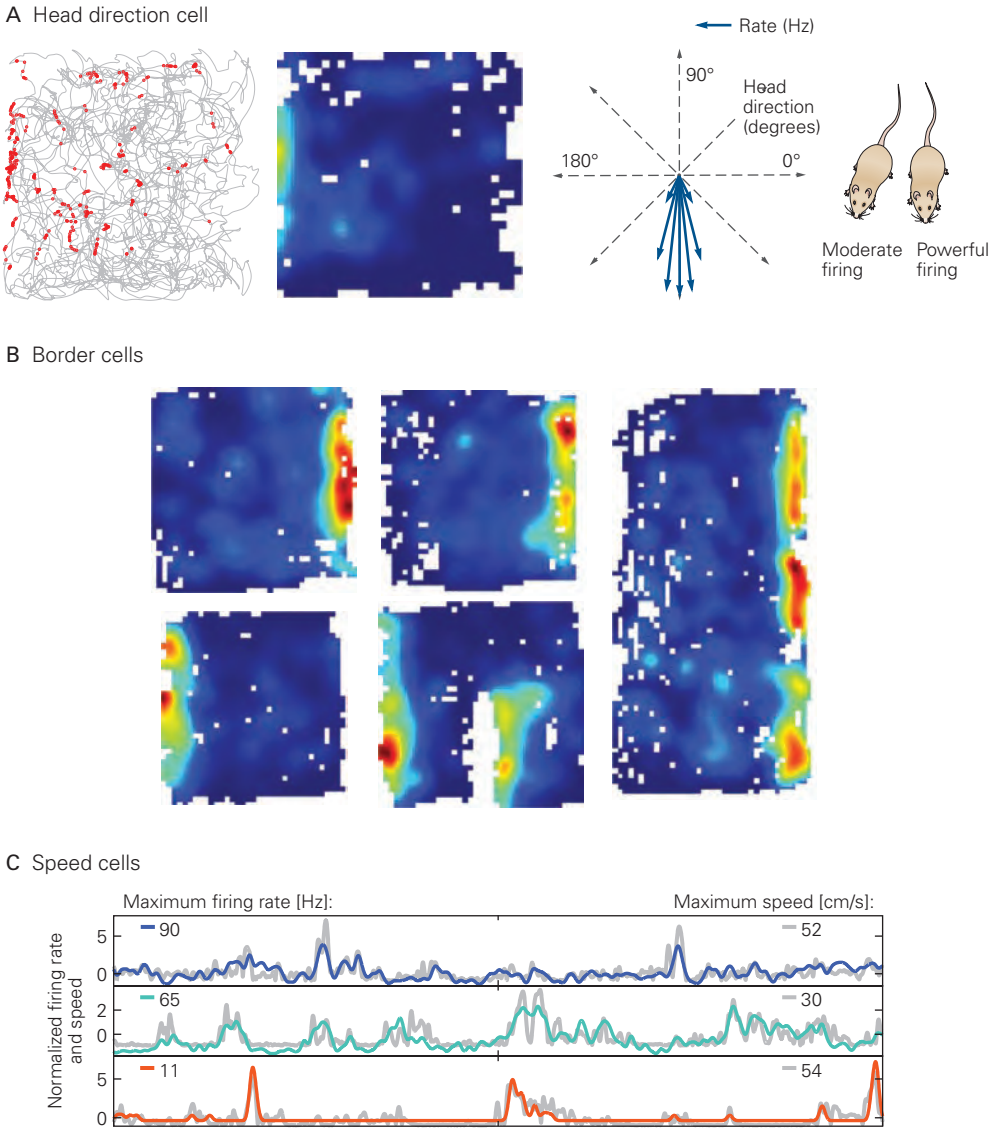

Figure 54–14 The medial entorhinal cortex contains several functional cell types tuned to distinct representations of an animal's navigation.

A. On the left is the trajectory of a rat exploring a 100-cm-wide square enclosure (**red dots** indicate firing locations). A color-coded firing rate map is also shown (color scale as in previous figures). Note that the cell's firing is scattered across the enclosure. The plot on the right shows the same cell's firing rate as a function of head direction, in polar coordinates. The cell fires selectively when the rat faces south, anywhere in the box. (Adapted, with permission, from Sargolini et al. 2006.)

B. Firing rate maps for a representative border cell in enclosures with different geometric shapes (**red** = high rate; **blue** = low rate). **Top row:** The firing field map follows the walls when the enclosure is stretched from a square (left and middle maps) to a rectangle (right map). **Bottom row:** The firing field of the same border cell in another environment. Introduction of a discrete wall (**white pixels**, right map) inside the square enclosure causes a new border field to appear to the right of the wall. (Reproduced, with permission, from Solstad et al. 2008.)

C. Speed cells. Traces show normalized firing rate (**colored traces**) and speed (**gray**) for seven representative entorhinal speed cells during 2 minutes of free foraging. Maximum values of firing rate and speed are indicated (left and right, respectively). Note high correspondence between speed and firing rate in these cells. (Reproduced, with permission, from Kropff et al. 2015.)

Taken together, these discoveries point to a network of functionally dedicated cells in the medial entorhinal cortex reminiscent of the feature detectors of the sensory cortices. The functional specificity of each cell type stems from the cell's representation of a specific feature of behavior. In this sense, the entorhinal cell types differ from cells in most other association cortices, which integrate information from many sources in ways that are not straightforward to decode.

What are the key differences between space-coding cells in the hippocampus and the medial entorhinal cortex? A striking property of all entorhinal cell types is the rigidity of their firing patterns. Ensembles of colocalized grid cells maintain the same intrinsic firing pattern regardless of context or environment. When a pair of grid cells has overlapping grid fields in one environment, their grid fields overlap also in other environments. If their grid fields are opposite, or "out of phase," they will be opposite in other environments as well. A similar rigidity is seen in head direction cells and border cells: Cells with similar orientation in one environment have similar orientations in other environments. Speed cells also maintain their unique tuning to running speed across environments. These findings suggest that the medial entorhinal cortex, or modules of this cortical circuit, may operate like a universal map of space that disregards the details of the environment. By doing so, the entorhinal map differs strongly from the place-cell map of the hippocampus.

The firing pattern of a hippocampal place cell is very sensitive to changes in the environment. The place fields of a given place cell in the hippocampus often switch to encode a completely different spatial locale when an animal's environment undergoes a major change, a process referred to as "remapping." Sometimes even minor changes in sensory or motivational inputs are sufficient to elicit remapping. The lack of correlation of hippocampal place maps for different environments (Figure 54–15) is thought to facilitate storage of discrete memories and minimize the risk that one memory will be confused with another, a process termed interference. For an explicit memory system like the hippocampus, with millions of events to be stored, this may be a huge advantage. For accurate and fast representation of an animal's position in space, as occurs in the medial entorhinal cortex, it may instead be beneficial to use a more stereotyped code that is less sensitive to environmental context or nonspatial sensory stimuli.

Place Cells Are Part of the Substrate for Spatial Memory

In addition to representing the animal's current location, place cells are thought to also store the memory of a location in position-related firing patterns that are evoked in the absence of the sensory inputs that originally elicited the firing. For example, as an animal sleeps after running repeated laps along a linear maze,

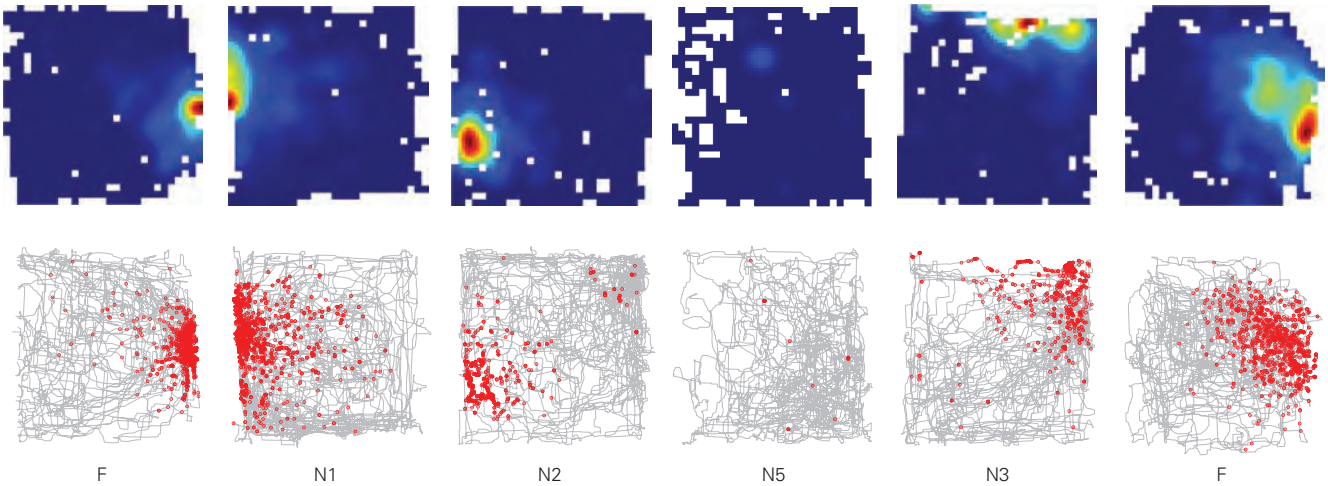

Figure 54–15 Place cells form independent maps for different environments. Rate maps showing firing patterns of a single hippocampal place cell in different square enclosures, each located in a different room. The rat was tested in one familiar (**F**) and 11 novel (**N**) rooms (recordings only shown for four of the novel rooms). The top row shows firing rate maps, whereas the bottom row shows trajectories of the animal's movement with firing locations in **red**. The cell was active only in some of the rooms (F, N1, N2, N3), where the firing locations were different. When the rat was returned to the familiar room at the end of the experiment, the cell's firing field had a similar location to the initial recording in the familiar room, indicating that a given cell's spatial firing pattern in the same environment is stable. (Adapted, with permission, from Alme et al. 2014.)

place cells spontaneously fire in the same order that they did in the maze, a phenomenon called "replay." Similarly, past trajectories and experiences may influence firing rates at particular locations in the environment. The ability of place cells to represent events and locations experienced in the past likely underlies the ability of the hippocampus to encode complex memories of events.

Once the firing pattern of a population of hippocampal neurons is formed for a given environment, how is it maintained? Because the place cells are the same hippocampal pyramidal neurons that undergo experimental LTP, a natural question is whether LTP is important. This question was addressed in experiments in mice in which LTP was disrupted.

In mice lacking the NR1 subunit of the NMDA receptor, hippocampal pyramidal neurons still fire in place fields despite the fact that LTP is blocked. Thus, this form of LTP is not required for the transformation of spatial sensory information into place fields. However, the place fields of the mutant mice are larger and fuzzier in outline than those in normal animals. In a second experiment with mutant mice, late LTP and long-term spatial memory were selectively disrupted by expression of a transgene that encodes a protein inhibitor of PKA. In these mice, place fields also form, but the firing patterns of individual cells are stable only for an hour or so (Figure 54–16). Thus, late LTP is required for long-term stabilization of place fields but not their formation.

To what degree do these maps of an animal's surroundings mediate explicit memory? In humans, explicit memory is defined as the conscious recall of facts about people, places, and objects. Although consciousness cannot be studied empirically in the mouse, selective attention, which is required for conscious recall, can be examined.

When mice are presented with different behavioral tasks, the long-term stability of place fields correlates strongly with the degree of attention required to

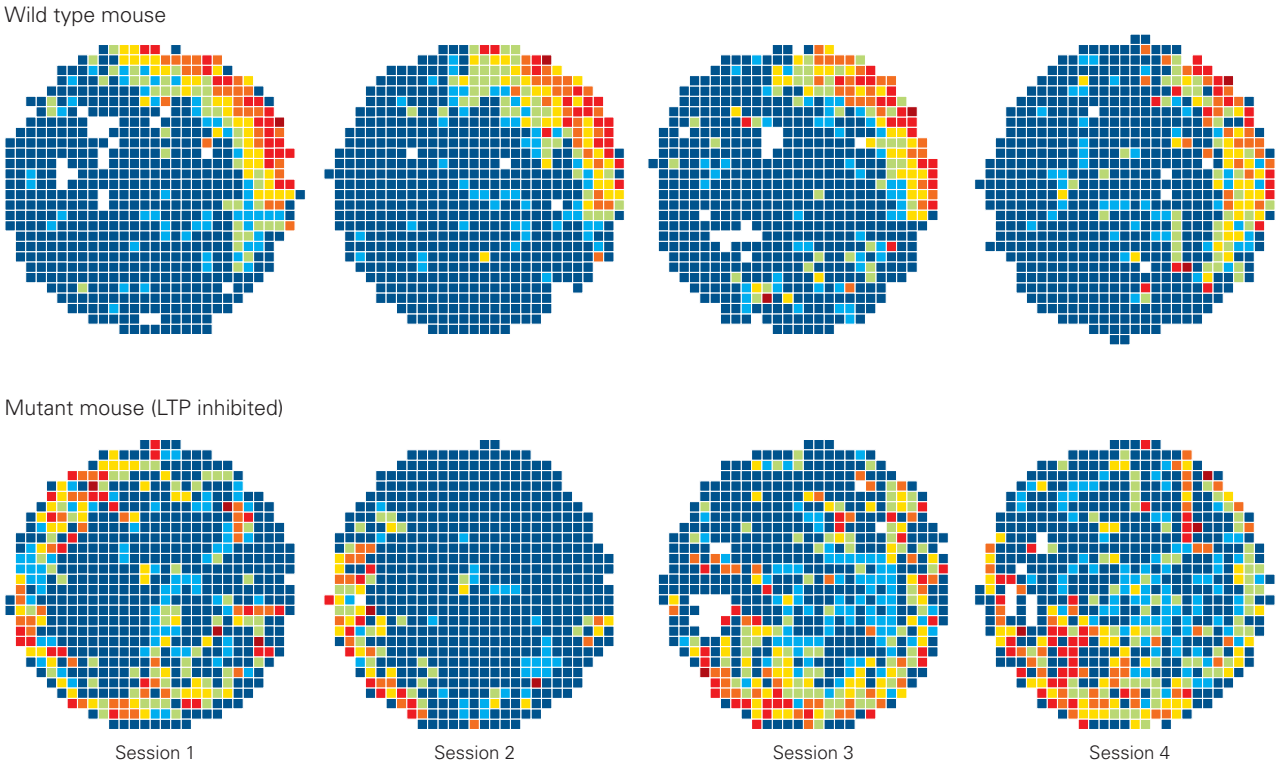

Figure 54–16 Disruption of long-term potentiation (LTP) degrades the stability of place field formation in the hippocampus. Color-coded firing rate maps (see Figure 54–12) show place fields recorded in four successive sessions from a single hippocampal pyramidal neuron in a wild type mouse and from a neuron in a mutant mouse that expresses the persistently active CaMKII (which inhibits the induction of LTP). Before each recording session, the animal is taken out of the enclosure and sometime later reintroduced into it. In each of the four sessions, the place field for the cell in the wild type animal is stable; the cell fires whenever the animal is in the upper right region of the enclosure. By contrast, the place field for the cell in the mutant mouse is unstable across the four sessions. (Reproduced, with permission, from Rotenberg et al. 1996.)

perform the task. When a mouse does not attend to the space it walks through, place fields form but are unstable after 3 to 6 hours. Animals with unstable place fields are unable to learn a spatial task. However, when a mouse is forced to attend to the space, for example, when trained to run to a specific location, the place fields are stable for days.

How does this attentional mechanism work? Studies in primates have shown the importance of the prefrontal cortex and the modulatory dopaminergic system during attention. Indeed, the formation of stable place fields in mice requires the activation of the dopamine D_1/D_5 type of receptor, which has been shown to enhance the formation of late LTP through production of cAMP and activation of PKA. These results suggest that long-term memory of a place field, rather than being a form of implicit memory that is stored and recalled without conscious effort, requires the animal to attend to its environment, as is the case for explicit memory in humans.

Disorders of Autobiographical Memory Result From Functional Perturbations in the Hippocampus

Our sense of identity is greatly dependent on our store of explicit autobiographical memories and our ability to recognize and navigate through familiar spatial environments. Neurological and psychiatric disorders that disrupt these abilities often occur as a result of changes in neural circuitry and plasticity mechanisms within the hippocampus and related regions in the temporal lobe.

There is now substantial evidence that the devastating memory loss associated with Alzheimer disease is associated with an accumulation of extracellular plaques of the protein fragment β-amyloid (Aβ) and intracellular neurofibrillary tangles of tau, a microtubule associated protein (Chapter 64). However, even before plaques and tangles are apparent, elevated levels of soluble Aβ and tau are thought to disrupt a number of cellular processes, particularly by reducing the magnitude of both early and late LTP at certain synapses. Mouse models of Alzheimer disease also show alterations in hippocampal place cell stability and population-level synchrony, which may contribute to memory loss and spatial disorientation. Changes in grid-cell function have also been observed in electrophysiological recordings in mouse disease models and in humans through functional magnetic resonance imaging studies. Although a number of preclinical studies have shown that agents that decrease levels of Aβ can rescue synaptic function and memory in rodents, so far these treatments have been less successful in treating patients with Alzheimer disease, perhaps because treatment must be initiated at early stages prior to irreversible synaptic changes.

Altered hippocampal function may also contribute to cognitive problems experienced by individuals with schizophrenia, including disturbances in working memory (Chapter 60). Recent studies using a genetic mouse model of schizophrenia report reduced synchrony between the hippocampus and prefrontal cortex associated with working memory. Furthermore, the place fields of place cells in the hippocampus CA1 region may be overly rigid in this mouse, suggesting that the ability of the hippocampus to distinguish different contexts may be impaired. Finally, a deficit in social memory in these mice has been linked to a reduction of parvalbumin-positive inhibitory neurons in the CA2 region; a similar loss of inhibitory neurons has been observed in postmortem brain tissue from individuals with schizophrenia and bipolar disorder.

Thus, studies of the hippocampus and related temporal lobe structures offer the great promise of providing fundamental insight into how explicit memories are stored and recalled and how functional alterations in these structures may contribute to neuropsychiatric disease. In turn, such insight may aid in the discovery of new treatments for these devastating disorders.

Highlights

1. Explicit memory has both a short-term component, termed working memory, and a long-term component. Both forms depend on the prefrontal cortex and hippocampus.
2. Long-term memory is thought to depend on activity-dependent long-term synaptic plasticity at synapses within the cortico-hippocampal circuit. A brief high-frequency train of tetanic stimulation leads to long-term potentiation (LTP) of excitatory synaptic transmission at each stage of the cortico-hippocampal circuit.
3. LTP at many synapses depends on calcium influx into the postsynaptic cell mediated by the *N*-methyl-D-aspartate (NMDA) type of glutamate receptor. This receptor acts as a coincidence detector: It requires both glutamate release and strong postsynaptic depolarization to conduct calcium.
4. The expression of LTP depends on either the insertion of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type of

glutamate receptors in the postsynaptic membrane or an increase in presynaptic glutamate release, depending on the type of synapse and intensity of tetanic stimulation.

5. LTP has both early and late phases. Early LTP depends on covalent modifications, whereas late LTP depends on new protein synthesis, gene transcription, and growth of new synaptic connections.
6. Pharmacological and genetic manipulations that disrupt LTP often lead to an impairment of long-term memory, indicating that LTP may provide an important cellular mechanism for memory storage.
7. Memories are stored by cell assemblies. LTP may be required for forming event-specific assemblies. Recall of memory may reflect reactivation of the same assemblies that were active during the original event.
8. The hippocampus encodes both spatial and nonspatial signals. Many hippocampal neurons act as place cells, firing action potentials when an animal visits a particular location in its environment.
9. The entorhinal cortex, the area of the cortex that provides most of the input to hippocampus, also encodes both nonspatial and spatial information. The medial portion of entorhinal cortex contains neurons, called grid cells, that fire when an animal crosses the vertices of a hexagonal grid-like lattice of spatial locales. Grid cells are organized into semi-independent semi-topographically organized modules with distinct grid frequencies. The entorhinal map also contains border cells, object-vector cells, head direction cells, and speed cells.
10. Within a grid-cell module, pairs of grid cells maintain firing relationships rigidly across environments and experiences, suggesting that grid cells form a universal map that is expressed similarly in all environments. In contrast, place cells in the hippocampus form maps that are plastic as they are completely uncorrelated between environments.
11. Neuropsychiatric disorders such as Alzheimer disease and schizophrenia have been associated with deficits in hippocampal and entorhinal synaptic function, place-cell properties, and learning and memory. Treatments aimed at restoring such function may yield new therapeutic approaches to disease.
12. Despite their clear differences, implicit (Chapter 53) and explicit memory storage rely on a common logic. Both activity-dependent presynaptic facilitation for storing implicit memory and associative long-term potentiation for storing explicit memory rely on the associative properties of specific proteins: Adenylyl cyclase activation in implicit memory requires neurotransmitter plus intracellular Ca^{2+}, whereas NMDA receptor activation in explicit memory requires glutamate plus postsynaptic depolarization. Such similarities indicate the fundamental importance of associative learning rules for memory storage.

Edvard I. Moser
May-Britt Moser
Steven A. Siegelbaum

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55

Language

Language is uniquely human and arguably our greatest skill and our highest achievement. Despite its complexity, all typically developing children master it by the age of 3. What causes this universal developmental phenomenon, and why are children so much better at acquiring a new language than adults? What brain systems are involved in mature language processing, and are these systems present at birth? How does brain damage produce the various disorders of language known as the aphasias?

For centuries, these questions about language and the brain have prompted vigorous debate among theorists. In the last decade, however, an explosion of information regarding language has taken us beyond the nature–nurture debates and beyond the standard view that a few specialized brain areas are responsible for language. Two factors have brought about this change.

First, functional brain imaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) have allowed us to examine activation patterns in the brain while a person carries out language tasks—naming objects or actions, listening to sounds or words, and detecting grammatical anomalies. The results of these studies reveal a far more complex picture than the one first proposed by Carl Wernicke in 1874. Moreover, structural

brain imaging techniques, such as diffusion tensor imaging (DTI), tractography, and quantitative magnetic resonance imaging (qMRI), have revealed a network of connections that link specialized language areas in the brain. These discoveries are taking us beyond previous, simpler views of the neural underpinnings of language processing and production that assumed involvement of only a few specific brain areas and connections.

Second, behavioral and brain studies of language acquisition show that infants begin to learn language earlier than previously thought, and in ways that had not been previously envisioned. Well before children produce their first words, they learn the sound patterns underlying the phonetic units, words, and phrase structure of the language they hear. Listening to language alters the infant brain early in development, and early language learning affects the brain for life.

Taken together, these advances are shaping a new view of the functional anatomy of language in the brain as a complex and dynamic network in the adult brain, one in which multiple, spatially distributed brain systems cooperate functionally via long-distance neural fascicles (axon fiber bundles). This mature network arises from the considerable brain structure and function in place at birth and develops in conjunction with powerful innate learning mechanisms responsive to linguistic experience. This new view of language encompasses not only its development and mature state, but also its dissolution when brain damage leads to aphasia.

Humans are not the only species to communicate. Passerine birds attract mates with songs, bees code the distance and direction to nectar by dancing, and monkeys signal a desire for sexual contact or fear at the approach of an enemy with coos and grunts. With language, we accomplish all of the above and more. We use language to provide information and express our emotions, to comment on the past and future, and to create fiction and poetry. Using sounds that have only an arbitrary association with the meanings they convey, we talk about anything and everything. No animal has a communication system that parallels human language either in form or in function. Language is the defining characteristic of humans, and living without it creates a totally different world, as patients with aphasia following a stroke experience so heartbreakingly.

Language Has Many Structural Levels: Phonemes, Morphemes, Words, and Sentences

What distinguishes language from other forms of communication? The key feature is a finite set of distinctive speech sounds or phonemes that can be combined with infinite possibilities. Phonemes are the building blocks of units of significance called morphemes. Each language has a distinctive set of phonemes and rules for combining them into morphemes and words. Words can be combined according to the rules of syntax into an infinite number of sentences.

Understanding language presents an interesting set of puzzles, ones that challenge supercomputers. The advent of virtual personal assistants such as Siri and Alexa, based on machine-learning algorithms, has allowed electronic devices to respond to select kinds of human utterances. However, we are still not conversing with computers. Fundamental advances will need to be made before humans can expect to have a conversation with a machine that resembles a conversation you can have with any 3-year-old. Machine-learning solutions do not accomplish their limited responses by mimicking human brain systems used for language, nor do they learn in the ways that human infants learn. Comparing machine-learning approaches (artificial intelligence) and human approaches is of theoretical and practical interest (Chapter 39) and is a hot topic for future research.

Language presents such a complex puzzle because it involves many functionally interconnected levels, starting at the most basic level with the sounds that distinguish words. For example, in English, the sounds /r/ and /1/ differentiate the words *rock* and *lock*. In Japanese, however, this sound change does not distinguish words because the /r/ and /l/ sounds are used interchangeably. Similarly, Spanish speakers distinguish between the words *pano* and *bano*, whereas English speakers treat the /p/ and /b/ sounds at the beginning of these words as the same sounds. Given that many languages use identical sounds but group them differently, children must discover how sounds are grouped to make meaningful distinctions in their language.

Phonetic units are subphonemic. As we have illustrated above with /r/ and /l/, these two sounds are both phonetic units, but their phonemic status differs in English and Japanese. In English, the two are phonemically distinct, meaning that they change the meaning of a word. In Japanese, /r/ and /l/ belong to the same phonemic category and are not distinct. Phonetic units are distinguished by subtle acoustic variations caused by the shape of the vocal tract called *formant frequencies* (Figure 55–1). The patterns and timing of formant frequencies distinguish words that differ in only one phonetic unit, such as the words *pat* and *bat*. In normal speech, formant changes occur very rapidly, on the order of milliseconds. The auditory system has to track these rapid changes in order for an individual

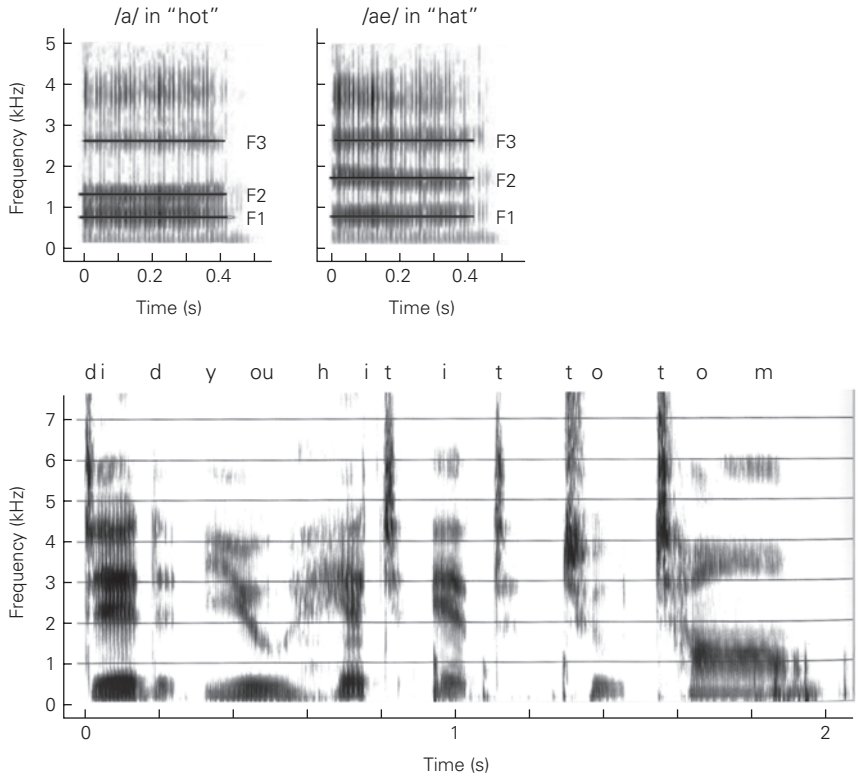

Figure 55–1 Formant frequencies. Formants are systematic variations in the concentration of energy at various sound frequencies and represent resonances of the vocal tract. They are shown here as a function of time in a spectrographic analysis of speech. The formant patterns for two simple vowels (/a/ and /ae/) spoken in isolation are distinguished by differences in formant 2 (F2). Formant patterns for the sentence "Did you hit it to Tom?" spoken slowly and clearly illustrate the rapid changes that underlie normal speech. (Data from Patricia Kuhl.)

to distinguish semantically different sounds and thus understand speech. Whereas in written language, spaces are customarily inserted between words, in speech, there are no acoustic breaks between words. Thus, speech requires a process that can detect words on the basis of something other than sounds bracketed by silence. Computers have a great deal of trouble recognizing words in the normal flow of speech.

Phonotactic rules specify how phonemes can be combined to form words. Both English and Polish use the phonemes /z/ and /b/, for example, but the combination /zb/ is not allowed in English, whereas in Polish, it is common (as in the name *Zbigniew*).

Morphemes are the smallest structural units of a language, best illustrated by prefixes and suffixes. In English, for example, the prefix *un* (meaning *not*) can be added to many adjectives to convey the opposite meaning (eg, *unimportant*). Suffixes often signal the tense or number of a word. For example, in English, we add *s* or *es* to indicate more than one of something (*pot* becomes *pots*, *bug* becomes *bugs*, or box becomes *boxes*). To indicate the tense of a regular verb, we add an ending to the word (eg, *play* can become *plays*, *playing*, and *played*). Irregular verbs do not follow the rule (eg, *go* becomes *went* rather than *goed* and *break* becomes *broke* rather than *breaked*). Every language has a different set of rules for altering the tense and number of a word.

Finally, to create language, words have to be strung together. *Syntax* specifies word and phrase order for a given language. In English, for example, sentences typically conform to a subject-verb-object order (eg, *He eats cake*), whereas in Japanese, it is typically subject-object-verb (eg, *Karewa keeki o tabenzasu*, literally *He cake eats*). Languages have systematic differences in the order of larger elements (noun phrases and verb phrases) of a sentence, and in the order of words within phrases, as illustrated by the difference between English and French noun phrases. In English, adjectives precede the noun (eg, *a very intelligent man*), whereas in French, most follow the noun (eg, *un homme tres intelligent*).

Language Acquisition in Children Follows a Universal Pattern

Regardless of culture, all children initially exhibit universal patterns of speech perception and production that do not depend on the specific language children hear (Figure 55–2). By the end of the first year, infants have learned through exposure to a specific language which phonetic units convey meaning in that language and to recognize likely words, even though they do not yet understand those words. By 12 months of age,