Making choices: the neurophysiology of visual-saccadic decision making

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Imagine the decisions you might make while playing a simple game like 'matching pennies'. At each play, you and your opponent, say the mathematician John vonNeumann, each lay down a penny heads or tails up. If both pennies show the same side, vonNeumann wins, if not, you win. Before each play, you have the subjective experience of deciding what to do: of choosing whether to play heads or tails. Although decisions like these are not yet understood at a physiological level, progress has been made towards understanding simple decision making in at least one model system: the primate neural architecture that uses visual data and prior knowledge about patterns in the environment to select and execute saccades. Both the visual system and the brainstem circuits that control saccadic eye movements are particularly well understood, making it possible for physiologists to begin to study the connections between these sensory and motor processes at a level of complexity that would be impossible in other less well understood systems.

Many stimuli appear in the richly textured visual world, but we can only look at these targets one at a time, picking some as important and ignoring others. At a purely anatomical level, this must be accomplished by passing visual information from the sensory systems to the motor systems of the brain (Fig. 1). Images of the visual world fall on the retina and induce a topographically organized pattern of excitation in the visual cortices. These visual maps project both to parietal association areas and to eye movement control areas like the frontal eye fields (FEF) and the superior colliculus (SC)[2]. The FEF and the SC are also topographically organized, containing precisely aligned maps of every location in the sensory world and of the saccadic movements that can direct gaze to any of those locations[3,4]. The FEF, in turn, projects both to the SC and to the eye movement control areas of the deep brainstem, areas that also receive projections from the SC (Ref. 5). Activity in these deep brainstem areas governs eye muscle tension, mechanically shifting the line of sight.

We know that when multiple visual targets are presented, each stimulus is represented in sensory maps like those in the FEF and the SC. But when a subject looks at a specific target, only a single locus in the saccadic movement maps within these structures becomes active[6–9]. How do these areas, and the other brain regions with which they are interconnected, accomplish this selection process? How do we decide where to look? Physiologists have approached this question by breaking sensory–motor decision making into two related sub-problems:

(1) How does a particular visual input result in a particular saccade being produced?

(2) How does stored prior knowledge of the environment influence the connection between visual inputs and eye movement outputs?

How does a visual input guide saccade production?
Consider yourself matching pennies against vonNeumann. Should you play heads or tails? On each play you watch carefully. Occasionally you may catch a glimpse of the coin heads up as he prepares to play, unambiguous visual data that should cause you to execute the muscular contractions to play tails. Consider a monkey performing an analogous visual-saccadic task (Fig. 2). The monkey stares straight ahead until an array of eight visual stimuli are presented. Seven of these stimuli appear in a common color but one is different, an 'oddball'. Only a saccade to the oddball will yield a reward. When the targets illuminate, eight locations in the topographically mapped visual cortices become active. Signals that originate at these eight locations propagate through the visual system to the FEF and the SC, but only one of these locations represents the oddball and ultimately leads to activation of the saccadic movement maps in these same structures. To examine how this is accomplished, Jeffrey Schall and his colleagues[9–14] recorded the activity of neurons in the

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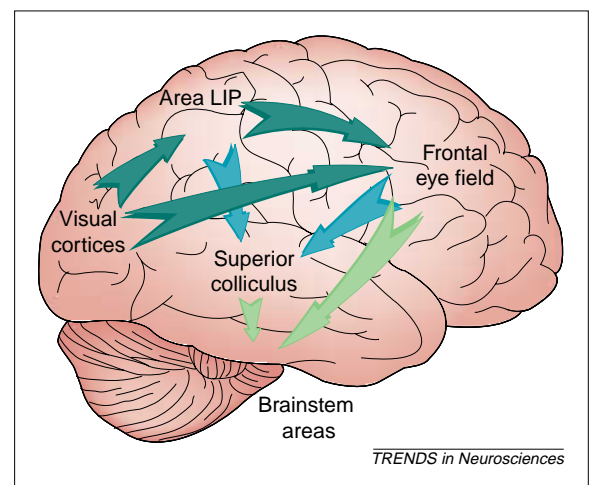e-mail: glimcher@ cns.nyu.edu

Fig. 1. Basic connectivity of the visual-saccadic system as we understand it. Sensory information from the visual cortices is passed to both parietal and frontal areas. Parietal areas project to frontal areas and to the midbrain superior colliculus. Frontal areas project to both the superior colliculus and directly to the brainstem eye movement control areas of the pons and mesencephalic tegmentum. The superior colliculus also projects to these brainstem areas. Brainstem areas control the patterns of motoneuron activation that govern eye position, velocity and acceleration. For an overview of saccadic anatomy, see Ref. 1.

Fig. 2. A profile of decision-related activity in the frontal eye fields during a simple oddball detection task. (a) Monkeys detect the oddball and shift gaze towards it with a variety of reaction times. (b) The black line plots average firing rate for frontal eye field neurons during trials on which the location of the oddball target was positioned to elicit the best movement of the neuron under study. The red line plots average firing rate on trials in which the oddball was positioned to elicit movements for which the neuron was unmodulated. For movements with fast reaction times, neuronal firing rates on these two types of trials begin to diverge about 80 ms after target onset. Surprisingly, for medium and slow movements, firing rates for best movement and other movement trials also diverge at about 80 ms (data not shown). (c) When average firing rates on best movement trials are plotted for fast, medium and slow movements, it is found that movements (data not shown) begin a fixed interval after the neurons reach a crucial firing rate or threshold. Adapted, with permission, from Ref. 10.
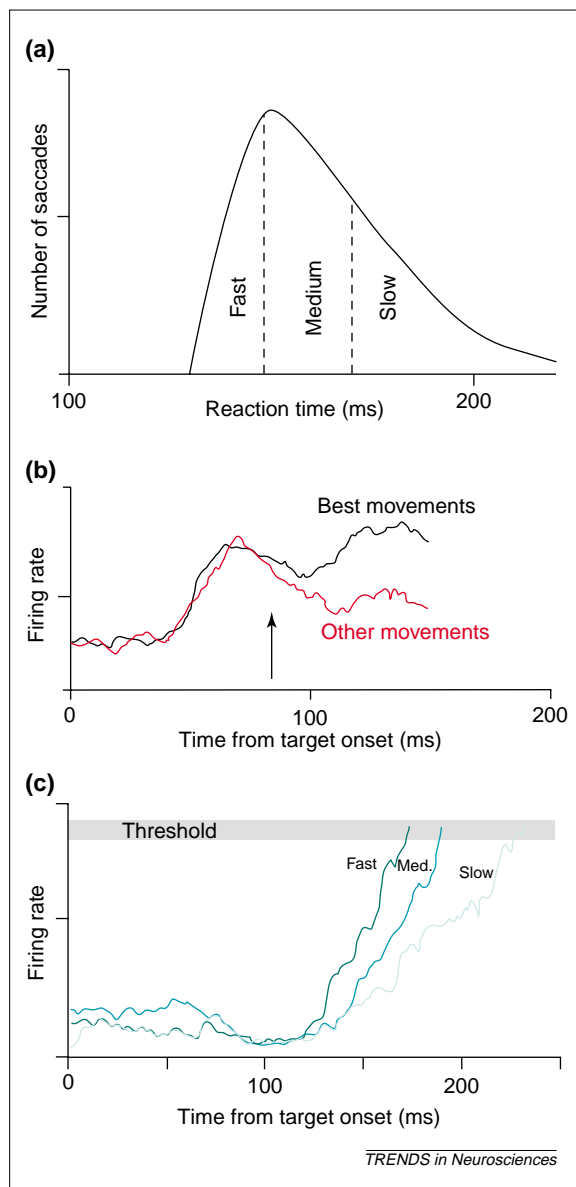
saccadic movement maps of the FEF while monkeys performed the oddball task. They noted that when monkeys executed hundreds of trials, there was a natural variability in saccadic reaction time: trials could be divided into fast, medium and slow groups. In addition, because each neuron existed within a topographic map of all possible eye movements, each neuron was most active before a specific, or best, movement. Fast, medium and slow trials could therefore be further subdivided into those trials in which the movement acquiring the oddball was the best movement for the neuron being studied, and those trials on which any other movement was produced.

During all trials, the firing rate of the neurons rose quickly to an early peak shortly after visual stimulus onset. About 80 ms after stimulus onset, the firing rate continued to grow if the monkey was deciding to make the best movement, but dropped if the monkey was deciding to make any other movement. This change in activity therefore reflected the neural

signature of a decision about which movement to produce. Schall and his colleagues also found that after these firing rates diverged, firing rates on fast reaction time trials increased more quickly than on slow reaction time trials. But regardless of how quickly or slowly the firing rate increased, the movement seemed to occur a fixed interval after the firing rate reached a threshold level. All of this suggests that the activity of these neurons is a neurophysiological marker for the time at which the complete process of making a decision, about where and when to look, starts and ends. Furthermore, the observation that the decision is complete when a threshold is reached, might have biophysical implications for models of neuronal decision making.

Are decisions about where and when to saccade separable?

The oddball task, however, actually required two decisions: where to saccade and when to saccade. Could topographically mapped sensory–motor areas like the FEF and the SC make these decisions separately? One class of collicular movement encoding neurons, the prelude bursters, was known to fire at a low frequency after visual target onset, but not to increase towards a higher threshold level until right before movement onset[15]. This raised the possibility that the topographic location of neurons active in the collicular map at prelude levels might encode a decision about where to look, independently of the sudden increase in firing rate that signals a movement is about to occur.

To examine the possibility that decisions about where and when to look might be separable, Glimcher and Sparks trained animals to fixate a central yellow target while one red and one green eccentric stimulus were illuminated[16]. The fixation light then turned either red or green and, after a delay of up to 10 s, was extinguished. Animals were rewarded for shifting gaze towards the target matching the color of the fixation light. If prelude activity in the SC reflected a decision about where to look independently of the decision about when to look, then prelude activity would be expected to: (1) predict which movement would be made irrespective of when that movement occurred; (2) arise when an animal was told where to look; (3) persist until the animal was told when to look. In fact, prelude activity does predict the movement the animal will make even if a 10 s delay intervenes between the decision about where and when to look. If the monkey (Fig. 3a) was told to select an upwards movement (and she did), then prelude activity suggested that her decision about where to look was complete almost immediately and persisted until just before the movement occurred.

Perhaps the most interesting aspect of this experiment was that the prelude activity allowed the experimenter to read the monkey's mind, predicting in advance the movement that the monkey would make at the end of the trial. But the most important
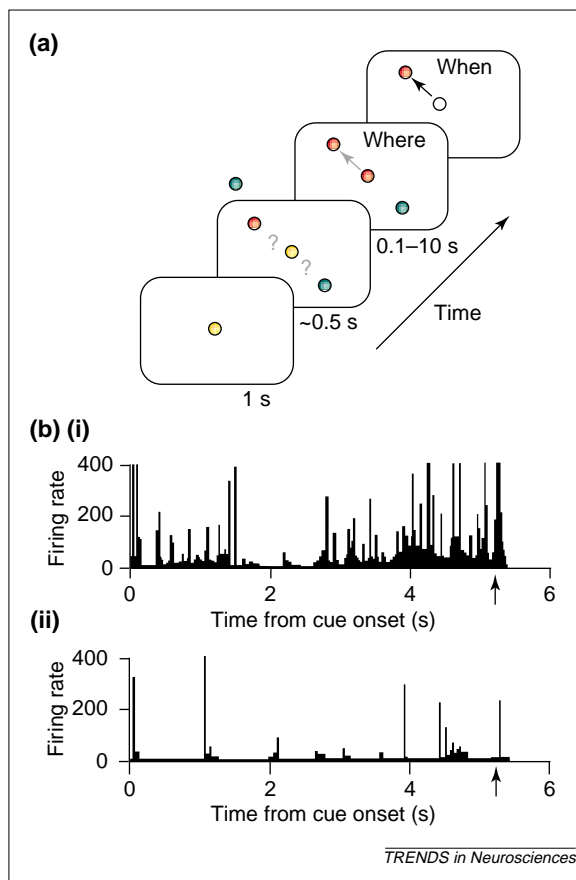
Fig. 3. The amplitude and direction of an upcoming saccade can be predicted seconds in advance from the activity of collicular prelude bursters during tasks that impose a delay between the decision about where to look and the decision about when to look. (a) The saccadic decision task separates the time at which a decision is made about where to look from the time at which a decision is made about when to look. (b)(i) 'Best Movement' plots the activity of a prelude burster when the monkey is instructed to prepare the best movement of the neuron under study but is required to withhold the movement for almost 6 s. (ii) 'Other Movement' plots a trial that is identical, except that the monkey is instructed to prepare another movement, a movement for which the neuron under study is not active. Arrows indicate time of movement onset. When the monkey makes errors (data not shown) the activity of the neuron during the long delay predicts the behavior of the animal not the instruction presented by the experimenter. Adapted, with permission, from Ref. 16.

aspect of this experiment was the suggestion that decisions about where and when to look are both behaviorally and neurophysiologically separable. Further support for this separability comes from experiments in which electrical stimulation of the SC at low frequencies can be shown to affect where saccades go, without affecting when saccades are produced, influencing the 'where to look' circuitry without influencing the 'when to look' circuitry[17].

Decisions based on ambiguous visual signals
At roughly the same time that these studies of the SC and FEF were being performed, William Newsome and his colleagues were attempting to understand how the perceptual analysis of visual data might be accomplished, and how this analysis might give rise to signals that could be used to guide a decision about
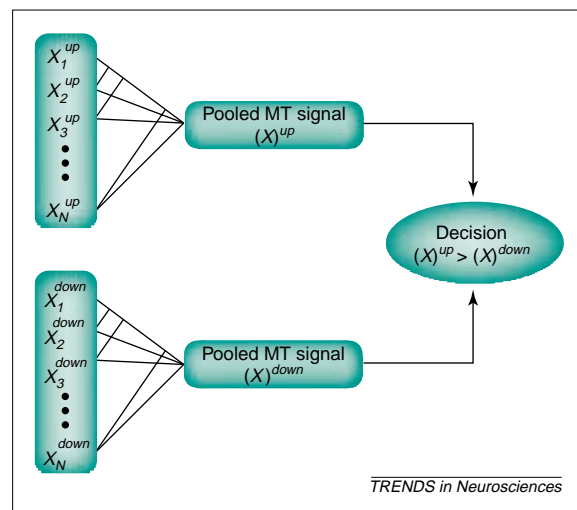

Fig. 4. Outline of the visual-saccadic decision-making model proposed by Shadlen and his colleagues. On each trial, the responses of *N* neurons responding to upwards visual stimulus motion and *N* neurons responding to downwards motion are pooled. Intersecting lines indicate that the responses of neurons responding to the same direction of motion are weakly correlated. Average responses are compared and the larger signal elicits the movement required by the task for that direction of stimulus motion. Reproduced, with permission, from Ref. 22.

where to look[18–21]. In these experiments, monkeys viewed a display of chaotically moving spots of light in which, on any given trial, a subset of the spots moved coherently in a single direction while the remaining spots moved randomly. The monkey was rewarded for identifying the direction of coherent spot motion with a saccadic eye movement. If the monkey perceived the coherent spots as moving to the left, for example, the monkey indicated this by making a leftwards saccade. These experiments indicated that the firing rates of single neurons in the middle temporal area of cortex were correlated with the fraction of spots that moved coherently – a visual stimulus used by the monkeys to decide where to look at the end of each trial.

In 1996, Michael Shadlen proposed a model of the visual-saccadic decision-making process under these conditions[22]. In his model (Fig. 4), visual motion was analyzed by middle temporal neurons that output an instantaneous estimate of the current strength and direction of image motion at each location in the retinotopic map. The instantaneous estimates of 30–100 neurons analyzing motion in each direction, at each topographic location, were then pooled during the 2 s motion display, in order to derive an estimate of the average motion observed at that location during the trial. At the end of the display, the pooled directional signal with the highest value was used to select the direction of the upcoming saccade.

One interesting aspect of this model is the prediction that neuronal elements should exist that sum the instantaneous motion signal during the 2 s display. In a series of electrophysiological experiments, Shadlen verified this prediction[23], showing that, on average, the saccade-related

Box 1. Mathematical models of decision making

Mathematicians and microeconomists have studied decision making for over 300 years by first defining a problem, such as 'how do I maximize my gain?', and then defining the mathematically optimal solution to that problem. In this paradigm, the goal of the scientist is to understand both how closely an organism approximates the optimal solution and how the fully defined computation is approximated by the brain. Economic models thus serve as computational descriptions of the decision-making process in much the same way that ideal observer theory guides research in sensory perception.

Mathematical models of decision making can be divided into two categories: classical microeconomics[a] and game theory[b]. Classical microeconomics seeks to model decisions of the type described in this article; situations in which an animal selects a course of action in a stationary environment. Game theory, by contrast, attempts to define the computations required when an animal must consider the non-stationarities associated with the strategies of intelligent opponents. Although neither classical microeconomics nor game theory has had much impact on physiological studies of brain function, both have had a tremendous impact in psychology and ecological biology. In ecological biology, classical microeconomic models have been used successfully to describe the decisions animals make when foraging for food[c,d]. And game theoretic models have been used successfully to analyze situations in which conspecifics compete for access to resources, such as potential mates[c,e]. Given that animal behavior can be well described using these mathematical tools, it seems clear that in the future they will also prove useful for understanding how the brain produces that behavior.

References
a Kreps, D.M. (1990) *A Course in Microeconomic Theory*, Princeton University Press
b Funderberg, D. and Tirole, J. (1991) *Game Theory*, MIT Press
c Krebs, J.R. and Davies, N.B. (1997) *Behavioural Ecology*, Blackwell
d Stephens, D.W. and Krebs, J.R. (1986) *Foraging Theory*, Princeton University Press
e Maynard Smith, J. (1982) *Evolution and the Theory of Games*, Cambridge University Press

neurons of the posterior parietal cortex produce a gradually increasing firing rate during the motion display that often plateaus before the movement is elicited. This firing rate predicts the saccade made at the end of the trial. Even more interesting is the observation that if the fraction of spots moving coherently was increased, average firing rates increase more quickly during the display interval. This is exactly what one would expect if these neurons were actually gathering motion-related evidence in support of the decision to make a particular saccade.

It has even been shown that these parietal signals are integrated with saccade-related signals in the SC and FEF. If, while a monkey is performing the motion discrimination task, a movement is elicited by electrical stimulation of the movement map of the FEF, then the direction of the stimulation-induced movement is altered by the presentation of the motion display. And the magnitude of this alteration is a function of the fraction of spots moving coherently in the display[24]. This is exactly what would be predicted if the neurons in the parietal cortex that sum the motion signal were affecting the amplitude and direction of the stimulation-induced saccade.

How does stored prior knowledge of the environment influence decision making?

When matching pennies against vonNeumann, you might occasionally catch a glimpse of his coin in advance, but in the absence of that sensory information, only a pre-existing, or prior, estimate of the probability that vonNeumann will play heads or tails can be used to select a course of action. How, if at all, is prior knowledge represented and how is it used by the primate nervous system to guide visual-saccadic decision making? We know that knowledge of prior probabilities can influence visual-saccadic decision making from the work of Roger Carpenter and colleagues[25,26]. In a series of experiments they asked human observers simply to look, as quickly as possible, at a stimulus that could appear at more than one possible location. Saccades elicited by targets presented at highly probable locations occurred with shorter reaction times than saccades elicited by targets at unlikely locations; reaction time was a function of the log of the likelihood that the target would appear at a specific location.

These experiments established that prior knowledge of the likelihood of a future event could influence visual-saccadic decision making; but how might this influence be instantiated in the nervous system and then combined with sensory data during actual decision making? General purpose mathematical models of decision making developed by economists, psychologists and ecological biologists suggest that any rational decision making must be based on a combination of sensory data and prior knowledge of two crucial environmental variables: the gain expected to result from an action and the probability that the expected gain will be realized (Box 1). Single neurons that participate in, or reflect, actual decision making might therefore be expected to reflect both expected gain and the probability of gain.

How does stored prior knowledge of the environment influence parietal decision-making circuits?

Apparently the saccade-related neurons of the posterior parietal cortex carry exactly these types of signals. Platt and Glimcher demonstrated this by training animals to perform the same red–green two-target task that was used to study collicular prelude bursters[27] (Fig. 3a). In this experiment, however, animals were presented with several sequential blocks of trials, during which either the magnitude of reward associated with each of the two possible movements, or the probability that each of the two movements would be required, was systematically varied. By analyzing only those trials on which the animal correctly made the best movement for the neuron under study, a database of trials across which the stimulus and the response were identical was produced. Sensory and motor variables were thus held constant while one of two decision variables, probability or gain, was manipulated. Under these conditions, the firing rates of many parietal neurons
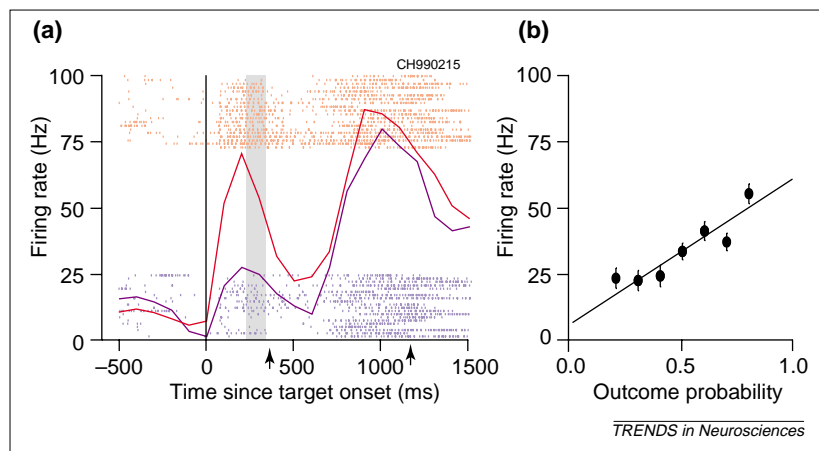
Fig. 5. The probability that a monkey will be instructed to make a particular movement modulates the neuronal activity associated with that movement in the lateral intraparietal area. (a) Average firing rate of an intraparietal neuron on trials that all elicited the best movement for the neuron under study. The red line plots trials on which the best movement was instructed with an 80% probability. The blue line plots trials on which the best movement was instructed with a 20% probability. Raster panels show spike times during the first 20 trials of each type. Black arrows indicate, from left to right, average time of the cue that indicated which movement would actually be required on that trial, and average time of saccade onset. (b) Mean firing rate for the same neuron after stimulus onset. Graph plots neuronal firing rate against the seven different prior probabilities studied in this neuron. Gray bar in (a) shows approximate time of the measured interval. Adapted, with permission, from Ref. 27.

were found to be proportional to the decision variables being manipulated.

One further test of the physiological value of economic models of decision making would be to show that a classical decision variable can influence both neural activity and behavioral decision making in a similar manner. In one such test, monkeys were presented with trials in which a central yellow fixation light was presented and two eccentric yellow targets were illuminated[27] (Fig. 5). After a delay, the fixation light was simply extinguished. Animals were free to look at either eccentric target, and were rewarded for either movement, but the reward differed depending on which movement they made. Under these conditions, both the probability that a movement would be chosen and the firing rates of parietal neurons were a function of the relative magnitudes of the two available rewards. These results, combined with the studies of motion discrimination conducted by Shadlen and his colleagues in these same neurons, suggest that these parietal neurons are influenced by both sensory information and prior knowledge, a combination that occurs in the final stages of most mathematical models of decision making.

Updating knowledge of prior probabilities in visual-saccadic decision making

Until this point, decision making has been described as though it were a static problem. But what happens when the prior probabilities that describe the environment change? How do we learn and assess the response patterns from which we derive the prior probabilities for a new strategy? Neurons of the basal ganglia might be specialized to extract this class of information, and decision theory could provide tools for understanding these components of the neural architecture. Wolfram Shultz and colleagues, for example, have shown that the activity of midbrain dopaminergic neurons might carry a post-decisional error signal, an indication of whether the decision made by the animal yielded more or less reward than expected[28,29]. Neurons in the caudate, the globus pallidus, other basal ganglia nuclei[30–32] and the supplemental eye fields[33] have also been shown to carry task-related signals that are influenced by reward contingencies and decision outcomes. Placed within the framework of classical decision theory, these results suggest that the basal ganglia might well be a region involved in updating the stored prior probabilities that influence decision making. Although the details of this work lie outside the scope of this article, it is worth noting that decision theory could offer an opportunity to unite studies of parietal, frontal and collicular decision making with studies of reward contingency in the basal ganglia.

Understanding stochastic decisions

Return one last time to matching pennies, a game that requires a decision about what to do on each play. Although a good player has a strong sense that they decide freely what side to play on each round, at a mathematical level, matching pennies has been well studied and described by game theorists. To play matching pennies well you must provide your opponent with no sensory data and no biased prior probabilities, selecting heads with a perfect prior probability of 50%. Your decisions must reflect a process that defies prediction on a play-by-play basis, but that operates with a lawful fixed probability over many trials.

The decisions that neurophysiologists have studied to date are not really like these decisions at an introspective level. The decisions that we are beginning to understand are much more deterministic: stimulus and prior probabilities influencing behavior in a predictable fashion. So how does the human brain accomplish decision making that defies play-by-play prediction? VonNeumann believed that the theory of games was a mathematical tool for describing the process by which humans make even the most complex decisions. The challenge ultimately facing neurophysiologists will be to test that proposal.

References

1 Glimcher, P.W. (1998) Eye movements. In *Fundamental Neuroscience* (Zigmond, M.J. *et al.*, eds), pp. 993–1010, Academic Press

2 Buttner-Ennever, J.A., ed. (1988) *Neuroanatomy of the Oculomotor System*, Elsevier

3 Sparks, D.L. (1986) Translation of sensory signals into commands for control of saccadic eye movements: role of primate superior colliculus. *Physiol. Rev.* 66, 118–171

4 Goldberg, M.E. and Segraves, M.A. (1989) The visual and frontal cortices. *Rev. Oculomotor Res.* 3, 283–313

5 Fuchs, A.F. *et al.* (1985) Brainstem control of saccadic eye movements. *Annu. Rev. Neurosci.* 8, 307–337

6 Stanton, G.B. *et al.* (1988) Frontal eye field efferents in the macaque monkey. I. Subcortical pathways and topography of striatal and thalamic

terminal fields. *J. Comp. Neurol.* 271, 473–492

7 Basso, M.A. and Wurtz, R.H. (1997) Modulation of neuronal activity by target uncertainty. *Nature* 389, 66–69

8 Dorris, M.C. and Munoz, D.P. (1998) Saccadic probability influences motor preparation signals and time to saccadic initiation. *J. Neurosci.* 18, 7015–7026

9 Schall, J.D. (2001) Neural basis of deciding, choosing and acting. *Nat. Rev. Neurosci.* 2, 33–42

10 Schall, J.D. and Thompson, K.G. (1999) Neural selection and control of visually guided eye movements. *Annu. Rev. Neurosci.* 22, 241–259

11 Schall, J.D. and Hanes, D.P. (1993) Neural basis of saccade target selection in frontal eye field during visual search. *Nature* 366, 467–469

12 Hanes, D.P. and Schall, J.D. (1996) Neural control of voluntary movement initiation. *Science* 247, 427–430

13 Thompson, K.G. *et al.* (1996) Perceptual and motor processing stages identified in the activity of macaque frontal eye field neurons during visual search. *J. Neurophysiol.* 76, 4040–4055

14 Thompson, K.G. *et al.* (1997) Dissociation of target selection from saccade planning in macaque frontal eye field. *J. Neurophysiol.* 77, 1046–1050

15 Sparks, D.L. (1978) Functional properties of neurons in the monkey superior colliculus:

coupling of neuronal activity and saccade onset. *Brain Res.* 156, 1–16

16 Glimcher, P.W. and Sparks, D.L. (1992) Movement selection in advance of action in the superior colliculus. *Nature* 355, 542–545

17 Glimcher, P.W. and Sparks, D.L. (1993) The effects of low-frequency stimulation of the superior colliculus on spontaneous and visually guided saccades. *J. Neurophysiol.* 69, 953–964

18 Newsome, W.T. *et al.* (1989) Neuronal correlates of a perceptual decision. *Nature* 7, 52–54

19 Salzman, C.D. *et al.* (1990) Cortical microstimulation influences perceptual judgements of motion direction. *Nature* 346, 174–177

20 Newsome, W.T. (1997) The King Solomon Lectures in Neuroethology. Deciding about motion: linking perception to action. *J. Comp. Physiol.* 181, 5–12

21 Newsome, W.T. *et al.* (1990) Neuronal mechanisms of motion perception. *Cold Spring Harbor Symp. Quant. Biol.* 55, 697–705

22 Shadlen, M.N. *et al.* (1996) A computational analysis of the relationship between neuronal and behavioral responses to visual motion. *J. Neurosci.* 15, 3870–3896

23 Shadlen, M.N. and Newsome, W.T. (1996) Motion perception: seeing and deciding. *Proc. Natl. Acad. Sci. U. S. A.* 93, 628–633

24 Gold, J.I. and Shadlen, M.N. (2000) Representation of a perceptual decision in

developing oculomotor commands. *Nature* 404, 390–394

25 Carpenter, R.H. and Williams, M.L. (1995) Neural computation of log likelihood in control of saccadic eye movements. *Nature* 377, 59–62

26 Reddi, B.A. and Carpenter, R.H. (2000) The influence of urgency on decision time. *Nat. Neurosci.* 3, 827–830

27 Platt, M.L. and Glimcher, P.W. (1999) Neural correlates of decision variables in parietal cortex. *Nature* 400, 233–238

28 Schultz, W. (2000) Multiple reward signals in the brain. *Nat. Rev. Neurosci.* 1, 199–207

29 Schultz, W. and Dickinson, A. (2000) Neuronal coding of prediction errors. *Annu. Rev. Neurosci.* 23, 473–500

30 Hikosaka, O. *et al.* (2000) Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol. Rev.* 80, 953–978

31 Shidara, M. *et al.* (1998) Neuronal signals in the monkey ventral striatum related to progress through a predictable series of trials. *J. Neurosci.* 18, 2613–2625

32 Handel, A. and Glimcher, P.W. (2000) Contextual modulation of substantia nigra pars reticulata neurons. *J. Neurophysiol.* 83, 3042–3048

33 Stuphorn, V. *et al.* (2000) Performance monitoring by the supplementary eye field. *Nature* 408, 857–860

The dephosphins: dephosphorylation by calcineurin triggers synaptic vesicle endocytosis

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When nerve terminals in the brain are stimulated, a group of phosphoproteins called the dephosphins are coordinately dephosphorylated by calcineurin, the Ca^{2+}-dependent protein phosphatase. Amazingly, the seven presently known dephosphins are not structurally related, yet each has been independently shown to be essential for synaptic vesicle endocytosis (SVE). Nowhere else in biology is there a similar example of the coordinated dephosphorylation of such a large group of proteins each sharing roles in the same biological response. This suggests that dephosphorylation and phosphorylation of the dephosphins is essential for SVE. Recent studies in synaptosomes have confirmed this view, with calcineurin-mediated dephosphorylation of the dephosphins essential for triggering SVE. The phosphorylation cycle of the dephosphins might regulate SVE by targeting the proteins to sites of action and by stimulating the assembly of several large essential endocytic protein complexes.

Nerve terminals are the primary sites for exocytosis in neurons, where neurotransmitter is released by the fusion of synaptic vesicles (SVs) with the presynaptic plasma membrane. After exocytosis, the vesicles are retrieved by endocytosis and recycled locally, so the process can begin again. Many of the proteins in nerve terminals are phosphoproteins, suggesting that protein phosphorylation should play an important role in SV recycling. However, intensive studies have shown an obligatory requirement for dynamic changes in protein phosphorylation at only one stage: endocytosis. Interestingly, it is the dephosphorylation, not the phosphorylation, of a group of nerve terminal phosphoproteins, collectively termed the dephosphins (Fig. 1), that stimulates the process.

The dephosphins
The dephosphins are nerve terminal proteins that have little structural relationship, but are grouped together by two criteria: (1) they are essential for SV endocytosis (SVE); and (2) they are rapidly and coordinately dephosphorylated in nerve terminals