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University of California
3210 Tolman Hall #1650
Berkeley, CA 94720-1650
Fax: 510.642.5293

Department of Psychology

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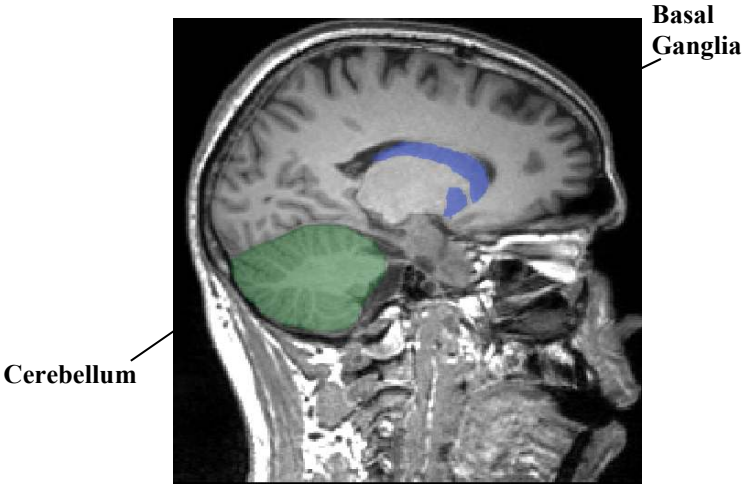
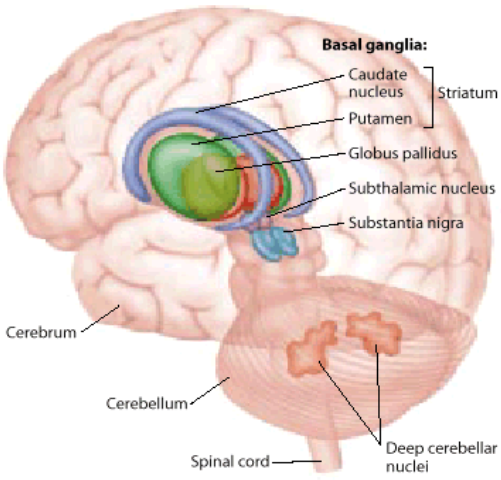
It's spring and warm in California, with the magnolia trees in full bloom. Spring also means that we're gearing up for the National Ataxia Foundation's Annual Meeting in Detroit, and part of our preparation is getting the annual newsletter from the Cognition and Action Lab in order. As always, I like 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 an update of some of the most recent results to emerge from our studies.

1. Skill learning: Using cognitive strategies to boost motor learning.

Many movement disorders disrupt skilled performance. Not only is skilled performance affected in people with Parkinson's disease and cerebellar ataxia, it can also be affected by cortical stroke or even degenerative disorders such as Alzheimer's disease. This observation underscores an obvious point: The performance of motor skills is not under the sole control of a single part of the brain, but requires the integrated activity of many different parts of the brain. This distributed view is especially true when we consider the acquisition of a new motor skill. Imagine you are learning how to high jump, facing a bar that is positioned 4' off the ground (or even 8' if you want to go for the world record). To do this, you are going to have to run fast to build up some momentum, figure out where you want to push off, and then make sure that all parts of your body make it over the bar. You can well imagine the hours of practice required to coordinate all of these movements. But even before you take off, you have to come up with a strategy. Do you approach the bar from the side and do a scissors kick, bringing one leg over the bar and then the other? Or do you rotate your body as you approach the bar, allowing your back to be the closet part of the body to the bar with the legs lifted high in the air? This example makes clear that motor skills require more than just extensive practice. If you keep doing the wrong thing over and over, you might become perform the action in a more coordinated fashion, but you won't get any closer to accomplishing your goal.

We don't, of course, ask people to come to our lab and hurl their bodies over a high jump bar. But we have developed simplified tasks that allow us to see how people use the combination of strategic planning and practice to learn a new skill. To this end, we have people perform reaching movements in distorted environments, ones in which the direction you reach is different from the direction you aimed. With practice, people can become quite good at learning to reach in these new environments. Our recent studies ask how strategies can boost the rate of learning.

This problem has been studied extensively in psychology and sports science. However, the traditional view is one that is best characterized as involving stages of processing. In this view, strategies are important during the early stages of learning when you are just trying to figure out what needs to be done. Once you have this problem solved, learning shifts to a stage of motor consolidation. Our results suggest otherwise. What we find is that strategies and motor consolidation are simultaneously operating at all stages of practice. The best evidence of this comes from some work by Jordan Taylor, our previous post-doc in the lab, who created virtual reality environments where strategy use and motor consolidation worked in opposition to one another. Under this condition, people show a very strange pattern of behavior where they actually get worse with practice, at least until they decide to change their strategy. Moreover, Jordan has shown that the balance between strategy use and motor consolidation can be altered by neurological disease. People with ataxia are most affected in the motor consolidation process and thus have to rely on strategies to learn new skills. In contrast, people with diseases affecting the cerebral cortex tend to have difficulty using and

modifying their strategies. It remains unclear how the basal ganglia fit into this picture. To shed some light on this question, we are currently extending this work to individuals with Parkinson's disease.

2. The impact of motor instability on learning.

Every neuroscience or neurology textbook will describe how the cerebellum is essential for skilled movement. People with ataxia have trouble coordinating movement: for some individuals, the problem is manifest in a wide range of movements including eye and finger movements, as well as walking and speech. For other individuals, the problem may be restricted to one class of movements (e.g., walking). Not only do people with ataxia have trouble producing movement, but they also have difficulty learning new movements. This has led to the view that the cerebellum is essential for motor learning.

One issue that has not been considered in a systematic manner is the relationship between coordination problems and learning problems. These two may be highly correlated: That is, people who have the most pronounced coordination problems may also have the greatest impairment in learning. However, there are some puzzling results in the neurology literature that suggest motor control and motor learning may not be correlated in people with ataxia.
We have been looking at this problem from a new perspective, one that we call the attribution question. Suppose in trying to reach to a visual target, you miss the target and end off to the right side of it. The brain now faces an attribution problem. It must decide if the error arose because the environment has changed (attribute the error to an unstable world) or the error arose because your muscles did not do what they were supposed to do (attribute the error to your unstable motor system). If the error is attributed to an unstable world, then the brain faces a learning problem—it needs to figure out how the world has changed and adjust to it. On the other hand, if the error is attributed to an unstable motor system, then the brain may choose to ignore the error. Rather, it provided the right commands and has to recognize that the motor system may just not be consistent in "carrying out its orders."

We have been conducting experiments to ask if the learning problems seen in people with coordination problems might reflect an attribution error. The basic idea is that ataxia or Parkinson's disease might lead individuals to attribute motor errors to their unstable motor system, even in situations where the error actually arose because the environment had changed. If this occurred, they might show poor motor learning, not because their learning capability was compromised, but because they had attributed the error to the wrong source (themselves rather than the world). We are just beginning to test this idea. John Schlerf and Jing Xu, two former grad students in the lab, conducted our first study on this issue, testing people with ataxia. Here our results suggest that the motor learning problem cannot be characterized as an attribution error. It appears that even when we account for the fact that these individuals' movements are more unstable, there remains a problem in using errors to adjust to changes in the world. With these tools in hand, we can now turn our attention to other neurological conditions. It may seem odd to talk about a changing "world". We can easily do this in the laboratory with our virtual reality systems. But these laboratory tests mimic the challenges we constantly face in the world. For example, the force we use to pick up a drinking glass has to be adjusted depending on whether the glass if full or empty (but the force should be the same if the glass is seen as half full or half empty!).

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.

Another 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, they learn to classify abstract pictures. The participants are tested twice, one after being given a dopamine (DA) agonist, Bromocriptine, a drug frequently used in the treatment of Parkinson's disease, and a second time after being 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.

News from CognAC

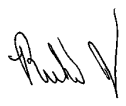
Let me end this newsletter with an update on the members of the Cognition and Action Lab. While I remain a constant presence, the other members move on to new positions when their training ends. Jing Xu is now in her 2nd year of a post-doc at Johns Hopkins University, one of the leading centers for the study of movement disorders. She is working on a major rehabilitation training project, one that could change the way we treat people who have suffered a stroke. Jordan Taylor left us this past summer, taking on a faculty position at Princeton University. He has set up his lab to study motor control and movement disorders. While he is sorely missed, he is actually a regular presence on lab email and Skype as we continue to work and collaborate together. After he finishes his dissertation, Peter Butcher will be joining Jordan in Princeton. And finally, Laura Hieber, our lab coordinator for the past three years will also be leaving the lab and California this summer. While we, and I know many of you will miss Laura's infectious smile, we should raise a toast and congratulate her: Laura will be starting a Ph.D. program in clinical psychology at Vanderbilt University in Nashville, Tennessee. She plans to shift her focus from movement disorders to psychopathology with an interest in understanding the neurological disorders that underlie schizophrenia.

Keep an eye out for some new faces in the CognAc lab. Two new post-docs have moved up the coast to join our team. Matt Crossley comes to us from UC Santa Barbara and Ian Greenhouse from UC San Diego. We also expect to have one or two new graduate students come September.

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
Professor of Psychology and Neuroscience
Cognition and Action Laboratory, UC Berkeley