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A Report on Ten Key Technologies and Their Policy Implications

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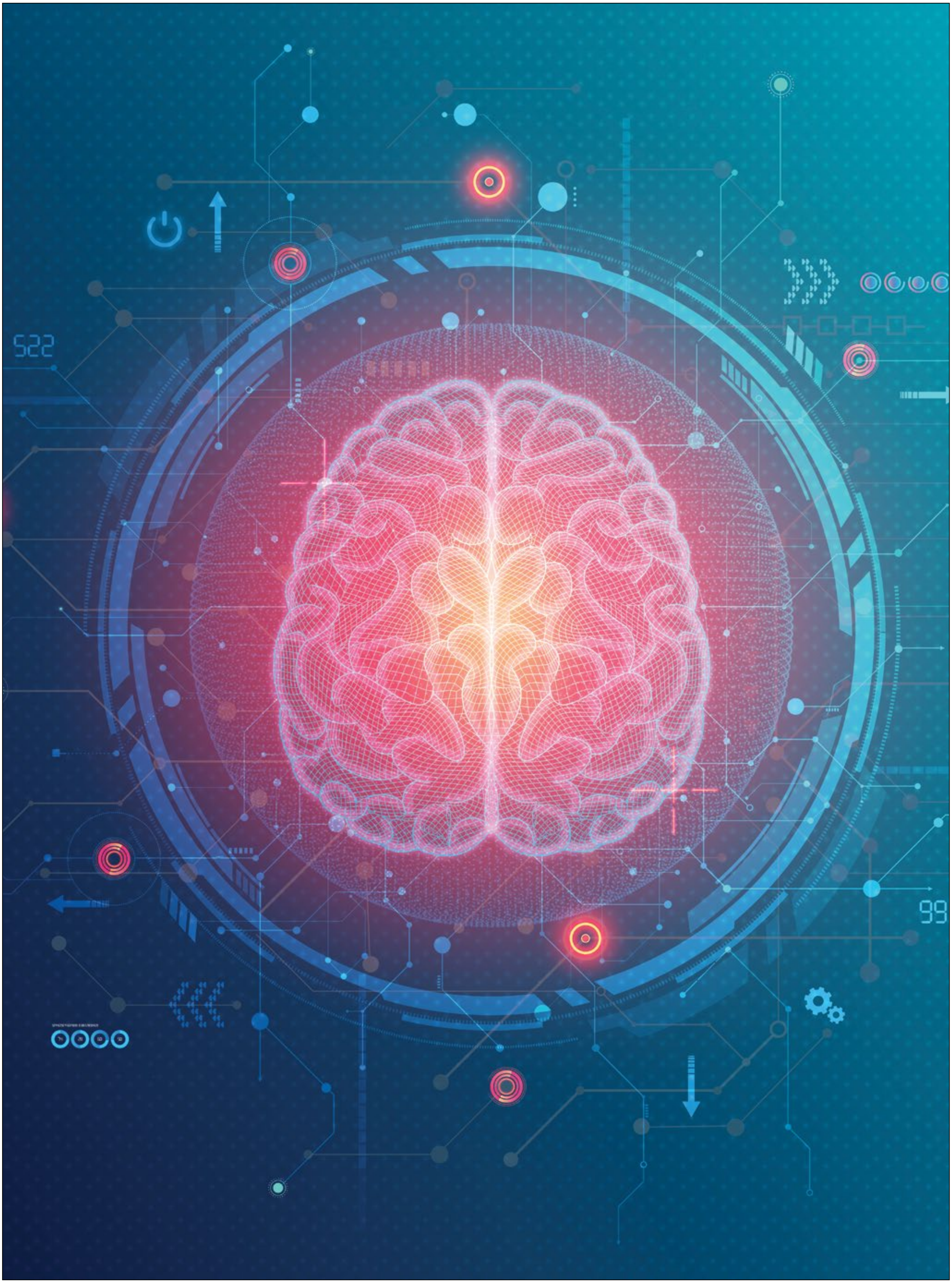
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NEUROSCIENCE

KEY TAKEAWAYS

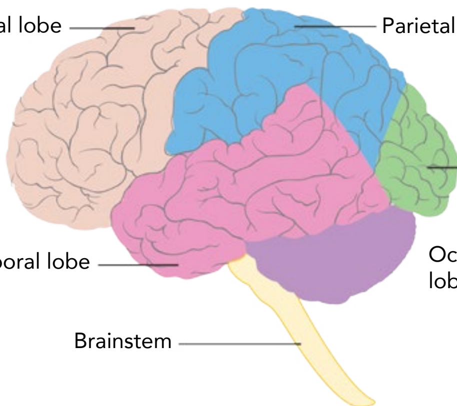
- Popular interest in neuroscience vastly exceeds the actual current scientific understanding of the brain, giving rise to overhyped claims in the public domain that revolutionary advances are just around the corner.
- Advances in computing have led to progress in several areas, including understanding and treating addiction and neurodegenerative diseases, and designing brain-machine interfaces.
- American leadership is essential for establishing and upholding global norms about ethics and human subjects research in neuroscience.

Overview

Neuroscience is the study of the human brain and the nervous system, their structure and function, healthy and diseased states, and life cycle from embryonic development to degeneration in later years.[1] Today's product applications of science support a growing market. Already a $32 billion market in 2021, the market for such products based on neuroscience is forecast to grow nearly 4 percent annually this decade to $41 billion, driven by increasing cases of neurological disorders like Parkinson's and Alzheimer's.[2]

The human brain (see figure 5.1) consumes 20 to 25 percent of the body's energy even though it constitutes only a small percentage of a human's body weight, a fact that underscores its outsize importance.[3] The power of the human brain is what has allowed us to become the dominant species on Earth without being the fastest, strongest, or biggest.

FIGURE 5.1 The human brain



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The brain contains some one hundred billion nerve cells, or neurons, which are the fundamental building blocks of the brain and nervous system. These cells sense the physical world, transmit information to the brain, process information, and send information from the brain to other parts of the body. The physical feature neurons use to connect to other neurons is called the synapse. Each neuron can have just a few or a hundred thousand synapses, though on average each neuron has several thousand synapses. Synapses are the structures that mediate most communication between neurons. The upstream neuron produces a chemical that is expelled at the synapse, diffuses for a very short distance, and finally is sensed by a receptor molecule on the downstream neuron. The prevalent view in the field is that memory is stored in the network of synapses.

Neuroscience covers a wide range of subfields: the nervous system's bodily structure (neuroanatomy), chemicals that modulate the nervous system (neurochemistry), nervous system functions (neurophysiology), the role of the nervous system in actions (behavioral neuroscience), and the role of the nervous system in thoughts (cognitive neuroscience). Many practical applications could benefit from neuroscience research, including the development of treatments for neurological and psychiatric disorders such as epilepsy, learning disabilities, cerebral palsy, and anxiety, as well as Alzheimer's disease and other neurodegenerative disorders.

Key Developments

This report focuses on three research areas in neuroscience that show major promise for concrete applications: brain-machine interfaces (neuroengineering), degeneration and aging (neurohealth), and the science of addiction (neurodiscovery). The most mature of these is the first.

Neuroengineering and the Development of Brain-Machine Interfaces

A brain-machine interface is a device that maps neural impulses from the brain to a computer, and vice versa. The potential applications for mature brain-machine interface technologies are wide ranging: sensory replacement or augmentation, limb replacement, direct mind-to-computer interfacing, and even computer-assisted memory recall and cognition are all within the theoretical realms of possibility. However, despite compelling headlines about mind-reading chip implants, that is still mostly science fiction. Even with tremendous interest and rapid progress in neuroscience and engineering, there are exceptionally few areas of the brain for which we have the necessary theoretical understanding of how neurocircuits work, and we also have not solved the technical problems of safely implanting electrodes in the brain.

An encouraging example of a brain-machine interface is the recent development of an artificial retina. The retina is the part of the eye that converts light into corresponding electrical signals sent to the brain. People who have certain incurable retinal

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diseases are blind because their light-detecting cells do not work. The artificial retina project aims to take video images and use electrodes implanted in the eye to simulate the electronic signals in a pattern that a functional retina would normally produce from those images, therefore bypassing the nonfunctional light-detecting cells.[4]

The theoretical side of this project—the science—involves recording spontaneous neural activity to identify cell types and their normal signals, identifying how electrodes activate cells, and understanding how to stimulate retinal ganglion cells to represent an image so that this information can be transmitted by the optic nerve. Solving the technical problems calls for significant engineering know-how in translating the scientific understanding of the stimulation algorithm into practical applications, experimental recordings, and fabrication and packaging of the electrode into the device—and in surgical techniques.

This effort requires a multidisciplinary team of neuroscientists, ophthalmologists, and surgeons working with electrical engineers and computer scientists.

The artificial retina project is the most mature brain-machine interface to date. The retina, a part of the central nervous system, is well suited as an experimental environment, as its stimuli (light) is experimentally controllable and can be captured by a digital camera. The retina is the best-understood neural circuit, and the theory of its function has developed to the point where much of retinal processing can be modeled. Compared to complex cognitive processes like learning and memory—where even the inputs aren't fully understood—the task of reconstructing vision is more achievable, albeit still challenging.

Other brain-machine interfaces are currently being developed, though they are less mature or less ambitious than the artificial retina project. Some of these interfaces decode brain activity without controlling a neural signal. For instance, one interface can translate brain activity in areas controlling motor functions into signals that can then be sent to an artificial limb prosthetic. Here, feeding high-dimensional patterns of neural activity into an AI algorithm suffices to control an artificial limb without requiring direct control of neural functions, a control that remains beyond our current scientific understanding. Another example of a unidirectional interface is the demonstrated use of data from functional magnetic resonance imaging (fMRI) studies of an individual to train a computer to reconstruct thoughts formulated as language from other fMRI data obtained in real time from that individual[5] and to measure emotional responses to informational stimuli in real time.[6]

Such demonstrations hint at the prospect of other brain-machine interfaces in the future, such as computer-assisted memory recall, even if the suite of specific future applications is unclear. The scope and feasibility of such applications will be determined by advances in neuroscientific theory and in technical solutions to engineering problems, such as probe density, spread, and penetration into deep-layer tissues.

Over the Horizon

The Impact of Neuroscience

NEUROHEALTH AND NEURODEGENERATION

Neurodegeneration is a major challenge as humans live longer. In the United States alone, the annual cost of Alzheimer's treatment is projected to explode from $305 billion today to $1 trillion by 2050.[7] Diseases like Alzheimer's and Parkinson's surge in frequency with age—while just 5 percent of 65–74-year-olds have Alzheimer's, this rises to 33 percent of those over 85.[8] The percentage of adults with Parkinson's disease demonstrates a similar rising frequency with age.[9] As modern medicine and society enable longer life spans, the human body and brain remain maladapted to maintaining nervous system function for decades past childbearing age.

Effective treatments for neurodegenerative disorders such as Alzheimer's are still far from sufficient despite decades of research. Alzheimer's disease occurs when two different types of proteins in the brain fold improperly, which eventually leads to neuron death. Only in the last two years have drugs aimed at clearing one of these proteins been approved by the FDA, albeit with limited though real therapeutic benefit and significant side effects. These drugs have also been subject to significant controversy. One drug, aducanumab, received approval in 2021 in the United States but not the European Union. A scientific advisory panel at the FDA voted against approval, citing minimal therapeutic benefits and high risk of complications. The FDA overruled the advisory panel, which led to three of the nine members resigning in protest.[10] A second drug, lecanemab, was approved in 2023, but again detractors suggest the treatment may not be worth the risks.[11] Still, these are the first drugs to suggest that the slowing of neurological disease progression is possible.

While current treatments for Alzheimer's disease are less effective than would be desired, there is reason for guarded optimism in the coming years. Gene therapy approaches targeting other proteins associated with Alzheimer's have recently entered clinical trials. Powerful diagnostic tools such as tau and amyloid PET scans, identification of biomarkers, and identification of genetic risk factors allow for increasing early detection and diagnosis, which might make it easier to fight the disease. Advances in personalized medicine also leave researchers and clinicians hopeful.

Another form of neurodegeneration results from traumatic brain injury (TBI), which can manifest itself in a range of complex symptoms and pathologies.[12] Traumatic impact to brain systems can affect cognitive and behavioral functions in ways that lead to long-term and severe psychiatric conditions requiring specialized care. This is particularly evident in the current surge of athletic and military brain injuries that predominantly exhibit psychiatric symptoms. A person's past medical and psychiatric records, as well as any coexisting conditions, play a vital role in diagnosis and treatment. TBI offers insights into other neuropsychiatric disorders and can pave the way for innovative concepts in neurodegenerative disease.

NEURODISCOVERY AND THE SCIENCE OF ADDICTION

Researchers are working to understand the neural basis of addiction and of chronic pain while working with psychiatrists and policymakers to address the opioid epidemic.[13] The economic costs of the opioid epidemic are difficult to calculate, but estimates range from $100 billion to $1 trillion a year when the loss of lifetime earnings of overdose victims is included.[14] The number of opioid deaths in the United States has risen sharply over the last ten to fifteen years, from 21,000 in 2010 to 80,000 in 2021,[15] which places opioid overdose as one of the top ten leading causes of death in the United States, comparable to diabetes and Alzheimer's disease.[16]

Economic, societal, and political factors all have a role in the epidemic. But neuroscience has a potentially important role to play as well. For example, a nonaddictive painkiller drug as effective as current-generation opioids would be transformative,[17] but detractors note that relief from pain itself is pleasurable and thus may be behaviorally addictive as well. Indeed, it is possible to become addicted to behaviors that do not involve consumption of a drug—consider gambling, sex, or technology addictions. Heroin and oxycontin themselves were famously initially marketed as nonaddictive alternatives to painkillers of the day.[18]

Though safer or less addictive painkillers would help reduce the burden of the opioid epidemic, other approaches are relevant to neuroscience, such as reducing the need for opioids or aiding in recovery from addiction. Consider the problem of relapse in tackling addiction. Particularly relevant for opioid use, scientists have found that the brain mechanisms leading to an initial opioid addiction differ significantly from those that trigger a relapse.

Neuroscientists may be able to assist in the social aspects of recovery from opioid addiction. It turns out that opioid receptors are found in many areas of the brain and affect diverse functions, including neural circuits related to the desire for social interaction. When an individual goes into opioid withdrawal, these areas of the brain are affected—and the individual often develops an aversion to social interactions. Such an aversion is a significant challenge to recovery since social interactions are often key to helping an individual to cope with the vulnerabilities associated with recovery. Essentially, their brains miscalculate the rewarding value of human connection, undermining their recovery process.

Stanford neuroscientists have recently identified a neurological pathway that is responsible for the onset of this social aversion.[19] If this study conducted in mice generalizes to humans, it may be possible to develop drugs that inhibit social aversion during withdrawal and thereby assist patients in seeking help or companionship from friends, families, recovery programs, and doctors.

Finally, it is widely recognized that chronic pain is a driver of opioid misuse.[20] Chronic pain is a widespread condition—an estimated 20 percent of adults in the United States experience chronic pain and around 7 percent have intense chronic pain that results in substantial impacts on daily life.[21] Compared to other alternatives, prescription opioids are unparalleled for managing acute pain, but rapid onset of tolerance and their addictive properties make them unsuitable for long-term use.

But what if it were possible to block the induction of chronic pain entirely? Soldiers with severe injuries, including compound fractures and open wounds, don't always report immediate pain. This fact suggests that pain isn't just governed by ascending signals—from the injury site to the brain—but also that the central nervous system can exert influence. That is, our brain can control whether we sense pain, a phenomenon known as descending pain control.[22] Certain neurons act as switches that control whether pain signals from the injured site reach the cortex. This is relevant to opioid use because opioid receptors are found in these neurons, and opioids inhibit pain by stimulating the neurons that block the ascending pain signals.[23]

On the other hand, opioids are addictive substances. Drug addiction is a compulsive use of a drug despite its long-term negative consequences. Regardless of the specific drug in question, the mechanism of drug addiction operates in the same way: consumption of the drug releases excessive amounts of dopamine in the brain, which then goes to the nucleus accumbens that are involved in reward and finally to the prefrontal cortex, which controls executive functions like goal selection and decision making. Similar mechanisms also appear to operate in behavioral addictions, such as addiction to gambling, technology, or video games.[24]

This reward mechanism evolved to reinforce activities that are crucial to survival, such as foraging for food and procreation. The release of dopamine serves as a robust positive signal, strengthening and reinforcing the activity that led to its release in the first place. But drugs appear to hijack this reward system, causing a surge in dopamine that far surpasses what the natural system can produce. This creates a potent lure that can make overcoming drug addiction particularly challenging, as the drugs tap into and significantly amplify this natural reinforcement system.

SCIENTIFIC THEORETICAL AND TECHNICAL ENGINEERING CHALLENGES

Contrasting the work on the artificial retina and the work on the science of neurodegeneration and addiction illustrates the dual-pronged nature of neuroscience applications. They have two primary components: a scientific component that focuses on identifying relevant brain circuits and understanding how they function and compute, and a technical engineering component that focuses on how to safely stimulate the relevant brain circuits to create the desired responses.

There is much about the brain's anatomy, physiology, and chemistry that is still not well understood, and addressing the theoretical issues in neuroscience is almost exclusively the purview of academia over industry. Certainly, there are research programs in industry that solve basic biological questions in neuroscience, but these are necessarily and economically tied to solving problems with a profit motive—usually the development of new drugs.

Once the basic science has been developed and a research area approaches an economically viable application, industry does a much better job. Consequently, helping to smooth the friction of moving a project from academia to industry is crucial to overcoming roadblocks in development. Incubators and accelerators can help transition the findings of basic research to application by aiding in high-throughput screening—the use of automated equipment to rapidly test samples—and prototyping. With viable prototypes, new companies can be created or licenses granted to existing companies to produce a final product. Such activities are critical in facilitating the integration of well-understood scientific theory, technical engineering, and final application.

DISCONNECT BETWEEN PUBLIC INTEREST AND CAPABILITY

The brain is perhaps the least understood yet most important organ in the human body. Demand for neuroscience research advances and applications—including understanding brain circuitry, developing new drugs, treating diseases and disorders, and creating brain-machine interfaces—is expected to continue to grow considerably over the coming years. The Society for Neuroscience's annual meeting draws close to thirty thousand attendees.[25]

Science fiction and fantastical headlines fuel beliefs that mind-reading technology, brains controlled by computers, and other dystopias are imminent. In reality, comprehending the brain's staggering complexity remains in its early stages. Most advances involve incremental progress expanding our theoretical foundations rather than revolutionary leaps to futuristic applications. This vast gap between public expectations and scientific reality creates an environment ripe for exploitation. Impatience for solutions to pressing medical problems like dementia and mental illness leave many open to dubious proclamations or pseudoscience.

Policy, Legal, and Regulatory Concerns

DRUG POLICY AND NEUROSCIENCE RESEARCH

The Controlled Substances Act (CSA) of 1970 as amended governs US policy regarding regulation of the manufacture, importation, possession, use, and distribution of certain substances. Substances on Schedule I are drugs or other substances with a high potential for abuse and not "currently accepted" for medical use in the United States. No research exceptions are provided for Schedule 1 substances such as cannabis or MDMA (often known as Ecstasy or Molly), which have potential for medical use that might be realized through research. (At the time of this writing, the Biden administration is reportedly considering the reassignment of marijuana to Schedule 3, a schedule with fewer restrictions.[26]) Placement of drugs on Schedule 1 sharply constrains researchers because these potentially helpful drugs are difficult to obtain. This constraint also denies the public the benefits that might flow from such research—such as better medical treatments—and potentially harms the public if, for example, individual states legalize certain drugs without adequate research into their safety, addictiveness, and public health impacts.

THE IMPACT OF COGNITIVE AND BEHAVIORAL NEUROSCIENCE ON LAW

Cognitive and behavioral neuroscience, which studies the biological basis of thoughts and actions, has broad implications for public policy. For example, a basic aspect of criminal law is the nature and extent of an individual's responsibility for a criminal act. Thus, under a 2005 US Supreme Court ruling, minors under eighteen years of age cannot be subject to the death penalty for crimes they committed because adolescent brains are not fully developed, putting minors at higher risk of impulsive, irrational thoughts and behaviors.[27]

THOUGHT IMPLANTS

The possibility that information can be implanted directly into a person's consciousness is a potential future problem. As government is still figuring out how to regulate internet forums that influence what people believe and how they feel—a problem that has existed for three decades—regulation will likely not come fast enough to guide even the later-stage promises of brain-machine interfaces. Establishing proper cultural norms at the outset and careful consideration of technologies is warranted.

FOREIGN COLLABORATION

As noted earlier, useful products emerge from neuroscience only after scientific issues have been resolved and engineering challenges have been met. Scientific research in neuroscience is in effect precompetitive, and this remains the major roadblock for most useful products. This point suggests that the primary capital in neuroscience is human expertise, and that future success continues to depend on the United States being the best place for international scientists to train, conduct research, and use their own expertise to train the next generation of scientists. Against this backdrop, the apparent targeting of US scientists with personal and familial links to China raises concerns,[28] and the United States only loses if these scientists leave and move their labs to China.

ETHICAL FRAMEWORKS

Neuroscience research naturally raises several ethical concerns that merit careful ongoing discussion and monitoring. Chief among these is human subjects research, of which there are many existing frameworks and regulations that guide neuroscience research in American academia today. Ethical guidelines for scientific research are usually national, not international. Some countries might allow particular types of brain research and drugs, while others might not; for example, a nation might permit experimentation on prisoners or on ethnic minorities. Managing differences in state research regimes will be critical to harnessing the power of international collaboration.

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