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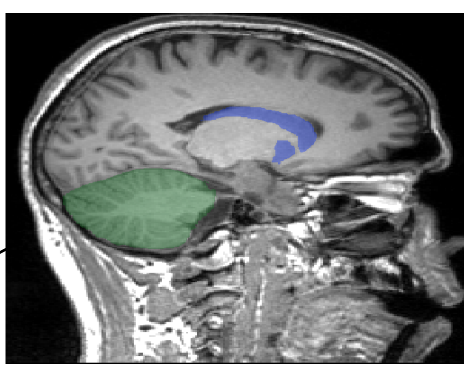
March 22, 2016

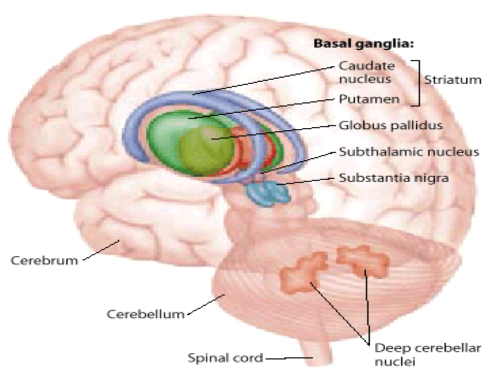
We're just about ready to head off to to Orlando for the National Ataxia Foundation's Annual Meeting next week. Our team this year will include a combination of individuals from the Cognition and Action lab at UC Berkeley and the Speech, Phonetics, and Phonology lab at the University of Delaware. We've joined forces to run a series of new experiments this year that focus on how well people with ataxia can adjust their movements to unexpected changes in the environment, as well as use that information to anticipate expected events. Our team also plans to stay an extra day after the conference and check out an environment with lots of unexpected events—Disneyworld!

As always, I'll 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. If a creature couldn't control its movement, it would be at a huge disadvantage in the world. It wouldn't be able to flee from enemies or 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 species.

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 dysfunction does not result from the loss of a particular brain chemical. Rather, various degenerative disorders, some of which have a known genetic basis, selectively attack cells in 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. The Cerebellum and Predictive Control in Speech.

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 control. 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.

We have conducted a number of studies in which we look at predictive control in reaching movements. In the past few years we have extended this line of study to look at speech. Speech is obviously one of the most amazing capabilities of humans, allowing us to share information with each other about the past, present, and future. In order to speak fluently at fast rates, 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 use feedback from our our own speech to determine if we produced the right sounds. 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 results from problems in this prediction. This project involves a collaboration between Ben Parrell, a former post-doc in the lab who is not an assistant professor at the University of Delaware and researchers at the University of California, San Francisco.

2. The Cerebellum and Temporal Predictions in Perception

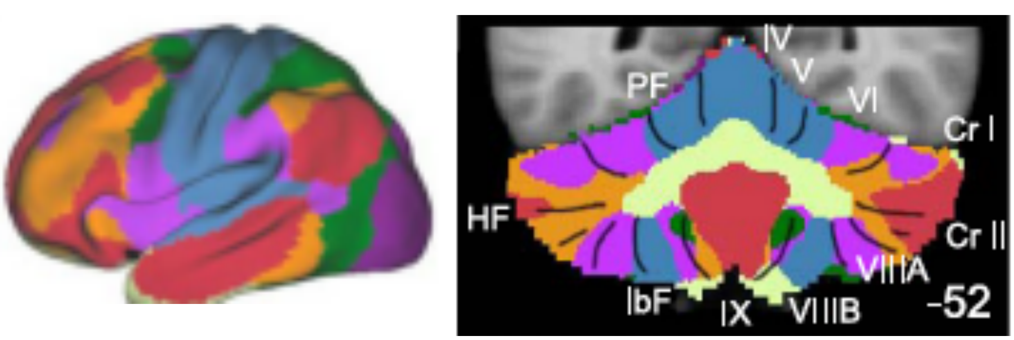
Predictive control may be essential, not only for coordinating movements, but also for efficient perception. When we are at a busy airport, we may be able to quickly spot a friend by having an internal mental image of what she looks like, allowing us to efficiently ignore people who look quite different to focus only on those who are a potential match. In our airport scanning example, we are using prediction to examine different regions in space.

We also use prediction to modulate how we process information in time. Music is a perfect example of this. When listening to a favorite song, we anticipate the upcoming lyrics and have have an excellent sense of the rhythm. DJ's in the hiphop dance world play on our memory for rhythm, introducing unexpected changes as a way to add a novel twist and beat to the sound. Indeed, variations in temporal prediction seems to be an important part of what makes us appreciate music. Humans like when things are predictable: Not only does this improve perception, but there seems to be something inherently satisfying about correcting anticipating what comes next. However, we also seem to take pleasure in violations of these predictions, finding things monotonous or unexciting if our predictions are always confirmed.

Given the role of the cerebellum in using predictive control to coordinate movement, researchers have also asked if this structure is essential for accurate prediction in perception. Our new research project is focusing on temporal predictions, asking if the ability to generate these is affected in people with cerebellar ataxia. In this work, we are examining a couple of different dimensions. One dimension will compare conditions in which temporal predictions are important for perceptual acuity with those in which the predictions are important for preparing movements? On the perceptual side, we know that people show improved perception when a stimulus is predictable in time. Will this enhancement effect also be observed in people with cerebellar degeneration? Will the enhancement effect depend on whether that perceptual information is used to facilitate movements (for example, if we measure how fast people can make a perceptual judgment rather than just their accuracy)? A second dimension gets back to our music example. Temporal predictions can be based on individual events such as when we know a clap of thunder will follow a bolt of lightning. Or it can be based on a repetitive beat as in a musical composition. Our studies are designed to examine if the cerebellum is important for all forms of timing or specific to certain types of temporal predictions.

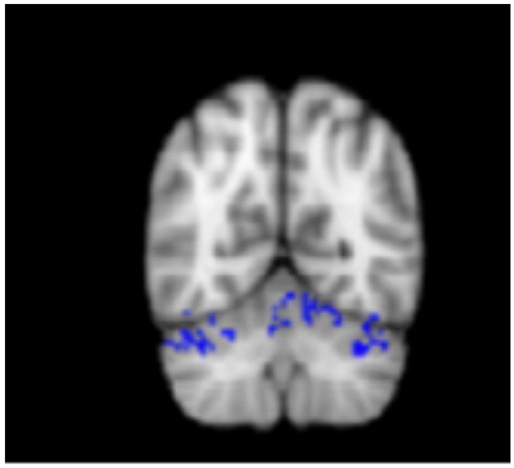
3. Insights into cerebellar function from psychiatry.

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. Two parts of the cerebellum (in blue) that show correlated activity with the sensorimotor parts of the cortex. 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. (from R. Buckner et al., Journal of Neurophysiology, 2011).

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 (from Roman-Urrrestrarazu et al., Schizophrenia Research, 2014). 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

There have been a lot of changes in the Cognition and Action Lab over the past year. Half of the lab members have moved on to new positions. Ryan Morehead and Sarah Hillenbrand received their Ph.Ds. this past May (yeah Ryan and Sarah!). Ryan has started a post-doctoral fellowship at Harvard University. He reports that he is enjoying his transition from California to Boston, but also recognizes that this has been a year without a real New England winter. Sarah Hillenbrand has moved down the bay to do a special post-doc at Stanford University, one that is designed to train scientists to become good communicators with the general public, perhaps as journalists or perhaps as public policy makers. The fellowship also lets her develop new classes on science education, something that Sarah has been passionate about for many years. You can follow her blog at http://sarahhillenbrand.com.

Two of our post-docs have also taken up new positions. As noted above, Ben Parrell, our speech specialist is now a professor of linguistics at the University of Delaware. He is busy setting up his own lab but will be taking time off to attend NAF this year. Matt Crossley is a research scientist at SRI International, a nonprofit research institute in Menlo Park, California that is perhaps most famous for inventing the computer mouse. We also continue to work with Jordan Taylor. Jordan is a professor at Princeton University and is doing ataxia research around New Jersey/New York through his collaborations with neurologists at Johns Hopkins University in Baltimore and Columbia University in New York City. Be sure to contact him if you are in the area, http://www.princeton.edu/~ipalab/.

While we can never replace Ryan, Sarah, Ben, and Matt, we have recruited some new folks to CognAc. Hyosub Kim received his Ph.D. in rehabilitation sciences from the University of Illinois. Hyosub's thesis was on recovery from spinal cord injury. He has come to the lab with an interest in moving up the nervous system, so to speak, and will now be working on motor learning in ataxia and Parkinson's disease. He brings an important clinical background to the lab from which we are all benefitting. Assaf Breska arrived in November after finishing his Ph.D. at Hebrew University in Israel. His thesis research studied how people generate and use temporal predictions, a project that he will now be extending to include individuals with ataxia. He'll be representing the lab at NAF this year. We also have a short-term visitor from Japan, Michi Hayashi who is an expert in functional brain imaging (fMRI).

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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