critical selection threshold (Figure 38–9B). However, a further important point when thinking about selection malfunctions is to appreciate that output inhibition and disinhibition are likely to be continuously variable rather than discrete on/off states. In that case, the difference between the disinhibited and inhibited channels would determine how "hard" or "soft" the selection is. When the difference is large (Figure 38–9D), competing options are likely to find the current selection is resistant to interruption—a larger than normal input salience would be required to cause the system to switch selections. Conversely, when the difference is small (Figure 38–9C), it would be comparatively easy for a competing option to initiate a selection switch.

Support for these ideas comes from behavioral observations showing that at the beginning of task learning there is frequently easy switching between strategies. However, as the task becomes well learned, the system becomes increasingly resistant to alternative strategies. Appreciation of the concepts of hard and soft selection could therefore play an important role when thinking about how a selection mechanism might become dysfunctional in the context of basal ganglia diseases.

### Parkinson Disease Can Be Viewed in Part as a Failure to Select Sensorimotor Options

The cardinal symptoms of Parkinson disease are akinesia (difficulties in initiating movement), bradykinesia (initiated movements are slow), and rigidity (stiffness and resistance to passive movement). Tremor is often but not always present. The principal neurological deficit responsible for the motor symptoms of Parkinson disease is thought to be the progressive degeneration of dopaminergic neurotransmission in the basal ganglia.

A consequence of this loss of dopamine is increased tonic and oscillatory activity in the recordings from basal ganglia output nuclei. Since the output of the basal ganglia is GABAergic and inhibitory, in Parkinson disease, targeted structures are receiving high and uneven levels of inhibitory input. This condition impairs the normal selective (disinhibitory) function of the basal ganglia; movements are difficult to select and, when possible, are slow to execute.

Parkinson disease is, however, more nuanced than this. Over much of this progressive condition, the loss of dopaminergic transmission differentially affects the sensorimotor territories of the basal ganglia, leaving the limbic and associative territories comparatively unaffected. As discussed in the section on goal-directed and habitual control, the sensorimotor territories of the basal ganglia play an essential role in selecting habitual actions. Perhaps, therefore, it is not surprising that many of the motor features of Parkinson disease can be interpreted in terms of a loss of automatic habits. While patients can do things, they are trapped in the slower, serial, and voluntary mode of goal-directed control. In the future, it will be interesting to see if subtle losses of habitual control can be detected before clinical symptoms appear, thereby acting as an early marker for the condition.

### Huntington Disease May Reflect a Functional Imbalance Between the Direct and Indirect Pathways

Huntington disease is a genetically transmitted disorder, the initial symptoms of which are subtle changes in mood, personality, cognition, and physical skills. The abnormal movements are characterized by jerky, random, and uncontrollable movements called chorea. The disease is associated with neuronal degeneration. Damage in the early stage is most evident in the striatal medium spiny neurons, but later spreads to other regions of the nervous system.

Observations that neuronal degeneration is evident in limbic, associative, and sensorimotor territories of the striatum would explain why the disease is characterized by disturbances of affect, cognition, and sensorimotor function. Also noteworthy is that the most vulnerable neurons are those in the striatum that project to the external globus pallidus (the indirect pathway) rather than the neurons that project directly to the basal ganglia output nuclei. At the level of the output nuclei, this disturbance would tip the balance in favor of the striatal projection responsible for disinhibition. Consequently, the symptoms of Huntington disease could reflect interference with expression of the selected affective, cognitive, and sensorimotor behaviors by competitors not being sufficiently suppressed.

### Schizophrenia May Be Associated With a General Failure to Suppress Nonselected Options

Schizophrenic psychosis is a condition in which there are also disturbances of affect, cognition, and sensorimotor function. Typical symptoms include delusions (false beliefs not based in reality), hallucinations (hearing or seeing things that do not exist), disorganized thinking (inferred from disorganized speech), and abnormal motor behavior (unpredictable agitation, stereotypy, and failure to concentrate on the matter in hand). The disease is progressive, and in later stages, negative symptoms characterized by flattened affect, social withdrawal, absence of thought, and reduced motor behavior become evident (Chapter 60).

Understanding the neurobiological basis of schizophrenia has been complicated by many inconsistent experimental procedures, high variability in symptoms, the side effects of medications, substance abuse, and variability in response to treatments. There is, however, a consistent link between schizophrenia and the basal ganglia insofar as a major class of antipsychotic drugs acts to suppress dopaminergic neurotransmission. In terms of simple regional density of axon terminals and postsynaptic dopamine receptors, dopaminergic transmission within the basal ganglia is likely to be influenced most profoundly by dopamine-related pharmacological therapies. Moreover, there is evidence that dopamine dysregulation in the basal ganglia is intrinsic to the pathology of schizophrenia rather than a medication side effect; predates the psychosis; and is a risk factor for the illness. The implication here is that schizophrenia is associated with a net excess of dopaminergic transmission in the basal ganglia.

So how might dysregulation of this form distort the normal functions of selection and reinforcement? First, the observation that schizophrenia is characterized by disturbances of affect, cognition, and sensorimotor behavior again suggests that the neurobiological substrate will be present in each of the basal ganglia's functional territories. Second, a recurrent theme is that with the positive symptoms there seems to be too much of everything—intense emotional intrusions, too many ideas out of control, spontaneous sensory experiences, too many distracting stimuli, and unpredictable motor agitation. One way of unifying this confusing array of symptoms is to assume that they represent a similar basic fault playing out in different functional territories of the basal ganglia. Here, the basic fault could be a failure on the part of the mechanism responsible for suppressing the impact of competing but nonselected options. Consequently, in all functional territories, the currently selected option would be pathologically vulnerable to interruption (Figure 38–9C).

### Attention Deficit Hyperactivity Disorder and Tourette Syndrome May Also Be Characterized by Intrusions of Nonselected Options

Further examples of hyperactive conditions that have been linked to basal ganglia dysfunction may also be due to a faulty selection mechanism where the system in each case is vulnerable to intrusions. Attention deficit hyperactivity disorder (ADHD), like schizophrenia, could in part be the result of a failure in the mechanism responsible for suppressing nonselected sensory options, thereby making it difficult to maintain a focus of attention. Alternatively, the impulsive aspects of the condition could reflect a malfunction in the neural systems that generate behavioral options based on the value of likely consequences. In this situation, options driven by immediately desired sensory events would take precedence over competing representations of disadvantageous longer-term consequences.

In the case of Tourette syndrome, converging evidence indicates that the involuntary behavioral intrusions (verbal and motor tics) are associated with aberrant activity in the cortical–basal ganglia–thalamic loops. In animal models, similar motor tics can be evoked by blocking inhibitory neurotransmission in local areas of the sensorimotor striatum. Were the disease state also to cause a similar failure of inhibition or inappropriate excitation in parts of the striatum not engaged by the current selection, disruptive motor intrusions might be expected. Furthermore, were the locus of the excessive excitation to remain constant and the motor characteristics of the intrusion to be repeated, it is likely that the mechanism for establishing automatic habits would be engaged, thereby further enhancing the automatic involuntary nature of the intrusion.

### Obsessive-Compulsive Disorder Reflects the Presence of Pathologically Dominant Options

Persons with obsessive-compulsive disorder compulsively repeat specific actions (hand washing, counting things, checking things) or have particular thoughts repeatedly come to mind uninvited (obsessions). Studies using functional neuroimaging when the symptoms are present consistently report abnormal activation at various locations within the cortical-striatum-thalamus-cortical loops.

In terms of a selection mechanism dysfunction, the symptoms of obsessive-compulsive disorder would be expected when, for whatever reason, the input salience of relevant functional channels would be abnormally dominant, thereby making it difficult for competing options to interrupt or cause behavioral or attentional switching (hard selection). The fact that the obsessional and compulsive options are dominant behaviors that have been learned suggests that the fault responsible for obsessive-compulsive disorder may lie with the reinforcement mechanism capable of adjusting input salience. Of course, such a fault could be of genetic and/or environmental origin.

### Addictions Are Associated With Disorders of Reinforcement Mechanisms and Habitual Goals

Addiction to drugs and other behaviors (eg, gambling, sex, eating) represents a dramatic dysregulation of

motivational selections. This is caused by an exaggerated salience of addiction-related stimuli, binge indulgence, and withdrawal anxiety. When addictions are being acquired, changes in dopaminergic and opioid peptide transmission in the basal ganglia have been reported.

Insofar as these transmission systems have been linked with fundamental mechanisms of reinforcement, it might be expected that the selective reinforcement of addiction-related stimuli would lead to observed increases in the ability of these stimuli to capture behavior. Alternatively, the increases in negative emotional states and stress-like responses experienced during withdrawal have been associated with reductions in dopamine function. In the limbic territories of the basal ganglia, such reductions are typically associated with negative reinforcement.

A final point to note is that if addiction-associated stimuli can automatically trigger the motivation/goal to indulge (ie, an automatic stimulus–goal association), a similar kind of mechanism may be operating in the limbic territories as is currently assigned to stimulus–response habits in the sensorimotor territories. Thus, if in the case of drug addiction the goal of drug acquisition may be correctly described as a stimulus-driven habit, the practicalities of obtaining the drug can be highly goal directed (eg, robbing a convenience store, phoning the dealer) and not at all habitual.

From the above sections, it can be seen that interpreting disorders of the basal ganglia in terms of dysregulations of selection and reinforcement does not require implausible intellectual contortions. Indeed, this could be regarded as further support for the view that the systems-level function of the basal ganglia is to operate as a generic selection mechanism. Moreover, having an overriding conceptual framework based on potential disorders of normal function has an important advantage for guiding future research. Instead of fishing in the brains of patients and animal models for clues of what might have gone wrong, one is hunting within a specified network for a malfunction that would be expected to produce the observed disorder.

## Highlights

1. The basal ganglia are an interconnected group of nuclei located at the base of the forebrain and midbrain. There are three major input structures (the striatum, the subthalamic nucleus, and the dopamine cells of substantia nigra) and two major output structures (the internal globus pallidus and substantia nigra pars reticulata).
2. Input structures receive projections from most regions of the cerebral cortex, limbic system, and brain stem, many via relays in the thalamus. Inputs to the striatum and subthalamus are topographically organized.
3. The spatial topography is maintained throughout the intrinsic basal ganglia connections, as well as in projections back to the cortex, limbic system, and brain stem structures. Thus, an essential feature of systems-level basal ganglia architecture can be viewed as a series of reentrant loops.
4. The striatum was thought to be connected to the output nuclei via direct and indirect pathways. However, recent anatomical evidence suggests a more complex internal architecture.
5. Phasic excitatory input to the basal ganglia is mediated by the neurotransmitter glutamate. Tonic inhibitory output from the basal ganglia is mediated by the neurotransmitter GABA. The reentrant loops keep afferent structures under strong inhibitory control. For any task, the tonic inhibitory firing of some output neurons pauses, while for others, it is maintained or increased.
6. Basal ganglia architecture appeared at the outset of vertebrate evolution and has been highly conserved throughout. This suggests that the computational problems they solve are likely to be problems faced by all vertebrate species.
7. The internal microarchitecture of the intrinsic basal ganglia nuclei is largely the same throughout their motivational, affective, cognitive, and sensorimotor territories. This suggests that the same basal ganglia algorithm is applied to all general classes of brain function.
8. A recurring theme within the basal ganglia literature is their involvement in action selection and reinforcement learning.
9. The selection hypothesis is supported by the following: (1) Selection is a generic problem faced by all vertebrates. (2) A selection algorithm common to all basal ganglia territories could resolve competitions between incompatible motivational, affective, cognitive, and sensorimotor options. (3) Many intrinsic processes could support a selection function. (4) Selective removal of output inhibition within a multiple reentrant looped architecture is necessarily a selection process. (5) Computational models of basal ganglia architecture effectively select the actions of multifunctional robots.
10. Abundant evidence indicates that the basal ganglia are an essential substrate for reinforcement

learning where selections are biased by the valence/value of past outcomes.

11. The multidimensional aspects of action (what, where, when, and how to do something) can be independently modified by reinforcement learning. It will be important to determine whether these different aspects of action are learned within the same or different functional territories of the basal ganglia.
12. Recent optogenetic investigations have confirmed that phasic dopamine signaling can act as a training signal for reinforcement learning.
13. Within the reentrant looped architecture, future selections can be biased not only within the basal ganglia by dopamine but also at synapses in external afferent structures and the thalamic relays.
14. Reinforcement learning can bias selections on the basis of outcome value (goal-directed), or by operating on an acquired automatic stimulus–response association (habit). Goal-directed and habitual selections are made in different functional territories of the basal ganglia.
15. Insofar as diseases of the basal ganglia in humans can be interpreted as selection malfunctions, additional support is provided for the idea that the basal ganglia operate as a generic selection module.

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# 39

# Brain–Machine Interfaces



Understanding the normal function of the nervous system is central to understanding dysfunction caused by disease or injury and designing therapies. Such treatments include pharmacological agents, surgical interventions, and, increasingly, electronic medical devices. These medical devices fill an important gap between largely molecularly targeted and systemic medications and largely anatomically targeted and focal surgical lesions.

In this chapter, we focus on medical devices that measure or alter electrophysiological activity at the level of populations of neurons. These devices are referred to as brain–machine interfaces (BMIs), brain–computer interfaces, or neural prostheses. We use the term BMI to refer to all such devices because there is no standard distinction among them. BMIs can be organized into four broad categories: those that restore lost sensory capabilities, those that restore lost motor capabilities, those that regulate pathological neural activity, and those that restore lost brain processing capabilities.

BMIs can help people perform "activities of daily living," such as feeding oneself, physically dressing and grooming oneself, maintaining continence, and walking. A type of BMI that we will discuss extensively in this chapter converts electrical activity from neurons in the brain into signals that control prosthetic devices to help people with paralysis. By understanding how neuroscience and neuroengineering work together to create current BMIs, we can more clearly envision how many neurological diseases and injuries can be treated with medical devices.

## BMIs Measure and Modulate Neural Activity to Help Restore Lost Capabilities

### Cochlear Implants and Retinal Prostheses Can Restore Lost Sensory Capabilities

One of the earliest and most widely used BMIs is the cochlear implant. People with profound deafness can benefit from restoration of even some audition. Since the 1970s, several hundred thousand people who have a peripheral cause of deafness that leaves the cochlear nerve and central auditory pathways intact have received cochlear implants. These systems have restored considerable hearing and spoken language, even to children with congenital deafness who have learned to perceive speech using cochlear implants.

Cochlear implants operate by capturing sounds with a microphone that resides outside the skin and sending these signals to a receiver surgically implanted under the skin near the ear. After conversion (encoding) to appropriate spatial-temporal signal patterns, these signals electrically stimulate spiral ganglion cells in the cochlear modiolus (Chapter 26). In turn, signals from the activated cochlear cells are transmitted through the auditory nerve to the brain stem and higher auditory areas where, ideally, the neural signals are interpreted as the sounds captured by the microphone.

Another example of a BMI is a retinal prosthesis. Blindness can be caused by diseases such as retinitis pigmentosa, an inherited retinal degenerative disease. At present, there is no cure and no approved medical therapy to slow or reverse the disease. Retinal prostheses currently enable patients to recognize large letters and locate the position of objects. They operate by capturing images with a camera and sending these signals to a receiver positioned within the eye. After conversion to appropriate spatial-temporal patterns, these electrical signals stimulate retinal ganglion cells in the retina through dozens of electrodes. In turn, these cells send their signals through the optic nerve to the thalamus and higher visual areas where, ideally, the afferent signals are interpreted as the image captured by the camera.

### Motor and Communication BMIs Can Restore Lost Motor Capabilities

BMIs are also being developed to assist paralyzed people and amputees by restoring lost motor and communication function. This is the central topic of this chapter. First, electrical neural activity in one or more brain areas is measured using penetrating multielectrode arrays placed, for example, in the arm and hand region of the primary motor cortex, dorsal and ventral premotor cortex, and/or intraparietal cortex (particularly the parietal reach region and medial intraparietal area) (Figure 39–1).

Second, an arm movement is attempted but cannot be made in the case of people with paralysis. Action potentials and *local field potentials* are measured during these attempts. With 100 electrodes placed in the primary motor cortex and another 100 in the dorsal premotor cortex, for example, action potentials from approximately 200 neurons and local field potentials from 200 electrodes are measured. Local field potentials are lower-frequency signals recorded on the same electrodes as the action potentials and believed to arise from local synaptic currents of many neurons near the electrode tips. Together, these neural signals contain considerable information about how the person wishes to move her arm.

Third, the relationship between neural activity and attempted movements is characterized. This relationship makes it possible to predict the desired movement from new neural activity, a statistical procedure we refer to as *neural decoding*. Fourth, the BMI is then operated in its normal mode where neural activity is measured in real time and desired movements are decoded from the neural activity by a computer. The decoded movements can be used to guide prosthetic devices, such as a cursor on a computer screen or a robotic arm. It is also possible to electrically stimulate muscles in a paralyzed limb to enact the decoded movements, a procedure known as *functional electrical stimulation*. Many other prosthetic devices can be envisioned as we increasingly interact with the world around us electronically (eg, smart phones, automobiles, and everyday objects that are embedded with electronics so that they can send and receive data—known as the "internet of things").

Finally, because the person can see the prosthetic device, she can alter her neural activity by thinking different thoughts on a moment-by-moment basis so as to guide the prosthetic device more accurately. This closed-loop feedback control system can make use of nonvisual sensory modalities as well, including delivering pressure and position information from electronic sensors wrapped on or embedded in a prosthetic arm. Such surrogate sensory information can be transformed into electrical stimulation patterns that are delivered to proprioceptive and somatosensory cortex.

The BMIs described above include motor and communication BMIs. Motor BMIs aim to provide natural control of a robotic limb or a paralyzed limb. In the case of upper-limb prostheses, this involves the

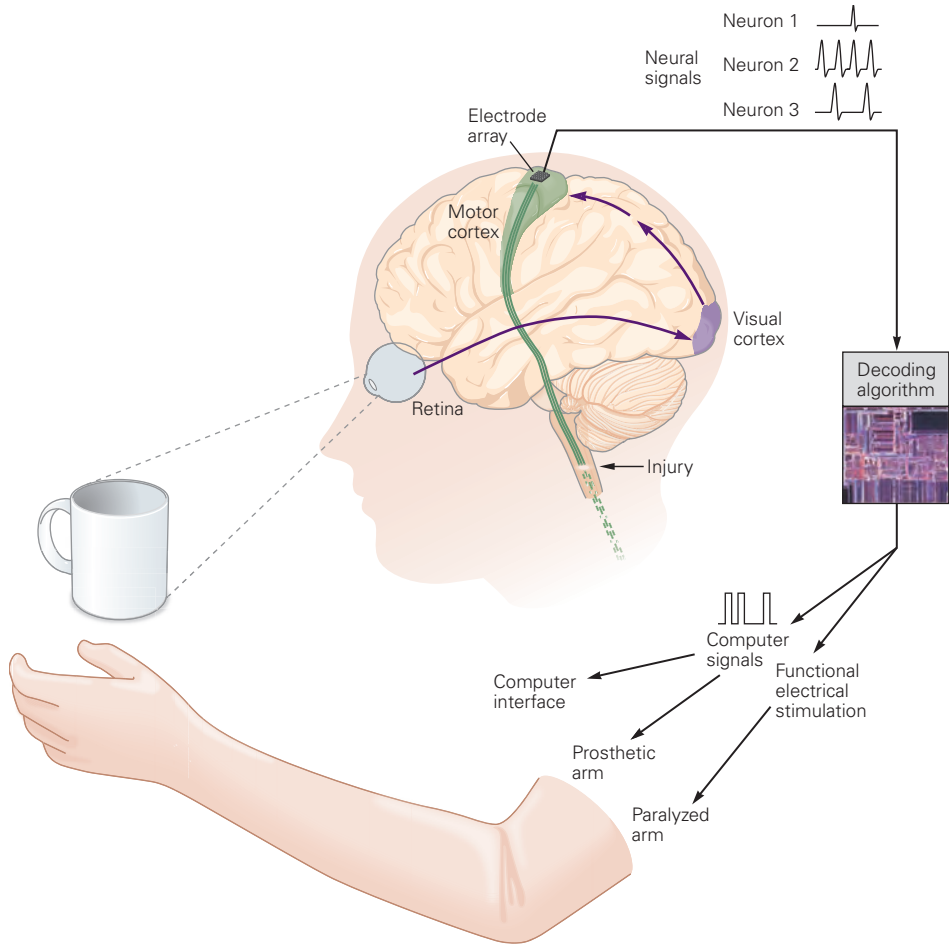


**Figure 39–1** Concept of motor and communication brain–machine interfaces. One or more electrode arrays are implanted in brain regions such as the primary motor cortex, dorsal and ventral premotor cortex, or intraparietal cortex. They record action potentials from tens to hundreds of neurons and local field potentials. The recorded neural activity is then converted by a decoding algorithm into (1) computer commands for controlling a computer interface or a prosthetic (robotic) arm, or (2) stimulation patterns for functional electrical stimulation of muscles in a paralyzed arm.

precise movement of the arm along a desired path and with a desired speed profile. Such control is indeed an ambitious ultimate goal, but even intermediate steps toward this goal could improve quality of life by restoring some lost motor function and improving the patient's ability to carry out "activities of daily living." For example, numerous people with tetraplegia could benefit from being able to feed themselves.

Communication BMIs are designed to provide a fast and accurate interface with a plethora of electronic devices. The ability to move a computer cursor around an on-screen keyboard allows a patient to type commands for computers, smart phones, voice synthesizers, smart homes, and the "internet of things." Ideally, communication BMIs would allow for a communication rate at which most people speak or type. Such BMIs would benefit people with amyotrophic lateral sclerosis (ALS), who often become "locked in" and unable to communicate with the outside world through any movements. Communication BMIs would also benefit people with other neurodegenerative diseases that severely compromise the quality of movement and speech, as well as those with upper spinal cord injury. The ability to reliably type several words per minute is a meaningful improvement in quality of life for many patients.

Motor and communication BMIs build on basic neuroscientific research in voluntary movement (Chapter 34). The design and development of BMIs have so far depended on laboratory animal research, largely with nonhuman primates; recently, however, pilot clinical trials with humans with paralysis have begun.

### Pathological Neural Activity Can Be Regulated by Deep Brain Stimulation and Antiseizure BMIs

BMIs have been developed to help people with disorders involving pathological neural activity in the brain, such as Parkinson disease and epilepsy. People with Parkinson disease benefit by having hand and arm tremor reduced. At present, there is no cure for Parkinson disease, and many people become resistant to pharmacological treatments. A deep brain stimulator (DBS) can help these people by delivering electrical pulses to targeted areas in the brain to disrupt the aberrant neural activity.

DBS is controlled by a neurostimulator implanted in the chest, with wires to stimulating electrodes in deep brain nuclei (eg, the subthalamic nucleus). The nuclei are continuously stimulated with these electrodes in order to alter the aberrant neural activity. This method can often greatly reduce Parkinson disease–related tremor for years. A DBS applied to different brain areas can also help people with essential tremor, dystonia, chronic pain, major depression, and obsessive-compulsive disorder.

Millions of people experiencing epileptic seizures are currently treated with antiseizure medications or neurosurgery, both of which often result in incomplete or impermanent seizure reduction. Antiseizure BMIs have shown considerable promise for further improving quality of life. These fully implanted BMIs operate by continuously monitoring neural activity in a brain region determined to be involved with seizures. They identify unusual activity that is predictive of seizure onset and then respond within milliseconds to disrupt this activity by electrically stimulating the same or a different brain region. This closed-loop response can be fast enough that seizure symptoms are not felt and seizures do not occur.

### Replacement Part BMIs Can Restore Lost Brain Processing Capabilities

BMIs are capable of restoring more than lost sensory or motor capabilities. They are, in principle, capable of restoring internal brain processing. Of the four categories of BMIs, this is the most futuristic. An example is a "replacement part" BMI. The central idea is that if enough is known about the function of a brain region, and if this region is damaged by disease or injury, then it may be possible to replace this brain region.

Once the normal input activity to a brain region is measured (see next section), the function of the lost brain region could then be modeled in electronic hardware and software, and the output from this substitute processing center would then be delivered to the next brain region as though no injury had occurred. This would involve, for example, reading out neural activity with electrodes, mimicking the brain region's computational functions with low-power microelectronic circuits, and then writing in electrical neural activity with stimulating electrodes.

This procedure might also be used to initiate and guide neural plasticity. A replacement part BMI that is currently being investigated focuses on restoring memory by replacing parts of the hippocampus that are damaged due to injury or disease. Another potential application would be to restore the lost functionality of a brain region damaged by stroke.

These systems represent the natural evolution of the BMI concept, a so-called "platform technology" because a large number of systems can be envisioned by mixing and matching various write-in, computational, and read-out components. The number of neurological diseases and injuries that BMIs should be able to help address ought to increase as our understanding of the functions of the nervous system and the sophistication of the technology continue to grow.

### Measuring and Modulating Neural Activity Rely on Advanced Neurotechnology

Measuring and modulating neural activity involves four broad areas of electronic technologies applied to the nervous system (so-called neurotechnology). The first area is the type of neural sensor; artificial neural sensors are designed with different levels of invasiveness and spatial resolution (Figure 39–2). Sensors that are external to the body, such as an *electroencephalogram* (EEG) cap, have been used extensively in recent decades. The EEG measures signals from many small metal disks (electrodes) applied to the surface of the scalp across the head. Each electrode detects average activity from a large number of neurons beneath it.

More recently, implantable electrode-array techniques, such as subdural *electrocorticography* (ECoG) and finely spaced micro-ECoG electrodes, have been used. Since ECoG electrodes are on the surface of the brain and are thus much closer to neurons than EEG electrodes, ECoG has higher spatial and temporal resolution and thus provides more information with which to control BMIs.

Most recently, arrays of *penetrating intracortical electrodes*, which we focus on in this chapter, have been used. The intracortical electrode arrays are made of silicon or other materials and coated with biocompatible materials. The arrays are implanted on the surface of the brain, with the electrode tips penetrating 1 to 2 mm