mational rearrangements are also part of the insertion pathway of α hemolysin (*1*), and the structure supports this view. Binding of the soluble protein to the membrane may result in the exposure of previously buried hydrophobic regions that could promote interaction with and insertion across the bilayer.

The role of the bilayer in this process is clearly important, but difficult to address experimentally. Occupancy of bilayer surface area by intermediates making hydrophobic contact with the lipid bilayer is likely to produce distortions of the bilayer structure; 10 amino acids in a β strand at the bilayer surface will occupy more space than the surface area of a typical lipid. Because the area per lipid molecule in a bilayer tends to be conserved (*12*), spreading the lipid headgroups at the surface of a lipid bilayer may cause the bilayer to thin locally, distorting the bilayer profile from its equilibrium position. Such effects, multiplied by protein oligomeric association, for example, could destabilize the bilayer and promote a relaxation to a state in which both the transmembrane form of a protein and of the bilayer have lower energy.

Understanding the energetics and possible intermediates of these spontaneous insertion processes can lead to important developments in our concepts of how membrane proteins may have arisen during evolution, how some membrane proteins are placed in position biosynthetically, and how membrane protein folding may proceed. Practical results may also ensue: study of transmembrane phenomena may lead to better drug delivery.

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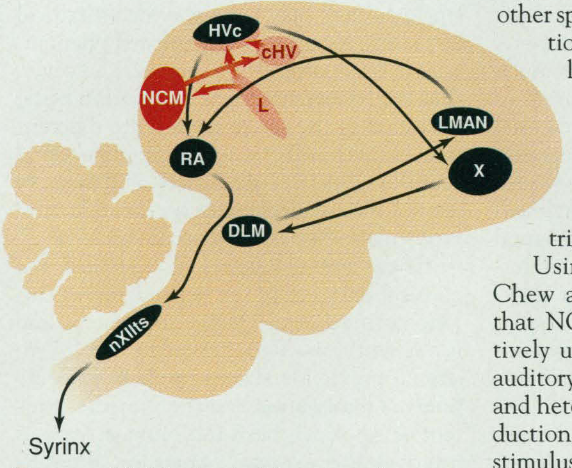
PSYCHOLOGY

Plasticity of a Different Feather?

Allison J. Doupe

Neuroscientists are keenly interested in understanding the neural mechanisms underlying learning and memory. On page 1909 of this issue, Chew *et al.* (*1*) describe an intriguing form of experience-dependent neural plasticity in songbirds, with some astonishing new twists: when a bird repeatedly hears a song, the response of certain neurons to this song progressively decreases and then recovers only at one of six fixed, "quantal" times. The duration of the decrease in neural response depends on the nature of the initial auditory experience and on the occurrence of episodes of protein synthesis at approximately the same fixed intervals. This phenomenon is quite surprising, which makes it all the more important to find out whether it exists in other brain systems and in other animal species. Even more critical is whether the decreased neural response and its quantized recovery underlie behavioral learning and forgetting. Songbirds are a particularly useful system for tackling this behavioral question, because they learn and remember for many months the songs of their own species (conspecific songs), both during juvenile life in order to sing them and as adults to identify other individual birds.



The songbird brain. In this schematic cross section, the traditionally defined song system is shown in black; these discrete brain areas form a network of neurons required for song learning and production. NCM is one of a number of high-level auditory areas (shown in red) that indirectly project to the song system.

The neuronal plasticity that Chew and colleagues observe occurs in the caudomedial neostriatum (NCM), a high-level auditory area in the brain of songbirds. NCM is not part of the "song system" known to be required for song learning and production (see figure), but is one indirect source of the song system's auditory inputs. Earlier work on gene expression from the Nottebohm laboratory showed that the immediate-early gene *ZENK* was induced in this area in both male and female songbirds when they were presented with songs (*2*). The auditory induction of *ZENK* expression in NCM was especially striking because, within the song system itself, the gene was resolutely resistant to activation by song playback, despite the presence of well-described song-responsive auditory neurons in those areas. Moreover, *ZENK* was much more strongly induced by songs of conspecific birds than by songs of other species (heterospecifics). Thus, induction of *ZENK* correlated with the biological relevance of the auditory stimuli. In addition, repeated presentation of a song would result in this song being ineffective at inducing *ZENK* for at least 24 hours, although a novel song could still trigger a full *ZENK* induction (*3*).

Using neurophysiological recordings, Chew and colleagues then demonstrated that NCM neurons have strong and relatively unselective responses to a variety of auditory stimuli, including both conspecific and heterospecific songs. As with *ZENK* induction, repeated presentations of the same stimulus led to a gradual and long-lasting decrease of multi-unit and single-unit neuronal responses; similar results have been reported by Stripling and co-workers (*4*). Chew *et al.* termed this decrease in neural responsiveness "habituation," a term borrowed from behavioral studies of response decrements (*5*), and showed that habituation was specific for each song presented, even for very similar stimuli such as forward and reversed versions of the same song.

The neuronal habituation in NCM may be most analogous to the loss of neural responsiveness to repeated visual stimuli described in primate inferotemporal (IT) cortex (*6*), and, like that adaptation, raises interesting questions about the possible mechanisms. For instance, does the habituation of the multi-unit response to multiple

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different songs reflect separate habituation of individual neurons in a population to each of the stimuli, or can single neurons habituate to multiple songs? And if the latter, to how many songs? Does the response adaptation reflect the habituation of other neurons in the auditory pathway? An advantage of studying adaptation to complex auditory stimuli such as song is that the stimuli have prominent temporal features, which can be easily manipulated to ask mechanistic questions. For example, do neurons habituate to the sequence of notes in a song as a whole, or does a portion of a habituated song or a song played out of order show the same diminished response? The answers to questions like these will make predictions about where and how synapses must be changing and will provide general insights into neuronal information processing.

The most surprising properties of NCM habituation emerged in the present study (*1*). In this work, the authors studied recovery from habituation by exposing birds to auditory stimuli at one time and then measuring the rate of neural habituation to the same stimuli in a single recording session at some later time. Songs that were familiar induced little decrease in neuronal response, whereas novel songs, or songs that had apparently become unfamiliar, induced rapid habituation. The rate of habituation, therefore, was used as an indirect measure of how much recovery from habituation had occurred. In agreement with other studies of neuronal plasticity and of memory across species ranging from flies and snails to humans (*7, 8*), Chew *et al.* found that habituation lasted longer when stimuli had been presented more often or at longer interstimulus intervals during the initial exposure. Most unexpectedly, however, recovery from habituation was not a continuous function, but occurred episodically, during only one or another of several narrow windows of time—depending on the nature of the initial experience, at 2 to 3, 6 to 7, 14 to 15, 17 to 19, 46 to 48, or 85 to 89 hours after first exposure to a stimulus. Even when stimulus parameters such as interstimulus interval or number of repetitions were altered gradually, the duration of habituation did not change continuously but instead showed stepwise change, always returning to the baseline rate of habituation during only one of the six recovery intervals. The authors termed this striking discontinuous decay of habituation "quantal." Different classes of auditory stimuli—such as conspecific song, heterospecific song, and human speech—also elicited habituation that recovered at one of these same fixed times, with the longest lasting habituation coming from the most biologically relevant stimulus, conspecific song, and the shortest from heterospecific stimuli.

The authors interpret their data as reflecting quantal duration of the habituated neural response. But what is quantal in length may be the resistance to further habituation, rather than the actual decrease in neural response. The authors calculate habituation rates from song responses normalized to the response to the first presentation of that song during testing; thus, information about the absolute magnitude of responses is overlooked. Neural responses at sites in NCM might actually be recovering gradually, but if the response of those neurons did not decrease when tested for habituation, the normalized habituation rate would not show any change, regardless of real response rates.

How general is the quantal process described here? To date, no other studies of neuronal adaptation or of memory, across numerous species, have suggested stepwise rather than gradual decay (*7*). In particular, careful investigations of human forgetting, over minutes to years, with manipulations of stimulus number and interstimulus interval analogous to those of Chew *et al.*, show exponential decay of memory with no hint of quantization (*8*). The clever experimental design of this songbird study, which made it possible to span a large number of stimulus parameters and durations of habituation in a single animal, may have provided a critical advantage for observing quantized phenomena. It is important to remember, however, that the passive neuronal habituation being measured in the songbirds is quite different from active recall of words and numbers, and that the properties of plasticity and memory are notoriously dependent on the induction protocols and tasks being studied.

Chew and colleagues also tackled the classical question of the dependence of this long-lasting neural change on protein and RNA synthesis. They exposed songbirds to stimuli previously shown to elicit 48 or 89 hours of habituation and then injected protein or RNA synthesis inhibitors at various intervals after exposure. Their initial results were again in line with observations on the initial consolidation of neural plasticity or long-term memory in other systems (*9*): inhibition of protein or RNA synthesis around the time of exposure eliminated subsequent long-term habituation. Inhibition at 6 to 7 hours after exposure, a period critical in some rat and chick memory systems (*10*), similarly eliminated habituation. Astonishingly, injection of synthesis inhibitors during periods 14 to 15, 17 to 18, 33 to 38, or 44 to 48 hours after induction of habituation also led to loss of habituation, but injections outside these periods did not. All of these sensitive periods (except the puzzling 33 to 38 hour time window) correspond to the quantal times when the habituation rate would spontaneously recover, suggesting that discrete sequential periods of RNA and protein synthesis may be required for maintenance of long-lasting neuronal habituation. This possibility raises fascinating questions about what mechanisms could trigger and regulate a neural process like this and how it relates to long-term memory.

A dependence of retention on so many periods of macromolecular synthesis has not been described in other plasticity systems, although memory, initially thought to be graded, is now known to consist of several phases, and at least two important waves of protein synthesis exist (*11*). Could a requirement for additional phases of protein synthesis have been missed in other animals? Generally, studies in many systems have shown that continuous blockade of protein synthesis from 2 to 20 hours does not affect long-term memories, facilitation, or habituation (*9*). This procedure should reveal any dependence of plasticity on later phases of synthesis, but perhaps continuous synthesis blockade in some way prevents the dependence of memory on later phases, just as blocking protein synthesis can prevent cell death induced by withdrawal of growth factors. It would be straightforward to test in NCM whether continuous blockade of protein or RNA synthesis had the same effects on habituation as the short-lived injections of synthesis inhibitors used by Chew *et al.* (*1*).

A crucial question remains. Although the authors call the neuronal habituation and recovery that they observe "learning" and "forgetting," they also point out that there is no evidence that the birds remember and forget these stimuli in their experiments. Psychophysical experiments and investigation of neuronal habituation in the context of behavior will be an important next step. Ideally, these birds could be tested for recognition and retention of the auditory stimuli, but even simple behavioral accompaniments of the neural habituation, such as changes in heart rate, would be informative. Simultaneous study of behavior and neurons is crucial to the interpretation of neural phenomena. For example, studies of visual adaptation in IT cortex of behaving monkeys showed that the decrease in neuronal response simply reflected stimulus repetition regardless of task relevance and differentiated it from the response enhancement observed in an active memory task (*12*); moreover, experiments using two different neural pathways to a single recording site in IT demonstrated that the habituation of single units could be dissociated from behavioral familiarity (*13*). The experiments to test for the behavioral relevance of neural habituation of NCM in songbirds will be well worth the effort: learning of song is a critical natural task for all songbirds, and the many different durations of habituation seen in these experiments should allow numerous tests of the relation between neural properties and learning, from the behavioral to the molecular levels.

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CONDENSED MATTER PHYSICS

The Metal-Insulator Transition in Correlated Disordered Systems

Elihu Abrahams and Gabriel Kotliar

Most substances in nature are either good metals (conductors) or good insulators. Continuous metal-to-insulator transitions are notably difficult to realize experimentally at very low temperatures. Coaxing materials to the proximity of the metal-to-insulator transition region requires clever experimental design, the choice of a suitable material, and the application of an external parameter to drive the system through the transition. Furthermore, in most systems, even a continuous change in external parameters results in a discontinuous first-order metal-to-insulator transition. Until now, continuous metal-to-insulator transitions have been realized only in amorphous alloys and in doped semiconductors. However, Husmann and colleagues have succeeded in observing a continuous metal-to-insulator transition at very low temperature by applying pressure to the chalcogenide compound $Ni(S,Se)_2$. Their results appear on page 1874 of this issue (*1*).

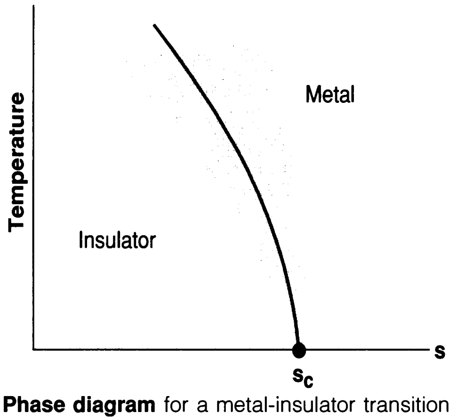
How a metal can be turned into an insulator by continuously varying external parameters has fascinated physicists for the last four decades. A metal-insulator transition is characterized by the localization of the charge carriers, which prevents them from transporting an electric current. The two basic mechanisms that cause electron localization are the correlations among the electrons and the disorder present in the sample. Mott demonstrated that electron-electron interactions can produce a metal-insulator transition even in a system without disorder (*2*). Anderson discovered that disorder, such as strong spatial fluctuations in the electrostatic potential caused by impurities, can drive a metal-insulator transition in a system of noninteracting electrons (*3*). The theoretical description of the situation when both effects are present is a central unsolved problem, especially when the electron-electron interactions are strong.

An important advance in our understanding came with the introduction of scaling ideas (*4*). The scaling approach had proved to be extraordinarily successful for understanding phase transformations driven by temperature. Near a continuous second-order phase transition, a simple and universal description of the transition emerges because the physics is controlled by a diverging length scale that is much larger than any of the microscopic lengths in the problem.

There is a sharp qualitative distinction between metal and insulator only at zero temperature because insulators can carry a (small) current at nonzero temperature owing to thermal excitations. Thus, a continuous metal-insulator transition can only take place at zero temperature. The metal insulator transition is therefore an example of a quantum phase transition—that is, a transition caused by a fundamental change in the ground state of a system as a parameter is varied.

A phase diagram can be constructed for such a transition (figure). A variety of parameters can be used to tune a system through the transition. In the figure, the abscissa is the control parameter. At nonzero temperature, two scenarios are possible. One is that there is a line of first-order metal-insulator transitions terminating in the critical point at $T = 0$ (solid line). The other is that there is simply a continuous crossover (shaded region) from metallic (resistivity decreases as T decreases) to insulating (resistivity increases) behavior.

The simplest scaling scenario gives the result that at low temperatures, and very near the metal-insulator transition, the electrical conductivity has a rather simple form: $\sigma(T, s) = \xi(s)^{-\mu\nu} f[T\tau(s)]$, where T is the absolute temperature. This formula is remarkable because it states that all of the dependence on material parameters of a system near the metal-insulator transition is contained in the value of a length scale ("localization length") $\xi(s)$ that diverges as $(s - s_c)^{-\nu}$ and a time scale $\tau(s)$ that diverges as temperature approaches zero as $(s - s_c)^{-\nu z}$; s is the critical parameter (for example, pressure or impurity concentration), which drives the metal-insulator transition when $s \rightarrow s_c$. The numbers μ, z, and ν introduced here are critical exponents. μ describes how the conductivity vanishes at zero temperature as s is varied through s_c, that is, $\sigma \propto (s - s_c)^{\mu}$. The slowing down in the relaxation that accompanies a phase transition is quantified by means of a "dynamical



Phase diagram for a metal-insulator transition at the quantum critical point. At $T = 0$, the behavior is metallic for critical parameter $s > s_c$ and insulating for $s < s_c$. The solid line indicates a line of first-order transitions; the shading shows the crossover region.

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