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SANTA BARBARA • SANTA CRUZ

PSYCHOLOGY DEPARTMENT
UNIVERSITY OF CALIFORNIA, BERKELEY
3210 TOLMAN HALL #1650
BERKELEY, CALIFORNIA 94720-3190

PHONE: (510) 642-5292
FAX: (510) 642-5293

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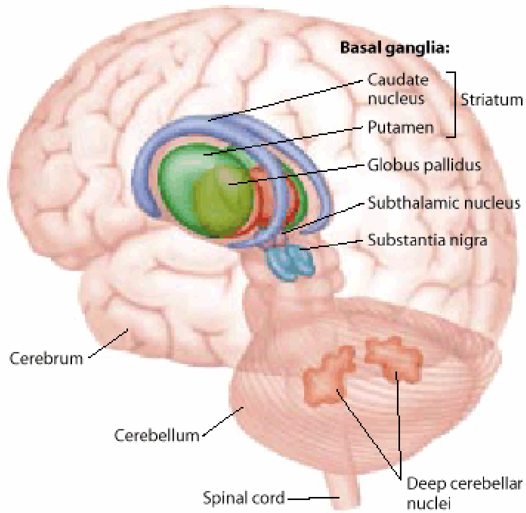
It's summer once again, the best time in academic life to catch up with everything that got pushed aside when the halls are filled with students. This letter provides a summary of some of the most recent research projects we've been conducting in the Cognition and Action lab at UC Berkeley. As always, I begin with a general overview to remind you 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 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). 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.

1. The temporal control of movement.

Many of you have participated in studies of rhythmic movements conducted by Bekki Spencer, a post-doc in the lab, and more recently, John Schlerf, one of the graduate students. The goal of this work is to explore the role of the cerebellum and basal ganglia in controlling movement timing. Timing is an essential aspect of most skilled actions. Indeed, the most fundamental of all actions, locomotion, requires that the same pattern of muscular activity be produced over and over again in a rhythmic manner. Some of the classic studies in neuroscience conducted at the beginning of the last century by the Nobel laureate, Charles Sherrington, demonstrated that such rhythmic activity could be controlled directly by the spinal cord. However, volitional skilled actions not only require consistent timing, but are also marked by their flexibility. We can choose to write our signature slowly or quickly, and the basic shape remains constant. Thus, the rate of the motor commands can be modified even though the organization or pattern of the commands remains fixed. Flexibility is one of the hallmarks of animals with larger brains.

In the work in our laboratory, we have shown that individuals with damage to the cerebellum have difficulty in controlling the timing of their movements. Whether it is a discrete action such as reaching for a glass of water or a rhythmic action such as brushing your teeth, these individuals are able to select the appropriate muscles and generate the necessary forces. However, their ataxia appears to arise from a problem in coordinating the timing between the different muscular events. Thus, they may knock over the glass of water because they fail to turn on the muscles that brake the reaching movement at the right point in time.

An important and unresolved question is whether the cerebellum is uniquely involved in controlling movement timing or whether it works in concert with other brain structures such as the basal ganglia. A number of laboratories around the world have shown that modulations in dopamine levels can affect the rate of movements. For example, one of the features of Parkinson's disease is that movements are produced slowly. Does this mean that the basal ganglia are directly involved in the control of timing, too, perhaps through interactions with the cerebellum? Or does the loss of dopamine slow movement in Parkinson's patients indirectly, perhaps because additional effort is required to send out motor commands? To explore this question, we performed a study in which Bekki directly compared people with Parkinson's disease or cerebellar injury on a set of tasks requiring precise timing. She found that, when the movement rate was set to that which all of the patients could maintain, only the individuals with cerebellar injury were more variable in their performance. Thus, this study would point to a special role for the cerebellum in the control of movement timing.

Bekki and I also joined forces with a group of researchers in France to test an individual with a very rare neurological disorder. Due to exposure to a toxic substance, this individual suffered peripheral nerve damage that severely affected her sensory nerves while having little impact on her motor nerves. Thus, she is able to produce movements, but is unable to feel the consequences of her movements (unless she uses her eyes). We tested her ability to coordinate rhythmic movements of the two arms. You can try our task yourself: simultaneously draw circles with your left and right arms. You will spontaneously move the two limbs in rhythm with one another as well as produce symmetric circles. We were interested in seeing if this form of coordination required sensory feedback. To our surprise, the patient was quite good at this task even when we asked her to close her eyes. Her limbs adopted a common pace and the timing was very consistent. Thus, it appears that motor timing does not require feedback from the moving limbs. Her spared ability provides another demonstration of how the brain has learned to produce skilled patterns. Of course in most of our behaviors, we need to use sensory information. Brain signals for controlling movement are modified by sensory signals. In fact, this patient with severe sensory loss has great difficulty using utensils such as a knife and fork because here the motor commands need to be constantly updated with sensory signals from the objects.

2. Planning and selection of actions.

In addition to our studies of neurological disorders, we have also been using brain imaging methods to examine how different brain structures contribute to skilled movement. The Berkeley campus now has a Brain Imaging Center, featuring a magnetic resonance imaging (MRI) system. Many of you have had MRIs, allowing your neurologist and radiologist to determine if there are structural abnormalities (usually resulting from stroke or degenerative disorders). In addition to this anatomical use, MRIs can also be used to look at brain function. The key here is that, as a person engages in some sort of activity, those areas of the brain that are most active require an increase in oxygen. Although these changes are small (just 1% or so), the powerful magnets in a MRI scanner can measure this redistribution of oxygen. We have employed this technique to look at brain activation when planning and executing skilled movements.

Our first studies here have focused on the cerebral cortex. The motor systems of the cortex control the body in what is called a contralateral manner: the left side of the cerebral cortex controls the right side of the body and the right side of the cerebral cortex controls the left side of the body. (Interestingly, while the same contralateral organization holds for the basal ganglia, the picture is reversed with the cerebellum.) However, the contralateral organization is not strictly followed. There also appears to be some contribution of the ipsilateral (or same) side of the cortex in controlling movement. This is especially apparent with movements of the left hand in most right-handers. Brain imaging studies show that both the left and right sides of the motor areas of the brain are active when right-handers produce left-handed movements. This also fits with what we have learned in neurology.

Damage to the left hemisphere not only produces language problems, but may also compromise a person's ability to produce skilled actions, a disorder known as apraxia. Apraxia is present when these individuals move either the right or left hand.

We performed an fMRI (functional MRI) study to specify the conditions that led to the recruitment of both halves of the brain during left-hand movements. In particular, we were interested in whether the left hemisphere was only recruited when the action involved some sort of sequential movement or whether the left hemisphere would also be recruited for other types of skilled actions. While lying in the brain scanner, we had right-handed individuals make different types of movements, all with the left hand. The movements could either be simple finger movements, sequential movements, or complex configural movements akin to what a pianist does when playing chords. We found that for the simple movements, activation was limited to the right side of the brain. In contrast, for both types of complex movements (sequences or chords), there was activation in motor areas of both halves of the brain. This study raises interesting questions about the relationship of language and motor control. Perhaps the special role of the left side of the brain is not for language per se, but rather reflects a more general specialization for skilled actions, with language being one type of skilled action.

We were not able to examine brain activation in the basal ganglia and cerebellum in this study. However, our upcoming plans are to extend this line of inquiry to include subcortical brain regions. Our interest here is to ask whether the two halves of the basal ganglia and cerebellum also show functional asymmetries. As I'm sure you've seen in the popular press, there is considerable interest in how the two halves of the cortex differ (for example, you can buy books that claim to train you to "think with the right side of your brain"). This type of question has rarely been applied to the subcortex, even though subcortical structures also come in pairs.

3. The cerebellum and language.

The preceding discussion leads to another issue we have been working on over the past few years: Specifically, is the role of the cerebellum limited to the control of movement, or does it also contribute to more cognitive aspects of human brain function. After 20 years of debate, I think we can safely say that damage to the cerebellum can lead to changes in cognition (and this is also supported by many brain imaging studies). The challenge now is to understand how the cerebellum contributes to cognition. One idea is that the cerebellum helps coordinate mental skills, similar to how it helps coordinate motor skills. By this view, the cerebellum might work in tandem with parts of the cerebral cortex that are involved in cognitive skills such as attention, memory, or language. A different idea is that the impact on cognition observed following cerebellar damage is indirect. People with cerebellar injury have to pay a lot more attention to controlling their movements than neurologically healthy individuals. Perhaps this comes at a cost in the amount of mental resources one has available for other cognitive activities. To take an extreme example, we all joke about being able to walk and chew gum at the same time, but if you have to have to monitor each step to make sure you don't tip over, it may prove difficult to chew gum. Of course that example involves two actions. But the same idea could hold for the combination of an action and some other cognitive task. (Having two teenage sons with driving permits, I apply these ideas by not letting them listen to the radio when we are out for a driving lesson.)

We have been investigating whether individuals with cerebellar damage have specific problems with language. It is well-documented that some people with ataxia have trouble speaking, a disorder known as cerebellar dysarthria. Our question was whether these individuals also have trouble with internal speech. Consider what happens when someone gives you their phone number. If you are paying attention and don't have a piece of paper handy, you will internally rehearse the number, chunking it into one group of three numbers and a second group of four numbers. You might repeat it a few times to make sure it gets into memory. This rehearsal is referred to as verbal working memory, reflecting the fact that we use covert, or internal speech, to remember the information. Our experiments, conducted by former lab members Susan Ravizza and Tim Justus, were designed to test if individuals with cerebellar damage had problems with verbal working memory and if so, was the problem one of difficulty with internal rehearsal. Alas, we don't have a clear answer. What we have learned to date is that there are subtle problems with verbal working memory. Our participants are not able to hold as much information in working memory as their matched control participants. However, the impairment is rather small. Moreover, it isn't clear at present if the problem is specifically related to difficulty in using internal speech or if it may be a problem in coding the information into internal sounds. Science can be, as you might imagine if you've been in a lot of our studies, a slow process where the results of a study not only might provide some answers but also open up a host of new questions. I would say that our work on the cerebellum and language, and indeed, cognition in general, is at a very early stage where there are many more questions than answers.

4. The basal ganglia and learning.

We have also been looking at changes in cognition associated with damage or degeneration of the basal ganglia. In this line of study, we've turned to tasks of cognitive learning, paralleling some older work we've done on motor learning. The tasks that we have used in our cognitive studies often require participants to learn, by trial and error, to classify stimuli into a number of contrasting groups. These tasks are designed to capture something that is essential to human cognition-- the ability to classify the things we encounter in our daily life. We recognize that there is something similar about all dogs, even though they come in vastly different sizes and shapes. The same holds for all sorts of categories: to name a few concrete ones, food, furniture, and tools.

In some of our studies, the emphasis has been on the learning process. We create novel categories and see how well people can learn the rules that divide one group of items from another. In other studies, the emphasis is on how well people can switch from using one rule to another. In one study conducted in collaboration with a researcher at the University of Texas (Todd Maddox), we used displays involving lines that varied in their length and horizontal position. The participants were asked to learn, by trial and error, to which of a number of contrasting groups each stimulus belonged. This task was particularly challenging because it required you to pay attention to one feature of the line (e.g., length) while simultaneously ignoring the other feature (e.g., position). As a group, individuals with Parkinson’s disease had difficulty learning this task (relative to control participants). Interestingly, they were able to learn to attend to the correct feature, but exhibited a bias when judging the value on that feature. This bias might be related to the one of the motor problems present in Parkinson's disease, a tendency to have difficulty in changing movement patterns. We also tested individuals with cerebellar injury in this same study and found that they were not impaired on this task. This indicates that the problem the individuals with Parkinson's disease had on the on this categorization task is related specifically to their neurological changes rather than associated with any sort of movement disorder.

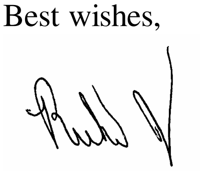
While Parkinson’s disease primarily affects the basal ganglia, it also affects the regions of the cerebral cortex, particularly the frontal lobe. This led us to conduct similar experiments in individuals with damage restricted to the basal ganglia. Shawn Ell, a post-doc in the lab, pursued this idea by testing individuals with damage in the basal ganglia due to stroke. Shawn’s study was similar to the one outlined above. Consistent with our previous results, Shawn found that basal ganglia damage due to stroke impaired classification abilities. More specifically, individuals with basal ganglia lesions tended to try a number of different, and fairly inaccurate, classification strategies before finally settling upon an accurate classification strategy. Shawn’s experiment also showed that this result is not a generic feature of all classification tasks; instead, it appears to be limited to tasks that tax short term memory and attention.

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 some websites that have provided press reports on our work over the past few years.

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. 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.

Finally, there have been notable developments on the personal side within the lab. There has been an increase in the international flavor of the lab with the additions of Julie Duque from Belgium, Flavio Oliveira from Brazil (via Canada), and Jing Xu from China. We also gained two newcomers of a different kind: Shawn Ell and his wife Shannon are the proud parents of one-year old Avery and Bekki Spencer and her husband Jim Chambers welcomed their daughter Noa this past May. Noa seems to be a real snoozer so you might notice her quietly sitting next to Bekki on your next visit to the lab. Alas, we won't be starting a daycare. Shawn and his family are leaving us this month to start new careers at the University of Maine. Neil Albert also had a significant addition this year: the lab joined him in celebrating his marriage to another graduate student, Alexandra List, earlier this month. Don't let them fool you into thinking it's all work around the lab!

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.

Contact Information:

Department of Psychology
University of California
Berkeley, CA 94720 USA

email: ivry@socrates.berkeley.edu lab: andrea.weinstein@gmail.com
phone: 510-642-7146 lab: 510-642-0135
webpage: http://socrates.berkeley.edu/~ivrylab/

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

Ell, S., Marchant, N., and Ivry, R.B. (2006). Focal putamen lesions impair learning in rule-based, but not information integration categorization tasks. Neuropsychologia, 44, 1737-1751.

Justus, T., Ravizza, S. M., Fiez, J. A., & Ivry, R. B. (2005). Reduced phonological similarity effects in patients with damage to the cerebellum. Brain and Language, 95, 304-318.

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.

Ravizza, S.M., McCormick, C.A., Schlerf, J.E., Justus, T., Ivry, R.B., and Fiez, J.A. (2006). Cerebellar damage produces selective deficits in verbal working memory. Brain, 129, 306-320.

Spencer, R.C.M. and Ivry, R.B. (2005). Comparison of patients with Parkinson's disease or cerebellar lesions in the production of periodic movements involving event-based or emergent timing. Brain and Cognition, 58, 84-93.

Spencer, R.C.M., Ivry, R.B., Cattaert, D., and Semjen, A. (2005). Bimanual coordination during rhythmic movements in the absence of somatosensory feedback. Journal of Neurophysiology, 94, 2901-2910.

Verstynen, T., Diedrichsen, J., Albert, N., Aparicio, P., and Ivry, R.B. (2005). Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. Journal of Neurophysiology, 93, 1209-1222.

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.

http://cognews.com/1139328519/index_html
This websites describe a new study from our lab on the relationship of language and perception. While not related to our work on motor systems, the results bear on the general question of how the two cerebral hemispheres are specialized to give us two different snapshots of the world. Our brain imaging work described above makes a similar point in terms of motor control.