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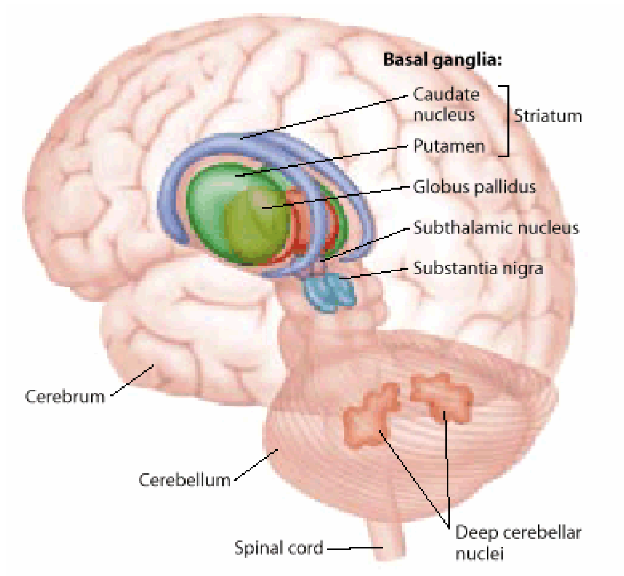
We're a few months delayed with our annual newsletter, but summer is always the best time in academic life to get caught up once again. I summarize below some of the most recent research projects that we've been conducting in the Cognition and Action lab here at UC Berkeley. As always, I begin with a general overview to remind you of our general mission.

We remain extremely indebted to all of our participants. Your willingness to be part of these studies is an essential part of our efforts to understand the mysteries of the brain. Neurological disorders present an extreme challenge for each individual— coping with fluctuating symptoms, having to work hard to learn new skills, and keeping an eye out for new treatments and developments. They also provide a rare opportunity for researchers to explore how damage to the human brain affects various aspects of our mental and physical life. A great deal of progress in understanding the brain has come about through research involving laboratory animals and computer models. However, there are always limitations in using such information to understand the human brain and for developing clinical interventions and rehabilitation strategies for different neurological disorders. The smartest rat or robot can't produce the kinds of skilled actions that approximate the complexity of those produced by people.

The research in the 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 on the next page). 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 or driving cars, they did require the neural machinery that allows 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 how movements are controlled across a range of different animals.

We have focused on two large structures within the subcortex, the basal ganglia and the cerebellum. Both have long been recognized to be part of the control of movement. Nonetheless, their specific functions remain a mystery. It is clear that if either structure is damaged, the 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



Our recruitment efforts are primarily oriented to enlist participants who have neurological disorders affecting the basal ganglia or cerebellar dysfunction, although we also work with individuals with other neurological problems that might affect the control of movement. We do not focus on specific disorders. Clinical researchers more frequently focus on a specific neurological disorder such as Parkinson's disease or spinocerebellar ataxia. In contrast, our emphasis is on understanding the neural systems required for skilled actions and this has led us to work with individuals with Parkinson's disease, ataxia, or strokes affecting the basal ganglia or 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. Indeed, there are a few different grants supporting the work, each with a distinct theme. Nonetheless, there are a number of central themes that guide our work. As I've already mentioned, we wish 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 or 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. The expert tennis player can't simply stand fixed on the center of the court and swat 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 for basketball; the professionals can all make shots from just about anyplace on the court when unguarded in practice. It's the challenge of doing the same thing 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, 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.

We've continued with our studies on the role of the cerebellum in skilled movements and in particular how this structure seems to be essential for movements that require precise timing. Many of you have been tested by Bekki Spencer, and more recently a new member of the lab, John Schlerf, on tasks that require you to produce rhythmic movements. Our recent work has followed up on one intriguing result I reported in last year's letter. Bekki had found that the timing problem is restricted to only certain types of movements, those in which there are abrupt transitions between different groups of muscles. If the action involves a continuous transition, for example, when drawing continuous circles, people with cerebellar ataxia perform as well as neurologically healthy individuals. We have been looking at why the transitions are so difficult. Is it because the brain must specify the exact timing for when each movement component must start and stop, and the cerebellum is essential for setting these times? Or is it that movement transitions require that the brain rapidly switch from one set of movement commands to another? Our results support the former hypothesis. In one study, we asked people to press and lift a finger. The lifting action was either performed as fast as possible or after a timed interval (for example, a half second). If the problem was in switching muscle commands from those required to press to those required to lift, then people with cerebellar damage should have had the most difficulty in the condition when the two gestures were made as fast as possible. However, the results showed that these individuals had the greatest problem when they had to insert the timed intervals between the two gestures.

We've also been exploring other, more subtle ways in which precise timing may be essential for coordinated movements. Consider actions that require the coordinated activity of the two arms. For example, in keeping with the tennis theme, serving requires using one hand to toss the ball while the other arm rotates the racquet above the head. It isn't sufficient to just do each action correctly on its own; the actions of each arm must be timed just right so that the racquet head meets the ball just as it begins to fall back down due to gravity.

Bimanual coordination is especially challenging given that each half of the body is controlled by only one side of the brain. For the cerebral cortex, the main part of the brain, the control is cross-wired: the right side of the brain controls the left side of the body and the left side of the brain controls the right side of the body. This cross wiring occurs because the nerve fibers connecting the brain to the spinal cord cross over near the base of the brain, at a structure called the "pyramids". Similarly, sensory fibers from the body cross over as they reach the brain resulting in a similar crossed organization. However, the cerebellum is different. For this structure, the nerve fibers cross the midline twice. Thus, each side of the cerebellum controls the same side of the body.

Interestingly, there is no good explanation for why the cerebellum is different. In terms of function, though, the fact that each half of the brain is associated with one half of the body, either opposite side for cortex or same side for cerebellum, raises an interesting question: How do the two halves communicate when an action requires the integrated action of our two hands? We have been doing a lot of work on bimanual coordination over the past few years to explore this problem.

One of our favorite tasks here involves a virtual reality environment in which you can see and feel objects, even though they don't really exist (thus, the term "virtual). Using this system, we've created what we call the "barmaid's challenge". Imagine the barmaid approaches your table with a three large mugs of beer balanced on a tray supported by her open hand. If you reach out to grab one of the beers, the tray becomes unbalanced and she is likely to spill the other beers. However, if she picks up one of the beers with her other hand, the tray remains stable. Somehow she is able to signal the supporting hand that the weight is about to change and make a very rapid adjustment to maintain stability. Jorn Diedrichsen created a version of the barmaid's challenge for our lab. He has now moved on to Johns Hopkins University and the project is being carried forward by Tim Verstynen and Neil Albert.

In our version of the barmaid's challenge, you were asked to lift and support a block with one hand, the postural hand, and then lift it up with the other hand, what we call the acting hand. If your two hands are well-coordinated, the upward force generated by the postural hand would be reduced just before the object is lifted by the acting hand. The virtual reality system allows us to precisely measure how rapidly communication occurs between the two hands. We have found that individuals with cerebellar ataxia are successful in coordinating the actions of the two hands.

However, there remains a timing problem. The change in the upward force does not occur exactly when it should. Interestingly, people with ataxia have developed a safe strategy here. They reduce the upward force generated by the postural hand earlier than people without ataxia. This ensures that the postural hand remains stable once the object is removed. But there is a potential danger: if the force is removed too soon, the object might fall off the hand. We think this task captures an important part of the stability problems that people with ataxia have.

We have recently been testing individuals with Parkinson's disease on the same task. They also have difficulty with this task, but the problem is quite different than that found in individuals with ataxia. People with Parkinson's are unable to anticipate the change in force. They can lift the object with the postural hand and then remove it with the acting hand. But they fail to show normal coordination between the two hands: when the acting hand lifts the object, the postural hand is deflected upward because the upward force is now terminated. At present, we are examining different ways to account for this problem. One idea is that the failure to reduce the upward force is another manifestation of the difficulty people with Parkinson's disease have in initiating movements, although here the movement is more a postural, unconscious change. Another idea is that the basal ganglia may be essential for these kinds of automatic, unconscious movements, similar to the way this structure has been associated with habitual, over learned movements. The basal ganglia changes that are associated with Parkinson's disease may lead to a loss of these habitual movements.

The barmaid's task requires that each hand be able to anticipate the action of the other hand. Anticipation is an important part of all movement; in the tennis example, we have to anticipate how the ball will bounce in order to position ourselves to strike it appropriately. In fact, making accurate predictions is an important part of much of our thinking. The tennis pro doesn't just anticipate the consequences of her own actions. She must also anticipate the actions of her opponent.

We've been doing various types of studies in the lab looking at how people generate predictions in order to either improve movements or learning in general. Some of you have worked with Shawn Ell and Roshan Cools on their studies on cognitive learning. Since that work is on-going, I'm going to hold off going into details here. Another study of prediction and learning has been conducted by Joel Mainland, a graduate student interested in the sense of smell, or what is called, olfaction. While we tend to pay very little attention to smell, it is an ancient system, perhaps the oldest of all our senses. Olfaction also provides another beautiful example of the linkage between perception and action. Brain imaging studies have shown that both the cerebellum and basal ganglia become active when people are smelling different odors. Joel's studies seek to understand what these structures are doing. As a starting point, he has been looking at whether the sense of smell is affected in people with ataxia or Parkinson's disease. It turns out that it is. People with Parkinson's disease can have a fairly severe loss of smell whereas people with ataxia tend to have a moderate loss of smell. Interestingly, for the latter group, the problem may be limited to a single nostril! We expect to begin testing individuals with focal lesions of the basal ganglia (due to stroke) soon on similar task to see if their problem is also limited to one nostril.

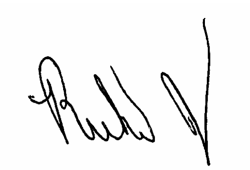
Smell is somewhat unique in that we can control the strength of an odor. We do this by adjusting the intensity of our sniffing. If a smell is rather subtle, we take a strong sniff. If the smell is strong, we take a weak sniff. These adjustments are constantly occurring at an automatic level. When you walk into a room that has just been scrubbed with ammonia, you very quickly reduce your sniff intensity to reduce the unpleasantness of the odor. Joel's work has been looking at this link between action and perception. In his first study on this problem, he discovered that people with cerebellar ataxia have difficulty making these adjustments. This seemed to fit with some new ideas about the cerebellum and how it provides an interface between perception and movement. However, this conclusion must be qualified because it turns out that the adjustment process becomes quite weak with age independent of whether or not there is a neurological problem. As we get older, the ability to modulate the intensity of a sniff to control smell becomes weaker. Future studies here will ask whether the aging effect is related to changes in the cerebellum or basal ganglia.

I hope this newsletter is useful in providing you with an overview of the general questions addressed by our research program and also some details about the specific studies you may have participated in over the past year. I, or any of the members of the lab, are always happy to answer any questions or provide additional information. All of our results are reported in scientific journals and I've listed below a few of the ones from this past year. These reports are available for free from our website (and if you don't like to use the WEB or download files, we are happy to send you copies). I will warn you that the reports are written at a technical level and don't make for the most exciting reading to someone outside the fields of neuroscience and neurology. I have also listed two websites that have provided press reports on our work this past year.

Let me close by thanking you once again for your time and energy. We are extremely grateful for your participation and look forward to continue to work with you in the coming year. While we know that the work doesn't really offer any medical benefits to you, we hope that there is a personal satisfaction from knowing that your participation contributes to scientific progress.

Finally, it is with some sadness that we say goodbye to Natalie Marchant. I know that all of you have enjoyed having Natalie around as much as I have. Alas, she is off to graduate school in England. Andrea Weinstein will be taking over and I expect you will be hearing from her over the coming months.

Best wishes,



Richard Ivry
Professor
Director, Institute of Cognitive and Brain Sciences

p.s. We are always looking for new participants, including individuals who have not had any neurological problems. These individuals can serve as "controls" to compare with the performance of our participants who have had neurological problems. Please pass on my contact information or card to anyone who might be interested.

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Recent Scientific Reports (that can be downloaded from our lab's website):

Ivry, R.B. and Spencer, R.C.M. (2004). The neural representation of time. Current Opinion in Neurobiology, 14, 225-232.

Aparicio, P., Diedrichsen, J., and Ivry, R.B. (2005). Effects of focal basal ganglia lesions on timing and force control. Brain and Cognition, 58, 62-74.

Spencer, R.C.M., Ivry, R.B., and Zelaznik, H.N. (2005). Role of the cerebellum in movements: Control of timing or movement transitions? Experimental Brain Research, 161, 383-396.

Diedrichsen, J., Verstynen, T., Lehman, S.L., and Ivry, R.B. (2005). Cerebellar involvement in anticipating the consequences of self-produced actions during bimanual movements. Journal of Neurophysiology., 93, 801-812.

Maddox, W.T., Aparicio, P., Marchant, N.L., and Ivry, R.B. (2005). Rule-based category learning is impaired in patients with Parkinson's Disease but not in patients with cerebellar disorders. Journal of Cognitive Neuroscience, 17, 707-723.

Press Reports on Our Research Reports

http://whyfiles.org/shorties/132cerebellum/
The whyfiles are published by the University of Wisconsin with financial support from the National Science Foundation. Their mission is to disseminate breakthroughs in science to the public. They did a feature piece on our work involving patients with cerebellar dysfunction.

http://ls.berkeley.edu/new/02/ivry.html
This is a piece written by the College of Letters & Sciences at UC, Berkeley for their website profiling faculty research programs on campus.