

IMAGING TECHNIQUES AT-A-GLANCE

Adapted from *Brain Imaging Technologies and Their Applications in Neuroscience*, by Carolyn Asbury, Ph.D.

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Adoptive transfer is used in molecular imaging to tag specific cells, such as in an animal model of a disease, and transfer those tagged cells into another laboratory animal to see how they work. The technique is used to label cells that are “naturally occurring probes” in the body, such as immune T cells, which produce antibodies that migrate to an infection. (Please also see Genetic Transfer, a related technique.)

Angiography uses a radiopaque dye injected through a catheter into a blood vessel to detect a blockage or narrowing of the vessel. The vessel is outlined on x-ray as white.

Arterial spin labeling (ASL) is a perfusion contrast used with fMRI. It is used to quantify regional cerebral blood flow noninvasively to provide absolute quantification of cerebral blood flow, which renders it sensitive to both static function and changes occurring over longer intervals.

Bioluminescent probes are used in molecular imaging. They utilize the enzyme luciferase to generate and emit light by an organism, providing real-time analyses of disease processes—particularly infections and cancer progression—at the molecular

level in living organisms, including laboratory animals. The enzyme is found in fireflies, glowworms, deep sea marine organisms and some bacteria and fungi.

BOLD (blood oxygenation level dependent) MRI is the contrast agent used in most fMRI imaging. (Please see “Functional MRI” below.) BOLD contrast reflects a complex interaction between the volume of blood, its flow, and its transport of oxygen by an iron-containing protein in red blood cells. Functional contrast is produced when the oxygen is released from the iron and taken up and used by brain cells (indicating that they are active). After the iron loses the oxygen, the iron becomes highly magnetized when exposed to the MRI magnetic field.

Computer Assisted Tomography (CT) uses special x-ray equipment to obtain three-dimensional anatomical images of bone, soft tissues and air. An x-ray emitter rotated around the head measures the rays’ intensities from different angles. Sensors measure the amount of radiation absorbed by different tissues; a computer uses the differences in X-ray absorption to form cross-sectional images or “slices” of brain called “tomograms.” CT can be done quickly, and so is used extensively in the ER to identify evidence of brain trauma, such as swelling or bleeding (as from hemorrhagic stroke or a ruptured brain aneurysm).

Confocal laser scanning microscopy is a molecular imaging technique that monitors dynamic processes such as synaptic activity and cell death. The technique enables simultaneous collection in digital form of multiple images from serial sections of thick tissue specimens that are flexibly displayed and analyzed via computer. The blur-free

images are taken point by point, and with sensitive and fast registration of the intensity of emitted light, are reconstructed via computer.

Deep brain stimulation (DBS) involves implanting electrodes in specific areas in the brain and externally stimulating the electrodes to measure electrical activities of neurons and their electrochemical pathways. DBS is used therapeutically to treat intractable Parkinson's disease and essential tremor, and is being studied for possible use in intractable depression and other brain conditions. It is also used in a few highly specialized centers to explore the neuronal underpinnings of cognition.

Dendrimer Nanoparticles are used in molecular imaging with fluorescent probes to label particles that travel to a target, especially a tumor. Dendrimer nanoparticles are compounds that are synthesized in the laboratory from materials (often polymers) and assembled into high molecular weight spherical particles. A fluorescent probe is added to the dendrimer nanoparticles which then target and light up specific cells. A therapeutic drug also can be added to dendrimer nanoparticles, which can cross the blood brain barrier and enter the brain. They are being intensively studied, therefore, as a means to deliver potential treatment targeted to brain tumor cells.

Diffusion-Perfusion-weighted MRI is a combination technique used to estimate the "ischemic penumbra." This is the brain tissue that has suffered from reduced blood flow following ischemic stroke but has not yet died and is the target of intensive therapy.

Diffusion-tensor MRI (DTMRI) measures microscopic water motion in tissues, and in the brain this motion is facilitated along white matter tracts that connect brain regions.

Computerized mathematical models construct the images of the white matter tracts. It is

used extensively pre-surgically to plan, such as to identify and spare these tracts during surgical removal of a brain tumor.

Diffusion-weighted MRI shows whether brain tissue has been damaged due to insufficient blood flow to the tissue.

Electroencephalography (EEG) measures the electrical activity that is produced by neurons as recorded from electrodes placed along the scalp.

Fluorescence resonance energy transfer (FRET) is a molecular imaging technique that reveals the interaction between two or more fluorescent probes in tissue cultures. It is used, for instance, to visualize a molecule binding to its receptor on a cell.

Functional MRI (fMRI) shows the brain in action. It is a highly sensitive but indirect measure that is used to elucidate processes involved in higher cognitive functioning, including identification of motor and task activation areas; and reorganization of function following injury to a single brain area. It is based on the principle that changes in regional cerebral blood flow and metabolism are coupled to changes in regional neural activity involved in brain functioning, such as memorizing a phrase or remembering a name. Almost all fMRI techniques use the contrast mechanism called BOLD (please see BOLD above).

Fluorescence microscopes are used with fluorescent probes that emit light of short wavelength to reveal biochemical activities within a cell in human and animal tissue cultures. These microscopes have the highest resolution of all cellular imaging devices. They can be used to identify a single fluorescently labeled molecule or differentiate activities of several differently colored fluorescent molecules in the same cell.

Fluorescent probes are used in molecular imaging to visualize molecules and their actions. The probes are green fluorescent protein, its yellow, blue and cyan-colored mutants, and red fluorescent proteins. Fluorescent probes that emit light of short wavelengths are used with fluorescent light microscopes to image molecules that are close to the surface in laboratory cultures of thin human or animal tissues. Fluorescent probes that emit light of longer wavelengths are introduced into small laboratory animals and used with other microscopes (please see Confocal laser scanning microscopy and Multi-photon laser microscopy) and excited by ultraviolet light to show molecules deeper in tissues, in the small laboratory animal or in thick animal tissues in laboratory cultures.

Intravital Light Microscopic technologies use light-emitting probes as contrast to visualize the activities of specific molecules and the cells they compose. Imaging is undertaken in tissues surgically biopsied from humans and laboratory animals. Imaging is also undertaken in small laboratory animals, but is confined to the specific location under view.

Genetic Transfer is used in molecular imaging to introduce bioluminescent and fluorescent probes into the animal. The gene that produces bioluminescence or fluorescence is cloned in the laboratory and introduced into a laboratory animal. The gene is introduced into the laboratory animal either by inserting it into a harmless virus (called a vector) that gets into a specific type of cell, or by inserting it into a stem cell that differentiates into a cell that expresses the luminescence or fluorescent protein. (Please also see Adoptive Transfer, a related technique.)

Intravital Macroscopic Imaging technologies use light-emitting probes as contrast to visualize specific molecules and the cells they compose in small laboratory animals and in a few larger laboratory animals. The molecules can be imaged everywhere they occur in body as opposed to a single location (please see intravital light microscope technologies); and, the molecules can be imaged as they move throughout the body, including the brain. (Please also see Macroscopic Optical Scanning techniques.)

Laser Doppler Ultrasound employs laser technology to combine information from both light and sound. It is a non-invasive and highly sensitive method for measuring even tiny changes in the rate of blood flow velocity (speed) within arteries throughout the body, including the brain. Its primary use in the brain is for monitoring severely head injured patients, especially those in coma, in intensive care units.

Macroscopic Optical Scanning techniques image the actions of molecules and cells that are illuminated with bioluminescent or fluorescent probes in live laboratory animals. These techniques enable scientists to visualize actions of cells or molecules anywhere they occur within living small laboratory animals, and in some cases in laboratory sheep and pigs. (Please also see Intravital Macroscopic Imaging Technologies.)

Magnetoencephalography (MEG) maps brain activity by measuring magnetic fields that are generated by neural activity in the brain. It is used to investigate the basis of sensory processing and motor planning in the brain.

Magnetic Resonance Imaging (MRI) is a non-invasive technology with high resolution that is used primarily to image brain structure and function. It is based on the principle that changes in regional cerebral blood flow and metabolism are coupled to changes in

regional neural activity involved in brain functioning. Significant contrast in tissue can be attributed to changes either in blood flow alone, or in metabolism alone, or in blood flow and metabolism. (Please also see Structural MRI.)

Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique that measures biochemical changes in the brain over time, characterizing brain diseases according to the natural history of the chemical changes produced. MRS is conducted in an MRI scanner, uses magnetization and radio waves from hydrogen protons in non-water atoms, such as carbon and nitrogen, and produces a color chart (“spectra”) that reflects the concentrations of molecules according to their chemical composition.

Multi-photon laser microscopy is a molecular imaging technology that is used to study the actions of specific cells in the brain over time. The technology relies on the simultaneous absorption of two or more photons by a molecule to image fluorescent probes with long wavelengths that penetrate deep into tissues. It is used in thick tissue cultures and small laboratory animals.

Optical Probes are used in cellular and molecular imaging. They are molecules that have been specially labeled to emit light of various wavelengths, to “contrast” the target cells of interest from other cells.

Optical tomographic imaging is a molecular imaging technology used to study biochemical activity that occurs deep within the tissues of live laboratory animals. Near infrared (NIR) light is used in combination with fluorescent probes. Light of a specific wavelength is shined on the animal; in turn this light excites the target molecule to emit light at a different wavelength, which is monitored by tomographic detectors placed in a

circle around the animal to collect light coming from various directions. Computers combine the multiple individual views into three-dimensional images.

Perfusion-weighted MRI shows areas of the brain in which blood flow has been altered.

Positron Emission Tomography (PET) measures physiological functioning in the brain. It provided the first opportunity to explore the parts of the brain that were activated in undertaking specific tasks; now it is primarily used to study neurotransmitters, actions of pharmaceutical drugs, and the expression of specific genes in the brain. PET is based on the principle that changes in regional cerebral flow and metabolism in brain regions are coupled to changes in neural activity in those regions. PET uses ionizing radiation (radioisotopes) as tracers. Each radioisotope attaches to a specific molecule (carbon, nitrogen, oxygen and fluorine). The regional distribution of exogenously administered positron-emitting tracers is measured using tomographic imaging. PET can quantify tiny concentrations of the radioisotope tracer so its measurements of change are exquisitely sensitive. PET, using new tracers that attach solely to the protein beta amyloid, may become a means to help diagnose Alzheimer's disease and identify patterns predictive of conversion from mild cognitive impairment to Alzheimer's.

Structural MRI measures the nuclear magnetic resonance of the body's own molecules, water protons, to create a computerized three-dimensional image of tissues. Variations in water located in different brain structures and compartments provide contrast, and the ability to see the spatial orientation of various brain structures. The contrast

differentiates the brain's gray matter (primarily nerve cell bodies) from white matter (primarily axons and their myelin sheaths) which are the nerve cell communication cables that connect brain regions. Many disease processes result in water content changes; these are reflected in the image produced to provide diagnostic information.

Single Photon Emission Computed Tomography (SPECT) measures physiological functioning in the brain and is similar to PET (Please see Positron Emission Tomography). In contrast to PET, SPECT uses commercially available stable low level radioisotopes and is therefore less expensive, more convenient for clinical use, is widely used clinically.

Transcranial magnetic stimulation (TMS) is a non-invasive technique that is used to map cortical functions in the brain, such as identifying motor or speech areas. With TMS, a large electromagnetic coil is placed on the scalp, near the forehead. An electromagnet is then used to create a rapidly changing magnetic field, inducing weak electric currents. Unlike the mapping function, a repetitive form of TMS, called rTMS, is used therapeutically to treat depression.

Ultrasound uses sound waves to determine the locations of surfaces within tissues, and differentiates surfaces from fluids. It does so by measuring the time that occurs between the production of an ultrasonic pulse to the production of the echo created when the surface reflects the pulse.

X-rays measure the density of tissues. They use photons, a quantum of visible light that possesses energy. The photons are passed through the body, deflected and absorbed to different degrees by tissues, and recorded as they pass out of the body onto a silver halide film. Dense structures such as bone, which block most of the photons, appear

white; structures containing air appear black; and muscle, fat and fluids appear in various shades of gray.

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