Playing tennis with the cerebellum

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A functional imaging study in which subjects tracked different targets with eye movements and a joystick provides evidence that the cerebellum is involved in eye–hand coordination. The data suggest that internal models used for motor control may also be involved in cognition.

I am a tennis fanatic, and the key to success on the tennis court is eye–hand coordination. The ability to coordinate the movements of one's eyes with one's hands is a critical skill not only in sport, but also in everyday life. How do our brains achieve this feat? We know a great deal about the brain areas that control hand movements and eye movements individually[1], but we still know very little about which brain areas are involved in coordinating these two activities. Several recent papers[2,3] have started to address this question, and in this issue, Miall and colleagues[4] report functional magnetic resonance imaging (fMRI) findings indicating that the cerebellum has a critical role in hand–eye coordination.

The authors asked their subjects to track a moving target with their eyes and to stabilize a cursor on a screen using a hand-held joystick. In some conditions, subjects had to perform only eye movements or only hand movements; in other conditions they had to perform both tasks simultaneously. The simultaneous task could be made more or less difficult by altering the time lag between eye and hand movements. In the easiest condition, eye and hand movements were coordinated—that is, the two movement trajectories had the same waveform and direction (with respect to up/down and left/right) and were synchronized in time. In the intermediate conditions, the trajectories were the same but were progressively staggered in time. In the most difficult condition, the eye and hand trajectories were unrelated to each other.

The authors first confirmed that the performance varied with task difficulty. Both the eye and the hand movements were most accurate in the simultaneous condition; performance deteriorated progressively as the lag time was increased, and was much worse in the independent tracking condition. The subjects then performed the same tasks as their brains were scanned by fMRI. During the individual tasks (eyes only or hand only), they showed the expected patterns of activation in oculomotor and motor cortical regions. When the two tasks were combined, the subjects showed a number of additional activations—interaction effects that would not be predicted by summation of the activations seen in the two individual tasks.

The most interesting of these interaction effects was seen in the cerebellum. It is not surprising that the cerebellum is activated when the two tasks are combined; a variety of considerations, both theoretical and neurophysiological[5], suggest the cerebellum as a likely candidate area for monitoring and perhaps regulating coordination between different motor effectors, in particular the hands and the eyes. What is surprising, however, is the way activation varies with task difficulty. The authors found that activity in some cerebellar structures, notably the posterior part of the cerebellar hemispheres, was directly correlated with task difficulty, decreasing as the time lag was increased and as the task became more difficult—in other words, the better the performance, the higher the activity. In the independent tracking task, however, cerebellar activity was anomalously high even though performance was very poor.

The non-monotonic relationship between cerebellar activation and performance seems puzzling at first sight, but it is possible to propose a unified explanation, in which increased or decreased activation signals reflect the selection or de-selection of so-called 'internal models' in the cerebellum. Internal models are representations of sensory-motor states that are useful either as predictors of the sensory consequences of motor plans (forward models) or as controllers of the motor plans necessary to produce a desired sensory outcome, for example a visually controlled action (inverse models)[6]. Internal models are thought to be generated by the cerebellum, and can be considered as hypotheses to be tested by sensorimotor experience. Those models that accurately describe real-world relationships will presumably be reinforced by experience. Although little is known about the neural basis of internal models, this conceptual framework offers a computationally simple and efficient way of generating appropriate sensory-motor behavior under different circumstances[7].

In the case of Miall and colleagues' data, the synchronous tracking task would presumably select internal models that are already strong as a result of prior experience—matching hand movements to eye movements is a commonplace requirement in normal life. The selection of these models is associated with high performance. As temporal asynchronies are introduced, the predictive power of these well-learned internal models is progressively reduced, and they are therefore deselected. New internal models, fitting the new sensory-motor parameters, are presumably not selected to the same extent, because the subjects lack pre-existing models for this highly artificial situation and are not exposed to any one condition for long enough to allow the formation of new models—in other words, they are not given sufficient time to learn the new transformation. This explains the reduction in cerebellar activity and the associated decrease in performance. In the most difficult task, however, the poor performance gives rise to a large error signal, and this is assumed to activate many internal models, in an attempt to find ones that fit the external conditions. The activation of these multiple models gives rise to the strong signal in the cerebellum.

The above interpretation remains speculative, but regardless of whether it is correct, the findings of Miall and colleagues represent the best demonstration to date of the role of the cerebellum in eye–hand coordination. They also provide the first empirical evidence for a link that until now was only hypothesized. It has been speculated that internal models might have a role not only in motor control but also in cognition, and that they might form the basis of cognitive process-

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es in which predictive and control functions are important[8]. However, previous imaging results with a task thought to activate internal models[9] revealed activation only in the anterior part of the cerebellum, which is canonically considered to be the 'motor' part of the cerebellum. In contrast, the new study reports that most of the activations are located in the posterior cerebellum, which is often activated by cognitive tasks[1]. This observation represents the first empirical support for the idea that internal models may be involved in cognition.

One puzzling feature of the new study is that no cortical areas show an activation pattern similar to that observed in the cerebellum. One might have expected parallel activations in the cortex, because cortico–cerebellar connections are extremely robust both anatomically (via the pons) and functionally, as has been repeatedly shown by imaging data in normal volunteers[10] and neurological patients[11]. Moreover, there is growing evidence that the posterior parietal cortex is a crucial structure for forward models of reaching movements and for eye–hand coordination[12,13]. In fact, if one looks at the data provided by Miall and colleagues, posterior parietal structures are the ones that most often follow the same functional pattern as cerebellar structures, albeit less systematically. This suggests that the posterior parietal cortex may have a role in selecting the activation or de-activation of internal models in the cerebellum.

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The diversity of synaptic plasticity

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In contrast to the hippocampus, low-frequency stimulation in the amygdala produces synaptic enhancement via kainate receptors that spreads to inactive synapses on the same cell.

It's official; the amygdala is not the hippocampus. It is tempting to focus on the similarities between the two structures. They are both found in the medial temporal lobes, they are heavily interconnected and share connections with many other structures, and perhaps most importantly, they have both been strongly implicated in learning and memory[1]. Although neuroscientists focusing on the biological substrates of learning and memory have recognized the anatomical differences between the amygdala and hippocampus, they have also demonstrated a tendency to assume that the synaptic physiology of these two limbic system structures is very similar, if not identical. A growing body of evidence, exemplified by the new report by Rogawski and colleagues[2], suggests that this is far from the case. Rogawski and colleagues find that low-frequency stimulation of synaptic inputs to the basolateral amygdala produces a long-lasting enhancement of synaptic transmission. In contrast to typical hippocampus-based synaptic plasticity, this enhancement is dependent upon kainate-type glutamate receptors, and spreads to adjacent, inactivated synapses. These unique physiological characteristics of amygdala-based plasticity may have important functional implications in behavior.

The canonical synapse for studying use-dependent changes in synaptic function is between the CA3 and CA1 pyramidal neurons of the hippocampus. At this synapse and at the perforant pathway synapses onto granule neurons of the dentate gyrus, long-term potentiation (LTP) can be induced by high-frequency stimulation through the activation of the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor[3]. This has become the *de facto* model for learning and memory in the mammalian brain; brief bursts of activity at much higher than normal frequency lead to NMDA receptor-dependent increases in synaptic efficacy, which alters network function to code for new memories. Pharmacological or genetic manipulations that block NMDA receptor function should (and generally do) prevent learning of behavioral tasks that depend on the hippocampus[4,5].

But the story cannot be that simple. High-frequency stimulation of mossy fiber inputs to CA3 pyramidal neurons produces LTP that does not depend on NMDA receptors, and some patterns of stimulation can produce NMDA receptor-independent LTP even at CA3–CA1 synapses[3]. Moreover, prolonged stimulation at a relatively low frequency (1–5 Hz, compared to the 100–400 Hz typically used for LTP induction) causes long-lasting decreases in synaptic efficacy in neurons of the hippocampus and neocortex, and this long-term depression (LTD) also depends on NMDA receptor activation[6]. So, blocking NMDA receptors *in vivo* could alter behavior by preventing either LTP or LTD; conversely, NMDA receptor-independent plasticity may or may not contribute to behavioral changes under these conditions.

Into this mix, we now must add the amygdala. Most LTP experiments in the amygdala have focused on the lateral and/or basolateral nuclei (LA/BLA), which receive inputs from adjacent polymodal neocortical regions, the thalamus, and other subnuclei within the amygdala. Although the stimulus parameters used to induce LTP have varied from study to

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