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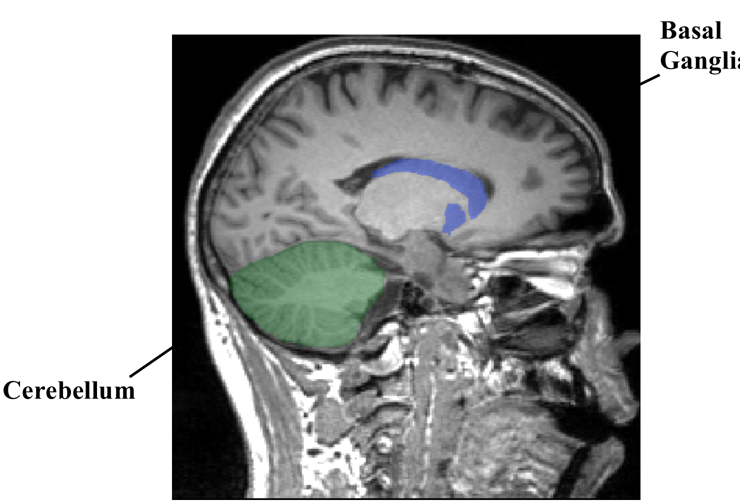
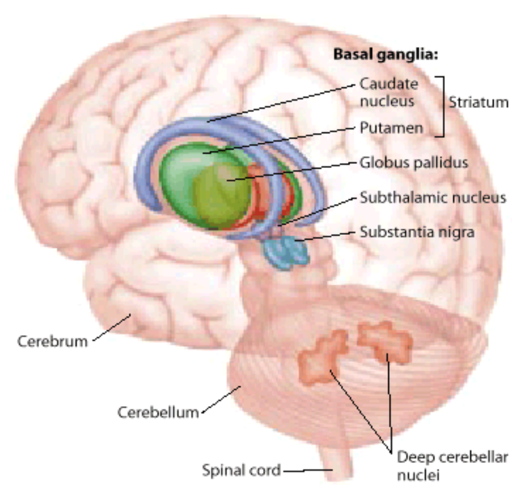
We're getting ready for the National Ataxia Foundation's Annual Meeting in Las Vegas this coming week. Not exactly a way to escape the California drought with a trip to the desert but a good motivation to get the annual newsletter from the Cognition and Action Lab in order. As always, I like to begin 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 recent projects.

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 much of what determines whether a movement is clumsy or skilled has more to do with the brain than the body. 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: Interaction of the cerebellum, cortex, and basal ganglia in motor learning.

Many movement disorders disrupt skilled performance. Not only is skilled movement affected in people with Parkinson's disease and cerebellar ataxia, but it can also be affected by cortical stroke or 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 require the integrated activity of many different parts of the brain.

Last year I described our work asking how motor skill learning requires a combination of strategy use and practice. For example, to high jump, you not only have to coordinate running and jumping movements, but you also have to come up with a good 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? 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. 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. We find that strategies and motor consolidation are simultaneously operating at all stages of practice. The clearest evidence for this comes from studies developed by a former lab member, Jordan Taylor, who is now a professor at Princeton University. Jordan created strange 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. Ryan Morehead, a graduate student in the lab has been extending this work. We all have the sense that it is easier to relearn a skill compared to when we first learned the skill. For example, if I once learned to knit but have set aside my needles for 10 years, it will be easier to become proficient when I start again. Ryan has been running a series of studies to ask if the "savings" comes about because the movement patterns have remained dormant for many years and just need to be reactivated, or if the "savings" comes from being able to regenerate the appropriate strategy. Interestingly, his work suggests that the main benefit comes from recall of the appropriate strategy.

We have also shown how the balance between strategy use and motor consolidation can be altered by neurological disease. We had predicted that people with diseases affecting the cerebral cortex would have difficulty using and modifying their strategies whereas people with ataxia would be most affected in the motor consolidation process. While the prediction about the cerebral cortex appears to be correct, our recent studies indicate that individuals with ataxia have difficulty not only in motor consolidation, but also in employing strategies. In terms of brain function, these findings make sense when we consider that the cerebellum makes lots of neural connections with the cerebral cortex. It may be that it is hard for the brain to evaluate the success of a strategy if the person has difficulty executing the movements required to test out that strategy. Or it may be that developing a strategy requires anticipating its consequences and this ability is affected in individuals with ataxia. To return to our high jump example, deciding whether to jump over the bar legs first or headfirst might require anticipating the effects of these two options. The cerebellum may work with the cerebral cortex to perform this anticipatory function, generating what we call "internally predictions".

2. The cerebellum and prediction: Beyond motor control.

We have recently been examining if the cerebellum plays a more general role in prediction. Tor Moberget, a visiting scholar from Norway, led this work. It is well known that people with ataxia may have difficulty coordinating the fine gestures to speak. Tor, however, has been looking at a different aspect of our language abilities, asking if the cerebellum contributes to our ability to understand language in a fluid manner. Consider a situation where you are at a noisy restaurant with a friend and you hear her say, "Please pass the xkdoh". Of course she didn't say "xkdoh" but the last word was drowned out by all the chatter about your table. We can all make a reasonable guess that the last word might have been "salt" or "bread" or "ketchup". As with movement, language is highly predictive. As skilled comprehenders, we can use the context of the initial words to anticipate the final word. Tor's study asks if this predictive capability in the domain of language is also dependent on the cerebellum.

To answer this question, Tor used a brain imaging method involving an MRI machine. I'm sure many of you are familiar with MRI and how it can produce exquisite pictures of the brain. The machine though can also be used to measure the distribution and utilization of oxygen in the brain, a technique that is known as functional MRI, or fMRI. We looked at two questions. First, we compared brain activity when people listened to sentences that were highly predictable ("Please pass me the bread and _____") to sentences that were more open-ended ("At the store, please buy some _________"). While the word "butter" can be used to complete both sentences, it is highly expected in the first example. When we looked at brain activity patterns, we observed more activation of the cerebellum in the predictive condition, consistent with the idea that the cerebellum helps generate these predictions. Second, we looked at brain activity when predictions were violated ("Please pass the bread and elephant."). Violations of predictions also led to activation of the cerebellum. Thus, Tor's study provides initial evidence that the cerebellum may be essential for making a range of predictions. In motor control, this might be to anticipate the sensory consequences of our actions—when I reach for a glass, I anticipate feeling the glass surface on my fingers. In language, this might be to anticipate what the person is about to say. In both domains, being capable of predicting outcomes allows the system to operate much more efficiently.

One important issue for future study is to conduct similar studies in people with ataxia. We know from past work and clinical observations that these individuals have difficulty anticipating the consequences of their movements. That is, rather than be anticipate sensory information, they tend to be reactive. But are there similar problems with language comprehension? To date, this question has not been studied. A limitation with fMRI studies is that the machine is excellent for revealing the parts of the brain that are engaged during particular tasks, but is of limited value in revealing why there is a particular pattern of activity. This question is much better answered by studying people with neurological conditions.

3. Hearing your own voice: Ataxia and speech control.

A third new project is also in the language domain. Here we are have returned to motor control, investigating why people with ataxia have difficulty controlling the pitch and loudness of their voice. One idea relates to the prediction theme described above. The parts of the brain used for hearing face an interesting problem. It is essential that this system is active when someone is speaking; we need our auditory system to make sense of their speech, a challenging problem when you consider how we are capable of speaking at very fast rates. However, the same system would we wise to ignore the sounds generated by our own speech. Not only would it be inefficient to listen to yourself speak (since you are the one who produced the sound), but because neural processing takes time, the perception of your own speech would lag behind your production system. This would be disruptive, something we can show by delaying auditory feedback through the use of special headphones. We are testing the idea that the cerebellum is involved in some sort of "cancellation process" where the auditory system is able to anticipate (and ignore) self-produced sounds. The irregular speech produced by some individuals with ataxia may result from a loss of this capability.

We are also looking at a second idea here. Rather than assume a speaker's brain ignores the sound of his or her own voice, it may be that this information is used as one source of feedback to control speech. Another source might be our sense of proprioception, the sense of our body; for speech, this would be the position of the speech articulators (e.g., the tongue, lips, jaw) and how they change when speaking. Given that ataxia is known to disrupt the sense of proprioception for arm movements, we are asking if this also holds true for speech movements. Perhaps the disrupted speech observed in some individuals with ataxia comes about from an over-reliance on auditory feedback rather than the integrated use of proprioceptive and auditory feedback. This project involves a collaboration between members of my lab (including Laura Hieber) and researchers at the University of California, San Francisco. For those of you at this year's NAF, you may get to know Zarinah Agnew, a post-doc over at UCSF who is leading this study.

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. Jordan Taylor has settled in at Princeton University. He has been working with neurologists at Johns Hopkins University in Baltimore and Columbia University in New York City to recruit individuals with ataxia or Parkinson's disease for his research programs. We continue to talk on a regular basis, establishing a coast-to-coast collaboration to study these neurological conditions. Peter Butcher, a former grad student at Berkeley is one source of glue here as he has just started work as a postdoctoral fellow in Jordan's lab. Laura Hieber, our lab coordinator for the past three years (and regular attendee at NAF) left the lab last summer and is now working on her Ph.D. in clinical psychology at Vanderbilt University in Nashville, Tennessee. She has shifted her focus from movement disorders to psychopathology, working in a lab that seeks to understand the neural mechanisms that underlie schizophrenia.

We have had an infusion of some new faces. Of particular note here is Ian Greenhouse, a post-doc in the lab who has a lot of experience in research with Parkinson's disease. Ian has launched one study with these individuals. He is also gearing up for a second study that will look at the neural mechanisms of inhibitory control, something that is highly relevant in Parkinson's given the problems these individuals have in initiating movement.

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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