large—bodies scattered about the court. In any sport, or in fact, our everyday activities, skilled action requires accurate perception and memory. Thus, our lab doesn't study motor control in isolation, simply looking at how people activate and control their muscles. Rather, as the name Cognition and Action implies, we study action from a broad perspective, trying to see how skill builds on so many aspects of our mental abilities.

Let me now turn to a brief update of some of the most recent results to emerge from our studies.

1. The specificity of motor learning? When you acquire a new skill with one hand, does the other hand benefit?

Hemiparesis is the term used to describe the loss of control of one limb or one side of the body following a stroke. "Paresis" refers to muscle weakness, and "hemi" to the fact that only one side of the body is affected. A person with hemiparesis is able to move the limb, but these movements may be seriously compromised. Hemiparesis following stroke results in a significant impairment in everyday life. Common rehabilitation methods to improve motor function often focus on training the affected limb. An alternative method would be to train the unaffected limb in such a manner that promotes transfer of the skill across limbs. We know that some motor skills can be executed with either limb, while some skills seem specific to the trained limb. For example, I can type a phone number with either hand, but can only write legibly with my right hand. Despite years of research, there is no consensus on what types of skills can transfer, how the context of training affects transfer, and how the degree of transfer may change over time.

To study this problem, Jordan Taylor, a post-doc in the lab, employed a new method that provides a continuous assessment of transfer during a motor learning task. The basic task involves what we call a "visuomotor rotation", one in which we distort the visual feedback such that to move straight, you actually have to produce a slanted movement. People readily learn to move in this new "environment". Jordan set out to see what happens if feedback is only given after movements with one hand. Would the other hand also show learning? He also manipulated the awareness of the participants to the experimental manipulation by either changing the environment very slowly over time (unaware) or changing it all at once (aware). The idea here was that the degree of awareness may change how participants solve the task. If something changes quite slowly, the motor system may assume that something has changed internally (e.g. my movements are inaccurate because the muscles are fatigued). In contrast, if something changes very quickly, the motor system may assume that the world has changed (e.g. my movements are inaccurate because there are hurricane force winds outside).

Participants made movements to visual locations with their right and left hands, but they were only given feedback following right hand movements. Thus, left hand movements were always made in the dark. This allowed us to see how training with the right hand changed the behavior of the left hand. The results showed

conclusively that learning always transferred from the right to left hand. This was true independent of awareness. This suggests that the brain builds up the skill automatically, but that the learning is not in the muscles or arm, but rather occurs at a more abstract level, one that can control movements for either limb. Interestingly, the degree of transfer was always incomplete, hovering around 35-50% of skill transfer. Thus, training with the right hand will improve function of the left hand, but the left hand has to be used to achieve full learning.

These results provide a promising new method for rehabilitation following stroke. Training the unaffected limb can result in providing a nice initial boost to the affected limb. However, the results also suggest that the affected limb would require some degree of training as well to achieve full learning. This work may additionally be relevant for people with degenerative diseases in which the symptoms are more pronounced on just one side of the body (as occurs in many cases of Parkinson's disease).

2. Learning from rewards and errors to change motor and cognitive decisions.

A second project takes a different approach to studying the challenges facing people with hemiparesis, and examines how the basal ganglia and cerebellum might contribute to their recovery. Because of their disability, these patients frequently adopt compensatory strategies that actually end up encouraging the person to keep using their unaffected limb, and by inference, avoid use of the stroke-affected limb. Here, even after the person has recovered control of their muscles, they have developed a habit to favor the unaffected limb. This has been called "learned nonuse". This strategy becomes self-reinforcing. Learned nonuse may be reduced by forcing the person to use the affected limb, but the benefits of this tactic are not always long-lasting.

We have been working on developing an alternative approach towards overcoming learned nonuse. The basic idea is that reinforcement encouraging use of the stroke-affected limb should be presented intrinsically. By this, we mean that the person should experience the success of using the affected limb, and that this success will increase the likelihood that the limb will be used in the future. Rehabilitation procedures such as constraint-induced therapy can force a person to use their limb, but here the effect is extrinsic; the therapist prevents the person from using the nonaffected limb. We are interested to see whether manipulations of intrinsic reinforcement will prove to be more effective and lasting in the long run.

Becca Stoloff, a graduate student in the lab, is working on this project. In a first study, we had college aged participants reach for a visual target, using either their right or left hand. Using our virtual reality system, we were able to manipulate the success rate for the two hands, even though the participants were unaware of our manipulation (a bit devious, but we tell them about this afterwards).

We are now investigating the neural substrates of hand choice, asking how the basal ganglia and cerebellum contribute to this learning process. Both of these structures are associated with motor learning. Interestingly though, they seem to do so in very different ways. The basal ganglia are part of the "reward" system, providing a signal that indicates a selected action has been successful. The cerebellum, in contrast, seems to be part of a "punishment", or error-detection system. When an action is not successful, the cerebellum provides a signal that can be used to correct future actions. We are studying the contribution of these two systems, by testing people with Parkinson's disease and cerebellar ataxia on two tasks. In our "hand choice" task, you are free to reach for an object with either hand. In our "object choice" task, you always use one hand, but can use it to reach for one of two objects. An example of a hand choice decision would be when you have to decide if you pick up a cup of coffee with the right or left hand. An example of an object choice would be deciding to take out the orange juice or coke from the fridge. While the motivation for this project came from our concern about individuals with hemiparesis, the research will also tell us something new about how the basal ganglia and cerebellum interact with the cortex to produce fluid behavior.

We are also using functional magnetic resonance imaging (fMRI) to determine regions of the brain that may contribute to these types of decisions. Our results suggest that when the task requires choosing between the two hands, the prefrontal cortex, parietal lobe, and the cerebellum are all active. Other studies have shown that making decisions about objects activates different parts of the brain such as the orbitofrontal cortex and basal ganglia.

3. Neural systems for reward and punishment in non-motor learning.

As noted in the last section, we have become interested in how reinforcement influences learning and behavior. How to present reinforcement is something that is relevant to much of our behavior. Should you punish an employee for doing an inferior job? Or reward them when they exceed your expectations? Or, as proves challenging for any parent, should you punish your child when they behave badly or only reward them for behaving well? Huge amounts of money are spent each year on this problem; for example, in designing programs to treat addiction. With a better understanding of how individuals learn from positive and negative feedback, these behavioral programs could be improved.

One question we have been exploring is whether positive (reward) and negative (punishment) reinforcement signals involve similar neural mechanisms. As discussed above, in the motor domain, positive reinforcement is associated with the basal ganglia and negative reinforcement with the cerebellum. We are interested in exploring whether a similar distinction holds true in non-motor domains.

Peter Butcher, a current graduate student in the lab, has been looking at this question in a drug study using college students as participants. The experiment involves a simple game where, through trial-and-error, you learn how to classify abstract pictures. The participants are tested twice, one after given a dopamine (DA) agonist, Bromocriptine, a drug frequently used in the treatment of Parkinson's disease, and a second time after given a placebo. Bromocriptine boosts the sensitivity of the system to dopamine, a brain chemical that is associated with reward signaling. Interestingly, our results show that participants who had taken the drug learned better from negative feedback, whereas it actually hindered learning when they were given only positive feedback. Basic models of dopamine would predict the opposite result. It appears that the administration of the drug changed the sensitivity of the system to dopamine. Thus, a story in which "more dopamine equals more reward" is likely too simplistic. The brain has evolved to be tuned to respond to an optimal level of dopamine. Diseases such as Parkinson's disease do not just reduce our sensitivity to reward; they put the system out of balance. Treatments must be designed to restore this balance.

Since so many of you have gotten to know our lab members just as we've gotten to know you, I'd like to highlight some recent accomplishments. While I remain a constant presence, the students and post-docs come and go, which is always bittersweet, both for our participants and myself. But once their training is completed, they move on to the next phase in their careers. Over the past year, Jing Xu completed her Ph.D. She is now a postdoctoral fellow at Johns Hopkins University, one of the leading centers for the study of movement disorders. We will also say goodbye to post-doc Jordan this summer. He has been appointed as an assistant professor at Princeton University and will set up his own lab to study motor control and movement disorders. If you are ever back east, give him a shout. Finally, the baby boom continues in the lab! Alit Stark and Ludovica Labruna, two of our post-docs, have had babies over the past year and Alit is now expecting again—her second child.
We hope that this newsletter provides you with a general overview of the research we conduct in lab and, perhaps, some more details about a study in which you may have participated over the past year. We appreciate your willingness to work with us in exploring these research questions and we hope that you can take pride in the fact that you are literally an integral part of the research. The results of our work are published in scientific

reports. All of the reports can be found on our lab website: ivrylab.berkeley.edu. If you prefer, we can send you a copy in the mail. Fair warning: These reports are written at the technical level, so they may not make for the most exciting read...

I want to thank you for dedicating your time and energy to helping with this research. The immediate impact of these studies is not always obvious, but they do help us in understanding how the brain works and learns. We trust that this knowledge will prove useful in the developments of new treatments and rehabilitation protocols.

Best wishes from all of us,

Rich Ivry
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