TABLE 444e-4 A PRION-BASED CLASSIFICATION OF NEURODEGENERATIVE DISEASES

Neurodegenerative Diseases	Causative Prion Proteins
Creutzfeldt-Jakob disease (CJD)	PrP^{Sc}
Kuru	
Gerstmann-Sträussler-Scheinker (GSS)	
Fatal insomnia	
Bovine spongiform encephalopathy (BSE)	
Scrapie	
Chronic wasting disease (CWD)	
Feline spongiform encephalopathy	
Transmissible mink encephalopathy	
Alzheimer's disease (AD)	Aβ → tau
Parkinson's disease	α-Synuclein
Frontotemporal dementias (FTDs)	Tau, TDP43, FUS (C9orf72, progranulin)
Posttraumatic FTD, called chronic traumatic encephalopathy	
Amyotrophic lateral sclerosis	SOD1, TDP43, FUS (C9orf72)
Huntington's disease	Huntingtin

of Tg mice that replicate human CJD prions. Despite doubling the length of incubation times in mice inoculated with scrapie prions, all of the mice eventually succumb to illness. Because all of the treated mice develop neurologic dysfunction at the same time, the mutation rate as judged by drug resistance is likely to approach 100%, which is much higher than mutation rates recorded for bacteria and viruses. Mutations in prions seem likely to represent conformational variants that are selected for in mammals where survival becomes limited by the fastest-replicating prions. The results of these studies make it likely that cocktails of drugs that attack a variety of prion conformers will be required for the development of effective therapeutics.

SYSTEMS NEUROSCIENCE

Systems neuroscience refers to study of the functions of neural circuits and how they relate to brain function, behavior, motor activity, and cognition. Brain imaging techniques, primarily functional magnetic resonance imaging (fMRI) and position emission tomography (PET), have made it possible to investigate, noninvasively and in awake individuals, cognitive processes such as perception, making judgments, paying attention, and thinking. This has allowed insights into how networks of neurons operate to produce behavior. Many of these studies at present are based on determining the connectivity of neural circuits and how they operate, and how this can be then modeled to produce improved understanding of physiologic processes. fMRI uses contrast mechanisms related to physiologic changes in tissue, and brain perfusion can be studied by observing the time course of changes in brain water signal as a bolus of injected paramagnetic gadolinium contrast moves through the brain. More recently, to study intrinsic contrast-related local changes in blood oxygenation with brain activity, blood-oxygen-level-dependent (BOLD) contrast has been used to provide a rapid noninvasive approach for functional assessment. These techniques have been reliably used in the field of both behavior and cognitive sciences. One example is the use of fMRI to demonstrate mirror neuron systems, imitative pathways activated when observing actions of others. Mirror neurons are thought to be important for social conditioning and for many forms of learning, and abnormalities in mirror neurons may underlie some autism disorders.

Both structural and functional connectivity methods show large-scale network dysfunction in AD and frontotemporal dementia. The networks targeted have been defined as the default network in AD and the salience network in frontotemporal dementia. The default network is characterized by an area of reduced glucose metabolism in the temporoparietal cortex, which precedes the onset of dementia and which is an area preferentially affected by amyloid deposition. These networks are now thought to be pathways accounting for the spread of abnormally templated proteins (prions; see above), including β-amyloid, tau, and α-synuclein.

Other examples of the use of fMRI include the study of memory, revealing that not only is hippocampal activity correlated with declarative memory consolidation, but it also involves activation in the ventral medial prefrontal cortex. Consolidation of memory over time results in decreased activity of the hippocampus and progressively stronger activation in the ventral medial prefrontal region associated with retrieval of consolidated memories. fMRI has also been used to identify sequences of brain activation involved in normal movements and alterations in their activation associated with both injury and recovery, to plan neurosurgical operations, and remarkably, to reconstruct actual visual images from the occipital cortex. Noninvasive brain-computer interfaces have extraordinary potential to advance the development of robotics and exoskeleton devices guided by brain activity for patients with a variety of nervous system afflictions. Diffusion tensor imaging is a recently developed MRI technique that can measure macroscopic axonal organization in nervous system tissues; it appears to be useful in assessing myelin and axonal injuries as well as brain development. Advances in understanding neural processing have led to the development of the ability to demonstrate that humans have online voluntary control of human temporal lobe neurons.

Multitasking capabilities, including attention to tasks when faced with distractions, decline as we age due to a decline in medial prefrontal cognitive control system. When faced with a multitasking challenge, video game training can improve cognitive control capabilities by augmenting prefrontal suppression of the default network and, as measured by electroencephalography and fMRI, result in improved performance that is sustained and, importantly, transfers to other cognitive tasks not associated with the training paradigm.

A significant recent advance in neuropathology has discovered that sodium dodecyl sulfate (SDS) detergent treatment can render the brain transparent (CLARITY), removing lipids while preserving most protein and structural elements and providing opportunities to identify brain structures and neural networks with unprecedented detail.

A therapeutic technology that has long-reaching implications for the development of novel interventions for neurologic, including behavioral, conditions has been the development of deep-brain stimulation as a highly effective therapeutic intervention for treating excessively firing neurons in the subthalamic nucleus of patients with Parkinson's disease and the precingulate cortex in patients with depression.

BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES (BRAIN) INITIATIVE

The BRAIN initiative, grand in scope, was launched in 2013 to speed development of advances to understand, treat, repair, and prevent common neurologic disorders that, in aggregate, affect more than 1 billion people worldwide. The initial goal of BRAIN is to bring together experts in neurobiology (including optogenetics), engineering, information technology, and other fields to develop novel visualization and electrophysiologic methods to better define and understand neural circuits and all the connections among individual neurons. The announcement of the BRAIN initiative followed just weeks after a similarly ambitious program, the Human Brain Project (HBP), was unveiled by the European Union. The HBP seeks to model individual neurons, neural circuits, and ultimately the entire brain using computer technologies. Its architects also envision layering clinical and biomarker data from large health care databases to identify biosignatures associated with human phenotypes, possibly leading to a fundamental reclassification of disease, a concept also proposed by others, including in a 2011 report of the National Academy of Sciences (Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease). These two ambitious projects are expected to be complementary and over time will hopefully become increasingly