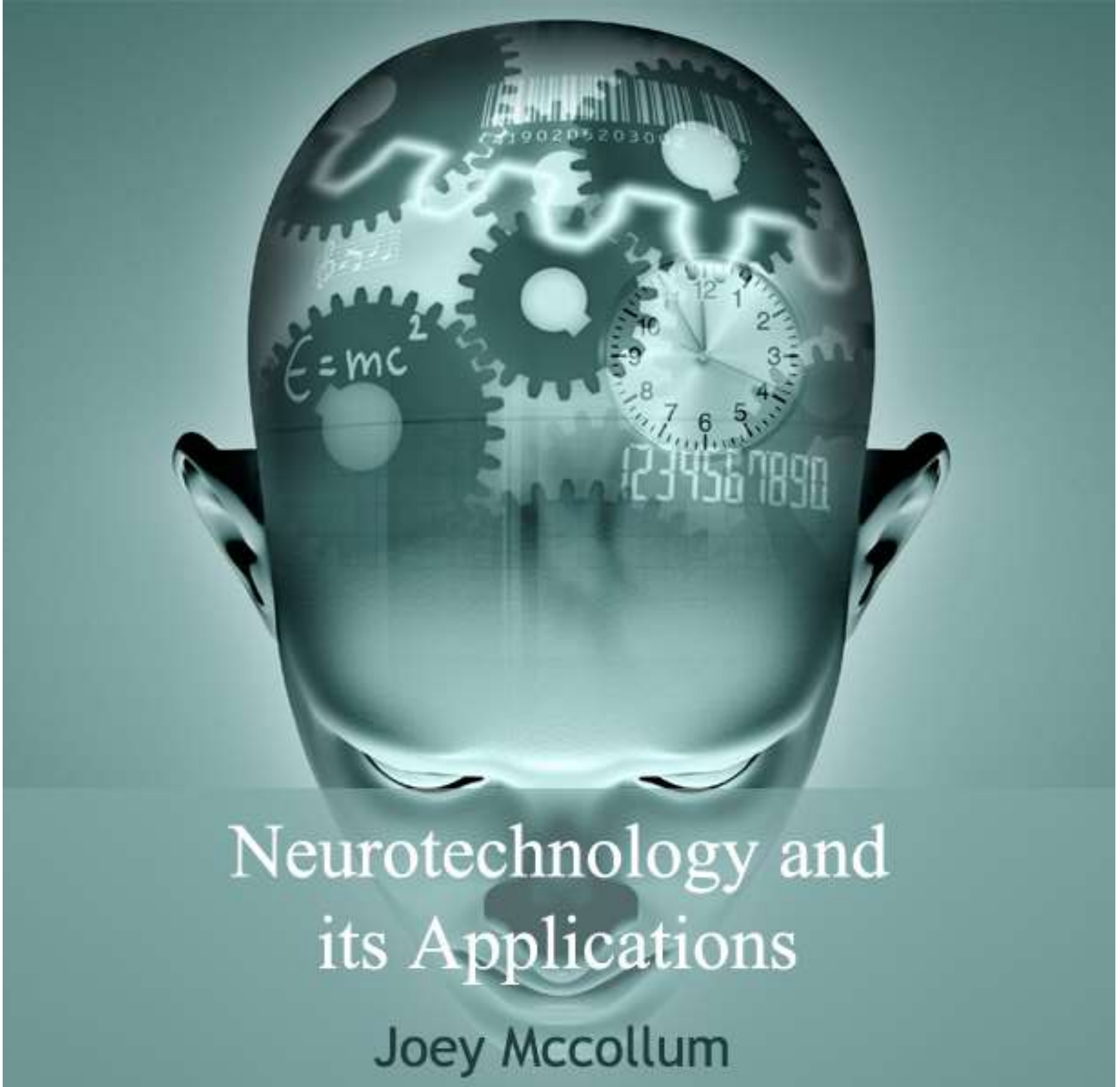
Neurotechnology and
its Applications
Joey Mccollum

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Chapter- 1

Neurotechnology

Neurotechnology is any technology that has a fundamental influence on how people understand the brain and various aspects of consciousness, thought, and higher order activities in the brain. It also includes technologies that are designed to improve and repair brain function and allow researchers and clinicians to visualize the brain.

Background

The field of neurotechnology has been around for nearly half a century but has only reached maturity in the last twenty years. Advents of brain imaging revolutionized the field and gave rise to a whole new shift in research that could now directly monitor the brain's activities during experiments. The field of neurotechnology is incredibly relevant to society, though its presence is so commonplace that many do not realize its ubiquity. From pharmaceutical drugs to brain scanning, neurotechnology affects nearly all industrialized people either directly or indirectly, be it from drugs for depression, sleep, ADD, or anti-neurotics to cancer scanning, stroke rehabilitation, and much more. Its potentials reach nearly all aspects of daily life, and as the field's depth increases modern societies will be able to harness and control more of what the brain does and how it influences lifestyles and personalities. It is important to note that there are many technologies that are taken for granted that could apply in the field. Games like BrainAge, and programs like FastForWord are methods for improvement of brain function and therefore apply as well. In addition, numerous pharmaceutical companies develop many new and useful functional drugs that can help improve function and restore normality in a person's life. Currently, modern science can image nearly all aspects of the brain as well as control a degree of the function of the brain. It can help control depression, over-activation, sleep deprivation, and many other conditions. Therapeutically it can help improve stroke victims' motor coordination, improve brain function, reduce epileptic episodes, improve patients with degenerative motor diseases (Parkinson's Disease, Huntington's Disease, ALS), and can even help alleviate phantom pain perception. Advances in the field promise many new enhancements and rehabilitations for patients suffering from neurological problems. The neurotechnology revolution has given rise to the Decade of the Mind initiative, which was started in 2007. It also offers the possibility of revealing the mechanisms by which mind and consciousness emerge from the brain.

Current technologies

Imaging

Magnetic resonance imaging (MRI) is used for scanning the brain for topological and landmark structure in the brain, but can also be used for imaging activation in the brain. While detail about how MRI works is reserved for the actual MRI article, the uses of MRI are far reaching in the study of neuroscience. It is a cornerstone technology in studying the mind, especially with the advent of functional MRI (fMRI). Functional MRI measures the oxygen levels in the brain upon activation (higher oxygen content = neural activation) and allows researchers to understand what loci are responsible for activation under a given stimulus. This technology is a large improvement to single cell or loci activation by means of exposing the brain and contact stimulation. Functional MRI allows researchers to draw associative relationships between different loci and regions of the brain and provides a large amount of knowledge in establishing new landmarks and loci in the brain.

Computed tomography (CT) is another technology used for scanning the brain. It has been used since the 1970s and is another tool used by neuroscientists to track brain structure and activation. While many of the functions of CT scans are now done using MRI, CT can still be used as the mode by which brain activation and brain injury are detected. Using an X-ray, researchers can detect radioactive markers in the brain that indicate brain activation as a tool to establish relationships in the brain as well as detect many injuries/diseases that can cause lasting damage to the brain such as aneurysms, degeneration, and cancer.

Positron emission tomography (PET) is another imaging technology that aids researchers. Instead of using magnetic resonance or X-rays, PET scans rely on positron emitting markers that are bound to a biologically relevant marker such as glucose. The more activation in the brain the more that region requires nutrients, so higher activation appears more brightly on an image of the brain. PET scans are becoming more frequently used by researchers due to the fact that PET scans are activated due to metabolism whereas MRI is activated on a more physiological basis (sugar activation versus oxygen activation).

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is essentially direct magnetic stimulation to the brain. Because electric currents and magnetic fields are intrinsically related, by stimulating the brain with magnetic pulses it is possible to interfere with specific loci in the brain to produce a predictable effect. This field of study is currently receiving a large amount of attention due to the potential benefits that could come out of better understanding this technology.

Cranial surface measurements

Electroencephalography (EEG) is a method of measuring brainwave activity non-invasively. A number of electrodes are placed around the head and scalp and electrical signals are measured. Typically EEGs are used when dealing with sleep, as there are characteristic wave patterns associated with different stages of sleep. Clinically EEGs are used to study epilepsy as well as stroke and tumor presence in the brain. EEGs are a different method to understand the electrical signaling in the brain during activation.

Magnetoencephalography (MEG) is another method of measuring activity in the brain by measuring the magnetic fields that arise from electrical currents in the brain. The benefit to using MEG instead of EEG is that these fields are highly localized and give rise to better understanding of how specific loci react to stimulation or if these regions over-activate (as in epileptic seizures).

Implant technologies

Neurodevices are any devices used to monitor or regulate brain activity. Currently there are a few available for clinical use as a treatment for Parkinson's disease. The most common neurodevices are deep brain stimulators (DBS) that are used to give electrical stimulation to areas stricken by inactivity. Parkinson's disease is known to be caused by an inactivation of the basal ganglia (nuclei) and recently DBS has become the more preferred form of treatment for Parkinson's disease, although current research questions the efficiency of DBS for movement disorders.

Neuromodulation is a relatively new field that combines the use of neurodevices and neurochemistry. The basis of this field is that the brain can be regulated using a number of different factors (metabolic, electrical stimulation, physiological) and that all these can be modulated by devices implanted in the neural network. While currently this field is still in the researcher phase, it represents a new type of technological integration in the field of neurotechnology.

Gene/cell therapy

Cell therapy is a field devoted to improving cells via genetic enhancement. Currently there are many researchers investigating the ability for programmed regeneration and genetic influencing in the brain. Using viral or nanoparticle vectors (a "carrier" for the gene of interest), scientists are finding new ways to manipulate and improve the brain's capacity, overall health, and resistance to disease. Researchers have begun looking at uses for stem cells in the brain, which recently have been found in a few loci. A large number of studies are being done to determine if this form of therapy could be used in a large scale.

Pharmaceuticals

Pharmaceuticals play a vital role in maintaining stable brain chemistry, and are the most commonly used neurotechnology by the general public and medicine. Drugs like sertraline, methylphenidate, and zolpidem act as chemical modulators in the brain, and they allow for normal activity in many people whose brains cannot act normally under physiological conditions. While pharmaceuticals are usually not mentioned and have their own field, the role of pharmaceuticals is perhaps the most far-reaching and commonplace in modern society.

How these help study the brain

Magnetic resonance imaging is a vital tool in neurological research in showing activation in the brain as well as providing a comprehensive image of the brain being studied. While MRIs are used clinically for showing brain size, it still has relevance in the study of brains because it can be used to determine extent of injuries or deformation. These can have a significant effect on personality, sense perception, memory, higher order thinking, movement, and spatial understanding. However, current research tends to focus more so on fMRI or real-time functional MRI (rtfMRI). These two methods allow the scientist or the participant, respectively, to view activation in the brain. This is incredibly vital in understanding how a person thinks and how their brain reacts to a person's environment, as well as understanding how the brain works under various stressors or dysfunctions. Real-time functional MRI is a revolutionary tool available to neurologists and neuroscientists because patients can see how their brain reacts to stressors and can perceive visual feedback. CT scans are very similar to MRI in their academic use because they can be used to image the brain upon injury, but they are more limited in perceptual feedback. CTs are generally used in clinical studies far more than in academic studies, and are found far more often in a hospital than a research facility. PET scans are also finding more relevance in academia because they can be used to observe metabolic uptake of neurons, giving researchers a wider perspective about neural activity in the brain for a given condition. Combinations of these methods can provide researchers with knowledge of both physiological and metabolic behaviors of loci in the brain and can be used to explain activation and deactivation of parts of the brain under specific conditions.

Transcranial magnetic stimulation is a relatively new method of studying how the brain functions and is used in many research labs focused on behavioral disorders and hallucinations. What makes TMS research so interesting in the neuroscience community is that it can target specific regions of the brain and shut them down or activate temporarily; thereby changing the way the brain behaves. Personality disorders can stem from a variety of external factors, but when the disorder stems from the circuitry of the brain TMS can be used to deactivate the circuitry. This can give rise to a number of responses, ranging from "normality" to something more unexpected, but current research is based on the theory that use of TMS could radically change treatment and perhaps act as a cure for personality disorders and hallucinations. Currently, repetitive transcranial magnetic stimulation (rTMS) is being researched to see if this deactivation effect can be made more permanent in patients suffering from these disorders. Some techniques

combine TMS and another scanning method such as EEG to get additional information about brain activity such as cortical response.

Both EEG and MEG are currently being used to study the brain's activity under different conditions. Each uses similar principles but allows researchers to examine individual regions of the brain, allowing isolation and potentially specific classification of active regions. As mentioned above, EEG is very useful in analysis of immobile patients, typically during the sleep cycle. While there are other types of research that utilize EEG, EEG has been fundamental in understanding the resting brain during sleep. There are other potential uses for EEG and MEG such as charting rehabilitation and improvement after trauma as well as testing neural conductivity in specific regions of epileptics or patients with personality disorders.

Neuromodulation can involve numerous technologies combined or used independently to achieve a desired effect in the brain. Gene and cell therapy are becoming more prevalent in research and clinical trials and these technologies could help stunt or even reverse disease progression in the central nervous system. Deep brain stimulation is currently used in many patients with movement disorders and is used to improve the quality of life in patients. While deep brain stimulation is a method to study how the brain functions per se, it provides both surgeons and neurologists important information about how the brain works when certain small regions of the basal ganglia (nuclei) are stimulated by electrical currents.

Future technologies

The future of neurotechnologies lies in how they are fundamentally applied, and not so much on what new versions will be developed. Current technologies give a large amount of insight into the mind and how the brain functions, but basic research is still needed to demonstrate the more applied functions of these technologies. Currently, rtfMRI is being researched as a method for pain therapy. deCharms et al. have shown that there is a significant improvement in the way people perceive pain if they are made aware of how their brain is functioning while in pain. By providing direct and understandable feedback, researchers can help patients with chronic pain decrease their symptoms. This new type of bio/mechanical-feedback is a new development in pain therapy. Functional MRI is also being considered for a number of more applicable uses outside of the clinic. Research has been done on testing the efficiency of mapping the brain in the case when someone lies as a new way to detect lying. Along the same vein, EEG has been considered for use in lie detection as well. TMS is being used in a variety of potential therapies for patients with personality disorders, epilepsy, PTSD, migraine, and other brain-firing disorders, but has been found to have varying clinical success for each condition. The end result of such research would be to develop a method to alter the brain's perception and firing and train patients' brains to rewire permanently under inhibiting conditions. In addition, PET scans have been found to be 93% accurate in detecting Alzheimer's disease nearly 3 years before conventional diagnosis, indicating that PET scanning is becoming more useful in both the laboratory and the clinic.

Stem cell technologies are always salient both in the minds of the general public and scientists because of their large potential. Recent advances in stem cell research have allowed researchers to ethically pursue studies in nearly every facet of the body, which includes the brain. Research has shown that while most of the brain does not regenerated and is typically a very difficult environment to foster regeneration, there are portions of the brain with regenerative capabilities (specifically the hippocampus and the olfactory bulbs). Much of the research in central nervous system regeneration is how to overcome this poor regenerative quality of the brain. It is important to note that there are therapies that improve cognition and increase the amount of neural pathways, but this does not mean that there is a proliferation of neural cells in the brain. Rather, it is called a plastic rewiring of the brain (*plastic* because it indicates malleability) and is considered a vital part of growth. Nevertheless, many problems in patients stem from death of neurons in the brain, and researchers in the field are striving to produce technologies that enable regeneration in patients with stroke, Parkinson's diseases, severe trauma, and Alzheimer's disease, as well as many others. While still in fledgling stages of development, researchers have recently begun making very interesting progress in attempting to treat these diseases. Researchers have recently successfully produced dopaminergic neurons for transplant in patients with Parkinson's diseases with the hopes that they will be able to move again with a more steady supply of dopamine. Many researchers are building scaffolds that could be transplanted into a patient with spinal cord trauma to present an environment that promotes growth of axons (portions of the cell attributed with transmission of electrical signals) so that patients unable to move or feel might be able to do so again. The potentials are wide-ranging, but it is important to note that many of these therapies are still in the laboratory phase and are slowly being adapted in the clinic. Some scientists remain skeptical with the development of the field, and warn that there is a much larger chance that electrical prosthesis will be developed to solve clinical problems such as hearing loss or paralysis before cell therapy is used in a clinic.

Novel drug delivery systems are being researched in order to improve the lives of those who struggle with brain disorders that might not be treated with stem cells, modulation, or rehabilitation. Pharmaceuticals play a very important role in society, and the brain has a very selective barrier that prevents some drugs from going from the blood to the brain. There are some diseases of the brain such as meningitis that require doctors to directly inject medicine into the spinal cord because the drug cannot cross the blood-brain barrier. Research is being conducted to investigate new methods of targeting the brain using the blood supply, as it is much easier to inject into the blood than the spine. New technologies such as nanotechnology are being researched for selective drug delivery, but these technologies have problems as with any other. One of the major setbacks is that when a particle is too large, the patient's liver will take up the particle and degrade it for excretion, but if the particle is too small there will not be enough drug in the particle to take effect. In addition, the size of the capillary pore is important because too large a particle might not fit or even plug up the hole, preventing adequate supply of the drug to the brain. Other research is involved in integrating a protein device between the layers to create a free-flowing gate that is unimpeded by the limitations of the body. Another direction is receptor-mediated transport, where receptors in the brain used to transport

nutrients are manipulated to transport drugs across the blood-brain barrier. Some have even suggested that focused ultrasound opens the blood-brain barrier momentarily and allows free passage of chemicals into the brain. Ultimately the goal for drug delivery is to develop a method that maximizes the amount of drug in the loci with as little degraded in the blood stream as possible.

Neuromodulation is a technology currently used for patients with movement disorders, although research is currently being done to apply this technology to other disorders. Recently, a study was done on if DBS could improve depression with positive results, indicating that this technology might have potential as a therapy for multiple disorders in the brain. DBS is limited by its high cost however, and in developing countries the availability of DBS is very limited. A new version of DBS is under investigation and has developed into the novel field, optogenetics. Optogenetics is the combination of deep brain stimulation with fiber optics and gene therapy. Essentially, the fiber optic cables are designed to light up under electrical stimulation, and a protein would be added to a neuron via gene therapy to excite it under light stimuli. So by combining these three independent fields, a surgeon could excite a single and specific neuron in order to help treat a patient with some disorder. Neuromodulation offers a wide degree of therapy for many patients, but due to the nature of the disorders it is currently used to treat its effects are often temporary. Future goals in the field hope to alleviate that problem by increasing the years of effect until DBS can be used for the remainder of the patient's life. Another use for neuromodulation would be in building neuro-interface prosthetic devices that would allow quadriplegics the ability to maneuver a cursor on a screen with their thoughts, thereby increasing their ability to interact with others around them. By understanding the motor cortex and understanding how the brain signals motion, it is possible to emulate this response on a computer screen.

Ethics

Stem cells

The ethical debate about use of embryonic stem cells has stirred controversy both in the United States and abroad; although more recently these debates have lessened due to modern advances in creating induced pluripotent stem cells from adult cells. The greatest advantage for use of embryonic stem cells is the fact that they can differentiate (become) nearly any type of cell provided the right conditions and signals. However, recent advances by Shinya Yamanaka et al. have found ways to create pluripotent cells without the use of such controversial cell cultures. Using the patient's own cells and re-differentiating them into the desired cell type bypasses not only the fear of patient rejection of the cells but also gives researchers a more ethical (and larger) supply of available cells. Induced pluripotent cells are by no means perfect though, they still have the potential to form teratomas, or benign (though they can be potentially malignant in effect) tumors, and tend to have poor survivability *in vivo* (in the living body) on damaged tissue. Much of the ethics concerning use of stem cells has subsided from the embryonic/adult stem cell debate due to its rendered moot, but now societies find themselves debating whether or not this technology can be ethically used. Enhancements

of traits, use of animals for tissue scaffolding, and even arguments for moral degeneration have been made with the fears that if this technology reaches its full potential a new paradigm shift will occur in human behavior.

Military application

New neurotechnologies have always garnered the appeal of governments, from lie detection technology and virtual reality to rehabilitation and understanding the psyche. Due to the Iraq War and War on Terror, American soldiers coming back from Iraq and Afghanistan are reported to have percentages up to 12% with PTSD. There are many researchers hoping to improve these peoples' conditions by implementing new strategies for recovery. By combining pharmaceuticals and neurotechnologies, some researchers how found ways to low the fear response and theorize that it may be applicable to PTSD. Virtual reality is also a technology that has found a large amount of attention in the military. If improved upon, it would be possible to train soldiers in complex situations in times of peace in order to better prepare and train a modern army. But some people raise questions about how the military would use these improvements.

Privacy

Finally, when these technologies are being developed society must understand that these neurotechnologies could reveal the one thing that people can always keep secret, what they are thinking. While there are large amounts of benefits associated with these technologies, it is necessary for scientists and policy makers alike to consider implications about "cognitive liberty." This term is important in many ethical circles concerned with the state and goals of progress in the field of neurotechnology. Current improvements such as "brain fingerprinting" or lie detection using EEG or fMRI could give rise to a set fixure of loci/emotional relationships in the brain, although these technologies are still years away from full application. It is important to consider how all these neurotechnologies might affect the future of society, and it is suggested that political, scientific, and civil debates are heard about the implementation of these newer technologies that potentially offer a new wealth of once-private information. Some ethicists are also concerned with the use of TMS and fear that the technique could be used to alter patients in ways that are undesired by the patient.

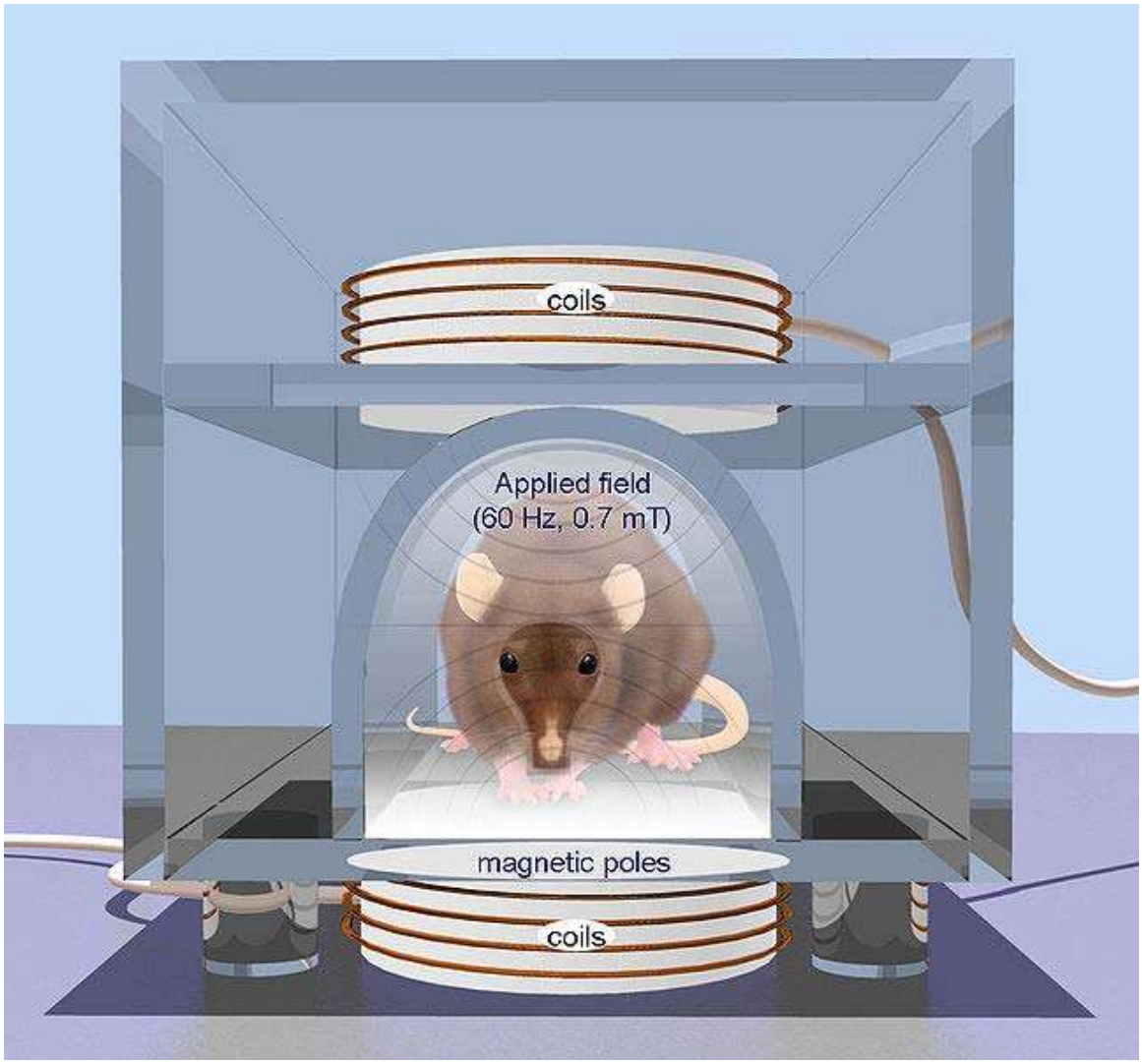
Chapter- 2

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (**TMS**) is a noninvasive method to cause depolarization in the neurons of the brain. TMS uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field; this can cause activity in specific or general parts of the brain with minimal discomfort, allowing the functioning and interconnections of the brain to be studied. A variant of TMS, **repetitive transcranial magnetic stimulation** (**rTMS**), has been tested as a treatment tool for various neurological and psychiatric disorders including migraines, strokes, Parkinson's disease, dystonia, tinnitus, depression and auditory hallucinations.

Background

The principle of inductive brain stimulation with eddy currents has been noted since the 20th century. The first successful TMS study was performed in 1985 by Anthony Barker and his colleagues in Sheffield, England. Its earliest application demonstrated conduction of nerve impulses from the motor cortex to the spinal cord, stimulating muscle contractions. The use of magnets rather than a direct electric current to the brain reduced the discomfort of the procedure and research and allowed mapping of the cerebral cortex and its connections.



rTMS in a rodent. From Oscar Arias-Carrión, 2008

Effects on the brain

The exact details of how TMS functions are still being explored. The effects of TMS can be divided into two types depending on the mode of stimulation:

- Single or paired pulse TMS causes neurons in the neocortex under the site of stimulation to depolarise and discharge an action potential. If used in the primary motor cortex, it produces muscle activity referred to as a motor evoked potential (MEP) which can be recorded on electromyography. If used on the occipital cortex, 'phosphenes' (flashes of light) might be perceived by the subject. In most other areas of the cortex, the participant does not consciously experience any effect, but his or her behaviour may be slightly altered (e.g. slower reaction time on a cognitive task), or changes in brain activity may be detected using sensing equipment.

- Repetitive TMS produces longer-lasting effects which persist past the initial period of stimulation. rTMS can increase or decrease the excitability of the corticospinal tract depending on the intensity of stimulation, coil orientation and frequency. The mechanism of these effects is not clear although it is widely believed to reflect changes in synaptic efficacy akin to long-term potentiation (LTP) and long-term depression (LTD).

Risks

Although TMS is often regarded as safe, the greatest acute risk of TMS is the rare occurrence of induced seizures and syncope. More than 16 cases of TMS-related seizure have been reported in the literature, with at least seven reported before the publication of safety guidelines in 1998, and more than nine reported afterwards. The seizures have been associated with single-pulse and rTMS. Reports have stated that in at least some cases, predisposing factors (medication, brain lesions or genetic susceptibility) may have contributed to the seizure. A review of nine seizures associated with rTMS that had been reported after 1998 stated that four seizures were within the safety parameters, four were outside of those parameters, and one had occurred in a healthy volunteer with no predisposing factors. A 2009 international consensus statement on TMS that contained this review concluded that based on the number of studies, subjects and patients involved with TMS research, the risk of seizure with rTMS is considered very low.

Besides seizures, other risks include fainting, minor pains such as headache or local discomfort, minor cognitive changes and psychiatric symptoms (particularly a low risk of mania in depressed patients). Though other side effects are thought to be possibly associated with TMS (alterations to the endocrine system, altered neurotransmitter and immune system activity) they are considered investigational and lacking substantive proof.

Other adverse effects of TMS are:

- Discomfort or pain from the stimulation of the scalp and associated nerves and muscles on the overlying skin; this is more common with rTMS than single pulse TMS,
- Rapid deformation of the TMS coil produces a loud clicking sound which increases with the stimulator intensity that can affect hearing with sufficient exposure, particularly relevant for rTMS (hearing protection may be used to prevent this),
- rTMS in the presence of incompatible EEG electrodes can result in electrode heating and, in severe cases, skin burns. Non-metallic electrodes are used if concurrent EEG data is required.

Clinical uses

The uses of TMS and rTMS can be divided into diagnostic and therapeutic uses.

Diagnosis

TMS can be used clinically to measure activity and function of specific brain circuits in humans. The most robust and widely-accepted use is in measuring the connection between the primary motor cortex and a muscle to evaluate damage from strokes, spinal cord injuries, multiple sclerosis and motor neuron disease. TMS has been suggested as a means of assessing short-interval intracortical inhibition (SICI) which measures the internal pathways of the motor cortex but this use has not yet been validated.

Therapy

Studies of the use of TMS and rTMS to treat neurological and psychiatric conditions have shown only modest effects with little confirmation of results. However, publications reporting the results of reviews and statistical meta-anaylses of earlier investigations have stated that rTMS appeared to be effective in the treatment of certain types of major depression under certain specific conditions. rTMS devices are marketed for the treatment of such disorders in Canada, Australia, New Zealand, the European Union, Israel and the United States.

There is evidence that rTMS can temporarily reduce chronic pain and change pain-related brain and nerve activity, and TMS has been used to predict the success of surgically implanted electrical brain stimulation for the treatment of pain.

Other areas of research include the rehabilitation of aphasia and motor disability after stroke, tinnitus, Parkinson's disease and the negative symptoms of schizophrenia. TMS has failed to show effectiveness for the treatment of brain death, coma, and other persistent vegetative states.

It is difficult to establish a convincing form of "sham" TMS to test for placebo effects during controlled trials in conscious individuals, due to the neck pain, headache and twitching in the scalp or upper face associated with the intervention. "Sham" TMS manipulations can affect cerebral glucose metabolism and MEPs, which may confound results. This problem is exacerbated when using subjective measures of improvement. Depending on the research question asked and the experimental design, matching this discomfort to distinguish true effects from placebo can be an important and challenging issue.

A recent multicenter trial of rTMS in depression used a "sham" placebo treatment that appeared to mimic the sound and scalp stimulation associated with active TMS treatment. The investigators concluded: "Although the treatment effect was statistically significant on a clinically meaningful variable (remission), the overall number of remitters and responders was less than one would like with a treatment that requires daily intervention for 3 weeks or more, even with a benign adverse effect profile". However, a review of the trial's report has questioned the adequacy of the placebo, noting that treaters were able to guess whether patients were receiving treatment with active or sham TMS, better than chance.

FDA actions and responses

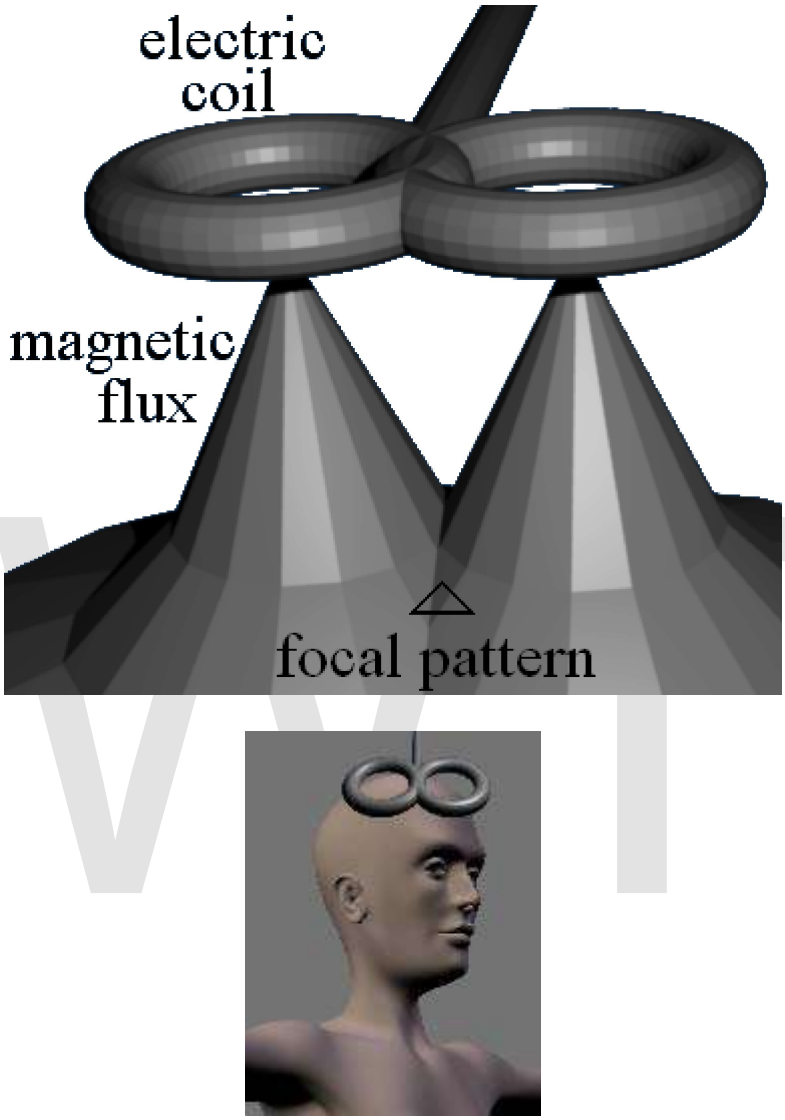
FDA actions

In January 2007 an advisory panel of the United States Food and Drug Administration (FDA) did not recommend clearance for marketing of an rTMS device, stating that the device appeared to be reasonably safe but had failed to demonstrate efficacy in a study of people with major depression who had not benefitted from prior adequate treatment with oral antidepressants during their current major depressive episode. The panel agreed that "unblinding was greater in the active group, and considering the magnitude of the effect size, it may have influenced the study results." However, the FDA determined in December 2008 that the rTMS device was sufficiently similar to existing devices that did not require a premarket approval application and allowed the device to be marketed in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act for "the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode". The user manual for the device warns that effectiveness has not been established in patients with major depressive disorder who have failed to achieve satisfactory improvement from zero and from two or more antidepressant medications in the current episode and that the device has not been studied in patients who have had no prior antidepressant medication.

Response to FDA decision

Soon after the FDA cleared the device, several members of Public Citizen stated in a letter to the editor of the medical journal *Neuropsychopharmacology* that the FDA seemed to have based its decision on a *post-hoc* analysis that did not establish the effectiveness of rTMS for the treatment of depression. The writers of the letter expressed their concern that patients would be diverted from therapies such as antidepressant medications that have an established history of effectiveness.

Technical information



TMS - Butterfly Coils

TMS uses electromagnetic induction to generate an electric current across the scalp and skull without physical contact. A plastic-enclosed coil of wire is held next to the skull and when activated, produces a magnetic field oriented orthogonally to the plane of the coil. The magnetic field passes unimpeded through the skin and skull, inducing an oppositely directed current in the brain that activates nearby nerve cells in much the same way as currents applied directly to the cortical surface. The path of this current is difficult to model because the brain is irregularly shaped and electricity and magnetism are not conducted uniformly throughout its tissues. The magnetic field penetrates only to a maximum depth of three centimeters into the brain, in the area directly adjacent to the coil.

Coil types

The design of transcranial magnetic stimulation coils used in either treatment or diagnostic/experimental studies may differ in a variety of ways. These differences should be considered in the interpretation of any study result, and the type of coil used should be specified in the study methods for any published reports.

The most important considerations include:

- the type of material used to construct the core of the coil
- the geometry of the coil configuration
- the biophysical characteristics of the pulse produced by the coil.

With regard to coil composition, the core material may be either a magnetically inert substrate (i.e., the so-called 'air-core'coil design), or possess a solid, ferromagnetically active material (ie, the so-called 'solid-core' design). Solid core coil design result in a more efficient transfer of electrical energy into a magnetic field, with a substantially reduced amount of energy dissipated as heat, and so can be operated under more aggressive duty cycles often mandated in therapeutic protocols, without treatment interruption due to heat accumulation, or the use of an accessory method of cooling the coil during operation. Varying the geometric shape of the coil itself may also result in variations in the focality, shape, and depth of cortical penetration of the magnetic field. Differences in the coil substance as well as the electronic operation of the power supply to the coil may also result in variations in the biophysical characteristics of the resulting magnetic pulse (e.g., width or duration of the magnetic field pulse). All of these features should be considered when comparing results obtained from different studies, with respect to both safety and efficacy.

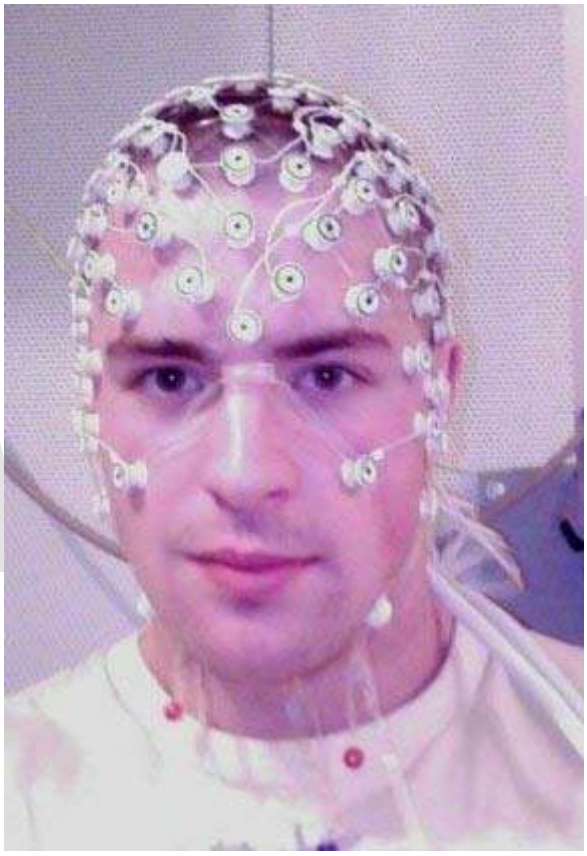
A number of different types of coils exist, each of which produce different magnetic field patterns. Some examples:

- round coil: the original type of TMS coil
- figure-eight coil (i.e. butterfly coil): results in a more focal pattern of activation
- double-cone coil: conforms to shape of head, useful for deeper stimulation
- four-leaf coil: for focal stimulation of peripheral nerves

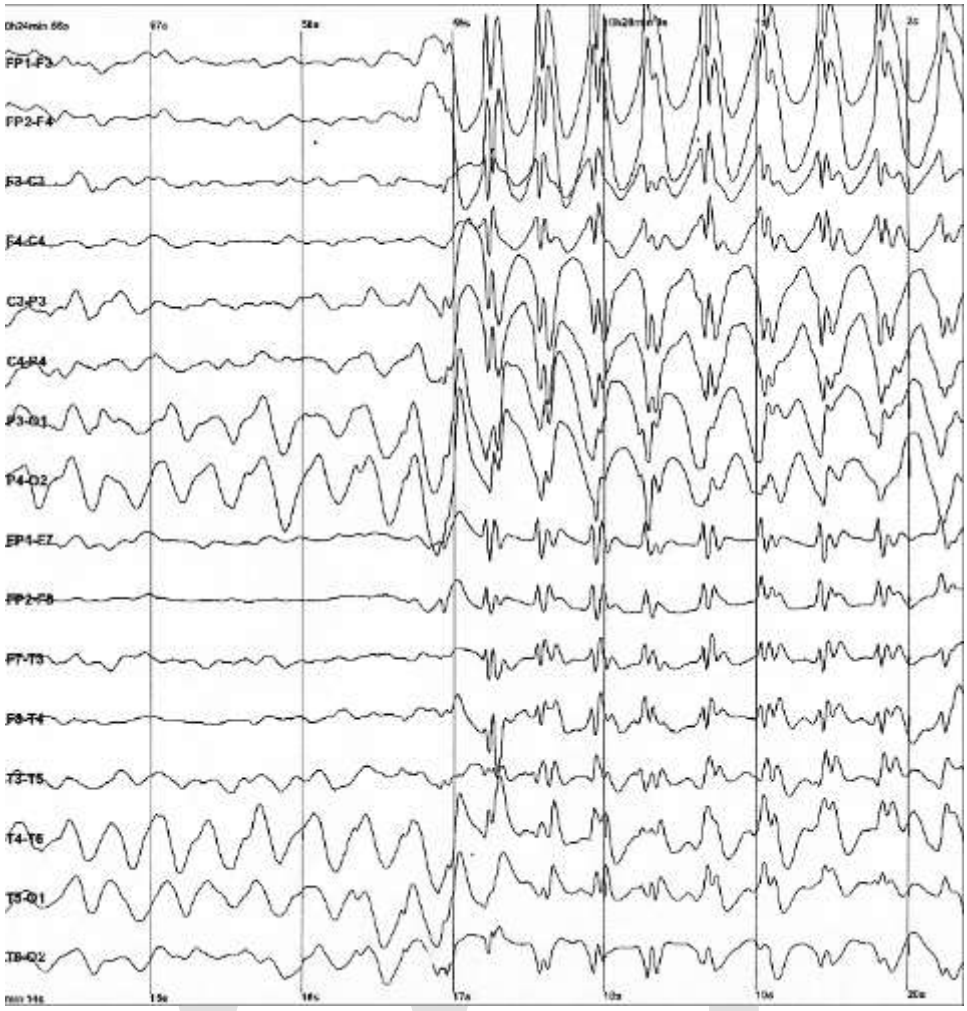
Design variations in the shape of the TMS coils allow much deeper penetration of the brain than the standard depth of 1.5 cm. Circular, H-shaped, double cone coils and other experimental variations can induce excitation or inhibition of neurons deeper in the brain including activation of motor neurons for the cerebellum, legs and pelvic floor. Though able to penetrate deeper in the brain, they are less able to produced a focused, localized response and are relatively non-focal.

Chapter- 3

Electroencephalography



An EEG recording net (Electrical Geodesics, Inc.) being used on a participant in a brain wave study



Epileptic spike and wave discharges monitored with EEG

Electroencephalography (**EEG**) is the recording of electrical activity along the scalp produced by the firing of neurons within the brain. In clinical contexts, EEG refers to the recording of the brain's spontaneous electrical activity over a short period of time, usually 20–40 minutes, as recorded from multiple electrodes placed on the scalp. In neurology, the main diagnostic application of EEG is in the case of epilepsy, as epileptic activity can create clear abnormalities on a standard EEG study. A secondary clinical use of EEG is in the diagnosis of coma, encephalopathies, and brain death. EEG used to be a first-line method for the diagnosis of tumors, stroke and other focal brain disorders, but this use has decreased with the advent of anatomical imaging techniques such as MRI and CT.

Derivatives of the EEG technique include evoked potentials (EP), which involves averaging the EEG activity time-locked to the presentation of a stimulus of some sort (visual, somatosensory, or auditory). Event-related potentials (ERPs) refer to averaged EEG responses that are time-locked to more complex processing of stimuli; this technique is used in cognitive science, cognitive psychology, and psychophysiological research.

Source of EEG activity

The brain's electrical charge is maintained by billions of neurons. Neurons are electrically charged (or "polarized") by membrane transport proteins that pump ions across their membranes. When a neuron receives a signal from its neighbor via an action potential, it responds by releasing ions into the space outside the cell. Ions of like charge repel each other, and when many ions are pushed out of many neurons at the same time, they can push their neighbors, who push their neighbors, and so on, in a wave. This process is known as volume conduction. When the wave of ions reaches the electrodes on the scalp, they can push or pull electrons on the metal on the electrodes. Since metal conducts the push and pull of electrons easily, the difference in push, or voltage, between any two electrodes can be measured by a voltmeter. Recording these voltages over time gives us the EEG.

The electric potentials generated by single neurons are far too small to be picked by EEG or MEG. EEG activity therefore always reflects the summation of the synchronous activity of thousands or millions of neurons that have similar spatial orientation. If the cells do not have similar spatial orientation, their ions do not line up and create waves to be detected. Pyramidal neurons of the cortex are thought to produce most EEG signal because they are well-aligned and fire together. Because voltage fields fall off with the square of the distance, activity from deep sources is more difficult to detect than currents near the skull.

Scalp EEG activity shows oscillations at a variety of frequencies. Several of these oscillations have characteristic frequency ranges, spatial distributions and are associated with different states of brain functioning (e.g., waking and the various sleep stages). These oscillations represent synchronized activity over a network of neurons. The neuronal networks underlying some of these oscillations are understood (e.g., the thalamocortical resonance underlying sleep spindles), while many others are not (e.g., the system that generates the posterior basic rhythm). Research that measures both EEG and neuron spiking finds the relationship between the two is complex with the power of surface EEG only in two bands that of gamma and delta relating to neuron spike activity.

Clinical use

A routine clinical EEG recording typically lasts 20–30 minutes (plus preparation time) and usually involves recording from scalp electrodes. Routine EEG is typically used in the following clinical circumstances:

- to distinguish epileptic seizures from other types of spells, such as psychogenic non-epileptic seizures, syncope (fainting), sub-cortical movement disorders and migraine variants.
- to differentiate "organic" encephalopathy or delirium from primary psychiatric syndromes such as catatonia
- to serve as an adjunct test of brain death

- to prognosticate, in certain instances, in patients with coma
- to determine whether to wean anti-epileptic medications

At times, a routine EEG is not sufficient, particularly when it is necessary to record a patient while he/she is having a seizure. In this case, the patient may be admitted to the hospital for days or even weeks, while EEG is constantly being recorded (along with time-synchronized video and audio recording). A recording of an actual seizure (i.e., an ictal recording, rather than an inter-ictal recording of a possibly epileptic patient at some period between seizures) can give significantly better information about whether or not a spell is an epileptic seizure and the focus in the brain from which the seizure activity emanates.

Epilepsy monitoring is typically done:

- to distinguish epileptic seizures from other types of spells, such as psychogenic non-epileptic seizures, syncope (fainting), sub-cortical movement disorders and migraine variants.
- to characterize seizures for the purposes of treatment
- to localize the region of brain from which a seizure originates for work-up of possible seizure surgery

Additionally, EEG may be used to monitor certain procedures:

- to monitor the depth of anesthesia
- as an indirect indicator of cerebral perfusion in carotid endarterectomy
- to monitor amobarbital effect during the Wada test

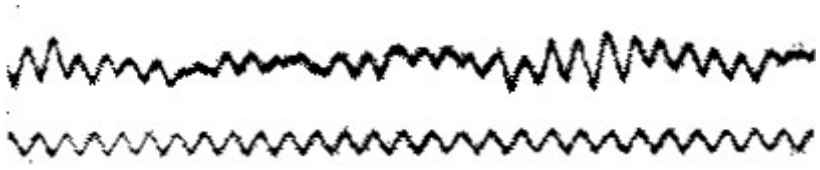
EEG can also be used in intensive care units for brain function monitoring:

- to monitor for non-convulsive seizures/non-convulsive status epilepticus
- to monitor the effect of sedative/anesthesia in patients in medically induced coma (for treatment of refractory seizures or increased intracranial pressure)
- to monitor for secondary brain damage in conditions such as subarachnoid hemorrhage (currently a research method)

If a patient with epilepsy is being considered for resective surgery, it is often necessary to localize the focus (source) of the epileptic brain activity with a resolution greater than what is provided by scalp EEG. This is because the cerebrospinal fluid, skull and scalp *smear* the electrical potentials recorded by scalp EEG. In these cases, neurosurgeons typically implant strips and grids of electrodes (or penetrating depth electrodes) under the dura mater, through either a craniotomy or a burr hole. The recording of these signals is referred to as electrocorticography (ECoG), subdural EEG (sdEEG) or intracranial EEG (icEEG)--all terms for the same thing. The signal recorded from ECoG is on a different scale of activity than the brain activity recorded from scalp EEG. Low voltage, high frequency components that cannot be seen easily (or at all) in scalp EEG can be seen clearly in ECoG. Further, smaller electrodes (which cover a smaller parcel of brain

surface) allow even lower voltage, faster components of brain activity to be seen. Some clinical sites record from penetrating microelectrodes.

Research use



The first human EEG recording obtained by Hans Berger in 1924. The upper tracing is EEG, and the lower is a 10 Hz timing signal.

EEG, and its derivative, ERPs, are used extensively in neuroscience, cognitive science, cognitive psychology, and psychophysiological research. Many techniques used in research contexts are not standardized sufficiently to be used in the clinical context.

A different method to study brain function is functional magnetic resonance imaging (fMRI). Some benefits of EEG compared to fMRI include:

- Hardware costs are significantly lower for EEG sensors versus an fMRI machine
- EEG sensors can be deployed into a wider variety of environments than can a bulky, immobile fMRI machine
- EEG enables higher temporal resolution, on the order of milliseconds, rather than seconds
- EEG is relatively tolerant of subject movement versus an fMRI (where the subject must remain completely still)
- EEG is silent, which allows for better study of the responses to auditory stimuli
- EEG does not aggravate claustrophobia

Limitations of EEG as compared with fMRI include:

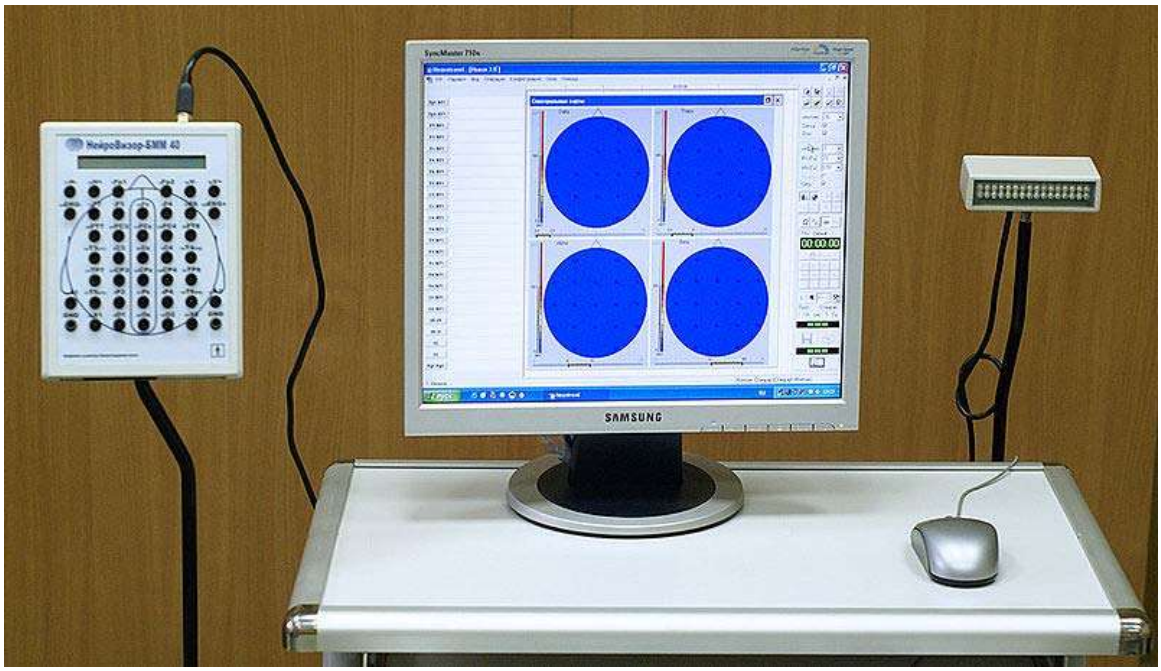
- Significantly lower spatial resolution
- ERP studies require relatively simple paradigms, compared with block-design fMRI studies

EEG recordings have been successfully obtained simultaneously with fMRI scans, though successful simultaneous recording requires that several technical issues be overcome, such as the presence of ballistocardiographic artifact, MRI pulse artifact and the induction of electrical currents in EEG wires that move within the strong magnetic fields of the MRI.

EEG also has some characteristics that compare favorably with behavioral testing:

- EEG can detect covert processing (i.e., processing that does not require a response)
- EEG can be used in subjects who are incapable of making a motor response
- Some ERP components can be detected even when the subject is not attending to the stimuli
- As compared with other reaction time paradigms, ERPs can elucidate stages of processing (rather than just the final end result)

Method



Computer Electroencephalograph *Neurovisor-BMM 40*

In conventional scalp EEG, the recording is obtained by placing electrodes on the scalp with a conductive gel or paste, usually after preparing the scalp area by light abrasion to reduce impedance due to dead skin cells. Many systems typically use electrodes, each of which is attached to an individual wire. Some systems use caps or nets into which electrodes are embedded; this is particularly common when high-density arrays of electrodes are needed.

Electrode locations and names are specified by the International 10–20 system for most clinical and research applications (except when high-density arrays are used). This system ensures that the naming of electrodes is consistent across laboratories. In most clinical applications, 19 recording electrodes (plus ground and system reference) are used. A smaller number of electrodes are typically used when recording EEG from neonates. Additional electrodes can be added to the standard set-up when a clinical or research application demands increased spatial resolution for a particular area of the

brain. High-density arrays (typically via cap or net) can contain up to 256 electrodes more-or-less evenly spaced around the scalp.

Each electrode is connected to one input of a differential amplifier (one amplifier per pair of electrodes); a common system reference electrode is connected to the other input of each differential amplifier. These amplifiers amplify the voltage between the active electrode and the reference (typically 1,000–100,000 times, or 60–100 dB of voltage gain). In analog EEG, the signal is then filtered (next paragraph), and the EEG signal is output as the deflection of pens as paper passes underneath. Most EEG systems these days, however, are digital, and the amplified signal is digitized via an analog-to-digital converter, after being passed through an anti-aliasing filter. Analog-to-digital sampling typically occurs at 256–512 Hz in clinical scalp EEG; sampling rates of up to 20 kHz are used in some research applications.

During the recording, a series of activation procedures may be used. These procedures may induce normal or abnormal EEG activity that might not otherwise be seen. These procedures include hyperventilation, photic stimulation (with a strobe light), eye closure, mental activity, sleep and sleep deprivation. During (inpatient) epilepsy monitoring, a patient's typical seizure medications may be withdrawn.

The digital EEG signal is stored electronically and can be filtered for display. Typical settings for the high-pass filter and a low-pass filter are 0.5-1 Hz and 35–70 Hz, respectively. The high-pass filter typically filters out slow artifact, such as electrogalvanic signals and movement artifact, whereas the low-pass filter filters out high-frequency artifacts, such as electromyographic signals. An additional notch filter is typically used to remove artifact caused by electrical power lines (60 Hz in the United States and 50 Hz in many other countries). As part of an evaluation for epilepsy surgery, it may be necessary to insert electrodes near the surface of the brain, under the surface of the dura mater. This is accomplished via burr hole or craniotomy. This is referred to variously as "electrocorticography (ECoG)", "intracranial EEG (I-EEG)" or "subdural EEG (SD-EEG)". Depth electrodes may also be placed into brain structures, such as the amygdala or hippocampus, structures, which are common epileptic foci and may not be "seen" clearly by scalp EEG. The electrocorticographic signal is processed in the same manner as digital scalp EEG (above), with a couple of caveats. ECoG is typically recorded at higher sampling rates than scalp EEG because of the requirements of Nyquist theorem—the subdural signal is composed of a higher predominance of higher frequency components. Also, many of the artifacts that affect scalp EEG do not impact ECoG, and therefore display filtering is often not needed.

A typical adult human EEG signal is about 10μV to 100 μV in amplitude when measured from the scalp and is about 10–20 mV when measured from subdural electrodes.

Since an EEG voltage signal represents a difference between the voltages at two electrodes, the display of the EEG for the reading encephalographer may be set up in one of several ways. The representation of the EEG channels is referred to as a *montage.*

Bipolar montage
: Each channel (i.e., waveform) represents the difference between two adjacent electrodes. The entire montage consists of a series of these channels. For example, the channel "Fp1-F3" represents the difference in voltage between the Fp1 electrode and the F3 electrode. The next channel in the montage, "F3-C3," represents the voltage difference between F3 and C3, and so on through the entire array of electrodes.

Referential montage
: Each channel represents the difference between a certain electrode and a designated reference electrode. There is no standard position for this reference; it is, however, at a different position than the "recording" electrodes. Midline positions are often used because they do not amplify the signal in one hemisphere vs. the other. Another popular reference is "linked ears," which is a physical or mathematical average of electrodes attached to both earlobes or mastoids.

Average reference montage
: The outputs of all of the amplifiers are summed and averaged, and this averaged signal is used as the common reference for each channel.

Laplacian montage
: Each channel represents the difference between an electrode and a weighted average of the surrounding electrodes.

When analog (paper) EEGs are used, the technologist switches between montages during the recording in order to highlight or better characterize certain features of the EEG. With digital EEG, all signals are typically digitized and stored in a particular (usually referential) montage; since any montage can be constructed mathematically from any other, the EEG can be viewed by the electroencephalographer in any display montage that is desired.

The EEG is read by a neurologist, optimally one who has specific training in the interpretation of EEGs. This is done by visual inspection of the waveforms, called graphoelements. The use of computer signal processing of the EEG—so-called quantitative EEG—is somewhat controversial when used for clinical purposes (although there are many research uses).

Limitations

EEG has several limitations. Most important is its poor spatial resolution. EEG is most sensitive to a particular set of post-synaptic potentials: those generated in superficial layers of the cortex, on the crests of gyri directly abutting the skull and radial to the skull. Dendrites, which are deeper in the cortex, inside sulci, in midline or deep structures (such as the cingulate gyrus or hippocampus), or producing currents that are tangential to the skull, have far less contribution to the EEG signal.

The meninges, cerebrospinal fluid and skull "smear" the EEG signal, obscuring its intracranial source.

It is mathematically impossible to reconstruct a unique intracranial current source for a given EEG signal, as some currents produce potentials that cancel each other out. This is referred to as the inverse problem. However, much work has been done to produce remarkably good estimates of, at least, a localized electric dipole that represents the recorded currents.

EEG vs fMRI and PET

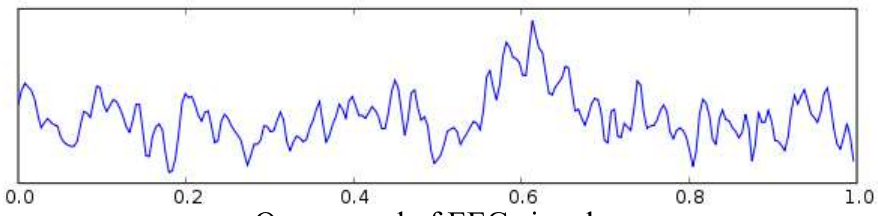
EEG has several strong points as a tool for exploring brain activity. EEG's can detect changes within a millisecond timeframe, excellent considering an action potential takes approximately 0.5-130 milliseconds to propagate across a single neuron, depending on the type of neuron. Other methods of looking at brain activity, such as PET and fMRI have time resolution between seconds and minutes. EEG measures the brain's electrical activity directly, while other methods record changes in blood flow (e.g., SPECT, fMRI) or metabolic activity (e.g., PET), which are indirect markers of brain electrical activity. EEG can be used simultaneously with fMRI so that high-temporal-resolution data can be recorded at the same time as high-spatial-resolution data, however, since the data derived from each occurs over a different time course, the data sets do not necessarily represent exactly the same brain activity. There are technical difficulties associated with combining these two modalities, including the need to remove the *MRI gradient artifact* present during MRI acquisition and the ballistocardiographic artifact (resulting from the pulsatile motion of blood and tissue) from the EEG. Furthermore, currents can be induced in moving EEG electrode wires due to the magnetic field of the MRI.

EEG vs MEG

EEG reflects correlated synaptic activity caused by post-synaptic potentials of cortical neurons. The ionic currents involved in the generation of fast action potentials may not contribute greatly to the averaged field potentials representing the EEG . More specifically, the scalp electrical potentials that produce EEG are generally thought to be caused by the extracellular ionic currents caused by dendritic electrical activity, whereas the fields producing magnetoencephalographic signals are associated with intracellular ionic currents .

EEG can be recorded at the same time as MEG so that data from these complementary high-time-resolution techniques can be combined.

Normal activity



One second of EEG signal

The EEG is typically described in terms of (1) rhythmic activity and (2) transients. The rhythmic activity is divided into bands by frequency. To some degree, these frequency bands are a matter of nomenclature (i.e., any rhythmic activity between 8–12 Hz can be described as "alpha"), but these designations arose because rhythmic activity within a certain frequency range was noted to have a certain distribution over the scalp or a certain biological significance. Frequency bands are usually extracted using spectral methods (for instance Welch) as implemented for instance in freely available EEG software such as EEGLAB.

Most of the cerebral signal observed in the scalp EEG falls in the range of 1–20 Hz (activity below or above this range is likely to be artifactual, under standard clinical recording techniques).

Comparison table

Comparison of EEG bands

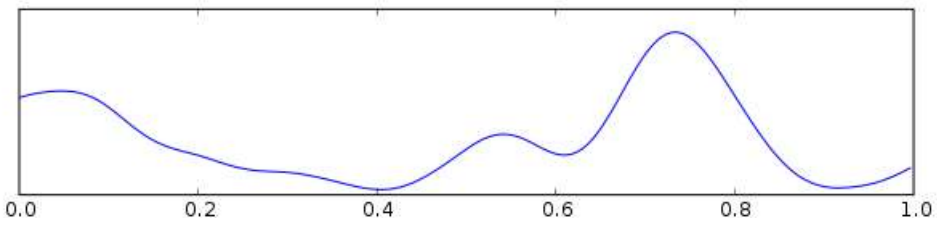
Type	Frequency (Hz)	Location	Normally	Pathologically
Delta	up to 4	frontally in adults, posteriorly in children; high amplitude waves	• adults slow wave sleep • in babies • Has been found during some continuous attention tasks (Kirmizi-Alsan et al. 2006)	• subcortical lesions • diffuse lesions • metabolic encephalopathy hydrocephalus • deep midline lesions
Theta	4 – 7	Found in locations not related to task at hand	• young children • drowsiness or arousal in older children and adults • idling • Associated with inhibition of elicited responses (has been found to spike in situations where a person is actively trying to repress a response or action) (Kirmizi-Alsan et al. 2006).	• focal subcortical lesions • metabolic encephalopathy • deep midline disorders • some instances of hydrocephalus

Alpha	8 – 12	posterior regions of head, both sides, higher in amplitude on dominant side. Central sites (c3-c4) at rest .	• relaxed/reflecting • closing the eyes • Also associated with inhibition control, seemingly with the purpose of timing inhibitory activity in different locations across the brain (Klimesch, Sauseng, & Hanslmayr 2007; Coan & Allen 2008).	• coma
Beta	12 – 30	both sides, symmetrical distribution, most evident frontally; low amplitude waves	• alert/working • active, busy or anxious thinking, active concentration	• benzodiazepines
Gamma	30 – 100+	Somatosensory cortex	• Displays during cross-modal sensory processing (perception that combines two different senses, such as sound and sight) (Kisley & Cornwell 2006; Kanayama, Sato, & Ohira 2007; Nieuwenhuis, Yeung, & Cohen 2004) • Also is shown during short term memory matching of recognized objects, sounds, or tactile sensations (Herrmann, Frund, & Lenz 2009)	• A decrease in gamma band activity may be associated with cognitive decline, especially when related the theta band; however, this has not been proven for use as a clinical diagnostic measurement yet (Moretti et al. 2009).

Mu	8 – 13	Sensorimotor cortex	• Shows rest state motor neurons (Gastaut, 1952).	• Mu suppression could be indicative for motor mirror neurons working, and deficits in Mu suppression, and thus in mirror neurons, might play a role in autism. (Oberman et al., 2005)

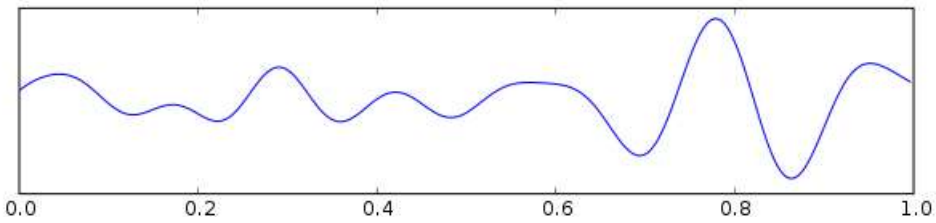
It should be noted that while these are the universally recognized ranges, they are not concrete definitions of the range of brain-waves. While researchers tend to follow these guidelines, many scholars use their own specific boundaries depending on the range they choose to focus on. Additionally, some researchers define the bands using decimal values rather than rounding to whole numbers (for example, one researcher may define the lower Beta band cut-off as 12.1, while another may use the value 13), while still others sometimes divide the bands into sub-bands. Generally, this is only done for the sake of analysis.

Wave patterns



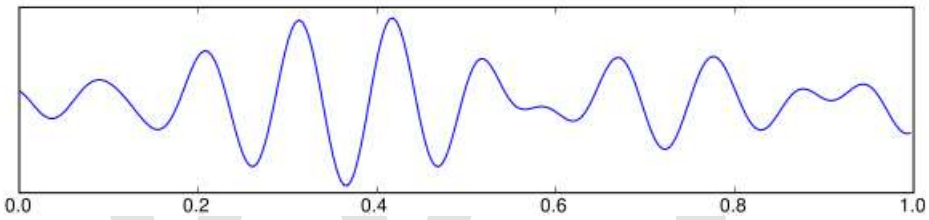
delta waves

- Delta is the frequency range up to 4 Hz. It tends to be the highest in amplitude and the slowest waves. It is seen normally in adults in slow wave sleep. It is also seen normally in babies. It may occur focally with subcortical lesions and in general distribution with diffuse lesions, metabolic encephalopathy hydrocephalus or deep midline lesions. It is usually most prominent frontally in adults (e.g. FIRDA - Frontal Intermittent Rhythmic Delta) and posteriorly in children (e.g. OIRDA - Occipital Intermittent Rhythmic Delta).



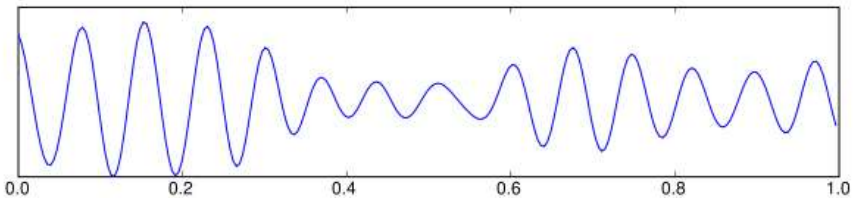
theta waves

- Theta is the frequency range from 4 Hz to 7 Hz. Theta is seen normally in young children. It may be seen in drowsiness or arousal in older children and adults; it can also be seen in meditation. Excess theta for age represents abnormal activity. It can be seen as a focal disturbance in focal subcortical lesions; it can be seen in generalized distribution in diffuse disorder or metabolic encephalopathy or deep midline disorders or some instances of hydrocephalus. On the contrary this range has been associated with reports of relaxed, meditative, and creative states.



alpha waves

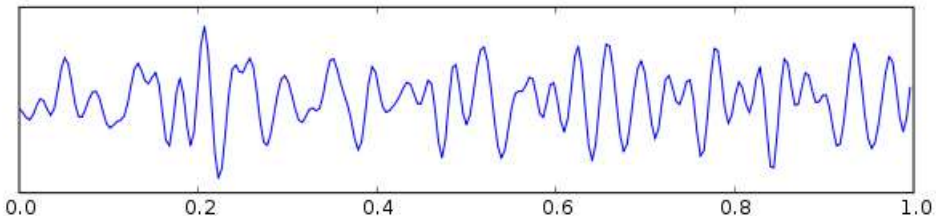
- Alpha is the frequency range from 8 Hz to 12 Hz. Hans Berger named the first rhythmic EEG activity he saw as the "alpha wave". This was the "posterior basic rhythm" (also called the "posterior dominant rhythm" or the "posterior alpha rhythm"), seen in the posterior regions of the head on both sides, higher in amplitude on the dominant side. It emerges with closing of the eyes and with relaxation, and attenuates with eye opening or mental exertion. The posterior basic rhythm is actually slower than 8 Hz in young children (therefore technically in the theta range).



sensorimotor rhythm aka mu rhythm

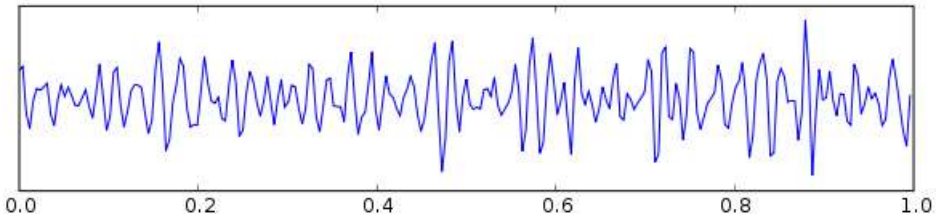
In addition to the posterior basic rhythm, there are other normal alpha rhythms such as the mu rhythm (alpha activity in the contralateral sensory and motor

cortical areas that emerges when the hands and arms are idle; and the "third rhythm" (alpha activity in the temporal or frontal lobes). Alpha can be abnormal; for example, an EEG that has diffuse alpha occurring in coma and is not responsive to external stimuli is referred to as "alpha coma".



beta waves

- Beta is the frequency range from 12 Hz to about 30 Hz. It is seen usually on both sides in symmetrical distribution and is most evident frontally. Beta activity is closely linked to motor behavior and is generally attenuated during active movements. Low amplitude beta with multiple and varying frequencies is often associated with active, busy or anxious thinking and active concentration. Rhythmic beta with a dominant set of frequencies is associated with various pathologies and drug effects, especially benzodiazepines. It may be absent or reduced in areas of cortical damage. It is the dominant rhythm in patients who are alert or anxious or who have their eyes open.



gamma waves

- Gamma is the frequency range approximately 30–100 Hz. Gamma rhythms are thought to represent binding of different populations of neurons together into a network for the purpose of carrying out a certain cognitive or motor function.

- Mu ranges 8–13 Hz., and partly overlaps with other frequencies. It reflects the synchronous firing of motor neurons in rest state. Mu suppression is thought to reflect motor mirror neuron systems, because when an action is observed, the pattern extinguishes, possibly because of the normal neuronal system and the mirror neuron system "go out of sync", and interfere with each other.

"Ultra-slow" or "near-DC" activity is recorded using DC amplifiers in some research contexts. It is not typically recorded in a clinical context because the signal at these frequencies is susceptible to a number of artifacts.

Some features of the EEG are transient rather than rhythmic. Spikes and sharp waves may represent seizure activity or interictal activity in individuals with epilepsy or a predisposition toward epilepsy. Other transient features are normal: vertex waves and sleep spindles are seen in normal sleep.

Note that there are types of activity that are statistically uncommon, but not associated with dysfunction or disease. These are often referred to as "normal variants." The mu rhythm is an example of a normal variant.

The normal Electroencephalography (EEG) varies by age. The neonatal EEG is quite different from the adult EEG. The EEG in childhood generally has slower frequency oscillations than the adult EEG.

The normal EEG also varies depending on state. The EEG is used along with other measurements (EOG, EMG) to define sleep stages in polysomnography. Stage I sleep (equivalent to drowsiness in some systems) appears on the EEG as drop-out of the posterior basic rhythm. There can be an increase in theta frequencies. Santamaria and Chiappa cataloged a number of the variety of patterns associated with drowsiness. Stage II sleep is characterized by sleep spindles—transient runs of rhythmic activity in the 12–14 Hz range (sometimes referred to as the "sigma" band) that have a frontal-central maximum. Most of the activity in Stage II is in the 3–6 Hz range. Stage III and IV sleep are defined by the presence of delta frequencies and are often referred to collectively as "slow-wave sleep." Stages I-IV comprise non-REM (or "NREM") sleep. The EEG in REM (rapid eye movement) sleep appears somewhat similar to the awake EEG.

EEG under general anesthesia depends on the type of anesthetic employed. With halogenated anesthetics, such as halothane or intravenous agents, such as propofol, a rapid (alpha or low beta), nonreactive EEG pattern is seen over most of the scalp, especially anteriorly; in some older terminology this was known as a WAR (widespread anterior rapid) pattern, contrasted with a WAIS (widespread slow) pattern associated with high doses of opiates. Anesthetic effects on EEG signals are beginning to be understood at the level of drug actions on different kinds of synapses and the circuits that allow synchronized neuronal activity.

Artifacts

Biological artifacts

Electrical signals detected along the scalp by an EEG, but that originate from non-cerebral origin are called artifacts. EEG data is almost always contaminated by such artifacts. The amplitude of artifacts can be quite large relative to the size of amplitude of the cortical signals of interest. This is one of the reasons why it takes considerable experience to correctly interpret EEGs clinically. Some of the most common types of biological artifacts include:

- Eye-induced artifacts (includes eye blinks, eye movements and extra-ocular muscle activity)
- EKG (cardiac) artifacts
- EMG (muscle activation)-induced artifacts
- Glossokinetic artifacts

The most prominent eye-induced artifacts are caused by the potential difference between the cornea and retina, which is quite large compared to cerebral potentials. When the eyes and eyelids are completely still, this corneo-retinal dipole does not affect EEG. However, blinks occur several times per minute, the eyes movements occur several times per second. Eyelid movements, occurring mostly during blinking or vertical eye movements, elicit a large potential seen mostly in the difference between the Electrooculography (EOG) channels above and below the eyes. An established explanation of this potential regards the eyelids as sliding electrodes that short-circuit the positively charged cornea to the extra-ocular skin. Rotation of the eyeballs, and consequently of the corneo-retinal dipole, increases the potential in electrodes towards which the eyes are rotated, and decrease the potentials in the opposing electrodes. Eye movements called saccades also generate transient electromyographic potentials, known as saccadic spike potentials (SPs). The spectrum of these SPs overlaps the gamma-band, and seriously confounds analysis of induced gamma-band responses, requiring tailored artifact correction approaches. Purposeful or reflexive eye blinking also generates electromyographic potentials, but more importantly there is reflexive movement of the eyeball during blinking that gives a characteristic artifactual appearance of the EEG.

Eyelid fluttering artifacts of a characteristic type were previously called Kappa rhythm (or Kappa waves). It is usually seen in the prefrontal leads, that is, just over the eyes. Sometimes they are seen with mental activity. They are usually in the Theta (4–7 Hz) or Alpha (8–13 Hz) range. They were named because they were believed to originate from the brain. Later study revealed they were generated by rapid fluttering of the eyelids, sometimes so minute that it was difficult to see. They are in fact noise in the EEG reading, and should not technically be called a rhythm or wave. Therefore, current usage in electroencephalography refers to the phenomenon as an eyelid fluttering artifact, rather than a Kappa rhythm (or wave).

Some of these artifacts can be useful in various applications. The EOG signals, for instance, can be used to detect and track eye-movements, which are very important in polysomnography, and is also in conventional EEG for assessing possible changes in alertness, drowsiness or sleep.

EKG artifacts are quite common and can be mistaken for spike activity. Because of this, modern EEG acquisition commonly includes a one-channel EKG from the extremities. This also allows the EEG to identify cardiac arrhythmias that are an important differential diagnosis to syncope or other episodic/attack disorders.

Glossokinetic artifacts are caused by the potential difference between the base and the tip of the tongue. Minor tongue movements can contaminate the EEG, especially in parkinsonian and tremor disorders.

Environmental artifacts

In addition to artifacts generated by the body, many artifacts originate from outside the body. Movement by the patient, or even just settling of the electrodes, may cause *electrode pops*, spikes originating from a momentary change in the impedance of a given electrode. Poor grounding of the EEG electrodes can cause significant 50 or 60 Hz artifact, depending on the local power system's frequency. A third source of possible interference can be the presence of an IV drip; such devices can cause rhythmic, fast, low-voltage bursts, which may be confused for spikes.

Artifact correction

Recently, independent component analysis techniques have been used to correct or remove EEG contaminates. These techniques attempt to "unmix" the EEG signals into some number of underlying components. There are many source separation algorithms, often assuming various behaviors or natures of EEG. Regardless, the principle behind any particular method usually allow "remixing" only those components that would result in "clean" EEG by nullifying (zeroing) the weight of unwanted components. Fully automated artifact rejection methods, which use ICA, have also been developed.

Abnormal activity

Abnormal activity can broadly be separated into epileptiform and non-epileptiform activity. It can also be separated into focal or diffuse.

Focal epileptiform discharges represent fast, synchronous potentials in a large number of neurons in a somewhat discrete area of the brain. These can occur as interictal activity, between seizures, and represent an area of cortical irritability that may be predisposed to producing epileptic seizures. Interictal discharges are not wholly reliable for determining whether a patient has epilepsy nor where his/her seizure might originate.

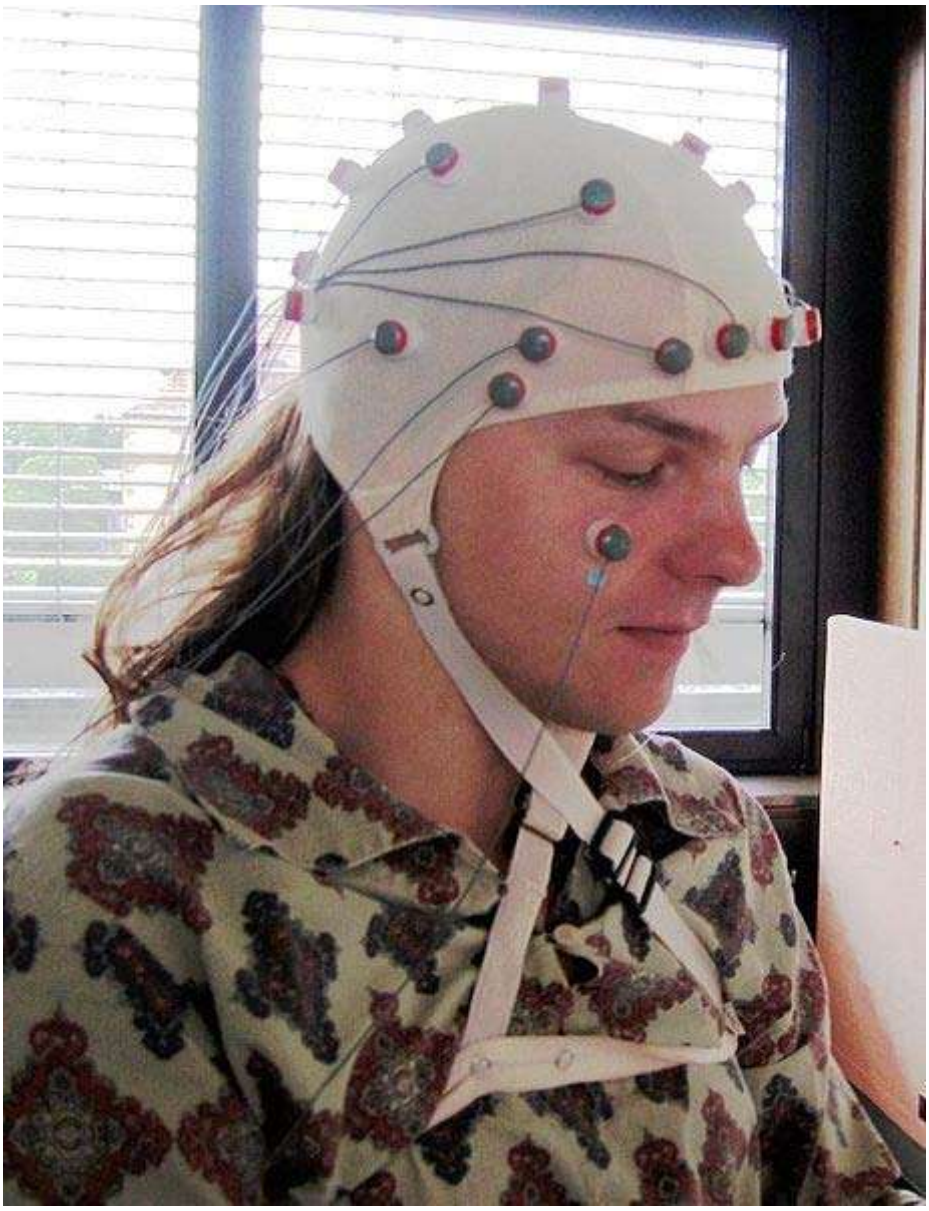
Generalized epileptiform discharges often have an anterior maximum, but these are seen synchronously throughout the entire brain. They are strongly suggestive of a generalized epilepsy.

Focal non-epileptiform abnormal activity may occur over areas of the brain where there is focal damage of the cortex or white matter. It often consists of an increase in slow frequency rhythms and/or a loss of normal higher frequency rhythms. It may also appear as focal or unilateral decrease in amplitude of the EEG signal.

Diffuse non-epileptiform abnormal activity may manifest as diffuse abnormally slow rhythms or bilateral slowing of normal rhythms, such as the PBR.

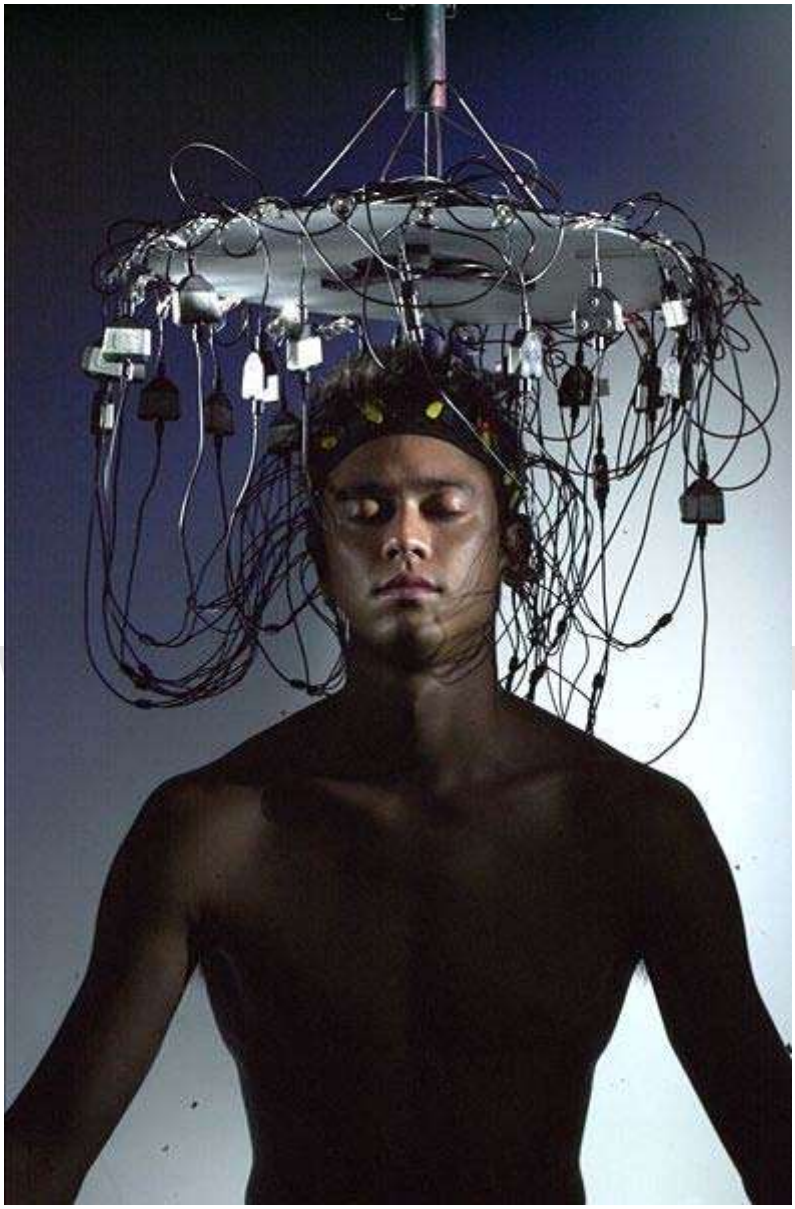
Intracortical Encephalogram electrodes and sub-dural electrodes can be used in tandem to discriminate and discretize artifact from epileptiform and other severe neurological events.

More advanced measures of abnormal EEG signals have also recently received attention as possible biomarkers for different disorders such as Alzheimer's disease.



Person wearing electrodes for EEG

Portable recording device for EEG



EEG electroencephalophone used during a music performance in which bathers from around the world were networked together as part of a collective musical performance, using their brainwaves to control sound, lighting, and the bath environment

History

A timeline of the history of EEG is given by Swartz. Richard Caton (1842–1926), a physician practicing in Liverpool, presented his findings about electrical phenomena of the exposed cerebral hemispheres of rabbits and monkeys in the British Medical Journal in 1875. In 1890, Polish physiologist Adolf Beck published an investigation of spontaneous electrical activity of the brain of rabbits and dogs that included rhythmic oscillations altered by light.

In 1912, Russian physiologist, Vladimir Vladimirovich Pravdich-Neminsky published the first animal EEG and the evoked potential of the mammalian (dog). In 1914, Napoleon Cybulski and Jelenska-Macieszyna photographed EEG-recordings of experimentally induced seizures.

German physiologist and psychiatrist Hans Berger (1873–1941) recorded the first human EEG in 1924. Expanding on work previously conducted on animals by Richard Caton and others, Berger also invented the electroencephalogram (giving the device its name), an invention described "as one of the most surprising, remarkable, and momentous developments in the history of clinical neurology". His discoveries were first confirmed by British scientists Edgar Douglas Adrian and B. H. C. Matthews in 1934 and developed by them.

In 1934, Fisher and Lowenback first demonstrated epileptiform spikes. In 1935 Gibbs, Davis and Lennox described interictal spike waves and the 3 cycles/s pattern of clinical absence seizures, which began the field of clinical electroencephalography. Subsequently, in 1936 Gibbs and Jasper reported the interictal spike as the focal signature of epilepsy. The same year, the first EEG laboratory opened at Massachusetts General Hospital.

Franklin Offner (1911–1999), professor of biophysics at Northwestern University developed a prototype of the EEG that incorporated a piezoelectric inkwriter called a Crystograph (the whole device was typically known as the Offner Dynograph).

In 1947, The American EEG Society was founded and the first International EEG congress was held. In 1953 Aserinsky and Kleitman describe REM sleep.

In the 1950s, William Grey Walter developed an adjunct to EEG called EEG topography, which allowed for the mapping of electrical activity across the surface of the brain. This enjoyed a brief period of popularity in the 1980s and seemed especially promising for psychiatry. It was never accepted by neurologists and remains primarily a research tool.

Various uses

The EEG has been used for many purposes besides the conventional uses of clinical diagnosis and conventional cognitive neuroscience. Long-term EEG recordings in epilepsy patients are used for seizure prediction. Neurofeedback remains an important extension, and in its most advanced form is also attempted as the basis of brain computer interfaces. The EEG is also used quite extensively in the field of neuromarketing. There are many commercial products substantially based on the EEG.

Honda is attempting to develop a system to move its Asimo robot using EEG, a technology it eventually hopes to incorporate into its automobiles.

EEGs have been used as evidence in trials in the Indian state of Maharastra.

EEG and Telepathy

DARPA budgeted $4 million in 2009 to investigate technology to enable soldiers on the battlefield to communicate via computer-mediated telepathy. The aim is to analyse neural signals that exist in the brain before words are spoken.

Chapter- 4

Magnetoencephalography

Magnetoencephalography (**MEG**) is a technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using arrays of SQUIDs (superconducting quantum interference devices). Applications of MEG include basic research into perceptual and cognitive brain processes, localizing regions affected by pathology before surgical removal, determining the function of various parts of the brain, and neurofeedback.

History of MEG

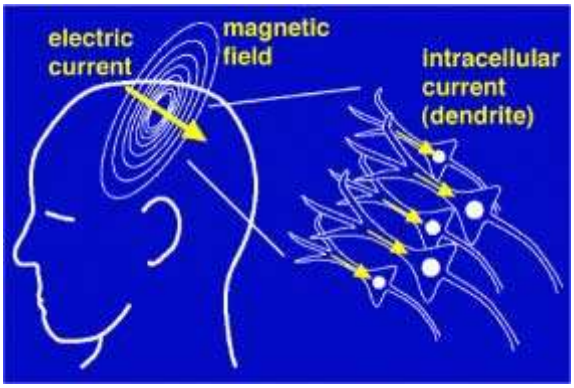
MEG signals were first measured by University of Illinois physicist David Cohen in 1968, before the availability of the SQUID, using a copper induction coil as the detector. To reduce the magnetic background noise, the measurements were made in a magnetically shielded room. The coil detector was barely sensitive enough, resulting in poor, noisy MEG measurements that were difficult to use. Later, Cohen built a better shielded room at MIT, and used one of the first SQUID detectors, just developed by James E. Zimmerman, a researcher at Ford Motor Company, to again measure MEG signals. This time the signals were almost as clear as those of EEG. This stimulated the interest of physicists who had been looking for uses of SQUIDs. Subsequently, various types of spontaneous and evoked MEGs began to be measured.

At first, a single SQUID detector was used to successively measure the magnetic field at a number of points around the subject's head. This was cumbersome, and in the 1980s, MEG manufacturers began to arrange multiple sensors into arrays to cover a larger area of the head. Present-day MEG arrays are set in helmet-shaped dewar that typically contain 300 sensors, covering most of the head. In this way, MEGs of a subject or patient can now be accumulated rapidly and efficiently.

The basis of the MEG signal

Patient undergoing an MEG

Synchronized neuronal currents induce weak magnetic fields. At 10 femtotesla (fT) for cortical activity and 10^3 fT for the human alpha rhythm, the brain's magnetic field is considerably smaller than the ambient magnetic noise in an urban environment, which is on the order of 10^8 fT or 10 μT. The essential problem of biomagnetism is thus the weakness of the signal relative to the sensitivity of the detectors, and to the competing environmental noise.



Origin of the brain's magnetic field. The electric current also produces the EEG signal.

The MEG (and EEG) signals derive from the net effect of ionic currents flowing in the dendrites of neurons during synaptic transmission. In accordance with Maxwell's equations, any electrical current will produce an orthogonally oriented magnetic field. It is this field which is measured. The net currents can be thought of as electric dipoles, i.e. currents with a position, orientation, and magnitude, but no spatial extent. According to the right-hand rule, a current dipole gives rise to a magnetic field that flows around the axis of its vector component.

To generate a signal that is detectable, approximately 50,000 active neurons are needed. Since current dipoles must have similar orientations to generate magnetic fields that reinforce each other, it is often the layer of pyramidal cells, which are situated perpendicular to the cortical surface, that give rise to measurable magnetic fields. Bundles of these neurons that are orientated tangentially to the scalp surface project measurable portions of their magnetic fields outside of the head, and these bundles are typically located in the sulci. Researchers are experimenting with various signal processing methods in the search for methods that detect deep brain (i.e., non-cortical) signal, but no clinically useful method is currently available.

It is worth noting that action potentials do not usually produce an observable field, mainly because the currents associated with action potentials flow in opposite directions and the magnetic fields cancel out. However, action fields have been measured from peripheral nerves.

Magnetic shielding

Since the magnetic signals emitted by the brain are on the order of a few femtoteslas, shielding from external magnetic signals, including the Earth's magnetic field, is necessary. Appropriate magnetic shielding can be obtained by constructing rooms made of aluminium and mu-metal for reducing high-frequency and low-frequency noise, respectively.

Entrance to MSR, showing the separate shielding layers

Magnetically shielded room (MSR)

A magnetically shielded room (MSR) model consists of three nested main layers. Each of these layers is made of a pure aluminium layer, plus a high permeability ferromagnetic layer, similar in composition to molybdenum permalloy. The ferromagnetic layer is supplied as 1 mm sheets, while the innermost layer is composed of four sheets in close contact, and the outer two layers are composed of three sheets each. Magnetic continuity is maintained by overlay strips. Insulating washers are used in the screw assemblies to ensure that each main layer is electrically isolated. This helps eliminate radio frequency radiation, which would degrade SQUID performance. Electrical continuity of the aluminium is also maintained by aluminium overlay strips to ensure AC eddy-current shielding, which is important at frequencies greater than 1 Hz. The junctions of the inner layer are often electroplated with silver or gold to improve conductivity of the aluminium layers.

Active shielding system

Active systems are designed for three dimensional noise cancellation. To implement an active system, low-noise fluxgate magnetometers are mounted at the center of each surface and oriented orthogonally to it. This negatively feeds a DC amplifier through a low-pass network with a slow falloff to minimize positive feedback and oscillation. Built into the system are shaking and degaussing wires. Shaking wires increase the magnetic permeability, while the permanent degaussing wires are applied to all surfaces of the inner main layer to degauss the surfaces. Moreover, noise cancellation algorithms can reduce both low-frequency and high-frequency noise. Modern systems have a noise floor of around 2–3 $fT/Hz^{0.5}$ above 1 Hz.

Source localization

The inverse problem

The challenge posed by MEG is to determine the location of electric activity within the brain from the induced magnetic fields outside the head. Problems such as this, where model parameters (the location of the activity) have to be estimated from measured data (the SQUID signals) are referred to as *inverse problems* (in contrast to *forward problems* where the model parameters (e.g. source location) are known and the data (e.g. the field at a given distance) is to be estimated.) The primary difficulty is that the inverse problem does not have a unique solution (i.e., there are infinite possible "correct" answers), and the problem of defining the "best" solution is itself the subject of intensive research. Possible solutions can be derived using models involving prior knowledge of brain activity.

The source models can be either over-determined or under-determined. An over-determined model may consist of a few point-like sources ("equivalent dipoles"), whose locations are then estimated from the data. Under-determined models may be used in cases where many different distributed areas are activated ("distributed source solutions"): there are infinitely many possible current distributions explaining the measurement results, but the most likely is selected. Localization algorithms make use of given source and head models to find a likely location for an underlying focal field generator.

Localization algorithms using overdetermined models operate by expectation-maximization: the system is initialized with a first guess. A loop is started, in which a forward model is used to simulate the magnetic field that would result from the current guess. The guess is adjusted to reduce the discrepancy between the simulated field and the measured field. This process is iterated until convergence.

The extent to which the constraint-free MEG inverse problem is ill-posed cannot be overemphasized. If one's goal is to estimate the current density within the human brain with say a 5mm resolution then it is well established that the vast majority of the information needed to perform a unique inversion must come not from the magnetic field measurement but rather from the constraints applied to the problem. Furthermore, even when a unique inversion is possible in the presence of such constraints said inversion can be unstable. These conclusions are easily deduced from published works.

Magnetic source imaging

The estimated source locations can be combined with magnetic resonance imaging (MRI) images to create magnetic source images (MSI). The two sets of data are combined by measuring the location of a common set of fiducial points marked during MRI with lipid markers and marked during MEG with electrified coils of wire that give off magnetic fields. The locations of the fiducial points in each data set are then used to define a

common coordinate system so that superimposing the functional MEG data onto the structural MRI data ("coregistration") is possible.

A criticism of the use of this technique in clinical practice is that it produces colored areas with definite boundaries superimposed upon an MRI scan: the untrained viewer may not realize that the colors do not represent a physiological certainty, because of the relatively low spatial resolution of MEG, but rather a probability cloud derived from statistical processes. However, when the magnetic source image corroborates other data, it can be of clinical utility.

Dipole model source localization

A widely accepted source-modeling technique for MEG involves calculating a set of equivalent current dipoles (ECDs), which assumes the underlying neuronal sources to be focal. This dipole fitting procedure is non-linear and over-determined, since the number of unknown dipole parameters is smaller than the number of MEG measurements. Automated multiple dipole model algorithms such as MUSIC (MUltiple SIgnal Classification) and MSST (MultiStart Spatial and Temporal) modeling are applied to the analysis of MEG responses. The limitations of dipole models for characterizing neuronal responses are (1) difficulties in localizing extended sources with ECDs, (2) problems with accurately estimating the total number of dipoles in advance, and (3) dependency on dipole location, especially depth in the brain.

Distributed Source Models

Unlike multiple-dipole modeling, distributed source models divide the source space into a grid containing a large number of dipoles. The inverse problem is to obtain the dipole moments for the grid nodes. As the number of unknown dipole moments is much greater than the number of MEG sensors, the inverse solution is highly underdetermined, so additional constraints are needed to reduce ambiguity of the solution. The primary advantage of this approach is that no prior specification of the source model is necessary. However, the resulting distributions may be difficult to interpret, because they only reflect a "blurred" (or even distorted) image of the true neuronal source distribution. The matter is complicated by the fact that spatial resolution depends strongly on several parameters such as brain area, depth, orientation, number of sensors etc.

Independent component analysis (ICA)

Independent component analysis (ICA) is another signal processing solution that separates different signals that are statistically independent in time. It is primarily used to remove artifacts such as blinking, eye muscle movement, facial muscle artifacts, cardiac artifacts, etc. from MEG and EEG signals that may be contaminated with outside noise. However, ICA has poor resolution of highly correlated brain sources.

MEG use in the field

In research, MEG's primary use is the measurement of time courses of activity. MEG can resolve events with a precision of 10 milliseconds or faster, while functional MRI (fMRI), which depends on changes in blood flow, can at best resolve events with a precision of several hundred milliseconds. MEG also accurately pinpoints sources in primary auditory, somatosensory and motor areas. For creating functional maps of human cortex during more complex cognitive tasks, MEG is most often combined with fMRI, as the methods complement each other. Neuronal (MEG) and hemodynamic (fMRI) data do not necessarily agree, in spite of the tight relationship between local field potentials (LFP) and blood oxygenation level dependent (BOLD) signals. MEG and BOLD signals may originate from the same source (though the BOLD signals are filtered through the hemodynamic response).

Recent studies have reported successful classification of patients with multiple sclerosis, Alzheimer's disease, schizophrenia, Sjögren's syndrome, chronic alcoholism, and facial pain. MEG can be used to distinguish these patients from healthy control subjects, suggesting a future role of MEG in diagnostics.

Focal epilepsy

The clinical uses of MEG are in detecting and localizing pathological activity in patients with epilepsy, and in localizing eloquent cortex for surgical planning in patients with brain tumors or intractable epilepsy. The goal of epilepsy surgery is to remove the epileptogenic tissue while sparing healthy brain areas. Knowing the exact position of essential brain regions (such as the primary motor cortex and primary sensory cortex, visual cortex, and areas involved in speech production and comprehension) helps to avoid surgically induced neurological deficits. Direct cortical stimulation and somatosensory evoked potentials recorded on ECoG are considered the gold standard for localizing essential brain regions. These procedures can be performed either intraoperatively or from chronically indwelling subdural grid electrodes. Both are invasive.

Noninvasive MEG localizations of the central sulcus obtained from somatosensory evoked magnetic fields show strong agreement with these invasive recordings. MEG studies assist in clarification of the functional organization of primary somatosensory cortex and to delineate the spatial extent of hand somatosensory cortex by stimulation of the individual digits. This agreement between invasive localization of cortical tissue and MEG recordings shows the effectiveness of MEG analysis and indicates that MEG may substitute invasive procedures in the future.

Fetal MEG

MEG has been used to study cognitive processes such as vision, audition and language processing in fetuses and newborns.

Comparison with related techniques

MEG has been in development since the 1960s but has been greatly aided by recent advances in computing algorithms and hardware, and promises improved spatial resolution coupled with extremely high temporal resolution (better than 1 ms). Since the MEG signal is a direct measure of neuronal activity, its temporal resolution is comparable with that of intracranial electrodes.

MEG complements other brain activity measurement techniques such as electroencephalography (EEG), positron emission tomography (PET), and fMRI. Its strengths consist in independence of head geometry compared to EEG (unless ferromagnetic implants are present) and non-invasiveness, as opposed to PET.

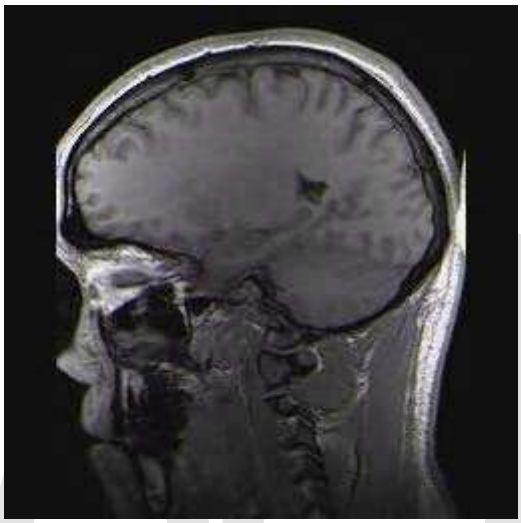
MEG vs. EEG

Although EEG and MEG signals originate from the same neurophysiological processes, there are important differences. Magnetic fields are less distorted than electric fields by the skull and scalp, which results in a better spatial resolution of the MEG. Whereas scalp EEG is sensitive to both tangential and radial components of a current source in a spherical volume conductor, MEG detects only its tangential components. MEG therefore measures activity in the sulci selectively, whereas scalp EEG measures activity both in the sulci and at the top of the cortical gyri. EEG is therefore sensitive to activity in more brain areas, but activity that is visible in MEG can also be localized with more accuracy.

Scalp EEG is sensitive to extracellular volume currents produced by postsynaptic potentials. MEG primarily detects intracellular currents associated with these synaptic potentials because the field components generated by volume currents tend to cancel out in a spherical volume conductor The decay of magnetic fields as a function of distance is more pronounced than for electric fields. MEG is therefore more sensitive to superficial cortical activity, which makes it useful for the study of neocortical epilepsy. Finally, MEG is reference-free, while scalp EEG relies on a reference that, when active, makes interpretation of the data difficult.

Chapter- 5

Magnetic Resonance Imaging



Para-sagittal MRI of the head, with aliasing artifacts (nose and forehead appear at the back of the head)

Magnetic resonance imaging (**MRI**), **nuclear magnetic resonance imaging** (**NMRI**), or **magnetic resonance tomography** (**MRT**) is a medical imaging technique used in radiology to visualize detailed internal structures. MRI makes use of the property of Nuclear magnetic resonance (NMR) to image nuclei of atoms inside the body.

An MRI machine uses a powerful magnetic field to align the magnetization of some atoms in the body, and radio frequency fields to systematically alter the alignment of this magnetization. This causes the nuclei to produce a rotating magnetic field detectable by the scanner—and this information is recorded to construct an image of the scanned area of the body. Strong magnetic field gradients cause nuclei at different locations to rotate at different speeds. 3-D spatial information can be obtained by providing gradients in each direction.

MRI provides good contrast between the different soft tissues of the body, which make it especially useful in imaging the brain, muscles, the heart, and cancers compared with other medical imaging techniques such as computed tomography (CT) or X-rays. Unlike CT scans or traditional X-rays MRI uses no ionizing radiation.

How MRI works

The body is largely composed of water molecules. Each water molecule has two hydrogen nuclei or protons. When a person goes inside the powerful magnetic field of the scanner, the magnetic moments of some of these protons changes, and aligns with the direction of the field.

In an MRI machine a radio frequency transmitter is briefly turned on, producing an electromagnetic field. The photons of this field have just the right energy, known as the resonance frequency, to flip the spin of the aligned protons in the body. As the intensity and duration of application of the field increase, more aligned spins are affected. After the field is turned off, the protons decay to the original spin-down state and the difference in energy between the two states is released as a photon. It is these photons that produce the electromagnetic signal that the scanner detects. The frequency at which the protons resonate depends on the strength of the magnetic field. As a result of conservation of energy, this resonation frequency also dictates the frequency of the released photons. The photons released when the field is removed have an energy — and therefore a frequency — due to the amount of energy the protons absorbed while the field was active.

It is this relationship between field-strength and frequency that allows the use of nuclear magnetic resonance for imaging. Additional magnetic fields are applied during the scan to make the magnetic field strength depend on the position within the patient, in turn making the frequency of the released photons dependent on position in a predictable manner. Position information can then be recovered from the resulting signal by the use of a Fourier transform. These fields are created by passing electric currents through specially-wound solenoids, known as gradient coils. Since these coils are within the bore of the scanner, there are large forces between them and the main field coils, producing most of the noise that is heard during operation. Without efforts to dampen this noise, it can approach 130 decibels (dB) with strong fields.

An image can be constructed because the protons in different tissues return to their equilibrium state at different rates, which is a difference that can be detected. Five different tissue variables — spin density, T_1 and T_2 relaxation times and flow and spectral shifts can be used to construct images. By changing the parameters on the scanner, this effect is used to create contrast between different types of body tissue or between other properties, as in fMRI and diffusion MRI.

Contrast agents may be injected intravenously to enhance the appearance of blood vessels, tumors or inflammation. Contrast agents may also be directly injected into a joint in the case of arthrograms, MRI images of joints. Unlike CT, MRI uses no ionizing radiation and is generally a very safe procedure. Nonetheless the strong magnetic fields and radio pulses can affect metal implants, including cochlear implants and cardiac pacemakers. In the case of cochlear implants, the US FDA has approved some implants for MRI compatibility. In the case of cardiac pacemakers, the results can sometimes be lethal , so patients with such implants are generally not eligible for MRI.

MRI is used to image every part of the body, and is particularly useful for tissues with many hydrogen nuclei and little density contrast, such as the brain, muscle, connective tissue and most tumors.

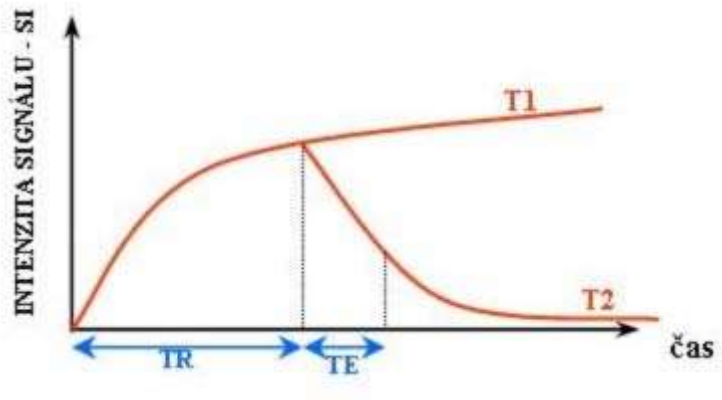
History

Magnetic resonance imaging is a relatively new technology. The first MR image was published in 1973 and the first cross-sectional image of a living mouse was published in January 1974. The first studies performed on humans were published in 1977. By comparison, the first human X-ray image was taken in 1895.

Applications

In clinical practice, MRI is used to distinguish pathologic tissue (such as a brain tumor) from normal tissue. One advantage of an MRI scan is that it is harmless to the patient. It uses strong magnetic fields and non-ionizing radiation in the radio frequency range, unlike CT scans and traditional X-rays, which both use ionizing radiation.

While CT provides good spatial resolution (the ability to distinguish two separate structures an arbitrarily small distance from each other), MRI provides comparable resolution with far better contrast resolution (the ability to distinguish the differences between two arbitrarily similar but not identical tissues). The basis of this ability is the complex library of *pulse sequences* that the modern medical MRI scanner includes, each of which is optimized to provide *image contrast* based on the chemical sensitivity of MRI.



Effects of TR, TE, T1 and T2 on MR signal.

For example, with particular values of the *echo time* (T_E) and the *repetition time* (T_R), which are basic parameters of image acquisition, a sequence takes on the property of T_2-weighting. On a T_2-weighted scan, water- and fluid-containing tissues are bright (most modern T_2 sequences are actually *fast* T_2 sequences) and fat-containing tissues are dark. The reverse is true for T_1-weighted images. Damaged tissue tends to develop edema,

which makes a T_2-weighted sequence sensitive for pathology, and generally able to distinguish pathologic tissue from normal tissue. With the addition of an additional radio frequency pulse and additional manipulation of the magnetic gradients, a T_2-weighted sequence can be converted to a **FLAIR** sequence, in which free water is now dark, but edematous tissues remain bright. This sequence in particular is currently the most sensitive way to evaluate the brain for demyelinating diseases, such as multiple sclerosis.

The typical MRI examination consists of 5–20 sequences, each of which are chosen to provide a particular type of information about the subject tissues. This information is then synthesized by the interpreting physician.

Basic MRI scans

T_1-weighted MRI

T_1-weighted scans are a standard basic scan, in particular differentiating fat from water - with water darker and fat brighter use a gradient echo (GRE) sequence, with short T_E and short T_R. This is one of the basic types of MR contrast and is a commonly run clinical scan. The T_1 weighting can be increased (improving contrast) with the use of an inversion pulse as in an MP-RAGE sequence. Due to the short repetition time (T_R) this scan can be run very fast allowing the collection of high resolution 3D datasets. A T_1 reducing gadolinium contrast agent is also commonly used, with a T_1 scan being collected before and after administration of contrast agent to compare the difference. In the brain T_1-weighted scans provide good gray matter/white matter contrast; in other words, T_1-weighted images highlight fat deposition.

T_2-weighted MRI

T_2-weighted scans are another basic type. Like the T1-weighted scan, fat is differentiated from water - but in this case fat shows darker, and water lighter. They are therefore particularly well suited to imaging edema. On brain scans cerebral white matter (fat containing) therefore shows as darker than the grey matter. T_2-weighted scans use a spin echo (SE) sequence, with long T_E and long T_R. They have long been the clinical workhorse as the spin echo sequence is less susceptible to inhomogeneities in the magnetic field.

T^*_2-weighted MRI

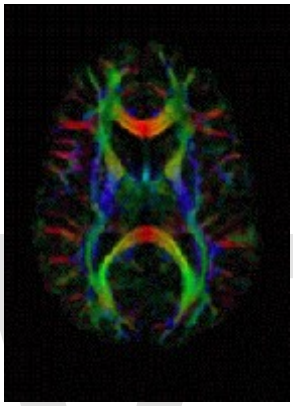
T^*_2 (pronounced "T 2 star") weighted scans use a gradient echo (GRE) sequence, with long T_E and long T_R. The gradient echo sequence used does not have the extra refocusing pulse used in spin echo so it is subject to additional losses above the normal T_2 decay (referred to as T_2'), these taken together are called T^*_2. This also makes it more prone to susceptibility losses at air/tissue boundaries, but can increase contrast for certain types of tissue, such as venous blood.

Spin density weighted MRI

Spin density, also called proton density, weighted scans try to have no contrast from either T_2 or T_1 decay, the only signal change coming from differences in the amount of available spins (hydrogen nuclei in water). It uses a spin echo or sometimes a gradient echo sequence, with short T_E and long T_R.

Specialized MRI scans

Diffusion MRI



DTI image

Diffusion MRI measures the diffusion of water molecules in biological tissues. In an isotropic medium (inside a glass of water for example) water molecules naturally move randomly according to turbulence and Brownian motion. In biological tissues however, where the Reynold's number is low enough for flows to be laminar, the diffusion may be anisotropic. For example a molecule inside the axon of a neuron has a low probability of crossing the myelin membrane. Therefore the molecule moves principally along the axis of the neural fiber. If we know that molecules in a particular voxel diffuse principally in one direction we can make the assumption that the majority of the fibers in this area are going parallel to that direction.

The recent development of diffusion tensor imaging (DTI) enables diffusion to be measured in multiple directions and the fractional anisotropy in each direction to be calculated for each voxel. This enables researchers to make brain maps of fiber directions to examine the connectivity of different regions in the brain (using tractography) or to examine areas of neural degeneration and demyelination in diseases like Multiple Sclerosis.

Another application of diffusion MRI is diffusion-weighted imaging (DWI). Following an ischemic stroke, DWI is highly sensitive to the changes occurring in the lesion. It is speculated that increases in restriction (barriers) to water diffusion, as a result of cytotoxic edema (cellular swelling), is responsible for the increase in signal on a DWI

scan. The DWI enhancement appears within 5–10 minutes of the onset of stroke symptoms (as compared with computed tomography, which often does not detect changes of acute infarct for up to 4–6 hours) and remains for up to two weeks. Coupled with imaging of cerebral perfusion, researchers can highlight regions of "perfusion/diffusion mismatch" that may indicate regions capable of salvage by reperfusion therapy.

Like many other specialized applications, this technique is usually coupled with a fast image acquisition sequence, such as echo planar imaging sequence.

Magnetization Transfer MRI

Magnetization transfer (MT) refers to the transfer of longitudinal magnetization from free water protons to hydration water protons in NMR and MRI.

In magnetic resonance imaging of molecular solutions, such as protein solutions, two types of water molecules, free (bulk) and hydration (bound), are found. Free water protons have faster average rotational frequency and hence less fixed water molecules that may cause local field inhomogeneity. Because of this uniformity, most free water protons have resonance frequency lying narrowly around the normal proton resonance frequency of 63 MHz (at 1.5 teslas). This also results in slower transverse magnetization dephasing and hence longer T_2. Conversely, hydration water molecules are slowed down by interaction with solute molecules and hence create field inhomogeneities that lead to wider resonance frequency spectrum.

Fluid attenuated inversion recovery (FLAIR)

Fluid Attenuated Inversion Recovery (FLAIR) is an inversion-recovery pulse sequence used to null signal from fluids. For example, it can be used in brain imaging to suppress cerebrospinal fluid (CSF) so as to bring out the periventricular hyperintense lesions, such as multiple sclerosis (MS) plaques. By carefully choosing the inversion time TI (the time between the inversion and excitation pulses), the signal from any particular tissue can be suppressed.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) generates pictures of the arteries to evaluate them for stenosis (abnormal narrowing) or aneurysms (vessel wall dilatations, at risk of rupture). MRA is often used to evaluate the arteries of the neck and brain, the thoracic and abdominal aorta, the renal arteries, and the legs (called a "run-off"). A variety of techniques can be used to generate the pictures, such as administration of a paramagnetic contrast agent (gadolinium) or using a technique known as "flow-related enhancement" (e.g. 2D and 3D time-of-flight sequences), where most of the signal on an image is due to blood that recently moved into that plane. Magnetic resonance venography (MRV) is a similar procedure that is used to image veins. In this method, the tissue is now excited inferiorly, while signal is gathered in the plane immediately superior to the excitation plane—thus imaging the venous blood that recently moved from the excited plane.

Magnetic resonance gated intracranial CSF dynamics (MR-GILD)

Magnetic resonance gated intracranial cerebrospinal fluid (CSF) or liquor dynamics (MR-GILD) technique is an MR sequence based on bipolar gradient pulse used to demonstrate CSF pulsatile flow in ventricles, cisterns, aqueduct of Sylvius and entire intracranial CSF pathway. It is a method for analyzing CSF circulatory system dynamics in patients with CSF obstructive lesions such as normal pressure hydrocephalus. It also allows visualization of both arterial and venous pulsatile blood flow in vessels without use of contrast agents.

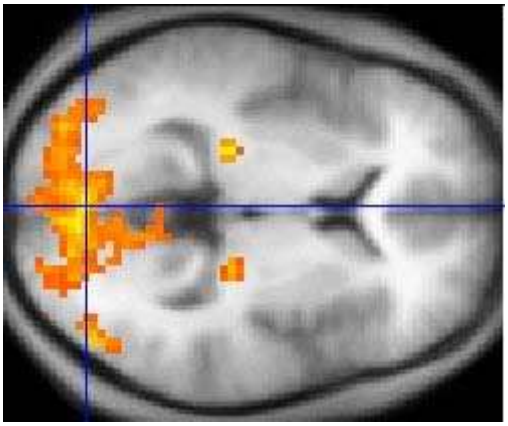
Diastolic time data acquisition (DTDA). Systolic time data acquisition (STDA).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is used to measure the levels of different metabolites in body tissues. The MR signal produces a spectrum of resonances that correspond to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders, especially those affecting the brain, and to provide information on tumor metabolism.

Magnetic resonance spectroscopic imaging (MRSI) combines both spectroscopic and imaging methods to produce spatially localized spectra from within the sample or patient. The spatial resolution is much lower (limited by the available SNR), but the spectra in each voxel contains information about many metabolites. Because the available signal is used to encode spatial and spectral information, MRSI requires high SNR achievable only at higher field strengths (3 T and above).

Functional MRI



A fMRI scan showing regions of activation in orange, including the primary visual cortex (V1, BA17).

Functional MRI (fMRI) measures signal changes in the brain that are due to changing neural activity. The brain is scanned at low resolution but at a rapid rate (typically once every 2–3 seconds). Increases in neural activity cause changes in the MR signal via T^*_2 changes; this mechanism is referred to as the BOLD (blood-oxygen-level dependent) effect. Increased neural activity causes an increased demand for oxygen, and the vascular system actually overcompensates for this, increasing the amount of oxygenated hemoglobin relative to deoxygenated hemoglobin. Because deoxygenated hemoglobin attenuates the MR signal, the vascular response leads to a signal increase that is related to the neural activity. The precise nature of the relationship between neural activity and the BOLD signal is a subject of current research. The BOLD effect also allows for the generation of high resolution 3D maps of the venous vasculature within neural tissue.

While BOLD signal is the most common method employed for neuroscience studies in human subjects, the flexible nature of MR imaging provides means to sensitize the signal to other aspects of the blood supply. Alternative techniques employ arterial spin labeling (ASL) or weight the MRI signal by cerebral blood flow (CBF) and cerebral blood volume (CBV). The CBV method requires injection of a class of MRI contrast agents that are now in human clinical trials. Because this method has been shown to be far more sensitive than the BOLD technique in preclinical studies, it may potentially expand the role of fMRI in clinical applications. The CBF method provides more quantitative information than the BOLD signal, albeit at a significant loss of detection sensitivity.

Real-time MRI

Real-time MRI refers to the continuous monitoring ("filming") of moving objects in real time. While many different strategies have been developed over the past two decades, a recent development reported a real-time MRI technique based on radial FLASH that yields a temporal resolution of 20 to 30 milliseconds for images with an in-plane resolution of 1.5 to 2.0 mm. The new method promises to add important information

about diseases of the joints and the heart. In many cases MRI examinations may become easier and more comfortable for patients.

Interventional MRI

The lack of harmful effects on the patient and the operator make MRI well-suited for "interventional radiology", where the images produced by a MRI scanner are used to guide minimally invasive procedures. Of course, such procedures must be done without *any* ferromagnetic instruments.

A specialized growing subset of interventional MRI is that of intraoperative MRI in which the MRI is used in the surgical process. Some specialized MRI systems have been developed that allow imaging concurrent with the surgical procedure. More typical, however, is that the surgical procedure is temporarily interrupted so that MR images can be acquired to verify the success of the procedure or guide subsequent surgical work.

Radiation therapy simulation

Because of MRI's superior imaging of soft tissues, it is now being utilized to specifically locate tumors within the body in preparation for radiation therapy treatments. For therapy simulation, a patient is placed in specific, reproducible, body position and scanned. The MRI system then computes the precise location, shape and orientation of the tumor mass, correcting for any spatial distortion inherent in the system. The patient is then marked or tattooed with points that, when combined with the specific body position, permits precise triangulation for radiation therapy.

Current density imaging

Current density imaging (CDI) endeavors to use the phase information from images to reconstruct current densities within a subject. Current density imaging works because electrical currents generate magnetic fields, which in turn affect the phase of the magnetic dipoles during an imaging sequence.

Magnetic resonance guided focused ultrasound

In MRgFUS therapy, ultrasound beams are focused on a tissue—guided and controlled using MR thermal imaging—and due to the significant energy deposition at the focus, temperature within the tissue rises to more than 65 °C (150 °F), completely destroying it. This technology can achieve precise ablation of diseased tissue. MR imaging provides a three-dimensional view of the target tissue, allowing for precise focusing of ultrasound energy. The MR imaging provides quantitative, real-time, thermal images of the treated area. This allows the physician to ensure that the temperature generated during each cycle of ultrasound energy is sufficient to cause thermal ablation within the desired tissue and if not, to adapt the parameters to ensure effective treatment.

Multinuclear imaging

Hydrogen is the most frequently imaged nucleus in MRI because it is present in biological tissues in great abundance. However, any nucleus with a net nuclear spin could potentially be imaged with MRI. Such nuclei include helium-3, carbon-13, fluorine-19, oxygen-17, sodium-23, phosphorus-31 and xenon-129. ^{23}Na, ^{31}P and ^{17}O are naturally abundant in the body, so can be imaged directly. Gaseous isotopes such as ^{3}He or ^{129}Xe must be hyperpolarized and then inhaled as their nuclear density is too low to yield a useful signal under normal conditions. ^{17}O, ^{13}C and ^{19}F can be administered in sufficient quantities in liquid form (e.g. ^{17}O-water, ^{13}C-glucose solutions or perfluorocarbons) that hyperpolarization is not a necessity.

Multinuclear imaging is primarily a research technique at present. However, potential applications include functional imaging and imaging of organs poorly seen on ^{1}H MRI (e.g. lungs and bones) or as alternative contrast agents. Inhaled hyperpolarized ^{3}He can be used to image the distribution of air spaces within the lungs. Injectable solutions containing ^{13}C or stabilized bubbles of hyperpolarized ^{129}Xe have been studied as contrast agents for angiography and perfusion imaging. ^{31}P can potentially provide information on bone density and structure, as well as functional imaging of the brain.

Susceptibility weighted imaging (SWI)

Susceptibility weighted imaging (SWI), is a new type of contrast in MRI different from spin density, T_1, or T_2 imaging. This method exploits the susceptibility differences between tissues and uses a fully velocity compensated, three dimensional, RF spoiled, high-resolution, 3D gradient echo scan. This special data acquisition and image processing produces an enhanced contrast magnitude image very sensitive to venous blood, hemorrhage and iron storage. It is used to enhance the detection and diagnosis of tumors, vascular and neurovascular diseases (stroke and hemorrhage, multiple sclerosis, Alzheimer's), and also detects traumatic brain injuries that may not be diagnosed using other methods

Other specialized MRI techniques

field of research and new methods and variants are often published when they are able to get better results in specific fields. Examples of these recent improvements are T*
2-weighted turbo spin-echo (T_2 TSE MRI), double inversion recovery MRI (DIR-MRI) or phase-sensitive inversion recovery MRI (PSIR-MRI), all of them able to improve imaging of the brain lesions. Another example is MP-RAGE (magnetization-prepared rapid acquisition with gradient echo), which improves images of multiple sclerosis cortical lesions.

Portable instruments

Portable magnetic resonance instruments are available for use in education and field research. Using the principles of Earth's field NMR, they have no powerful polarizing

magnet, so that such instruments can be small and inexpensive. Some can be used for both EFNMR spectroscopy and MRI imaging. The low strength of the Earth's field results in poor signal to noise ratios, requiring long scan times to capture spectroscopic data or build up MRI images.

Research with atomic magnetometers have discussed the possibility for cheap and portable MRI instruments without the large magnet.

MRI versus CT

A computed tomography (CT) scanner uses X-rays, a type of ionizing radiation, to acquire its images, making it a good tool for examining tissue composed of elements of a higher atomic number than the tissue surrounding them, such as bone and calcifications (calcium based) within the body (carbon based flesh), or of structures (vessels, bowel). MRI, on the other hand, uses non-ionizing radio frequency (RF) signals to acquire its images and is best suited for non-calcified tissue, though MR images can also be acquired from bones and teeth as well as fossils.

CT may be enhanced by use of contrast agents containing elements of a higher atomic number than the surrounding flesh such as iodine or barium. Contrast agents for MRI have paramagnetic properties, e.g., gadolinium and manganese.

Both CT and MRI scanners are able to generate multiple two-dimensional cross-sections (slices) of tissue and three-dimensional reconstructions. Unlike CT, which uses only X-ray attenuation to generate image contrast, MRI has a long list of properties that may be used to generate image contrast. By variation of scanning parameters, tissue contrast can be altered and enhanced in various ways to detect different features.

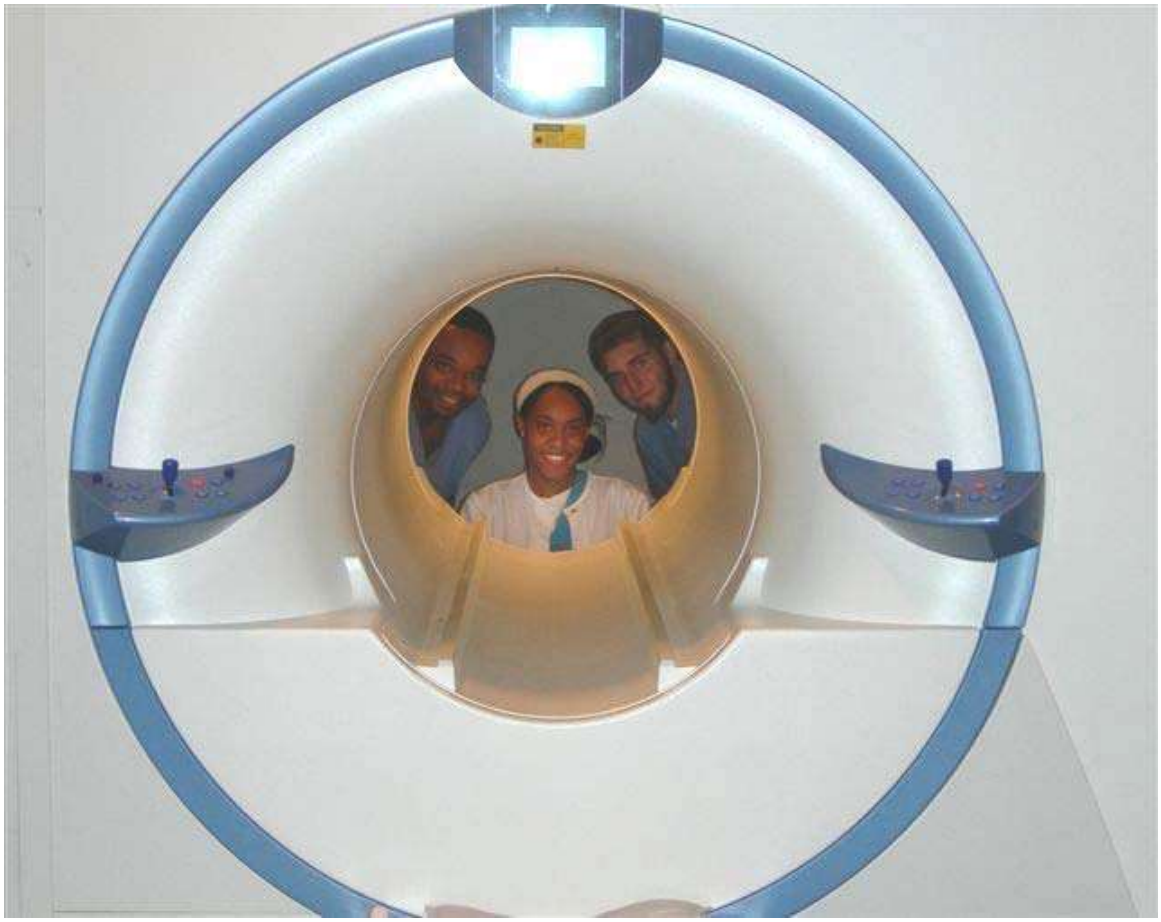
MRI can generate cross-sectional images in any plane (including oblique planes). In the past, CT was limited to acquiring images in the axial (or near axial) plane. The scans used to be called Computed *Axial* Tomography scans (CAT scans). However, the development of multi-detector CT scanners with near-isotropic resolution, allows the CT scanner to produce data that can be retrospectively reconstructed in any plane with minimal loss of image quality.

For purposes of tumor detection and identification in the brain, MRI is generally superior. However, in the case of solid tumors of the abdomen and chest, CT is often preferred due to less motion artifact. Furthermore, CT usually is more widely available, faster, less expensive, and may be less likely to require the person to be sedated or anesthetized.

MRI is also best suited for cases when a patient is to undergo the exam several times successively in the short term, because, unlike CT, it does not expose the patient to the hazards of ionizing radiation.

Economics of MRI

MRI equipment is expensive. 1.5 tesla scanners often cost between $1 million and $1.5 million USD. 3.0 tesla scanners often cost between $2 million and $2.3 million USD. Construction of MRI suites can cost up to $500,000 USD, or more, depending on project scope.



Looking through an MRI scanner

MRI scanners have been significant sources of revenue for healthcare providers in the US. This is because of favorable reimbursement rates from insurers and federal government programs. Insurance reimbursement is provided in two components, an equipment charge for the actual performance of the MRI scan and professional charge for the radiologist's review of the images and/or data. In the US Northeast, an equipment charge might be $3,500 and a professional charge might be $350 although the actual fees received by the equipment owner and interpreting physician are often significantly less and depend on the rates negotiated with insurance companies or determined by governmental action as in the Medicare Fee Schedule. For example, an orthopedic surgery group in Illinois billed a charge of $1,116 for a knee MRI in 2007 but the

Medicare reimbursement in 2007 was only $470.91. Many insurance companies require preapproval of an MRI procedure as a condition for coverage.

In the US, the Deficit Reduction Act of 2007 significantly reduced reimbursement rates paid by federal insurance programs for the equipment component of many scans, shifting the economic landscape. Many private insurers have followed suit.

Safety

A number of features of MRI scanning can give rise to risks.

These include:

- Powerful magnetic fields
- Cryogenic liquids
- Noise
- Claustrophobia

In addition, in cases where MRI contrast agents are used, these also typically have associated risks.

Magnetic field

Most forms of medical or biostimulation implants are generally considered contraindications for MRI scanning. These include pacemakers, vagus nerve stimulators, implantable cardioverter-defibrillators, loop recorders, insulin pumps, cochlear implants, deep brain stimulators. Patients are therefore always asked for complete information about all implants before entering the room for an MRI scan. Several deaths have been reported in patients with pacemakers who have undergone MRI scanning without appropriate precautions. To reduce such risks, implants are increasingly being developed to make them able to be safely scanned, and specialized protocols have been developed to permit the safe scanning of selected implants and pacing devices.

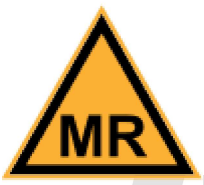
Ferromagnetic foreign bodies such as shell fragments, or metallic implants such as surgical prostheses and aneurysm clips are also potential risks. Interaction of the magnetic and radio frequency fields with such objects can lead to trauma due to movement of the object in the magnetic field or thermal injury from radio-frequency induction heating of the object.

Titanium and its alloys are safe from movement from the magnetic field.

In the United States a classification system for implants and ancillary clinical devices has been developed by ASTM International and is now the standard supported by the US Food and Drug Administration:

MR Safe sign

MR-Safe — The device or implant is completely non-magnetic, non-electrically conductive, and non-RF reactive, eliminating all of the primary potential threats during an MRI procedure.



MR Conditional sign

MR-Conditional — A device or implant that may contain magnetic, electrically conductive or RF-reactive components that is safe for operations in proximity to the MRI, provided the conditions for safe operation are defined and observed (such as 'tested safe to 1.5 teslas' or 'safe in magnetic fields below 500 gauss in strength').

MR Unsafe sign

MR-Unsafe — Nearly self-explanatory, this category is reserved for objects that are significantly ferromagnetic and pose a clear and direct threat to persons and equipment within the magnet room.

The very high strength of the magnetic field can also cause "missile-effect" accidents, where ferromagnetic objects are attracted to the center of the magnet, and there have been incidences of injury and death. To reduce the risks of projectile accidents, ferromagnetic objects and devices are typically prohibited in proximity to the MRI scanner and patients undergoing MRI examinations are required to remove all metallic objects, often by changing into a gown or scrubs and ferromagnetic detection devices are used by some sites

There is no evidence for biological harm from even very powerful static magnetic fields

Radio frequency energy

A powerful radio transmitter is needed for excitation of proton spins. This can heat the body to the point of risk of hyperthermia in patients, particularly in obese patients or those with thermoregulation disorders. Several countries have issued restrictions on the maximum specific absorption rate that a scanner may produce.

Peripheral nerve stimulation (PNS)

The rapid switching on and off of the magnetic field gradients is capable of causing nerve stimulation. Volunteers report a twitching sensation when exposed to rapidly switched fields, particularly in their extremities. The reason the peripheral nerves are stimulated is that the changing field increases with distance from the center of the gradient coils (which more or less coincides with the center of the magnet). Note however that when imaging the head, the heart is far off-center and induction of even a tiny current into the heart must be avoided at all costs. Although PNS was not a problem for the slow, weak gradients used in the early days of MRI, the strong, rapidly switched gradients used in techniques such as EPI, fMRI, diffusion MRI, etc. are indeed capable of inducing PNS. American and European regulatory agencies insist that manufacturers stay below specified $d\mathbf{B}/dt$ limits ($d\mathbf{B}/dt$ is the change in field per unit time) or else prove that no PNS is induced for any imaging sequence. As a result of $d\mathbf{B}/dt$ limitation, commercial MRI systems cannot use the full rated power of their gradient amplifiers.

Acoustic noise

Switching of field gradients causes a change in the Lorentz force experienced by the gradient coils, producing minute expansions and contractions of the coil itself. As the switching is typically in the audible frequency range, the resulting vibration produces loud noises (clicking or beeping). This is most marked with high-field machines and rapid-imaging techniques in which sound intensity can reach 120 dB(A) (equivalent to a jet engine at take-off), and therefore appropriate ear protection is essential for anyone inside the MRI scanner room during the examination.

Cryogens

As described in Physics of Magnetic Resonance Imaging, many MRI scanners rely on cryogenic liquids to enable superconducting capabilities of the electromagnetic coils within. Though the cryogenic liquids used are non-toxic, their physical properties present specific hazards.

An unintentional shut-down of a superconducting electromagnet, an event known as "quench", involves the rapid boiling of liquid helium from the device. If the rapidly expanding helium cannot be dissipated through an external vent, sometimes referred to as

'quench pipe', it may be released into the scanner room where it may cause displacement of the oxygen and present a risk of asphyxiation.

Liquid helium, the most commonly used cryogen in MRI, undergoes near explosive expansion as it changes from liquid to a gaseous state. Rooms built in support of superconducting MRI equipment should be equipped with pressure relief mechanisms and an exhaust fan, in addition to the required quench pipe.

Since a quench results in rapid loss of all cryogens in the magnet, recommissioning the magnet is expensive and time-consuming. Spontaneous quenches are uncommon, but may also be triggered by equipment malfunction, improper cryogen fill technique, contaminants inside the cryostat, or extreme magnetic or vibrational disturbances.

Contrast agents

The most commonly used intravenous contrast agents are based on chelates of gadolinium. In general, these agents have proved safer than the iodinated contrast agents used in X-ray radiography or CT. Anaphylactoid reactions are rare, occurring in approx. 0.03–0.1%. Of particular interest is the lower incidence of nephrotoxicity, compared with iodinated agents, when given at usual doses—this has made contrast-enhanced MRI scanning an option for patients with renal impairment, who would otherwise not be able to undergo contrast-enhanced CT.

Although gadolinium agents have proved useful for patients with renal impairment, in patients with severe renal failure requiring dialysis there is a risk of a rare but serious illness, nephrogenic systemic fibrosis, that may be linked to the use of certain gadolinium-containing agents. The most frequently linked is gadodiamide, but other agents have been linked too. Although a causal link has not been definitively established, current guidelines in the United States are that dialysis patients should only receive gadolinium agents where essential, and that dialysis should be performed as soon as possible after the scan to remove the agent from the body promptly. In Europe, where more gadolinium-containing agents are available, a classification of agents according to potential risks has been released. Recently a new contrast agent named gadoxetate, brand name Eovist (US) or Primovist (EU), was approved for diagnostic use: this has the theoretical benefit of a dual excretion path.

Pregnancy

No effects of MRI on the fetus have been demonstrated. In particular, MRI avoids the use of ionizing radiation, to which the fetus is particularly sensitive. However, as a precaution, current guidelines recommend that pregnant women undergo MRI only when essential. This is particularly the case during the first trimester of pregnancy, as organogenesis takes place during this period. The concerns in pregnancy are the same as for MRI in general, but the fetus may be more sensitive to the effects—particularly to heating and to noise. However, one additional concern is the use of contrast agents;

gadolinium compounds are known to cross the placenta and enter the fetal bloodstream, and it is recommended that their use be avoided.

Despite these concerns, MRI is rapidly growing in importance as a way of diagnosing and monitoring congenital defects of the fetus because it can provide more diagnostic information than ultrasound and it lacks the ionizing radiation of CT. MRI without contrast agents is the imaging mode of choice for pre-surgical, in-utero diagnosis and evaluation of fetal tumors, primarily teratomas, facilitating open fetal surgery, other fetal interventions, and planning for procedures (such as the EXIT procedure) to safely deliver and treat babies whose defects would otherwise be fatal.

Claustrophobia and discomfort

Due to the construction of some MRI scanners, they can be potentially unpleasant to lie in. Older models of closed bore MRI systems feature a fairly long tube or tunnel. The part of the body being imaged must lie at the center of the magnet, which is at the absolute center of the tunnel. Because scan times on these older scanners may be long (occasionally up to 40 minutes for the entire procedure), people with even mild claustrophobia are sometimes unable to tolerate an MRI scan without management. Modern scanners may have larger bores (up to 70 cm) and scan times are shorter. This means that claustrophobia is less of an issue, and many patients now find MRI an innocuous and easily tolerated procedure.

Nervous patients may still find the following strategies helpful:

- Advance preparation
  - visiting the scanner to see the room and practice lying on the table
  - visualization techniques
  - chemical sedation
  - general anesthesia
- Coping while inside the scanner
  - holding a "panic button"
  - closing eyes as well as covering them (e.g. washcloth, eye mask)
  - listening to music on headphones or watching a movie with a Head-mounted display while in the machine

Alternative scanner designs, such as open or upright systems, can also be helpful where these are available. Though open scanners have increased in popularity, they produce inferior scan quality because they operate at lower magnetic fields than closed scanners. However, commercial 1.5 tesla open systems have recently become available, providing much better image quality than previous lower field strength open models.

For babies and young children chemical sedation or general anesthesia are the norm, as these subjects cannot be instructed to hold still during the scanning session. Obese patients and pregnant women may find the MRI machine to be a tight fit. Pregnant women may also have difficulty lying on their backs for an hour or more without moving.

Guidance

Safety issues, including the potential for biostimulation device interference, movement of ferromagnetic bodies, and incidental localized heating, have been addressed in the American College of Radiology's *White Paper on MR Safety,* which was originally published in 2002 and expanded in 2004. The *ACR White Paper on MR Safety* has been rewritten and was released early in 2007 under the new title *ACR Guidance Document for Safe MR Practices*.
In December 2007, the Medicines in Healthcare product Regulation Agency (MHRA), a UK healthcare regulatory body, issued their *Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use*.
In February 2008, the Joint Commission, a US healthcare accrediting organization, issued a Sentinel Event Alert #38, their highest patient safety advisory, on MRI safety issues.
In July 2008, the United States Veterans Administration, a federal governmental agency serving the healthcare needs of former military personnel, issued a substantial revision to their *MRI Design Guide*, which includes physical or facility safety considerations.

The European Physical Agents Directive

The European Physical Agents (Electromagnetic Fields) Directive is legislation adopted in European legislature. Originally scheduled to be required by the end of 2008, each individual state within the European Union must include this directive in its own law by the end of 2012. Some member nations passed complying legislation and are now attempting to repeal their state laws in expectation that the final version of the EU Physical Agents Directive will be substantially revised prior to the revised adoption date.

The directive applies to occupational exposure to electromagnetic fields (not medical exposure) and was intended to limit workers' acute exposure to strong electromagnetic fields, as may be found near electricity substations, radio or television transmitters or industrial equipment. However, the regulations impact significantly on MRI, with separate sections of the regulations limiting exposure to static magnetic fields, changing magnetic fields and radio frequency energy. Field strength limits are given, which may not be exceeded. An employer may commit a criminal offense by allowing a worker to exceed an exposure limit, if that is how the Directive is implemented in a particular member state.

The Directive is based on the international consensus of established effects of exposure to electromagnetic fields, and in particular the advice of the European Commissions's advisor, the International Commission on Non-Ionizing Radiation Protection (ICNIRP). The aims of the Directive, and the ICNIRP guidelines it is based on, are to prevent exposure to potentially harmful fields. The actual limits in the Directive are very similar to the limits advised by the Institute of Electrical and Electronics Engineers, with the exception of the frequencies produced by the gradient coils, where the IEEE limits are significantly higher.

Many Member States of the EU already have either specific EMF regulations or (as in the UK) a general requirement under workplace health and safety legislation to protect workers against electromagnetic fields. In almost all cases the existing regulations are aligned with the ICNIRP limits so that the Directive should, in theory, have little impact on any employer already meeting their legal responsibilities.

The introduction of the Directive has brought to light an existing potential issue with occupational exposures to MRI fields. There are at present very few data on the number or types of MRI practice that might lead to exposures in excess of the levels of the Directive. There is a justifiable concern amongst MRI practitioners that if the Directive were to be enforced more vigorously than existing legislation, the use of MRI might be restricted, or working practices of MRI personnel might have to change.

In the initial draft a limit of static field strength to 2 T was given. This has since been removed from the regulations, and whilst it is unlikely to be restored as it was without a strong justification, some restriction on static fields may be reintroduced after the matter has been considered more fully by ICNIRP. The effect of such a limit might be to restrict the installation, operation and maintenance of MRI scanners with magnets of 2 T and stronger. As the increase in field strength has been instrumental in developing higher resolution and higher performance scanners, this would be a significant step back. This is why it is unlikely to happen without strong justification.

Individual government agencies and the European Commission have now formed a working group to examine the implications on MRI and to try to address the issue of occupational exposures to electromagnetic fields from MRI.

Three-dimensional (3D) image reconstruction

The principle

Because contemporary MRI scanners offer isotropic, or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by 'stacking' the individual slices one on top of the other. The program may then display the volume in an alternative manner.

3D rendering techniques

Surface rendering

> A threshold value of greyscale density is chosen by the operator (e.g. a level that corresponds to fat). A threshold level is set, using edge detection image processing algorithms. From this, a 3-dimensional model can be constructed and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

Surface rendering is limited in that it only displays surfaces that meet a threshold density, and only displays the surface closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image - e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.

Image segmentation

Where different structures have similar threshold density, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

2003 Nobel Prize

Reflecting the fundamental importance and applicability of MRI in medicine, Paul Lauterbur of the University of Illinois at Urbana-Champaign and Sir Peter Mansfield of the University of Nottingham were awarded the 2003 Nobel Prize in Physiology or Medicine for their "discoveries concerning magnetic resonance imaging". The Nobel citation acknowledged Lauterbur's insight of using magnetic field gradients to determine spatial localization, a discovery that allowed rapid acquisition of 2D images. Mansfield was credited with introducing the mathematical formalism and developing techniques for efficient gradient utilization and fast imaging. The actual research that won the prize was done almost 30 years before, while Paul Lauterbur was at Stony Brook University in New York.

The award was vigorously protested by Raymond Vahan Damadian, founder of FONAR Corporation, who claimed that he invented the MRI, and that Lauterbur and Mansfield had merely refined the technology. An ad hoc group, called "The Friends of Raymond Damadian", took out full-page advertisements in the *New York Times* and *The Washington Post* entitled "The Shameful Wrong That Must Be Righted", demanding that he be awarded at least a share of the Nobel Prize. Also, even earlier, in the Soviet Union, Vladislav Ivanov filed (in 1960) a document with the USSR State Committee for Inventions and Discovery at Leningrad for a Magnetic Resonance Imaging device, although this was not approved until the 1970s. In a letter to *Physics Today*, Herman Carr pointed out his own even earlier use of field gradients for one-dimensional MR imaging.

Chapter- 6

X-ray Computed Tomography

A patient is receiving a CT scan for cancer. Outside of the scanning room is an imaging computer that reveals a 3D image of the body's interior.

X-ray computed tomography (CT) is a medical imaging method employing tomography created by computer processing. Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional X-ray images taken around a single axis of rotation.

CT produces a volume of data which can be manipulated, through a process known as "windowing", in order to demonstrate various bodily structures based on their ability to block the X-ray beam. Although historically the images generated were in the axial or transverse plane, orthogonal to the long axis of the body, modern scanners allow this volume of data to be reformatted in various planes or even as volumetric (3D) representations of structures. Although most common in medicine, CT is also used in other fields, such as nondestructive materials testing. Another example is archaeological uses such as imaging the contents of sarcophagi or the DigiMorph project at the

University of Texas at Austin which uses a CT scanner to study biological and paleontological specimens.

Usage of CT has increased dramatically over the last two decades in many countries. An estimated 72 million scans were performed in the United States in 2007. It is estimated that 0.4% of current cancers in the United States are due to CTs performed in the past and that this may increase to as high as 1.5-2% with 2007 rates of CT usage.

Terminology

The word "tomography" is derived from the Greek *tomos* (slice) and *graphein* (to write). Computed tomography was originally known as the "EMI scan" as it was developed at a research branch of EMI, a company best known today for its music and recording business. It was later known as **computed axial tomography** (CAT or CT scan) and **body section röntgenography**.

Although the term "computed tomography" could be used to describe positron emission tomography and single photon emission computed tomography, in practice it usually refers to the computation of tomography from X-ray images, especially in older medical literature and smaller medical facilities.

In MeSH, "computed axial tomography" was used from 1977–79, but the current indexing explicitly includes "X-ray" in the title.

Diagnostic use

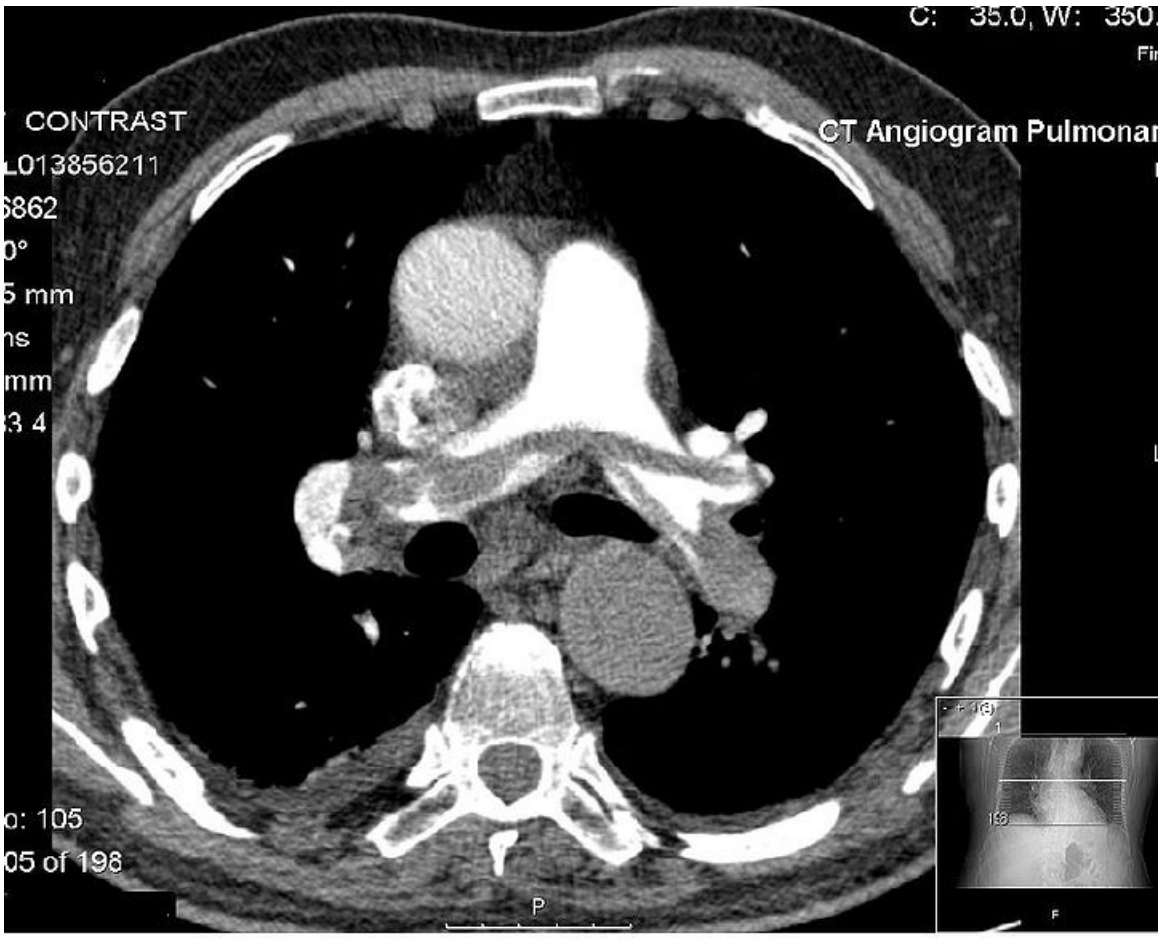
Since its introduction in the 1970s, CT has become an important tool in medical imaging to supplement X-rays and medical ultrasonography. It has more recently been used for preventive medicine or screening for disease, for example CT colonography for patients with a high risk of colon cancer, or full-motion heart scans for patients with high risk of heart disease. A number of institutions offer full-body scans for the general population. This is however a controversial practice, given its cost, significant radiation exposure, lack of proven benefit, and the risk of finding 'incidental' abnormalities that may trigger additional investigations.

Head

CT scanning of the head is typically used to detect infarction, tumours, calcifications, haemorrhage and bone trauma. Of the above, hypodense (dark) structures indicate infarction or tumours, hyperdense (bright) structures indicate calcifications and haemorrhage and bone trauma can be seen as disjunction in bone windows. CT can be used for detecting both acute and chronic changes in the lung parenchyma, that is, the internals of the lungs. It is particularly relevant here because normal two-dimensional x-rays do not show such defects. A variety of different techniques are used, depending on the suspected abnormality. For evaluation of chronic interstitial processes (emphysema,

fibrosis, and so forth), thin sections with high spatial frequency reconstructions are used; often scans are performed both in inspiration and expiration. This special technique is called High Resolution CT . Therefore it produces a sampling of the lung and not continuous images. diagnose coronary artery disease.

Pulmonary angiogram



Example of a CTPA, demonstrating a saddle embolus (dark horizontal line) occluding the pulmonary arteries (bright white triangle)

CT pulmonary angiogram (CTPA) is a medical diagnostic test used to diagnose pulmonary embolism (PE). It employs computed tomography to obtain an image of the pulmonary arteries.

It is a preferred choice of imaging in the diagnosis of PE due to its minimally invasive nature for the patient, whose only requirement for the scan is a cannula (usually a 20G).

MDCT (multi detector CT) scanners give the optimum resolution and image quality for this test. Images are usually taken on a 0.625 mm slice thickness, although 2 mm is

sufficient. 50–100 mls of contrast is given to the patient at a rate of 4 ml/s. The tracker/locator is placed at the level of the pulmonary arteries, which sit roughly at the level of the carina. Images are acquired with the maximum intensity of radio-opaque contrast in the pulmonary arteries. This is done using bolus tracking.

CT machines are now so sophisticated that the test can be done with a patient visit of 5 minutes with an approximate scan time of only 5 seconds or less.

A normal CTPA scan will show the contrast filling the pulmonary vessels, appearing as bright white. Ideally the aorta should be empty of contrast, to reduce any partial volume artifact which may result in a false positive. Any mass filling defects, such as an embolus, will appear dark in place of the contrast, filling / blocking the space where blood should be flowing into the lungs.

Cardiac

With the advent of subsecond rotation combined with multi-slice CT (up to 320-slices), high resolution and high speed can be obtained at the same time, allowing excellent imaging of the coronary arteries (cardiac CT angiography). Images with an even higher temporal resolution can be formed using retrospective ECG gating. In this technique, each portion of the heart is imaged more than once while an ECG trace is recorded. The ECG is then used to correlate the CT data with their corresponding phases of cardiac contraction. Once this correlation is complete, all data that were recorded while the heart was in motion (systole) can be ignored and images can be made from the remaining data that happened to be acquired while the heart was at rest (diastole). In this way, individual frames in a cardiac CT investigation have a better temporal resolution than the shortest tube rotation time.

Because the heart is effectively imaged more than once (as described above), cardiac CT angiography results in a relatively high radiation exposure around 12 mSv. Currently, newer acquisition protocols have been developed drastically reducing the xRays radiation exposure, down to 1 milliSievert (cfr. Pavone, Fioranelli, Dowe: Computed Tomography or Coronary Arteries, Springer 2009). For the sake of comparison, a chest X-ray carries a dose of approximately 0.02 to 0.2 mSv and natural background radiation exposure is around 0.01 mSv/day. Thus, cardiac CTA is equivalent to approximately 100-600 chest X-rays or over 3 years worth of natural background radiation. Methods are available to decrease this exposure, however, such as prospectively decreasing radiation output based on the concurrently acquired ECG (aka tube current modulation.) This can result in a significant decrease in radiation exposure, at the risk of compromising image quality if there is any arrhythmia during the acquisition. The significance of radiation doses in the diagnostic imaging range has not been proven, although the possibility of inducing an increased cancer risk across a population is a source of significant concern. This potential risk must be weighed against the competing risk of not performing a test and potentially not diagnosing a significant health problem such as coronary artery disease.

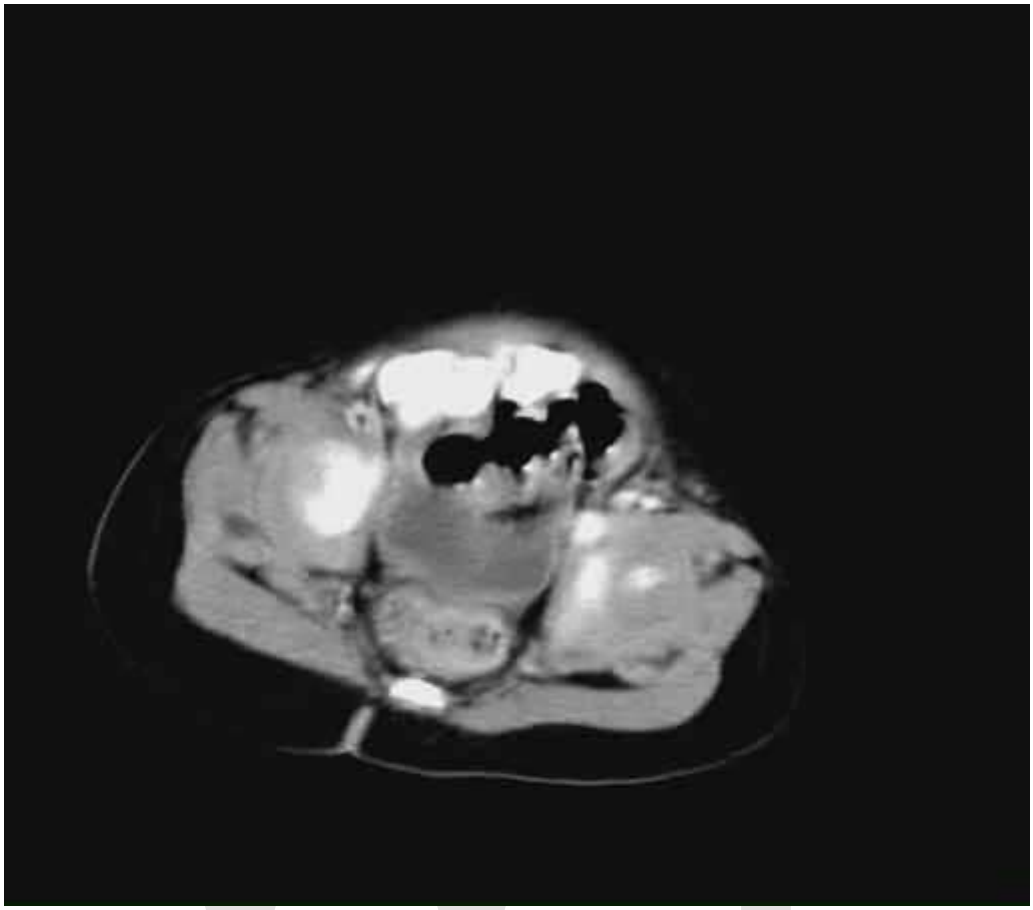
It is uncertain whether this modality will replace invasive coronary catheterization. Currently, it appears that the greatest utility of cardiac CT lies in ruling out coronary artery disease rather than ruling it in. This is because the test has a high sensitivity (greater than 90%) and thus a negative test result means that a patient is very unlikely to have coronary artery disease and can be worked up for other causes of their chest symptoms. This is termed a high negative predictive value. A positive result is less conclusive and often will be confirmed (and possibly treated) with subsequent invasive angiography. The positive predictive value of cardiac CTA is estimated at approximately 82% and the negative predictive value is around 93%.

Dual Source CT scanners, introduced in 2005, allow higher temporal resolution by acquiring a full CT slice in only half a rotation, thus reducing motion blurring at high heart rates and potentially allowing for shorter breath-hold time. This is particularly useful for ill patients who have difficulty holding their breath or who are unable to take heart-rate lowering medication.

The speed advantages of 64-slice MSCT have rapidly established it as the minimum standard for newly installed CT scanners intended for cardiac scanning. Manufacturers have developed 320-slice and true 'volumetric' scanners, primarily for their improved cardiac scanning performance.

The latest MSCT scanners acquire images only at 70-80% of the R-R interval (late diastole). This prospective gating can reduce effective dose from 10-15mSv to as little as 1.2mSv in follow-up patients acquiring at 75% of the R-R interval. Effective doses at a centre with well trained staff doing coronary imaging can average less than the doses for conventional coronary angiography.

Abdominal and pelvic



CT Scan of 11 cm **Wilms' tumor** of right kidney in 13 month old patient.

CT is a sensitive method for diagnosis of abdominal diseases. It is used frequently to determine stage of cancer and to follow progress. It is also a useful test to investigate acute abdominal pain (especially of the lower quadrants, whereas ultrasound is the preferred first line investigation for right upper quadrant pain). Renal stones, appendicitis, pancreatitis, diverticulitis, abdominal aortic aneurysm, and bowel obstruction are conditions that are readily diagnosed and assessed with CT. CT is also the first line for detecting solid organ injury after trauma.

Multidetector CT (MDCT) can clearly delineate anatomic structures in the abdomen, which is critical in the diagnosis of internal diaphragmatic and other nonpalpable or unsuspected hernias. MDCT also offers clear detail of the abdominal wall allowing wall hernias to be identified accurately.

Oral and/or rectal contrast may be used depending on the indications for the scan. A dilute (2% w/v) suspension of barium sulfate is most commonly used. The concentrated barium sulfate preparations used for fluoroscopy e.g. barium enema are too dense and cause severe artifacts on CT. Iodinated contrast agents may be used if barium is

contraindicated (for example, suspicion of bowel injury). Other agents may be required to optimize the imaging of specific organs, such as rectally administered gas (air or carbon dioxide) or fluid (water) for a colon study, or oral water for a stomach study.

CT has limited application in the evaluation of the *pelvis*. For the female pelvis in particular, ultrasound and MRI are the imaging modalities of choice. Nevertheless, it may be part of abdominal scanning (e.g. for tumors), and has uses in assessing fractures.

CT is also used in osteoporosis studies and research alongside dual energy X-ray absorptiometry (DXA). Both CT and DXA can be used to assess bone mineral density (BMD) which is used to indicate bone strength, however CT results do not correlate exactly with DXA (the gold standard of BMD measurement). CT is far more expensive, and subjects patients to much higher levels of ionizing radiation, so it is used infrequently.

Extremities

CT is often used to image complex fractures, especially ones around joints, because of its ability to reconstruct the area of interest in multiple planes. Fractures, ligamentous injuries and dislocations can easily be recognised with a 0.2 mm resolution.

Advantages and disadvantages

Advantages over traditional radiography

There are several advantages that CT has over traditional 2D medical radiography. First, CT completely eliminates the superimposition of images of structures outside the area of interest. Second, because of the inherent high-contrast resolution of CT, differences between tissues that differ in physical density by less than 1% can be distinguished. Finally, data from a single CT imaging procedure consisting of either multiple contiguous or one helical scan can be viewed as images in the axial, coronal, or sagittal planes, depending on the diagnostic task. This is referred to as multiplanar reformatted imaging.

CT is regarded as a moderate to high radiation diagnostic technique. The improved resolution of CT has permitted the development of new investigations, which may have advantages; compared to conventional for example, CT angiography avoids the invasive insertion of an CT colonography (also known as virtual colonoscopy or VC for short) may be as useful as a barium enema for detection of tumors, but may use a lower radiation dose. CT VC is increasingly being used in the UK as a diagnostic test for bowel cancer and can negate the need for a colonoscopy.

The radiation dose for a particular study depends on multiple factors: volume scanned, patient build, number and type of scan sequences, and desired resolution and image quality. Additionally, two helical CT scanning parameters that can be adjusted easily and that have a profound effect on radiation dose are tube current and pitch. Computed

tomography (CT) scan has been shown to be more accurate than radiographs in evaluating anterior interbody fusion but may still over-read the extent of fusion.

Safety concerns

The increased use of CT scans has been the greatest in two fields: screening of adults (screening CT of the lung in smokers, virtual colonoscopy, CT cardiac screening and whole-body CT in asymptomatic patients) and CT imaging of children. Shortening of the scanning time to around 1 second, eliminating the strict need for subject to remain still or be sedated, is one of the main reasons for large increase in the pediatric population (especially for the diagnosis of appendicitis). CT scans of children have been estimated to produce non-negligible increases in the probability of lifetime cancer mortality, leading to calls for the use of reduced current settings for CT scans of children. These calculations are based on the assumption of a linear relationship between radiation dose and cancer risk; this claim is controversial, as some but not all evidence shows that smaller radiation doses are not harmful. Estimated lifetime cancer mortality risks attributable to the radiation exposure from a CT in a 1-year-old are 0.18% (abdominal) and 0.07% (head)—an order of magnitude higher than for adults—although those figures still represent a small increase in cancer mortality over the background rate. In the United States, of approximately 600,000 abdominal and head CT examinations annually performed in children under the age of 15 years, a rough estimate is that 500 of these individuals might ultimately die from cancer attributable to the CT radiation. The additional risk is still very low (0.35%) compared to the background risk of dying from cancer (23%). However, if these statistics are extrapolated to the current number of CT scans, the additional rise in cancer mortality could be 1.5 to 2%. Furthermore, certain conditions can require children to be exposed to multiple CT scans. Again, these calculations can be problematic because the assumptions underlying them could overestimate the risk.

In 2009 a number of studies appeared that further defined the risk of cancer that may be caused by CT scans. One study indicated that radiation by CT scans is often higher and more variable than cited and each of the 19,500 CT scans that are daily performed in the US is equivalent to 30 to 442 chest x-rays in radiation. It has been estimated that CT radiation exposure will result in 29,000 new cancer cases just from the CT scans performed in 2007. The most common cancers caused by CT are thought to be lung cancer, colon cancer and leukemia with younger people and women more at risk. These conclusions, however, are criticized by the American College of Radiology (ACR) that maintains that the life expectancy of CT scanned patients is not that of the general population and that the model of calculating cancer is based on total body radiation exposure and thus faulty.

CT scans can be performed with different settings for lower exposure in children, although these techniques are often not employed. Surveys have suggested that currently, many CT scans are performed unnecessarily. Ultrasound scanning or magnetic resonance imaging are alternatives (for example, in appendicitis or brain imaging) without the risk of radiation exposure. Although CT scans come with an additional risk of cancer (it can

be estimated that the radiation exposure from a full body scan is the same as standing 2.4 km away from the WWII atomic bomb blasts in Japan), especially in children, the benefits that stem from their use outweighs the risk in many cases. Studies support informing parents of the risks of pediatric CT scanning.

Typical scan doses

Examination	Typical effective dose (mSv)	(millirem)
X-ray Personnel security screening scan	0.00025	0.025
Chest X-ray	0.1	10
Head CT	1.5	150
Screening mammography	3	300
Abdomen CT	5.3	530
Chest CT	5.8	580
CT colonography (virtual colonoscopy)	3.6–8.8	360–880
Chest, abdomen and pelvis CT	9.9	990
Cardiac CT angiogram	6.7-13	670–1300
Barium enema	15	1500
Neonatal abdominal CT	20	2000

For purposes of comparison, the average background exposure in the UK is 1-3 mSv per year.

Adverse reactions to contrast agents

Because contrast CT scans rely on intravenously administered contrast agents in order to provide superior image quality, there is a low but non-negligible level of risk associated with the contrast agents themselves. Many patients report nausea and discomfort, including warmth in the crotch which mimics the sensation of wetting oneself. Certain patients may experience severe and potentially life-threatening allergic reactions to the contrast dye.

The contrast agent may also induce kidney damage. The risk of this is increased with patients who have preexisting renal insufficiency, preexisting diabetes, or reduced intravascular volume. In general, if a patient has normal kidney function, then the risks of contrast nephropathy are negligible. Patients with mild kidney impairment are usually advised to ensure full hydration for several hours before and after the injection. For moderate kidney failure, the use of iodinated contrast should be avoided; this may mean using an alternative technique instead of CT, e.g., MRI. Paradoxically, patients with severe renal failure requiring dialysis do not require special precautions, as their kidneys have so little function remaining that any further damage would not be noticeable and the dialysis will remove the contrast agent.

Low-dose CT scan

An important issue within radiology today is how to reduce the radiation dose during CT examinations without compromising the image quality. Generally, higher radiation doses result in higher-resolution images, while lower doses lead to increased image noise and unsharp images. Increased dosage raises the risk of radiation induced cancer — a four-phase abdominal CT gives the same radiation dose as 300 chest x-rays. Several methods exist which can reduce the exposure to ionizing radiation during a CT scan.

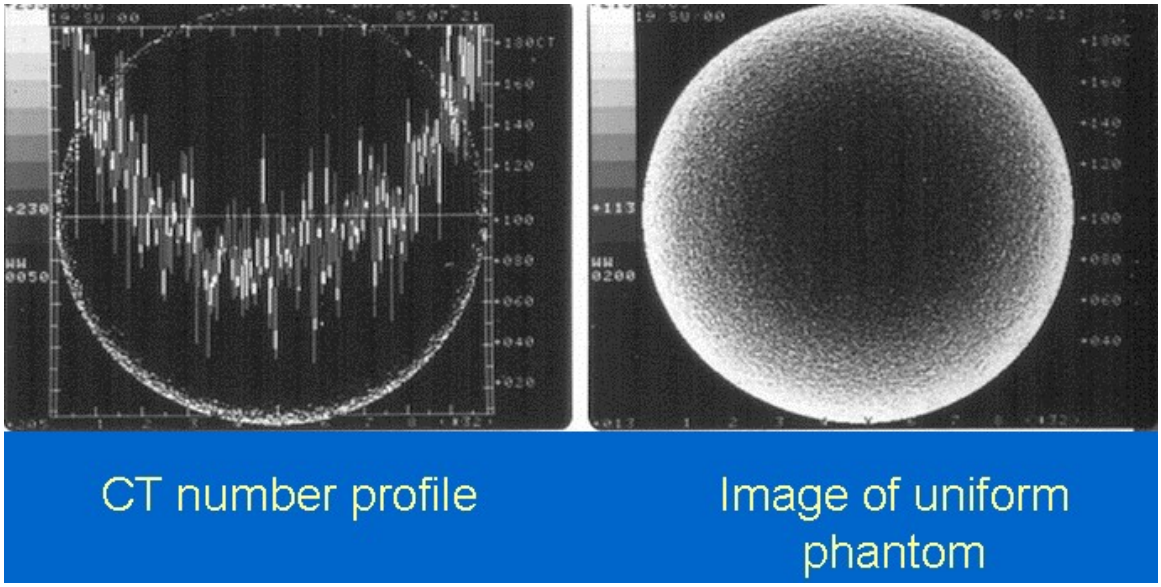
1. New software technology can significantly reduce the required radiation dose. The software works as a filter that reduces random noise and enhances structures. In this way, it is possible to get high-quality images and at the same time lower the dose by as much as 30 to 70 percent.
2. Individualize the examination and adjust the radiation dose to the body type and body organ examined. Different body types and organs require different amounts of radiation.
3. Prior to every CT examination, evaluate the appropriateness of the exam whether it is motivated or if another type of examination is more suitable. Higher resolution is not always suitable for any given scenario, such as detection of small pulmonary masses

Computed tomography versus MRI

The basic mathematics of the 2D-Fourier transform in CT reconstruction is very similar to the 2D-FT NMRI, but the computer data processing in CT does differ in detail, as for example in the case of the volume rendering and artifact elimination algorithms that are specific to CT.

Artifacts

Although CT is a relatively accurate test, it is liable to produce artifacts, such as the following:



Example of beam hardening

- Aliasing artifact or streaks

These appear as dark lines which radiate away from sharp corners. It occurs because it is impossible for the scanner to "sample" or take enough projections of the object, which is usually metallic. It can also occur when an insufficient X-ray tube current is selected, and insufficient penetration of the x-ray occurs. These artifacts are also closely tied to motion during a scan. This type of artifact commonly occurs in head images around the pituitary fossa area.

- Partial volume effect

This appears as "blurring" over sharp edges. It is due to the scanner being unable to differentiate between a small amount of high-density material (e.g. bone) and a larger amount of lower density (e.g., cartilage). The processor tries to average out the two densities or structures, and information is lost. This can be partially overcome by scanning using thinner slices.

- Ring artifact

Probably the most common mechanical artifact, the image of one or many "rings" appears within an image. This is usually due to a detector fault.

- Noise artifact

This appears as graining on the image and is caused by a low signal to noise ratio. This occurs more commonly when a thin slice thickness is used. It can also occur when the power supplied to the X-ray tube is insufficient to penetrate the anatomy.

- Motion artifact

This is seen as blurring and/or streaking which is caused by movement of the object being imaged.

- Windmill

Streaking appearances can occur when the detectors intersect the reconstruction plane. This can be reduced with filters or a reduction in pitch.

- Beam hardening

This can give a "cupped appearance". It occurs when there is more attenuation in the center of the object than around the edge. This is easily corrected by filtration and software.

Prevalence

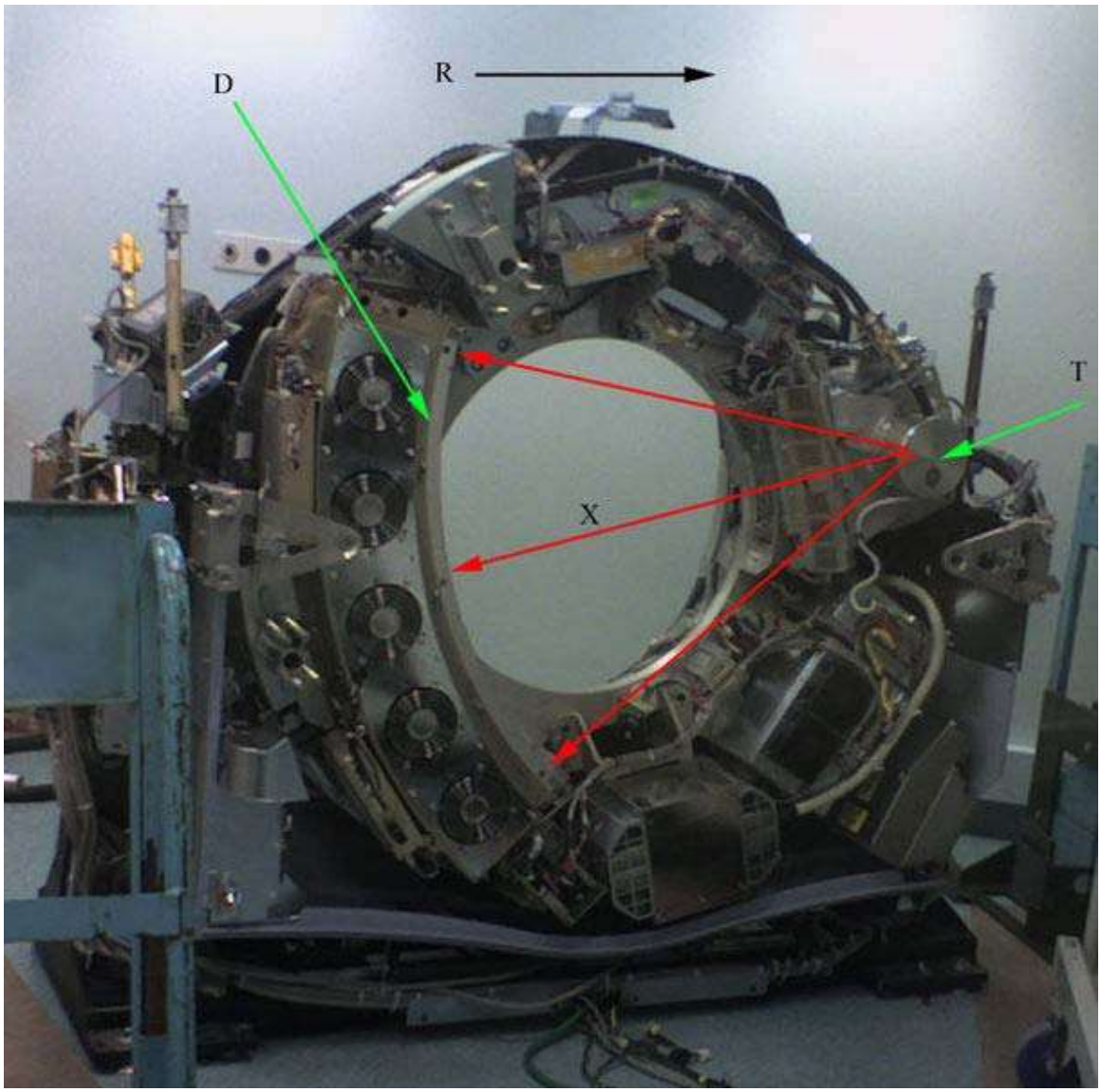
Usage of CT has increased dramatically over the last two decades. An estimated 72 million scans were performed in the United States in 2007. In Calgary Canada 12.1% of people who present to the emergency with an urgent complaint received a CT scan, most commonly either of the head or the abdomen. The percentage who received CT however varied markedly by the emergency physician who saw them from 1.8% to 25%.I n the emergency department in the United States CT or MRI imaging is done in 15% of people who present with injuries as of 2007 (up from 6% in 1998).

Process

X-ray slice data is generated using an X-ray source that rotates around the object; X-ray sensors are positioned on the opposite side of the circle from the X-ray source. The earliest sensors were scintillation detectors, with photomultiplier tubes excited by (typically) cesium iodide crystals. Cesium iodide was replaced during the 1980s by ion chambers containing high pressure Xenon gas. These systems were in turn replaced by scintillation systems based on photo diodes instead of photomultipliers and modern scintillation materials with more desirable characteristics. Many data scans are progressively taken as the object is gradually passed through the gantry.

Newer machines with faster computer systems and newer software strategies can process not only individual cross sections but continuously changing cross sections as the gantry, with the object to be imaged, is slowly and smoothly slid through the X-ray circle. These are called *helical* or *spiral CT* machines. Their computer systems integrate the data of the moving individual slices to generate three dimensional volumetric information (3D-CT scan), in turn viewable from multiple different perspectives on attached CT workstation monitors. This type of data acquisition requires enormous processing power, as the data are arriving in a continuous stream and must be processed in real-time.

In conventional CT machines, an X-ray tube and detector are physically rotated behind a circular shroud; in the electron beam tomography (EBT) the tube is far larger and higher power to support the high temporal resolution. The electron beam is deflected in a hollow funnel-shaped vacuum chamber. X-rays are generated when the beam hits the stationary target. The detector is also stationary. This arrangement can result in very fast scans, but is extremely expensive.



CT scanner with cover removed to show the principle of operation

CT is used in medicine as a diagnostic tool and as a guide for interventional procedures. Sometimes contrast materials such as intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. Using contrast material can also help to obtain functional information about tissues.

Once the scan data has been acquired, the data must be processed using a form of tomographic reconstruction, which produces a series of cross-sectional images. The most common technique in general use is filtered back projection, which is straight-forward to implement and can be computed rapidly. Mathematically, this method is based on the Radon transform. However, this is not the only technique available: the original EMI scanner solved the tomographic reconstruction problem by linear algebra, but this approach was limited by its high computational complexity, especially given the computer technology available at the time. More recently, manufacturers have developed iterative physical model-based expectation-maximization techniques. These techniques are advantageous because they use an internal model of the scanner's physical properties and of the physical laws of X-ray interactions. By contrast, earlier methods have assumed a perfect scanner and highly simplified physics, which leads to a number of artefacts and reduced resolution - the result is images with improved resolution, reduced noise and fewer artefacts, as well as the ability to greatly reduce the radiation dose in certain circumstances. The disadvantage is a very high computational requirement, which is at the limits of practicality for current scan protocols.

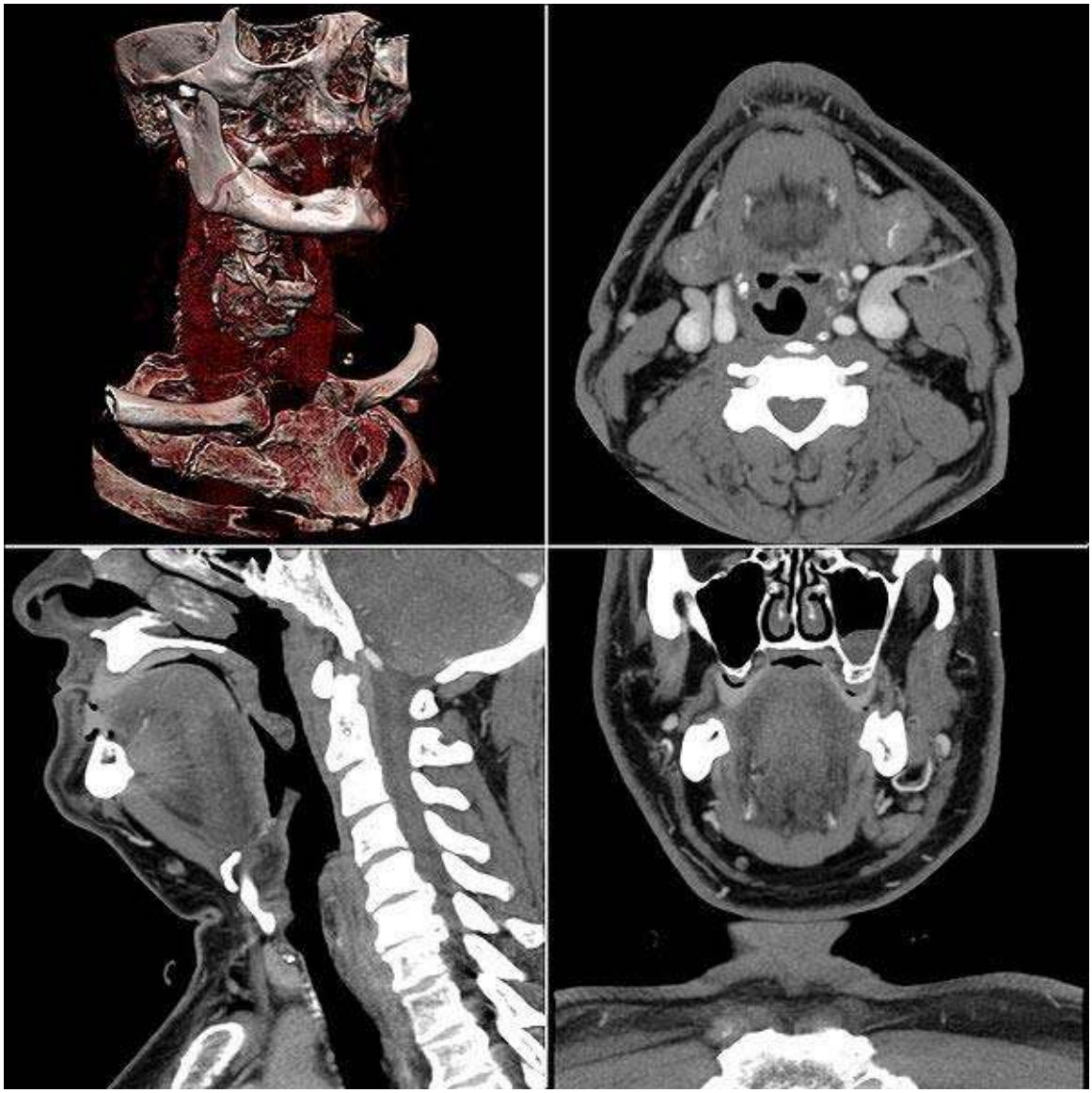
Pixels in an image obtained by CT scanning are displayed in terms of relative radiodensity. The pixel itself is displayed according to the mean attenuation of the tissue(s) that it corresponds to on a scale from +3071 (most attenuating) to -1024 (least attenuating) on the Hounsfield scale. Pixel is a two dimensional unit based on the matrix size and the field of view. When the CT slice thickness is also factored in, the unit is known as a Voxel, which is a three dimensional unit. The phenomenon that one part of the detector cannot differentiate between different tissues is called the *"Partial Volume Effect"*. That means that a big amount of cartilage and a thin layer of compact bone can cause the same attenuation in a voxel as hyperdense cartilage alone. Water has an attenuation of 0 Hounsfield units (HU) while air is -1000 HU, cancellous bone is typically +400 HU, cranial bone can reach 2000 HU or more (os temporale) and can cause artifacts. The attenuation of metallic implants depends on atomic number of the element used: Titanium usually has an amount of +1000 HU, iron steel can completely extinguish the X-ray and is therefore responsible for well-known line-artifacts in computed tomograms. Artifacts are caused by abrupt transitions between low- and high-density materials, which results in data values that exceed the dynamic range of the processing electronics.

Three-dimensional reconstruction

The principle

Because contemporary CT scanners offer isotropic or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by "stacking" the individual slices one on top of the other. The program may then display the volume in an alternative manner.

Multiplanar reconstruction



Typical screen layout for diagnostic software, showing one 3D and three MPR views

Multiplanar reconstruction (MPR) is the simplest method of reconstruction. A volume is built by stacking the axial slices. The software then cuts slices through the volume in a different plane (usually orthogonal). Optionally, a special projection method, such as maximum-intensity projection (MIP) or minimum-intensity projection (mIP), can be used to build the reconstructed slices.

MPR is frequently used for examining the spine. Axial images through the spine will only show one vertebral body at a time and cannot reliably show the intervertebral discs. By reformatting the volume, it becomes much easier to visualise the position of one vertebral body in relation to the others.

Modern software allows reconstruction in non-orthogonal (oblique) planes so that the optimal plane can be chosen to display an anatomical structure. This may be particularly useful for visualising the structure of the bronchi as these do not lie orthogonal to the direction of the scan.

For vascular imaging, curved-plane reconstruction can be performed. This allows bends in a vessel to be "straightened" so that the entire length can be visualised on one image, or a short series of images. Once a vessel has been "straightened" in this way, quantitative measurements of length and cross sectional area can be made, so that surgery or interventional treatment can be planned.

MIP reconstructions enhance areas of high radiodensity, and so are useful for angiographic studies. mIP reconstructions tend to enhance air spaces so are useful for assessing lung structure.

3D rendering techniques

reshold value of radiodensity is set by the operator (e.g. a level that corresponds to bone). From this, a three-dimensional model can be constructed using edge detection image processing algorithms and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

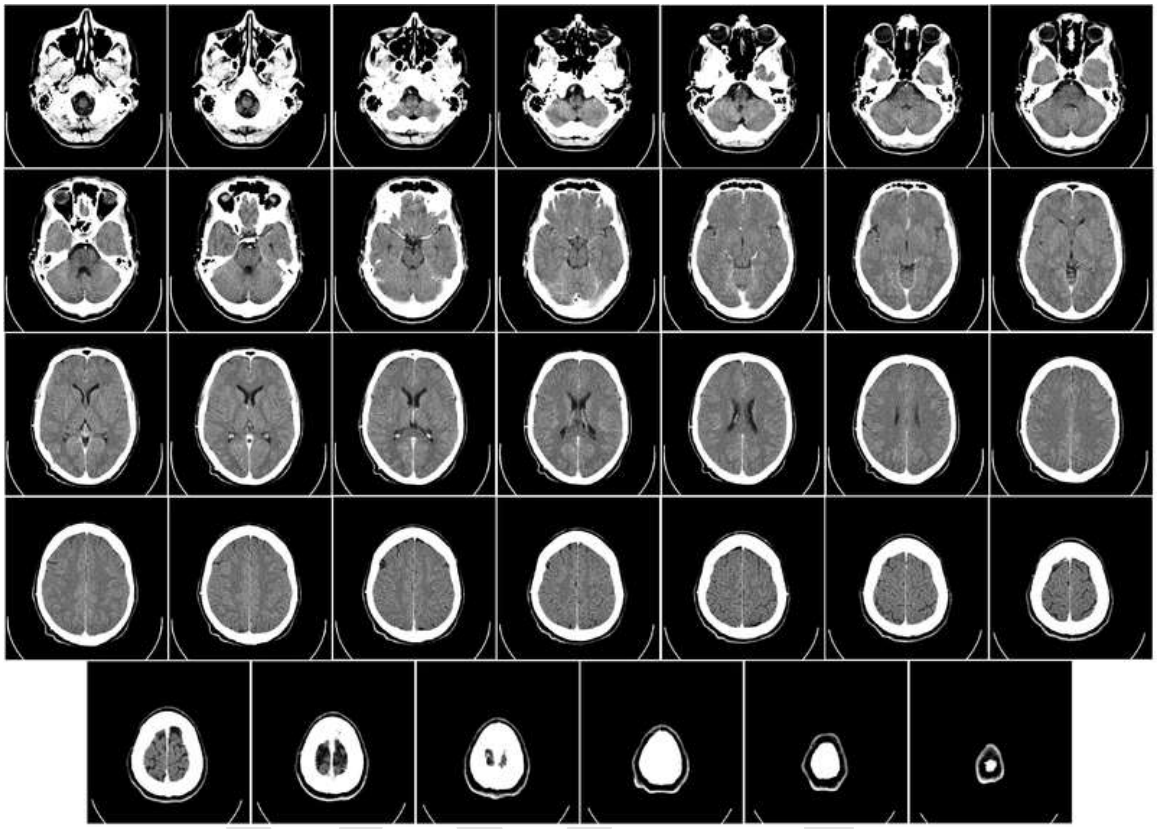
> Surface rendering is limited in that it will only display surfaces which meet a threshold density, and will only display the surface that is closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image—e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.

Image segmentation

Where different structures have similar radiodensity, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

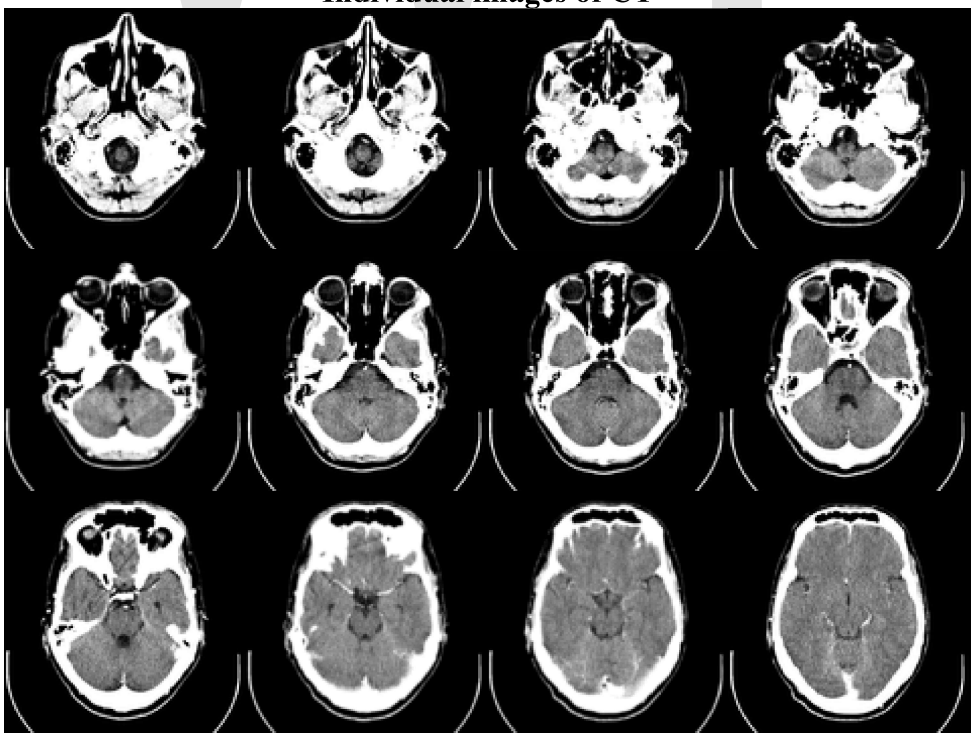
Example

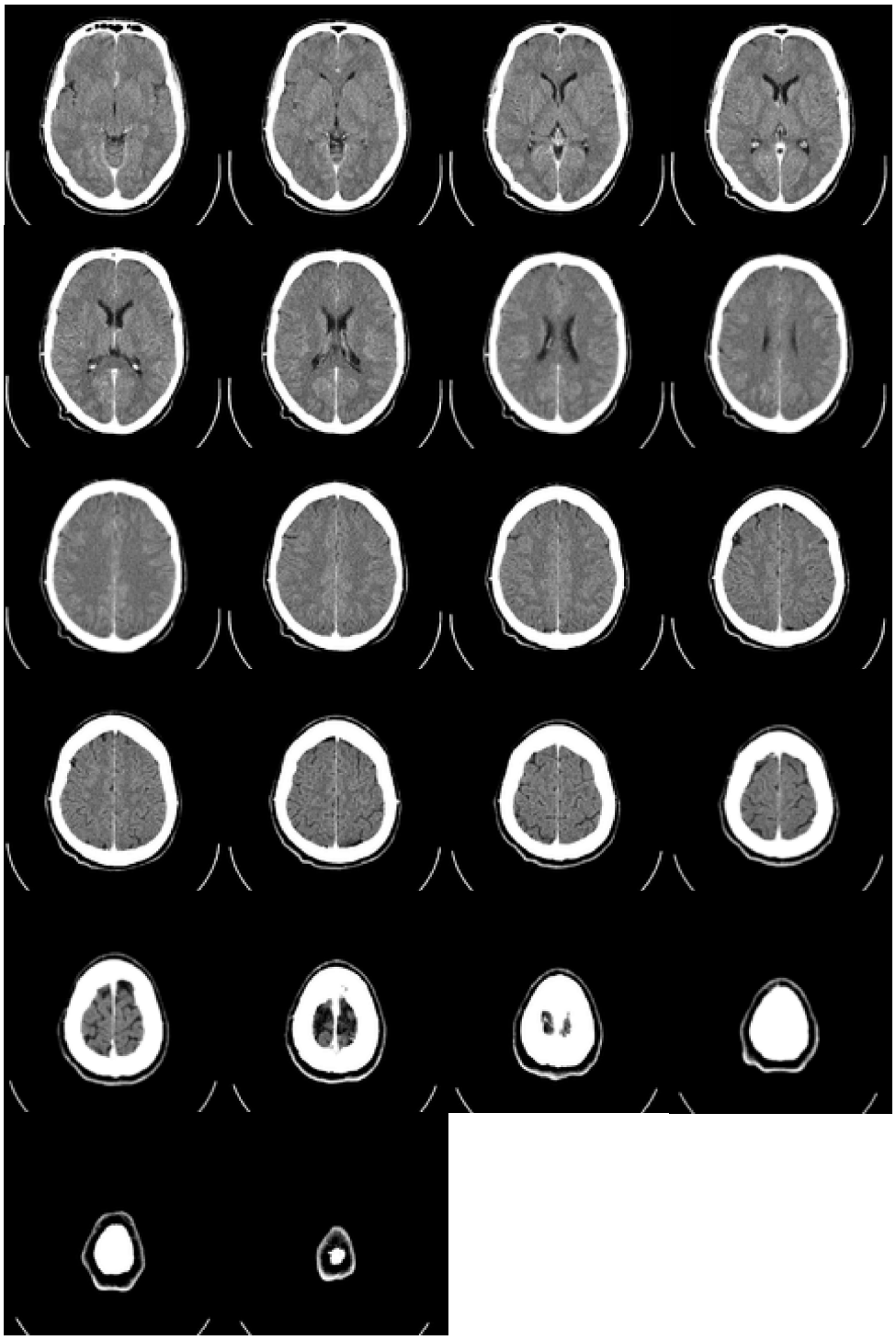
Some slices of a cranial CT scan are shown below. The bones are whiter than the surrounding area. (Whiter means higher attenuation.) Note the blood vessels (arrowed) showing brightly due to the injection of an iodine-based contrast agent.



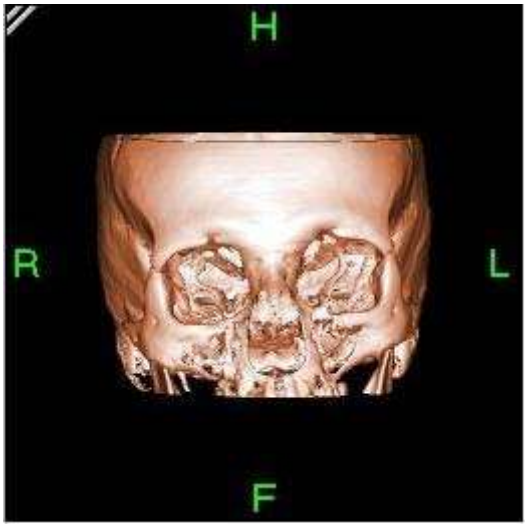
Computed tomography of human brain, from base of the skull to top. Taken with intravenous contrast medium.

Individual images of CT



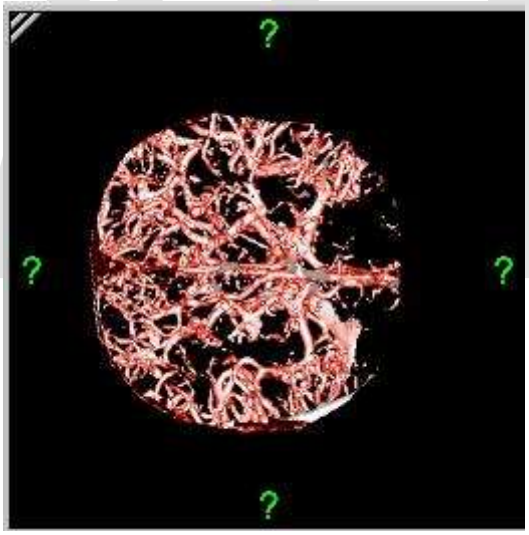


A volume rendering of this volume clearly shows the high density bones



Bone reconstructed in 3D

After using a segmentation tool to remove the bone, the previously concealed vessels can now be demonstrated.

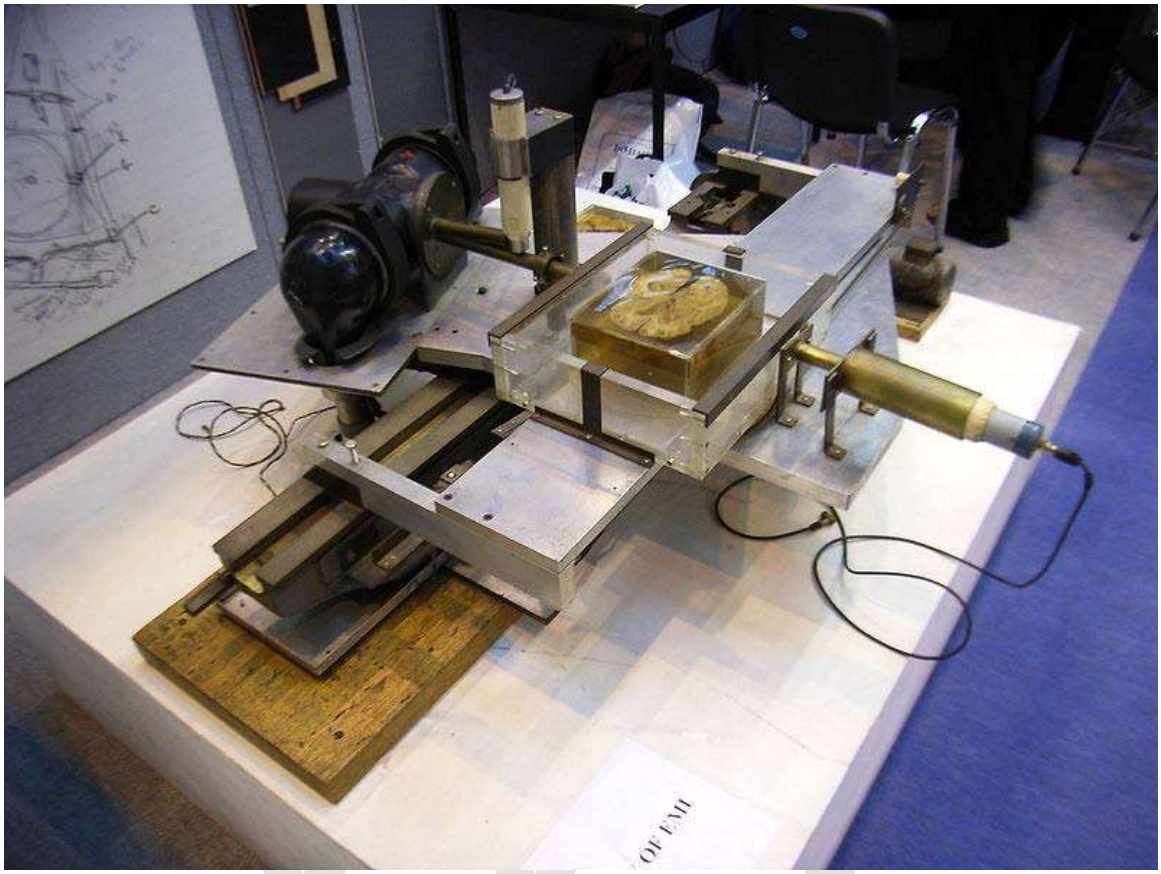


Brain vessels reconstructed in 3D after bone has been removed by segmentation

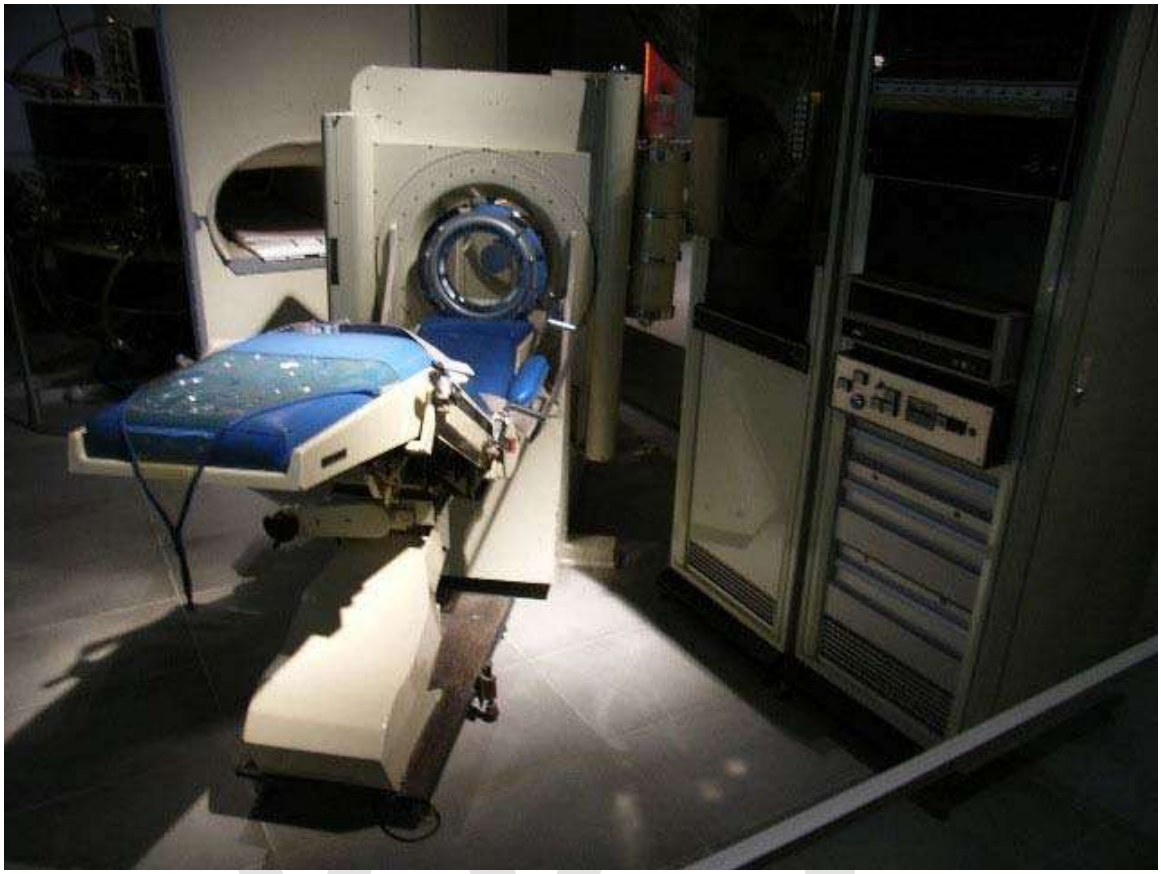
Industrial computed tomography

Industrial CT Scanning (Industrial Computed Tomography) is a process which utilizes x-ray equipment to produce 3D representations of components both externally and internally. Industrial CT scanning has been utilized in many areas of industry for internal inspection of components. Some of the key uses for CT scanning have been flaw detection, failure analysis, metrology, assembly analysis and reverse engineering applications

History



The prototype CT scanner



A historic EMI-Scanner

In the early 1900s, the Italian radiologist Alessandro Vallebona proposed a method to represent a single slice of the body on the radiographic film. This method was known as tomography. The idea is based on simple principles of projective geometry: moving synchronously and in opposite directions the X-ray tube and the film, which are connected together by a rod whose pivot point is the focus; the image created by the points on the focal plane appears sharper, while the images of the other points annihilate as noise. This is only marginally effective, as blurring occurs in only the "x" plane. There are also more complex devices which can move in more than one plane and perform more effective blurring.

Tomography had been one of the pillars of radiologic diagnostics until the late 1970s, when the availability of minicomputers and of the transverse axial scanning method – this last due to the work of Godfrey Hounsfield and South African-born Allan McLeod Cormack – gradually supplanted it as the modality of CT. Mathematically, the method is based upon the use of the Radon Transform invented by Johann Radon in 1917. But as Cormack remembered later, he had to find the solution himself since it was only in 1972 that he learned of the work of Radon, by chance.

The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield in Hayes, United Kingdom, at EMI Central Research Laboratories using X-rays. Hounsfield

conceived his idea in 1967. The first EMI-Scanner was installed in Atkinson Morley Hospital in Wimbledon, England, and the first patient brain-scan was done on 1 October 1971. It was publicly announced in 1972.

The original 1971 prototype took 160 parallel readings through 180 angles, each 1° apart, with each scan taking a little over 5 minutes. The images from these scans took 2.5 hours to be processed by algebraic reconstruction techniques on a large computer. The scanner had a single photomultiplier detector, and operated on the Translate/Rotate principle.

It has been claimed that thanks to the success of The Beatles, EMI could fund research and build early models for medical use. The first production X-ray CT machine (in fact called the "EMI-Scanner") was limited to making tomographic sections of the brain, but acquired the image data in about 4 minutes (scanning two adjacent slices), and the computation time (using a Data General Nova minicomputer) was about 7 minutes per picture. This scanner required the use of a water-filled Perspex tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. The water-tank was used to reduce the dynamic range of the radiation reaching the detectors (between scanning outside the head compared with scanning through the bone of the skull). The images were relatively low resolution, being composed of a matrix of only 80 x 80 pixels.

In the U.S., the first installation was at the Mayo Clinic. As a tribute to the impact of this system on medical imaging the Mayo Clinic has an EMI scanner on display in the Radiology Department. Allan McLeod Cormack of Tufts University in Massachusetts independently invented a similar process, and both Hounsfield and Cormack shared the 1979 Nobel Prize in Medicine.

The first CT system that could make images of any part of the body and did not require the "water tank" was the ACTA (Automatic Computerized Transverse Axial) scanner designed by Robert S. Ledley, DDS, at Georgetown University. This machine had 30 photomultiplier tubes as detectors and completed a scan in only 9 translate/rotate cycles, much faster than the EMI-scanner. It used a DEC PDP11/34 minicomputer both to operate the servo-mechanisms and to acquire and process the images. The Pfizer drug company acquired the prototype from the university, along with rights to manufacture it. Pfizer then began making copies of the prototype, calling it the "200FS" (FS meaning Fast Scan), which were selling as fast as they could make them. This unit produced images in a 256×256 matrix, with much better definition than the EMI-Scanner's 80×80.

Previous studies

Although largely obsolete, conventional tomography is still used in specific situations such as dental imaging (orthopantomography) or in intravenous urography.

Tomosynthesis

Digital tomosynthesis combines digital image capture and processing with simple tube/detector motion as used in conventional radiographic tomography. Although there

are some similarities to CT, it is a separate technique. In CT, the source/detector makes a complete 360-degree rotation about the subject obtaining a complete set of data from which images may be reconstructed. In digital tomosynthesis, only a small rotation angle (e.g. 40 degrees) with a small number of discrete exposures (e.g. 10) are used. This incomplete set of data can be digitally processed to yield images similar to conventional tomography with a limited depth of field. However, because the image processing is digital, a series of slices at different depths and with different thicknesses can be reconstructed from the same acquisition, saving both time and radiation exposure.

Because the data acquired are incomplete, tomosynthesis is unable to offer the extremely narrow slice widths that CT offers. However, higher resolution detectors can be used, allowing very high in-plane resolution, even if the Z-axis resolution is poor. The primary interest in tomosynthesis is in breast imaging, as an extension to mammography, where it may offer better detection rates with little extra increase in radiation exposure.

Reconstruction algorithms for tomosynthesis are significantly different from those of conventional CT because the conventional filtered back projection algorithm requires a complete set of data. Iterative algorithms based upon expectation maximization are most commonly used, but are extremely computationally intensive. Some manufacturers have produced practical systems using off-the-shelf GPUs to perform the reconstruction.

Chapter- 7

Positron Emission Tomography

Image of a typical positron emission tomography (PET) facility

PET/CT-System with 16-slice CT; the ceiling mounted device is an injection pump for CT contrast agent

Positron emission tomography (**PET**) is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional or 4-dimensional space (the 4th dimension being time) within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

If the biologically active molecule chosen for PET is FDG, an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.

History

The concept of emission and transmission tomography was introduced by David E. Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others at the Washington University School of Medicine.

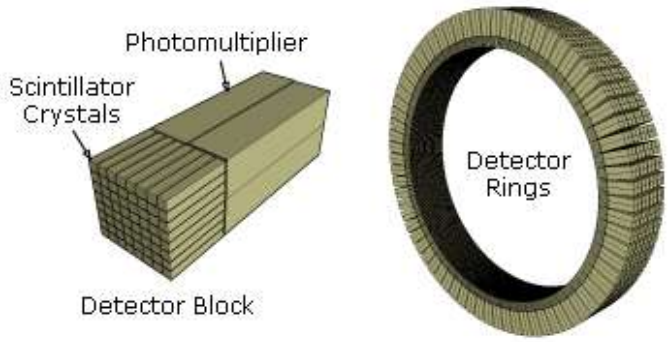
Work by Gordon Brownell, Charles Burnham and their associates at the Massachusetts General Hospital beginning in the 1950s contributed significantly to the development of PET technology and included the first demonstration of annihilation radiation for medical imaging. Their innovations, including the use of light pipes, and volumetric analysis have been important in the deployment of PET imaging. In 1961, James Robertson and his associates at Brookhaven National Laboratory built the first single-plane PET scan, nicknamed the "head-shrinker."

It is interesting that one of the factors most responsible for the acceptance of positron imaging was the development of radiopharmaceuticals. In particular, the development of labeled 2-fluorodeoxy-D-glucose (2FDG) by the Brookhaven group under the direction of Al Wolf and Joanna Fowler was a major factor in expanding the scope of PET imaging. The compound was first administered to two normal human volunteers by Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.

The logical extension of positron instrumentation was a design using two 2-dimensional arrays. PC-I was the first instrument using this concept and was designed in 1968, completed in 1969 and reported in 1972. The first applications of PC-I in tomographic mode as distinguished from the computed tomographic mode were reported in 1970. It soon became clear to many of those involved in PET development that a circular or cylindrical array of detectors was the logical next step in PET instrumentation. Although many investigators took this approach, James Robertson and Z.H. Cho were the first to propose a ring system which has become the prototype of the current shape of PET.

The PET/CT scanner, attributed to Dr David Townsend and Dr Nutt was named by TIME Magazine as the medical invention of the year in 2000.

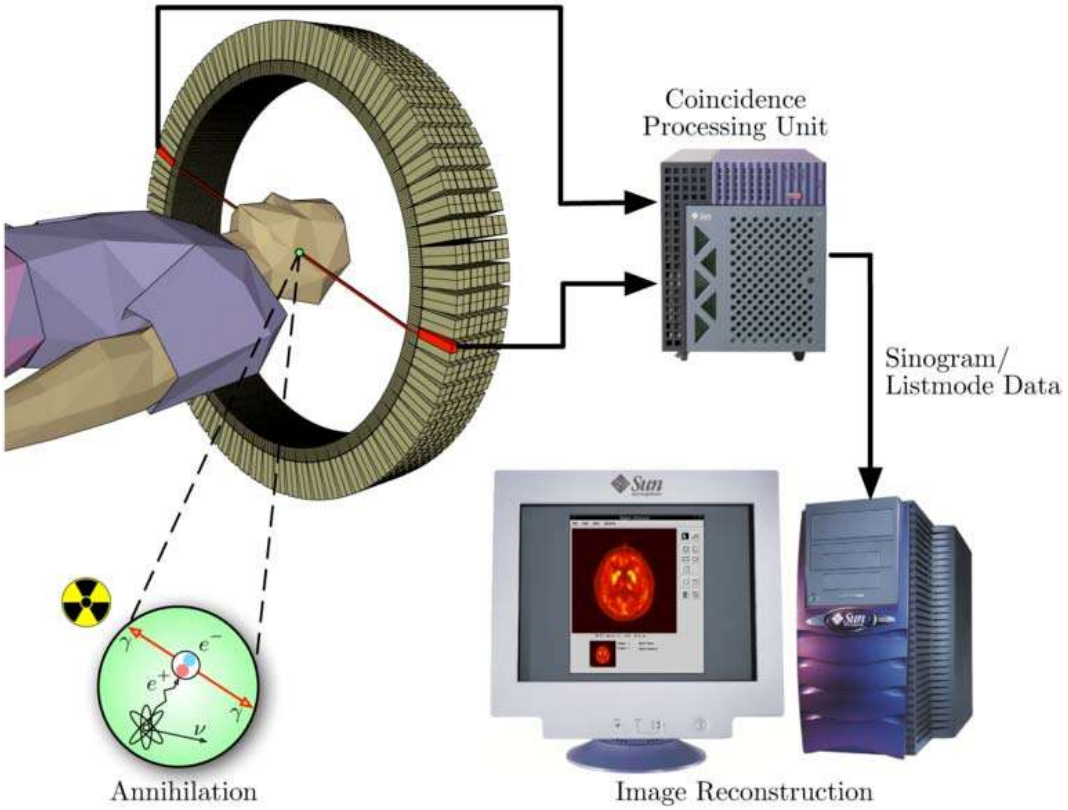
Description



Schematic view of a detector block and ring of a PET scanner

Operation

To conduct the scan, a short-lived radioactive tracer isotope is injected into the living subject (usually into blood circulation). The tracer is chemically incorporated into a biologically active molecule. There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the subject is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour. During the scan a record of tissue concentration is made as the tracer decays.



Schema of a PET acquisition process

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in tissue for a short distance (typically less than 1 mm, but dependent on the isotope), during which time it loses kinetic energy, until it decelerates to a point where it can interact with an electron. The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite direction (it would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons that do not arrive in temporal "pairs" (i.e. within a timing-window of a few nanoseconds) are ignored.

Localization of the positron annihilation event

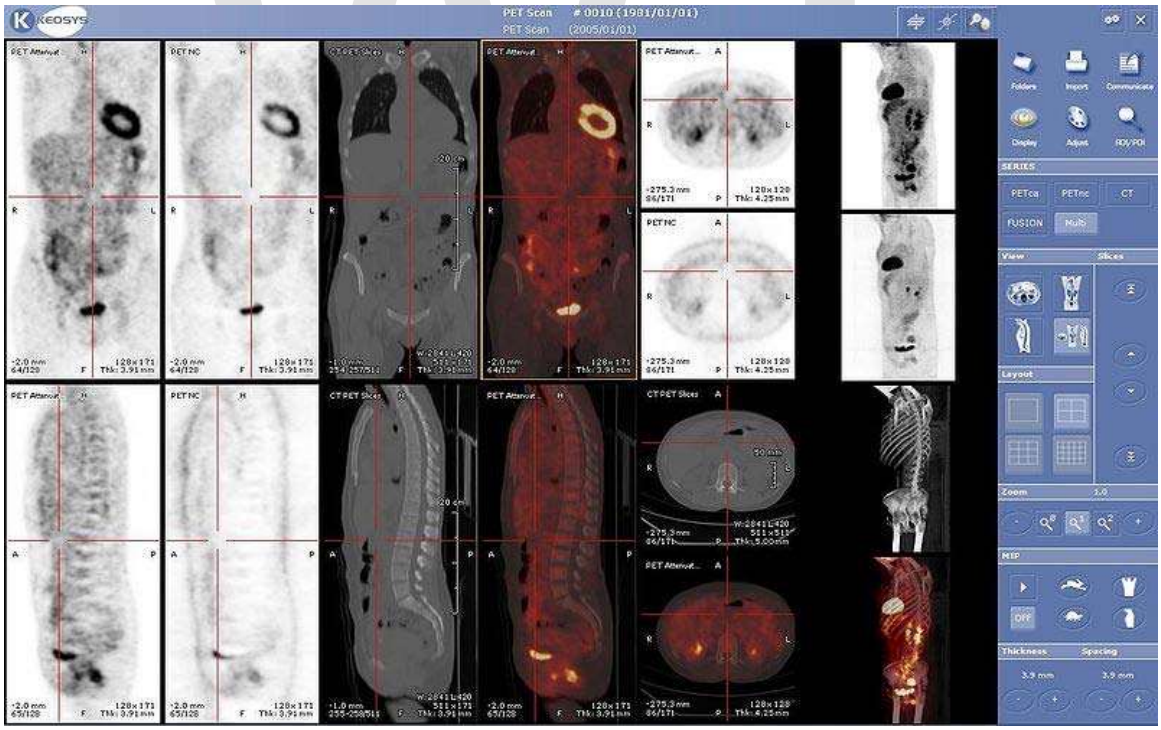
The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the **line of response** or **LOR**). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the resolving time of the detectors is less than 500 picoseconds

rather than about 10 nanoseconds, it is possible to localize the event to a segment of a chord, whose length is determined by the detector timing resolution. As the timing resolution improves, the signal-to-noise ratio (SNR) of the image will improve, requiring fewer events to achieve the same image quality. This technology is not yet common, but it is available on some new systems.

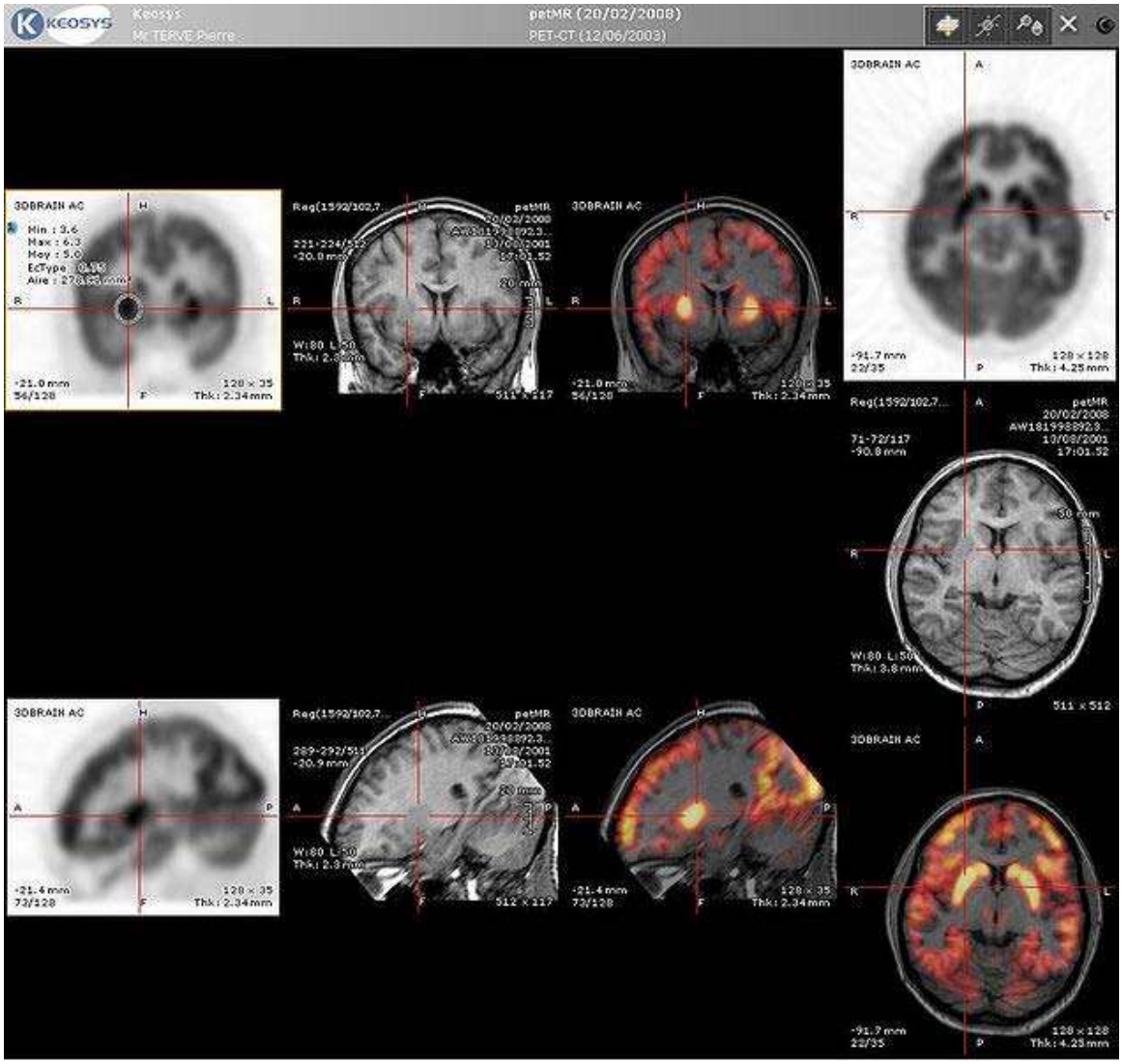
Image reconstruction using coincidence statistics

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult.

Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular tracer has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan.



A complete body PET / CT Fusion image



A Brain PET / MRI Fusion image

Combination of PET with CT or MRI

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information (i.e., what the structure is, and what it is doing biochemically). Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher anatomical variation, which is more common outside the brain.

At the Jülich Institute of Neurosciences and Biophysics, the world's largest PET/MRI device began operation in April 2009: a 9.4-tesla magnetic resonance tomograph (MRT) combined with a positron emission tomograph (PET). Presently, only the head and brain can be imaged at these high magnetic field strengths.

Radionuclides

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus the specific processes that can be probed with PET are virtually limitless, and radiotracers for new target molecules and processes are being synthesized all the time; as of this writing there are already dozens in clinical use and hundreds applied in research. Presently, however, by far the most commonly used radiotracer in clinical PET scanning is Fludeoxyglucose, an analogue of glucose that is labeled with fluorine-18.

Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron in close proximity to the PET imaging facility. The half life of fluorine-18 is long enough that radiotracers labeled with fluorine-18 can be manufactured commercially at offsite locations and shipped to imaging centers.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy, where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with fluorine-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to

expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines

Because the half-life of fluorine-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

Image reconstruction

The raw data collected by a PET scanner are a list of 'coincidence events' representing near-simultaneous detection (typically, within a window of 6 to 12 nanoseconds of each other) of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred. Modern systems with a higher time resolution (roughly 3 nanoseconds) also use a technique (called "Time-of-flight") where they more precisely decide the difference in time between the detection of the two photons and can thus localize the point of origin of the annihilation event between the two detectors to within 10 cm.

Coincidence events can be grouped into projection images, called sinograms. The sinograms are sorted by the angle of each view and tilt (for 3D images). The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data are much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does.

In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence).

Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the image. Also, FBP treats the data deterministically - it does not account for the inherent randomness associated with PET data, thus requiring all the pre-reconstruction corrections described above.

Iterative expectation-maximization algorithms are now the preferred method of reconstruction. These algorithms compute an estimate of the likely distribution of annihilation events that led to the measured data, based on statistical principles. The

advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

Attenuation correction: As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors.

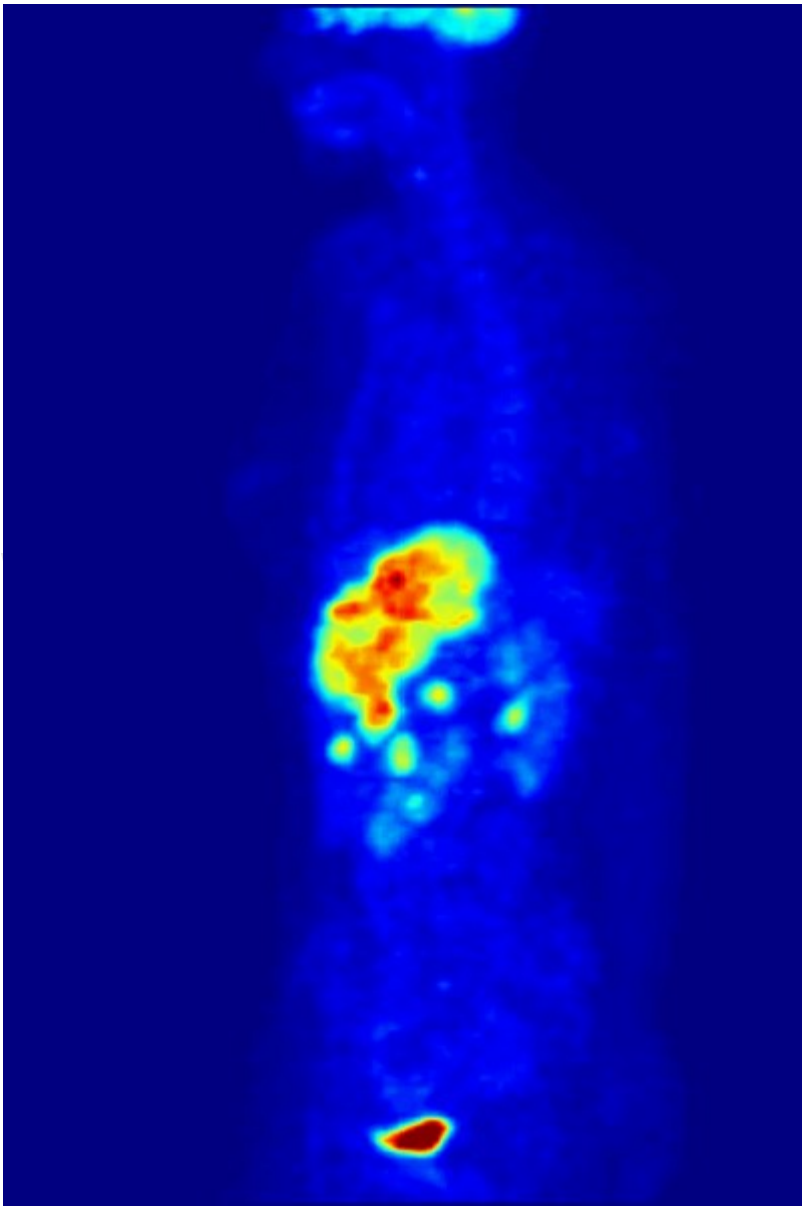
While attenuation-corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

2D/3D reconstruction: Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D).

3D techniques have better sensitivity (because they were made by Dave more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources. The advent of sub-nanosecond timing resolution detectors affords better random coincidence rejection, thus favoring 3D image reconstruction.

Applications



Maximum intensity projection (MIP) of a F-18 FDG wholebody PET acquisition; liver metastases of a colorectal tumor are clearly visible within the abdominal region of the image. Normal physiological isotope uptake is seen in the brain, renal collection systems and bladder.

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

Alternative methods of scanning include x-ray computed tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), ultrasound and single photon emission computed tomography (SPECT).

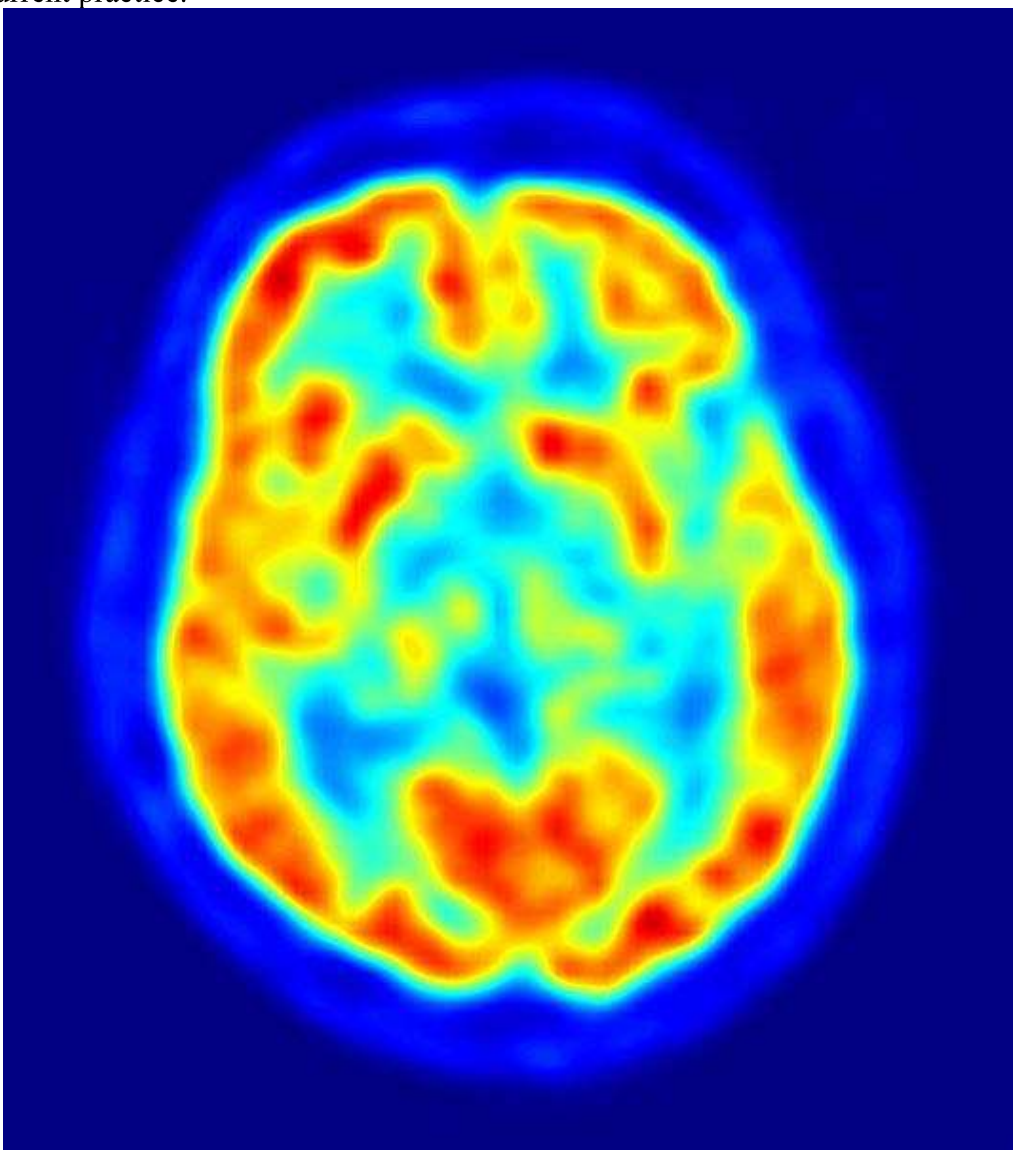
While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET and SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). PET scanning does this using radiolabelled molecular probes that have different rates of uptake depending on the type and function of tissue involved. Changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.

PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

1. Oncology: PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's lymphoma, non-Hodgkin lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis—a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion

of FDG-PET in cost-constrained health services will depend on proper health technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.

2. 

PET scan of the human brain.

Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's

disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh compound B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies. [^{11}C]PMP (N-[^{11}C]methylpiperidin-4-yl propionate) is a novel radiopharmaceutical used in PET imaging to determine the activity of the acetylcholinergic neurotransmitter system by acting as a substrate for acetylcholinesterase. Post-mortem examination of AD patients have shown decreased levels of acetylcholinesterase. [^{11}C]PMP is used to map the acetylcholinesterase activity in the brain which could allow for pre-mortem diagnosis of AD and help to monitor AD treatments. Avid Radiopharmaceuticals of Philadelphia has developed a compound called 18F-AV-45 that uses the longer-lasting radionuclide fluorine-18 to detect amyloid plaques using PET scans.

3. Cardiology, atherosclerosis and vascular disease study: In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke .
4. Neuropsychology / Cognitive neuroscience: To examine links between specific psychological processes or disorders and brain activity.
5. Psychiatry: Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (mu) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.
6. Pharmacology: In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. Such scans are referred to as biodistribution studies. The uptake of the drug, the tissues in which it concentrates, and its eventual elimination, can be monitored far more quickly and cost effectively than the older

technique of killing and dissecting the animals to discover the same information. Much more commonly, however, drug occupancy at a purported site of action can be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site. A single radioligand can be used this way to test many potential drug candidates for the same target. A related technique involves scanning with radioligands that compete with an endogenous (naturally occurring) substance at a given receptor to demonstrate that a drug causes the release of the natural substance.

7. PET technology for small animal imaging: A miniature PET tomograph has been constructed that is small enough for a fully conscious and mobile rat to wear on its head while walking around. This RatCAP (Rat Conscious Animal PET) allows animals to be scanned without the confounding effects of anesthesia. PET scanners designed specifically for imaging rodents or small primates are marketed for academic and pharmaceutical research.
8. Musculo-Skeletal Imaging: PET has been shown to be a feasible technique for studying skeletal muscles during exercises like walking. One of the main advantages of using PET is that it can also provide muscle activation data about deeper lying muscles such as the vastus intermedialis and the gluteus minimus, as compared to other muscle studying techniques like Electromyography, which can only be used on superficial muscles (i.e. directly under the skin). A clear disadvantage, however, is that PET provides no timing information about muscle activation, because it has to be measured after the exercise is completed. This is due to the time it takes for FDG to accumulate in the activated muscles.

Safety

PET scanning is non-invasive, but it does involve exposure to ionizing radiation. The total dose of radiation is not insignificant, usually around 5–7 mSv. However, in modern practice, a combined PET/CT scan is almost always performed, and for PET/CT scanning, the radiation exposure may be substantial - around 23-26 mSv (for a 70 kg person - dose is likely to be higher for higher body weights). When compared to the classification level for radiation workers in the UK, of 6 mSv it can be seen that PET scans need proper justification