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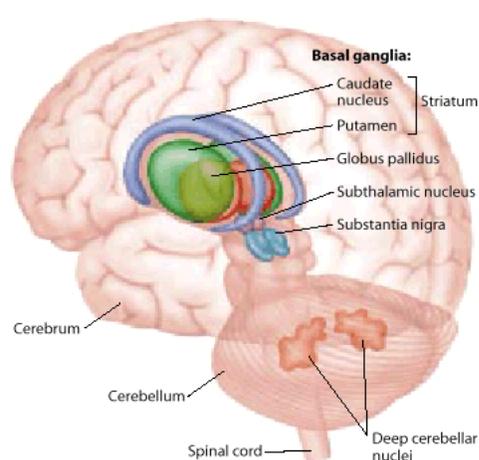
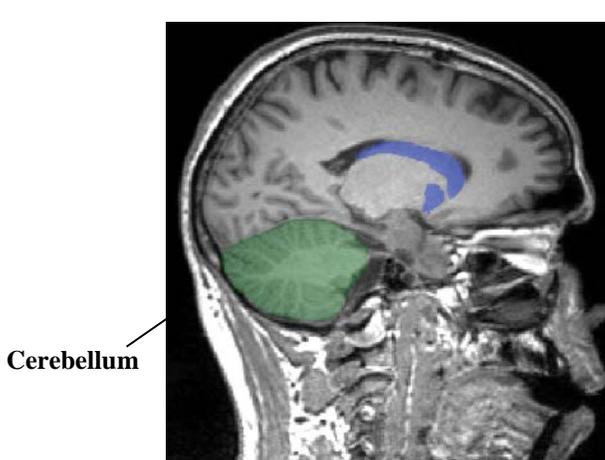
March 3, 2015

We're getting ready for the National Ataxia Foundation's Annual Meeting in Denver this coming week. There will be a group of us from the Cognition and Action lab at UC Berkeley and, this year, we will be joined by researchers from the Intelligent Performance and Adaptation Lab at Princeton University. Our two labs have joined forces and we will be running a series of experiments that look at the coordination challenges faced by individuals with ataxia.

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. Ataxia and speech control.

We are continuing our work on speech and language. Here we are investigating why people with ataxia have slowed speech, and difficulty controlling the pitch and loudness of their voice. One idea relates to the idea that the cerebellum is essential for anticipating the outcome of a movement, or what is referred to as “predictive control”. Consider what happens when you reach and grasp a glass of water. Your brain sends commands down the spinal cord to activate your muscles that will first cause your arm to first move forward and then close your fingers around the glass. The timing between these two events is tightly coordinated. How is this achieved? One idea would be that you use feedback from your arm and eyes to determine when the arm is positioned so that you can grasp the glass. However, feedback takes time—the signals must be transmitted from the arm and eyes to the brain and then processed. If we were dependent on using feedback in a continuous manner, our movements would be much slower. An alternative is that we control movements in a predictive manner, or what is called feedforward. That is, the brain sends the motor commands to make the arm move forward and predicts, based on those commands, when it will be appropriate to close the fingers around the glass. It is this predictive capability that allows movements to be so fluid and coordinated. By this view, one of the key problems in ataxia is a disruption of predictive control. People with ataxia have difficulty generating accurate predictions and thus either produce errors in their movements or have to slow down, relying on feedback to coordinate their movements.

Much of our reaching work has been on the issue of prediction in arm movements. In the past few years we have extended this line of study to look at speech. In order to speak fluently at the fast rates we are capable of, we need to be able to predict how the movements of our lips, tongue, and jaw will combine to create the sounds of speech. We can’t listen to our own speech to determine if we produced the right sounds because of the delays mentioned above. Indeed, it seems that our brains have learned to ignore the sounds we produce, even though those sounds reach our ears in the same manner as the sounds produced by other speakers. One idea here is that we ignore our own speech by anticipating those sounds, a form of predictive control. However, if this predictive ability is disrupted, we might have a tendency to slow down our speech, providing a way to overcome the neural delays and ensure we produced the right sounds. We are testing the idea that the cerebellum is crucial to predict the auditory consequences of speech movements, and that the slowed speech and difficulty controlling pitch and loudness of the voice in patients with ataxia may result from problems in this prediction.

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 Ben Parrell, a new post-doc in my lab, and researchers at the University of California, San Francisco.

2. How the cerebellum evaluates competency in movement execution to inform decision making.

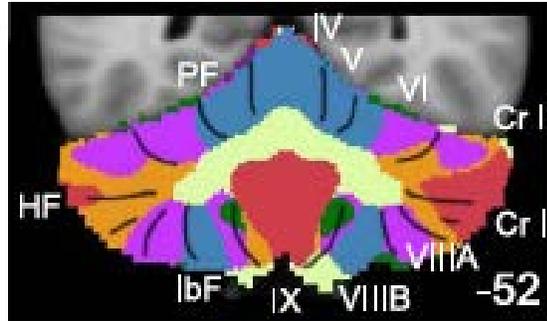
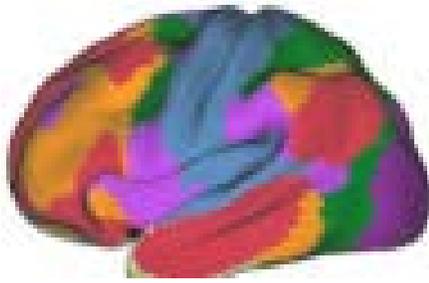
The only way in which we can interact with the world is to move: Every decision we make eventually requires a movement. We use those actions to evaluate whether or not we made the right decision. For example, if I think I will like the red wine offered at dinner, I take a sip and decide if the taste is good. If the taste is very bitter, I learn from my action—the particular bottle of wine has spoiled. Occasionally, we make the right decision but execute it poorly. For example, I might reach for the wine and knock over the glass. How do I evaluate this undesired outcome? It seems unlikely that I would decide the wine was bad—remember the saying about “not crying over spilled milk”. A more reasonable solution would be to recognize that it was my lack of coordination that resulted in the unexpected outcome. The challenge for us as neuroscientists is to determine how the brain might generate signals that allow us to determine if the bad outcome is due to a poor decision (choosing spoiled wine) or a poor action (bad coordination). We are exploring the idea that the cerebellum is critical for generating these signals.

The idea here again builds on the idea that prediction, or what we call “sensory-prediction errors,” the difference between a desired result of an action and the actual result, are used to not only control movements but also to learn from our actions. These sensory prediction errors could be used to provide information to decision-making circuits in other areas of the brain like the prefrontal cortex and the basal ganglia.

To this end, Sam McDougale a graduate student in Jordan Taylor’s lab at Princeton University is collaborating with us on a project to understand the role of the cerebellum in action-based decision making. In this experiment, participants chose between two different virtual ‘slot machines’, but have to make a reaching movement to the slot machine. Over the course of the experiment, we manipulate how easy it is to reach to the slot machine and how many points (or money) we get from the slot machine. We find that the simple requirement to move to the slot machine changes peoples behavior. We are currently enrolling individuals with spinocerebellar ataxia and Friedreich’s ataxia to understand how competency in action changes decision making and to determine if this involves the cerebellum.

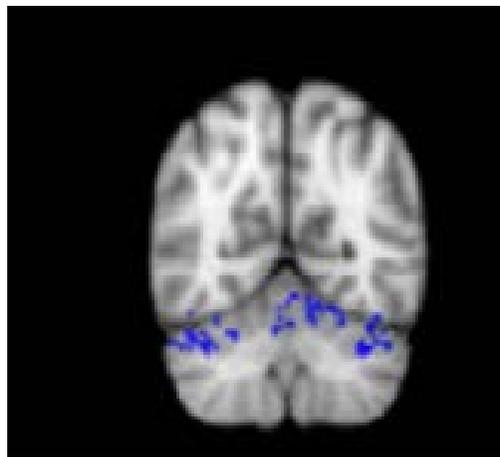
3. Insights into cerebellar function from psychiatry.

While our interest in the cerebellum and ataxia is motivated by our desire to understand how people perform coordinated actions, other researchers have been studying how abnormalities in the cerebellum may be related to psychiatric disorders such as schizophrenia and autism. This interest comes about from some surprising studies of brain anatomy. Using new methods to image the human brain, researchers have made new discoveries concerning how the cerebellum is connected to the cerebral cortex as well as how people with psychiatric abnormalities show developmental abnormalities in the organization of the cerebellum. The first surprising result comes from research using functional MRI (fMRI). Traditional MRI systems highlight the anatomy of the brain with exquisite detail. In contrast, fMRI studies physiology, looking at how the brain utilizes oxygen, the fuel required by active neurons. The picture below shows how oxygen utilization in the cerebellum is correlated to oxygen utilization in the cerebral cortex: regions sharing the same color indicate areas that tend to be co-active. As expected, there are large parts of the cerebellum that are co-active with the motor regions of the cerebral cortex. These are the regions shown in blue. More surprising, there are large parts of the cerebellum that show activity correlated with other parts of the cerebral cortex, and in particular, the prefrontal cortex (the regions shown in orange). Results such as these indicate that the cerebellum is not just “talking” to motor cortex; rather, the cerebellum is communicating with much of the brain, including those areas associated with higher complex thinking. Results such as this have made clear that we cannot just think about how the cerebellum contributes to motor function. It also appears to be well positioned to influence all aspects of brain function.



The left side is the cerebral cortex and the right side shows the different divisions of the cerebellum. Colors indicate regions that show correlated patterns of oxygen utilization. There are two parts of the cerebellum (in blue) that show correlated activity with the sensorimotor parts of the cortex. However, activity in other regions of the cerebellum are much more closely linked to non-motor regions of the cerebral cortex, including the frontal lobes (orange), areas associated with higher mental function.

The story becomes even more interesting when modern brain scanning methods are used to study people with psychiatric conditions. The blue regions in the picture shown below identify areas in the cerebellum that show reduced size in people with schizophrenia compared to matched control participants. This result is surprising because we think of schizophrenia as a “thought disorder.” These individuals do not have marked impairments in motor control. Other studies have shown abnormalities in the cerebellum in disorders such as autism or attention deficit/hyperactivity disorder (ADHD).



We have to remember that correlation does not equal causation. That is, we cannot conclude that these individuals have schizophrenia because of their abnormal cerebellum. In fact we know that having a degenerative disease of the cerebellum **does not** lead to schizophrenia. Ongoing research is designed to ask whether there is a functional link between cerebellar development and disorders such as schizophrenia or autism. We are beginning to collaborate with researchers at UC San Francisco who work with these populations. Our work is asking if ideas related to predictive control may help understand the thought problems observed in these individuals. For example, might auditory hallucinations, a common feature in schizophrenia, be related to a problem in distinguishing one’s own voice from that of others? This project shows how research involving people with ataxia can inform research in completely unrelated fields such as psychiatry.

News from CognAC

Let me end this newsletter with an update on the members of the Cognition and Action Lab. Jordan Taylor is now settled into his new life as a professor 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 work together and in fact, members from both of our labs will be at this year's NAF meeting.

New faces some of you will come to recognize include Ben Parnell, a new post-doc in the lab who is working on the speech studies and Matt Crossley, a post-doc in the lab at Berkeley who has been involved in the decision making research. Matt is working in tandem with Sam McDougle, a grad student at Princeton, helping cement our coast-to-coast collaboration.

Ryan Morehead is just finishing his dissertation at Berkeley, collecting the last data for his thesis during this year's NAF. He'll be leaving us this summer to do a post-doctoral fellowship at Harvard. Former lab members send their best wishes: Jing Xu is at Johns Hopkins working on stroke rehabilitation and Laura Hieber is making progress in her Ph.D. studies in clinical psychology at Vanderbilt University. Peter Butcher has left my lab but is still very much in the mix when it comes to ataxia research, now working as a post-doc at Princeton. Nice to have some continuity!

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. Check out our new look! Jordan has also put together a spiffy website to feature his work at Princeton: <http://www.princeton.edu/~ipalab/> 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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Cognition and Action Laboratory, UC Berkeley