Rethinking the thalamus

Paul W Glimcher & Brian Lau

Reward-sensitive neurons are present throughout the brain. A report in *Science* now shows that a subset of thalamic neurons respond selectively to the smaller of two rewards, as opposed to just reflecting reward magnitude, as do neurons in other brain areas.

Most neurobiologists working today were brought up to believe in a few fundamental truths: the neuron doctrine, the electrical nature of the action potential and that the thalamus is uninteresting. Recently, however, neuroscientists have been trying to explain why so many neural circuits seem to involve multiple, highly organized passes through this 'uninteresting' structure. Surely this indicates that the thalamus must do something, but what? One group of theoreticians proposed that striatal loops involving the thalamus may help select a single action for execution out of the multiple actions competing for access to the musculature[1,2]. In parallel, physiologists have recorded from neurons throughout these striatal loops in monkeys performing visuomotor tasks.

The most recent physiological study of these loops attempts to consolidate these two approaches by adding a twist to the competition hypothesis. In *Science*, Kimura and colleagues[3] present neurophysiological data from the intralaminar thalamus suggesting the existence of a previously unknown process that is activated when an animal must execute an action that yields a relatively small reward. To understand this new work, however, one has to place it within the context of other studies of the thalamus.

Besides containing sensory nuclei such as the lateral and medial geniculate nuclei, the thalamus seems to be locked into at least two interrelated sets of processing loops[4–6]. The first are the parallel corticostriatal loops proposed in ref. 4 and later elaborated upon anatomically[7]. These loops consist of cortical projections to the striatum, which, through the basal ganglia output nuclei, connect to the thalamus and then back to the originating cortical regions. These pathways are segregated into five largely independent functional subloops that have been the subject of much physiological inquiry[8,9].

There is also compelling evidence for the existence of five additional loops[6] that pass through midline regions of the thalamus (**Fig. 1a**). These connect the striatum, an area known to process reward-related information, to itself. The thalamostriatal loops involve the midline intralaminar nuclei, particularly the caudal intralaminar group, which is composed primarily of the centromedian-parafascicular complex. It is this complex that forms the main way station for most of the thalamostriatal loops. In the skeletomotor thalamostriatal loop, for example, the centromedian nucleus projects to the postcommisural putamen, a skeletomuscular nucleus of the basal ganglia. This region of the putamen projects, in turn, to the globus pallidus, which closes the loop by projecting back to the centromedian thalamus (**Fig. 1b**).

Kimura and colleagues have been examining the properties of neurons in the skeletomuscular thalamostriatal loop for some time now, focusing on neurons of the centromedian-parafascicular complex. Their initial studies[10,11] showed that these neurons are multimodal, responding to a variety of sensory signals both during and outside of operantly conditioned reaching tasks. They have classified neurons into two physiologically distinct groups on the basis of the speed with which they respond to visual or auditory stimuli: short-latency facilitatory neurons found mostly in the parafascicular nucleus (and thus associated with limbic and cognitive thalamostriatal loops) and long-latency facilitatory neurons found mostly in the centromedian nucleus (and thus associated primarily with the skeletomotor thalamostriatal loop). Furthermore, inactivation of the centromedian-parafascicular complex decreases the reward-related responses of tonically active neurons in the regions of the striatum to which they project[10].

Kimura and colleagues[3] now report recordings from long-latency facilitatory centromedian neurons in macaques trained to perform a traditional 'go'/'no-go' reaching task. In this task, the monkey placed one hand on a central button to begin each trial. After a delay, a second button was illuminated yellow at one of two possible locations; then it changed either to green or to red. As soon as the monkey detected the onset of the green button (a 'go' trial) he had to reach for it to earn a fluid reward. If, however, he detected a red button instead (a 'no-go' trial,) he had to hold position on the initial yellow button for 0.75 s to be rewarded. Across blocks of 60–120 trials, the authors varied which action was associated with a large reward (+R) and which was associated with a small reward (–R). Therefore, on the first block, the monkey might have earned a large reward for the go response on go trials and a small reward for the no-go response on no-go trials. This was then reversed in the next block. Of course, making the wrong response—for example, a go response on a no-go trial—earned the monkey no reward regardless of whether it was a +R or a –R condition.

The authors found that many neurons in the centromedian thalamus responded more vigorously on –R trials than on +R trials irrespective of trial type (go or no-go). This finding is important for three reasons. First, this is the first time that thalamic neurons—in this case, in the thalamostriatal loop associated with skeletal movements—have been shown to be influenced by reward magnitude. Second, the neurons responded strongly for both go and no-go trials that yielded low rewards, indicating that the neurons were not selective for the action that the monkey was required to produce, but rather for the more abstract value of the trial. Third, this modulation seems to be reversed compared with most of the reward-related responses that have been observed in other areas. For example, neurons in posterior and frontal cortex respond more strongly to larger rewards. In contrast, centromedian neurons responded more for small rewards than for large rewards, a phenomenon that has not been reported previously.

To interpret these findings, it is important to note that the activity of many neurons outside the thalamus has been correlated with response bias, the behavioral observation that subjects are often biased toward selecting one particular response over another. If reaching for a lighted button earns a large reward and withholding that action earns a small reward, then human and animal subjects are more likely to reach for the button than to withhold the movement; they show a response bias that favors reaching. Neurons

Paul Glimcher and Brian Lau are at the Center for Neural Science, New York University, New York, New York 10003, USA.
e-mail: glimcher@cns.nyu.edu

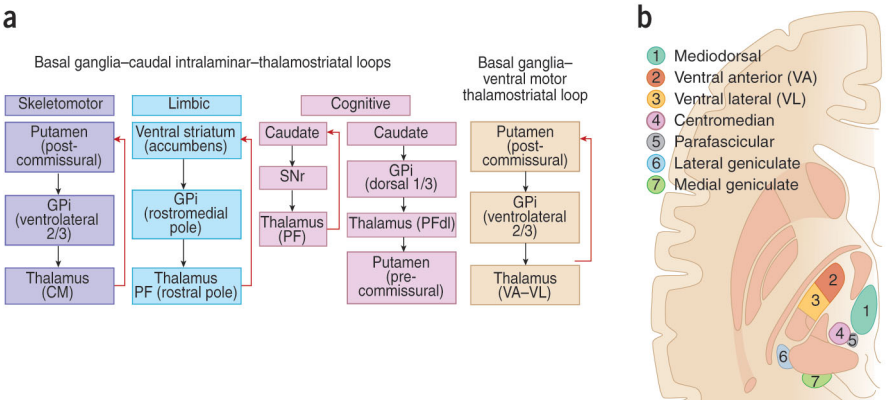

Figure 1 Parallel thalamostriatal loops involving the basal ganglia and the thalamus in monkeys (after ref. 6). (**a**) These loops have been classified on the basis of the anatomical segregation of neurons in the striatum, which project to distinct pallidal regions, either the internal segment of the globus pallidus (GPi) or the substantia nigra pars reticulata (SNr). The intralaminar loops are closed after passing through distinct nuclei of the centromedian (CM)-parafascicular (PF) complex. (**b**) Major thalamic nuclei involved in corticostriatal and thalamostriatal loops.

throughout the visual-oculomotor pathway, for example, show enhanced responses such as shifts in baseline activity[12,13] that are correlated with these behavioral biases.

The thalamic signal Kimura and colleagues have identified does not correspond directly to a response bias of this type. Their neuronal signal is strongest when the animal must choose between a movement that will yield a small reward and withholding that movement, where withholding the movement will yield no reward on this trial but has yielded large rewards on other trials. They therefore propose that the behaviorally observed phenomenon of response bias may be the product of two complementary underlying neural processes. The first of these would be, in essence, a pre-bias process (a process more strongly correlated with large rewards than the choice behavior of the animal), and the second would be a complementary pre-anti-bias process (a process that is active when an animal must choose a relatively small reward action). They hypothesize that it is the combination of these two signals that yields the overall response bias we observe in behavior and that the thalamic signals they have observed reflect this antibias process. Although the precise form of their hypothesis is unique in some ways, previous work[14] has identified signals in the basal ganglia that may be related to the pre-bias process that Kimura and colleagues propose, and another study[15] has identified signals in the frontal eye fields that can also be characterized as competing go and no-go processes. As well, signals in the supplementary eye fields are correlated with the interactions of these go and no-go processes.

Working with their notion that a pre-bias process would be most active whenever a large-reward go trial was imminent, one might expect that the complementary anti-bias process would also have to be more active if the monkey had to withhold that go response for some reason. To examine this prediction, they trained another monkey on a version of the go/no-go task where a large reward trial was guaranteed after a maximum of three small reward trials. They found that centromedian responses were strongest on small-reward no-go trials that were the third and last in a series of small-reward trials. So it was not just a small reward that activated these neurons; instead, a small reward certain to be followed by a large reward activated these neurons more than a small reward likely to be followed by another small reward. Kimura and colleagues hypothesize that this is the case specifically because thalamic activity serves as a compensatory anti-bias process that offsets a growing pre-bias signal, which was suggested by the error rate data in this version of the task.

If these centromedian neurons inhibit or counteract a pre-bias signal, then strong artificial activation of centromedian neurons should reveal the anti-bias process by eliciting the incorrect action—an action the monkeys know to be unreinforced. To test this, Kimura and colleagues microstimulated in the centromedian nucleus just before a small fraction of high-reward go trials. They found that stimulation on these trials did slow reaction times, although it only rarely stopped the go movement completely. This inhibition of a go response, in effect causing a no-go response, is consistent with the predictions of their model. The result, however, raises the question of whether stimulation during large-reward no-go trials might result in accidental go responses. It also leads one to ask what effect centromedian microstimulation has when the animal is equally reinforced on go and no-go trials? Is centromedian stimulation effective only when the rewards for two or more actions have different magnitudes?

Kimura and colleagues have suggested a bold new hypothesis for response selection. They have proposed that the tight linkage that has been observed between behavior and activity in a number of decision-making areas may reflect the activity of two processes: a pre-bias process and a complementary process driven by neurons of the centromedian thalamus. Even more exciting, however, is that they are exploring this hypothesis in the thalamus. Response bias–related signals have been observed throughout the cortex and basal ganglia, both of which are intimately connected with the thalamus. By exploring issues related to cognitive processes in the thalamus, Kimura and colleagues are helping to open a critical avenue for future research. Future experiments will have to be conducted to test this new model against its competitors, but now those tests will have to include physiological studies in the thalamus, a development that has been long overdue.

1. Redgrave, P., Prescott, T.J. & Gurney, K. *Neuroscience* **89**, 1009–1023 (1999).
2. Wise, S.P., Murray, E.A. & Gerfen, C.R. *Crit. Rev. Neurobiol.* **10**, 317–356 (1996).
3. Minamimoto, T., Hori, Y. & Kimura, M. *Science* **308**, 1798–1801 (2005).
4. Alexander, G.E., DeLong, M.R. & Strick, P.L. *Annu. Rev. Neurosci.* **9**, 357–381 (1986).
5. Parent, A. & Hazrati, L.N. *Brain Res. Rev.* **20**, 91–127 (1995).
6. Smith, Y., Raju, D.V., Pare, J.F. & Sidibe, M. *Trends Neurosci.* **27**, 520–527 (2004).
7. Middleton, F.A. & Strick, P.L. *Brain Res. Rev.* **31**, 236–250 (2000).
8. Sommer, M.A. *Curr. Opin. Neurobiol.* **13**, 663–670 (2003).
9. Wyder, M.T., Massoglia, D.P. & Stanford, T.R. *J. Neurophysiol.* **91**, 2628–2648 (2004).
10. Minamimoto, T. & Kimura, M. *J. Neurophysiol.* **87**, 3090–3101 (2002).
11. Matsumoto, N., Minamimoto, T., Graybiel, A.M. & Kimura, M. *J. Neurophysiol.* **85**, 960–976 (2001).
12. Platt, M.L. & Glimcher, P.W. *Nature* **400**, 233–238 (1999).
13. Shadlen, M.N. & Newsome, W.T. *J. Neurophysiol.* **86**, 1916–1936 (2001).
14. Lauwereyns, J., Watanabe, K., Coe, B. & Hikosaka, O. *Nature* **418**, 413–417 (2002).
15. Schall, J.D., Stuphorn, V. & Brown, J.W. *Neuron* **36**, 309–322 (2002).