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Neurology : Introduction

Neurology implies the branch of medicine pertaining to the study and treatment of disorders of the nervous system. The nervous system is a complex, sophisticated system that regulates and coordinates body activities. It consists of two major divisions:

- First is Central nervous system: the brain and spinal cord, and
- Second Peripheral nervous system: all other neural elements, such as eyes, ears, skin, and other "sensory receptors".

A doctor who has specialisation in neurology is known as a neurologist. The neurologist treats disorders that affect the brain, spinal cord, and nerves, such as:

- Demyelinating diseases of the central nervous system, such as multiple sclerosis
- Cerebrovascular disease, such as stroke
- Headache disorders
- Infections of the brain and peripheral nervous system
- Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis (Lou Gehrig's disease)
- Movement disorders, such as Parkinson's disease
- Seizure disorders, such as epilepsy
- Spinal cord disorders

- Speech and language disorders.

Neurologists do not perform surgery. If one of their patients requires surgery, they refer them to a neurosurgeon.

A number of neurologists also have additional training or interest in one area of neurology, such as stroke, epilepsy, neuromuscular, sleep medicine, pain management, or movement disorders.

WHO'S NEUROLOGIST

Neurologist is a medical doctor who possesses specialized training in diagnosing, treating and managing disorders of the brain and nervous system. Pediatric neurologists are doctors with specialized training in children's neurological disorders. A neurologist's educational background and medical training includes an undergraduate degree, four years of medical school, a one-year internship and three years of specialized training.

Many neurologists also have additional training in one area of neurology such as stroke, epilepsy or movement disorders.

Role Play by Neurologist

Neurologists are principal care providers or consultants. In comparison to other physicians a patient has a neurological disorder that requires frequent care, a neurologist is often the principal care provider. Patients with disorders such as Parkinson's disease, Alzheimer's disease or multiple sclerosis may use a neurologist as their principal care physician. In a consulting role, a neurologist will diagnosis and treat a neurological disorder and then advise the primary care physician managing the patient's overall health. For instance, a neurologist would act in a consulting role for conditions such as stroke, concussion or headache. Neurologists can recommend surgical treatment, but they do not perform surgery. When treatment includes surgery, neurologists will monitor surgically treated patients and supervise their continuing treatment.

Neurosurgeons are medical doctors who specialize in performing surgical treatments of the brain or nervous system.

Treatment by Neurologist

Disorders of the nervous system, brain, spinal cord, nerves, muscles and pain are mainly treated by Neurologist. Common neurological disorders include:
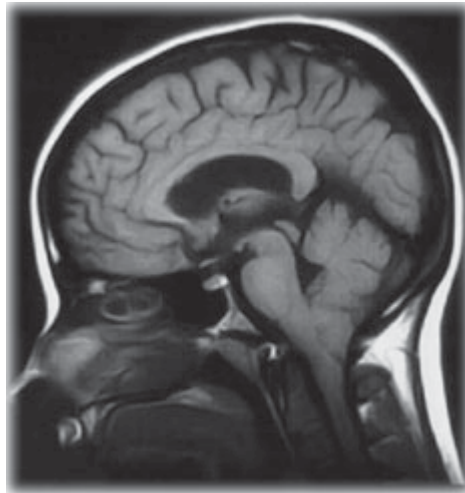
- Stroke
- Alzheimer's disease
- Headache
- Epilepsy
- Parkinson's disease
- Sleep disorders
- Multiple sclerosis
- Pain
- Tremor
- Brain and spinal cord injuries
- Brain tumours
- Peripheral nerve disorders
- Amyotrophic lateral sclerosis.

New Findings

In last few years, research has advanced understanding fundamental mechanism of the brain. With this new understanding, neurologists are finding new treatments and, ultimately, cures for many neurological diseases, which are among the most destructive and costly public health problems in the United States. For instance, research breakthroughs now permit neurologists to successfully treat stroke patients with clot-busting medication proven to reduce deaths and decrease disability.

Research developments have also produced new medications that relieve migraines, slow the progression of multiple sclerosis and improve movement in Parkinson's patients. These are just a few of the many advances gained from research that are improving the lives of millions of men and women around the world suffering from neurological disorders. To keep research advancing toward future cures and treatments, it's significant for patients to advocate for additional research funding. Contact your members of Congress and ask them to support neurology research.

NEUROLOGICAL EXAMINATION

During this examination, the health history of the patient is reviewed by neurologist with special attention to the current condition. The patient then takes a neurological exam. Typically, the exam tests mental status, function of the cranial nerves (including vision), strength, coordination, reflexes, and sensation. This information endorse the neurologist determine whether the problem exists in the nervous system and the clinical localization. Localization of the pathology is the key process by which neurologists develop their differential diagnosis. Further tests may be needed to confirm a diagnosis and ultimately guide therapy and appropriate management.

Neurologists Tasks

In the clinic the chief task of Neurologists is to examine patients who have been referred to them by other physicians in both the

inpatient and outpatient settings. A neurologist will start their interaction with a patient by taking a comprehensive medical history, and then perform a physical examination focusing on evaluating the nervous system. Components of the neurological examination include assessment of the patient's cognitive function, cranial nerves, motor strength, sensation, reflexes, coordination, and gait. In few examples, neurologists may order additional diagnostic tests as part of the evaluation. Commonly employed tests in neurology comprise imaging studies such as computed axial tomography (CAT) scans, magnetic resonance imaging (MRI), and ultrasound of major blood vessels of the head and neck. Neurophysiologic studies, including electroencephalography (EEG), needle electromyography (EMG), nerve conduction studies (NCSs) and evoked potentials are also commonly ordered.

Neurologists frequently perform lumbar punctures in order to assess characteristics of a patient's cerebrospinal fluid. Advances in genetic testing has made genetic testing and important tool in the classification of inherited neuromuscular disease.

The role of genetic influences on the development of acquired neuromuscular diseases is an active area of research.

Some of the conditions commonly encountered treated by neurologists include radiculopathy, neuropathy, headaches, stroke, dementia, seizures and epilepsy, Alzheimer's Disease, Attention deficit/hyperactivity disorder, Parkinson's Disease, Tourette's syndrome, multiple sclerosis, head trauma, sleep disorders, neuromuscular diseases, and different types of infections and tumours of the nervous system.

Neurologists are also asked to evaluate unresponsive patients on life support in order to confirm brain death. Treatment options vary depending on the neurological problem. They can include everything from referring the patient to a physiotherapist, to prescribing medications, to recommending a surgical procedure.

Some neurologists specialize in certain parts of the nervous system or in specific procedures. For example, clinical

neurophysiologists specialize in the use of EEG and intraoperative monitoring in order to diagnose certain neurological disorders. Other neurologists specialize in the use of electrodiagnostic medicine studies - needle EMG and NCSs. In the US, physicians do not typically specialize in all the aspects of clinical neurophysiology - i.e. sleep, EEG, EMG, and NCSs.

The American Board of Clinical Neurophysiology certifies US physicians in general clinical neurophysiology, epilepsy, and intraoperative monitoring. The American Board of Electrodiagnostic Medicine certifies US physicians in electrodiagnostic medicine and certifies technologists in nerve conduction studies. Sleep medicine is a subspecialty field in the US under several medical specialties including anesthesiology, internal medicine, family medicine, and neurology.

Neurosurgery is a distinct specialty that involves a different training path, and emphasizes the surgical treatment of neurological disorders. There are also many non-medical doctors, those with PhD degrees in subjects such as biology and chemistry, who study and research the nervous system. Working in labs in universities, hospitals, and private companies, these neuroscientists perform clinical and laboratory experiments and tests in order to learn more about the nervous system and find cures or new treatments for diseases and disorders.

There is a great deal of overlap between neuroscience and neurology. A large number of neurologists work in academic training hospitals, where they conduct research as neuroscientists in addition to treating patients and teaching neurology to medical students.

General Caseload

Neurologists are responsible for the diagnosis, treatment, and management of all the conditions mentioned above. When surgical intervention is required, the neurologist may refer the patient to a neurosurgeon. In some countries, additional legal responsibilities of a neurologist may include making a finding of brain death

when it is suspected that a patient has died. Neurologists frequently care for people with hereditary (genetic) diseases when the major manifestations are neurological, as is frequently the case.

Lumbar punctures are frequently performed by neurologists. Some neurologists may develop an interest in particular subfields, such as stroke, dementia, movement disorders, neurointensive care, headaches, epilepsy, sleep disorders, chronic pain management, multiple sclerosis, or neuromuscular diseases.

Overlapping with other Specialities

Overlaping with other specialties, varying from country to country and even within a local geographic area is also a case. Acute head trauma is most often treated by neurosurgeons, whereas sequelae of head trauma may be treated by neurologists or specialists in rehabilitation medicine. Although traditionally stroke cases have been managed by internal medicine or hospitalists, the emergence of vascular neurology and interventional neurologists has created a demand for stroke specialists. The establishment of JCAHO certified stroke centres has increased the role of neurologists in stroke care in many primary as well as tertiary hospitals. Some cases related to nervous system infectious diseases are treated by infectious disease specialists.

Most of cases related to headache are diagnosed and treated primarily by general practitioners, at least the less severe cases. Likewise, most cases of sciatica and other mechanical radiculopathies are treated by general practitioners, though they may be referred to neurologists or a surgeon (neurosurgeons or orthopedic surgeons).

Pulmonologists and psychiatrists also treat sleep disorders. Cerebral palsy is initially treated by pediatricians, but care may be transferred to an adult neurologist after the patient reaches a certain age. Physical medicine and rehabilitation physicians also in the US diagnosis and treat patients with neuromuscular diseases through the use of electrodiagnostic studies (needle EMG and nerve conduction studies) and other diagnostic tools. In the United

Kingdom and other countries, many of the conditions encountered by older patients such as movement disorders including Parkinson's Disease, stroke, dementia or gait disorders are managed predominantly by specialists in geriatric medicine.

Clinical neuropsychologists are often called upon to evaluate brain-behaviour relationships for the purpose of assisting with differential diagnosis, planning rehabilitation strategies, documenting cognitive strengths and weaknesses, and measuring change over time (e.g., for identifying abnormal aging or tracking the progression of a dementia).

Relationship to Clinical Neurophysiology

Neurologists in some countries, like USA and Germany, may subspecialize in clinical neurophysiology, the field responsible for EEG and intraoperative monitoring, or in electrodiagnostic medicine nerve conduction studies, EMG and evoked potentials. In other countries, this is an autonomous specialty (e.g., United Kingdom, Sweden, Spain).

Interaction with Psychiatry

Some are of the view that mental illnesses are neurological disorders affecting the central nervous system, traditionally they are classified separately, and treated by psychiatrists. In a 2002, Professor Joseph B. Martin, Dean of Harvard Medical School and a neurologist by training, wrote in an article that "the separation of the two categories is arbitrary, often influenced by beliefs rather than proven scientific observations. And the fact that the brain and mind are one makes the separation artificial anyway". Neurological disorders generally have psychiatric manifestations, such as post-stroke depression, depression and dementia associated with Parkinson's disease, mood and cognitive dysfunctions in Alzheimer's disease and Huntington disease, to name a few. Hence, there is not always a great distinction between neurology and psychiatry on a biological basis. The dominance of psychoanalytic theory in the first three quarters of the 20th century has since then been largely replaced by a focus on pharmacology. Inspite of the

shift to a medical model, brain science has not advanced to the point where scientists or clinicians can point to readily discernible pathologic lesions or genetic abnormalities that in and of themselves serve as reliable or predictive biomarkers of a given mental disorder.

EMERGING FIELD OF NEUROLOGICAL ENHANCEMENT

The rising field of neurological enhancement concentrates on the potential of therapies to improve such things as workplace efficacy, attention in school, and overall happiness in personal lives. However, this field has also led to questions about neuroethics and the psychopharmacology of lifestyle drugs.

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Neuro Anatomy

Neuroanatomy is the study of the structure and function of the nervous system. The nervous system is made up of many connected systems that work together to send and receive messages from the central nervous system, which is the brain and spinal cord, to the rest of the body. These systems comprised the central nervous system, peripheral nervous system, and somatic nervous system. They also include the autonomic nervous system, sympathetic nervous system, and parasympathetic nervous system. Within each of these systems, information is carried in electrical energy by nerve cells and neurons.

It is the brain which control our every thought and action. Brain is the most complex organ of our body. The brain is divided into functional units with particular function such as processing visual information or responding to fearful experiences. Each of these units is made up of brain cells that work together. These cells also form connections with cells in other functional units, creating communication routes for brain signals. Using new tools to tag and trace brain circuits, scientists are working to better understand how the human brain is organized to perform its many functions. Ongoing studies in animals and people are helping scientists recognize the many different types of brain cells and the roles they play. In addition, imaging technology is helping map brain regions responsible for specific functions and behaviors.

The physical structure of neuroanatomy is that of the nervous system. The central nervous system is made up of the brain and spinal cord. The peripheral nervous system is formed by the nerves and pathways that send messages from the central nervous system to the rest of the body.

The peripheral nervous system is divided into two subcategories: the somatic nervous system and the autonomic nervous system. The somatic nervous system is liable for carrying sensory information from the sense organs to the central nervous system as well as carrying motor instructions to the muscles. The autonomic nervous system can also be further divided into two subcategories. The sympathetic nervous system is the part of the autonomic nervous system that is responsible for fight or flight response, and the parasympathetic nervous system is in charge of resting states and conserving energy.

NERVOUS SYSTEM

THE NERVOUS SYSTEM considered to be the most complicated and highly organized of the various systems which make up the human body. It is the mechanism concerned with the correlation and integration of various bodily processes and the reactions and adjustments of the organism to its environment. In addition the cerebral cortex is related to conscious life. It is divided into two parts, central and peripheral.

The central nervous system have the encephalon or brain,contained within the cranium, and the medulla spinalis or spinal cord,lodged in the vertebral canal; the two portions are continuous with one another at the level of the upper border of the atlas vertebra.

The peripheral nervous system comprises a series of nerves by which the central nervous system is connected with the diverse tissues of the body. For descriptive purposes these nerves may be arranged in two groups, cerebrospinal and sympathetic, the arrangement, however, being an arbitrary one, since the two groups are intimately connected and closely intermingled. Both the

cerebrospinal and sympathetic nerves have nuclei of origin (the somatic efferent and sympathetic efferent) as well as nuclei of termination (somatic afferent and sympathetic afferent) in the central nervous system.

Tere are forty three cerebrospinal nerves on either side— twelve cranial, attached to the brain, and thirty-one spinal, to the medulla spinalis. They are associated with the functions of the special and general senses and with the voluntary movements of the body. The sympathetic nerves transmit the impulses which regulate the movements of the viscera, determine the caliber of the bloodvessels, and control the phenomena of secretion. Related to them are two rows ofcentral ganglia, situated one on either side of the middle line in front of the vertebral column; these ganglia are intimately related to the medulla spinalis and the spinal nerves, and are also joined to each other by vertical strands of nerve fibers so as to constitute a pair of knotted cords, the sympathetic trunks, which reach from the base of the skull to the coccyx. The sympathetic nerves issuing from the ganglia form three great prevertebral plexuses which supply the thoracic, abdominal, and pelvic viscera; in relation to the walls of these viscera intricate nerve plexuses and numerous peripheral ganglia are found.

Nervous System: Its Structure

Generally nervous tissues are made of nerve cells and their various processes, together with a supporting tissue called neuroglia, which, however, is found only in the brain and medulla spinalis. Some long processes of the nerve cells are of special significance, and it is convenient to consider them apart from the cells; they are known as nerve fibers. To the naked eye a difference is obvious between certain portions of the brain and medulla spinalis, viz., the gray substance and the white substance. The gray substance is largely composed of nerve cells, while the white substance contains only their long processes, the nerve fibers.

It is in the former that nervous impressions are received, stored, and transformed into efferent impulses, and by the latter

that they are conducted. Hence the gray substance forms the essential constituent of all the ganglionic centers, both those in the isolated ganglia and those aggregated in the brain and medulla spinalis; while the white substance forms the bulk of the commissural portions of the nerve centers and the peripheral nerves.

What is Neuroglia?

Neuroglia is the peculiar ground substance in which the true nervous constituents of the brain and medulla spinalis are imbedded. It consists of cells and fibers. Some of the cells are stellate in shape, with ill-defined cell body, and their fine processes become neuroglia fibers, which extend radially and unbranched among the nerve cells and fibers which they aid in supporting. Other cells give off fibers which branch repeatedly.

Some of the fibers start from the epithelial cells lining the ventricles of the brain and central canal of the medulla spinalis, and pass through the nervous tissue, branching repeatedly to end in slight enlargements on the pia mater. Thus, neuroglia is evidently a connective tissue in function but is not so in development; it is ectodermal in origin, whereas all connective tissues are mesodermal.

Nerve Cells

In the gray substance of the brain and medulla spinalis, but smaller collections of these cells also form the swellings, known as ganglia, seen on many nerves. These latter are found chiefly upon the spinal and cranial nerve roots and in connection with the sympathetic nerves.

There are different shape and size of nerve cells and have one or more processes. They may be divided for purposes of description into three groups, according to the number of processes which they possess:

(1) Unipolar cells are found in the spinal ganglia; the single process, after a short course, divides in a T-shaped manner

(2) Bipolar cells are also found in the spinal ganglia when the cells are in an embryonic condition. They are best demonstrated in the spinal ganglia of fish. Sometimes the processes come off from opposite poles of the cell, and the cell then assumes a spindle shape; in other cells both processes emerge at the same point.

In some cases where two fibers are explicity connected with a cell, one of the fibers is really derived from an adjoining nerve cell and is passing to end in a ramification around the ganglion cell, or, again, it may be coiled spirally around the nerve process which is issuing from the cell.

(3) Multipolar cells has pyramidal or stellate shape, and characterized by their large size and by the numerous processes which issue from them. The processes are of two types: one of them is termed the axis-cylinder process or axon because it becomes the axis-cylinder of a nerve fiber.

The others are termed the protoplasmic processes or dendrons; they start to divide and subdivide soon after they emerge from the cell, and finally end in minute twigs and become lost among the other elements of the nervous tissue.
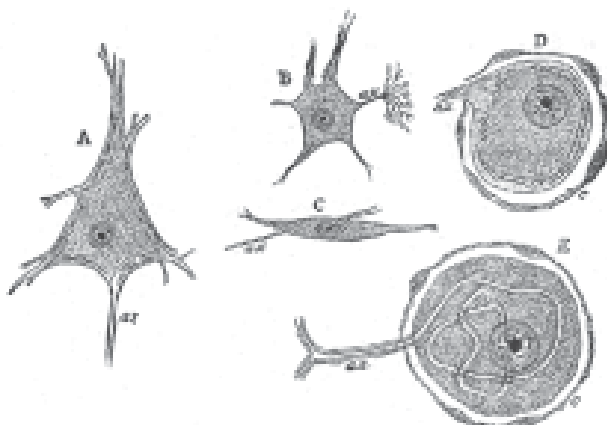

FIG. : Different forms of nerve cells. **A.** *Pyramidal cell.* **B.** *Small multipolar cell, in which the axon quickly divides into numerous branches.* **C.** *Small fusiform cell.* **D** *and* **E.** *Ganglion cells (*E *shows T-shaped division of axon).***ax.** *Axon.* **c.** *Capsule.*
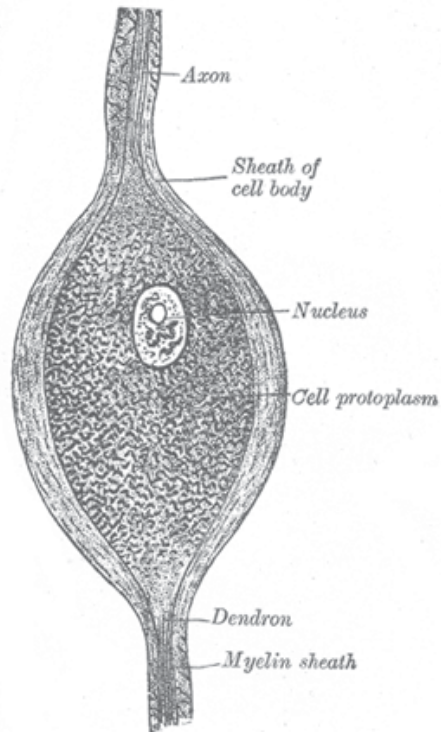
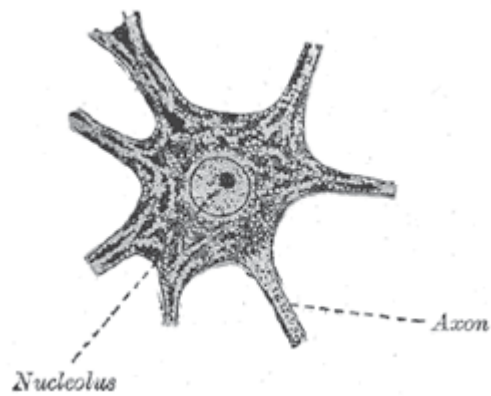*FIG. : Bipolar nerve cell from the spinal ganglion of the pike. (After Kölliker.)*

Fig. : Motor nerve cell from ventral horn of medulla spinalis of rabbit. The angular and spindle-shaped Nissl bodies are well shown.

The body of the nerve cell is called cyton, have a finely fibrillated protoplasmic material, of a reddish or yellowishbrown colour, which occasionally presents patches of a deeper tint, caused by the aggregation of pigment granules at one side of the nucleus, as in the substantia nigra and locus cæruleus of the brain.

The protoplasm also contains peculiar angular granules, which stain deeply with basic dyes, such as methylene blue; these are known as Nissl's granules . They extend into the dendritic processes but not into the axis-cylinder; the small clear area at the point of exit of the axon in some cell types is termed the cone of origin.

During fatigue or after prolonged stimulation of the nerve fibers connected with the cells. They are supposed to represent a store of nervous energy, and in different types of mental diseases are deficient or absent. The nucleus is, as a rule, a large, well-defined, spherical body, generally presenting an intranuclear network, and containing a well-marked nucleolus.
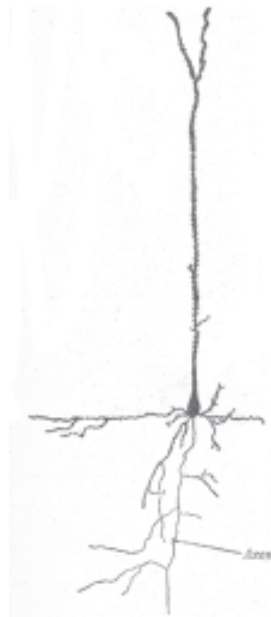
Fig. : Pyramidal cell from the cerebral cortex of a mouse.

Fig. : Cell of Purkinje from the cerebellum. Golgi method. (Cajal.)
**a.***Axon.* **b.** *Collateral.* **c** *and* **d.** *Dendrons.*

Besides the protoplasmic network as has been described above, each nerve cell may be shown to have delicate neurofibrils running through its substance; these fibrils are continuous with the fibrils of the axon, and are believed to convey nerve impulses. Golgi has also described an extracellular network, which is probably a supporting structure.

Nerve Fibers

In the peripheral nerves and in the white substance of the brain and medulla spinalis nerve fibers are found universally. They are of two kinds—viz., medullated or white fibers, and non-medullated orgray fibers.

The medullated fibers form the white part of the brain and medulla spinalis, and also the greater part of every cranial and spinal nerve, and give to these structures their opaque, white aspect. When perfectly fresh they appear to be similar; but soon after removal from the body each fiber presents, when examined by transmitted light, a double outline or contour, as if consisting of two parts. The central portion is named the axis-cylinder; around

this is a sheath of fatty material, staining black with osmic acid, named the white substance of Schwann ormedullary sheath, which gives to the fiber its double contour, and the whole is enclosed in a delicate membrane, the neurolemma, primitive sheath, or nucleated sheath of Schwann.
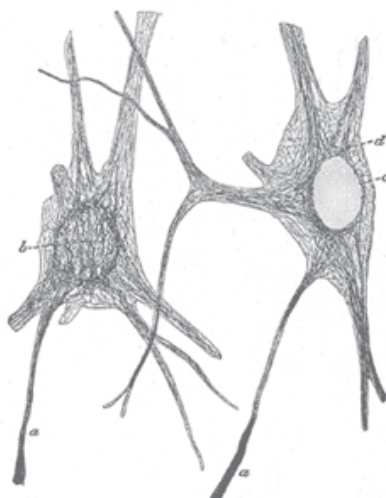
Fig. : Nerve cells of kitten, showing neurofibrils. (Cajal.) **a.** *Axon.* **b.***Cyton.* **c.** *Nucleus.* **d.** *Neurofibrils.*

The axis-cylinder is an integral part of the nerve fiber, and is always present; the medullary sheath and the neurolemma are occasionally absent, especially at the origin and termination of the nerve fiber. The axis-cylinder undergoes no interruption from its origin in the nerve center to its peripheral termination, and must be considered as a direct prolongation of a nerve cell. It constitutes about one-half or one-third of the nerve fiber, being greater in proportion in the fibers of the central organs than in those of the nerves.

It is rather transparent, and is therefore indistinguishable in a perfectly fresh and natural state of the nerve. It is made up of exceedingly fine fibrils, which stain darkly with gold chloride, and at its termination may be seen to break up into these fibrillæ. The fibrillæ have been termed as primitive fibrillæ of Schultze.

The axis-cylinder is said by some to be enveloped in a special reticular sheath, which separates it from the medullary sheath, and is composed of a substance calledneurokeratin. The more common opinion is that this network or reticulum is contained in the white matter of Schwann, and by some it is believed to be produced by the action of the reagents employed to show it.
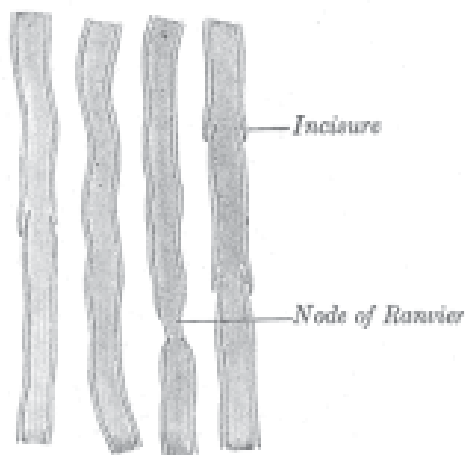

Fig. : Medullated nerve fibers. X 350.
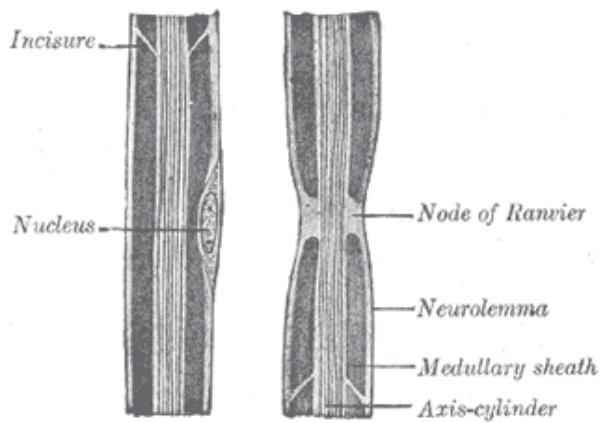
Fig. : Longitudinal sections of medullated nerve fibers. Osmic acid.
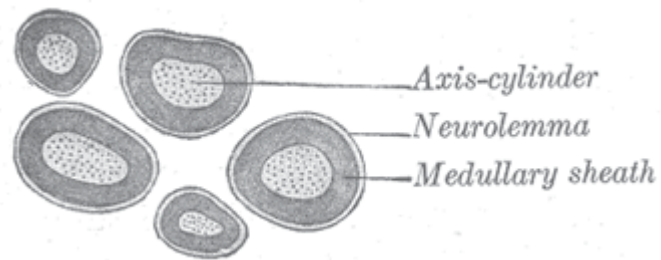
Fig. : Transverse sections of medullated nerve fibers. Osmic acid.

Fig. : Medullated nerve fibers stained with osmic acid. X 425.
*(Schäfer.) **R.** Nodes of Ranvier. **a.** Neurolemma. **c.** Nucleus.*

The medullary sheath, or white matter of Schwann , is a fatty matter in a fluid state, which insulates and protects the essential part of the nerve—the axis-cylinder. It is of diverse thickness, in some forming a layer of extreme thinness, so as to be scarcely

distinguishable, in others forming about one-half the nerve fiber. The variation in diameter of the nerve fibers (from 2 to 16ì) depends mainly upon the amount of the white substance, though the axis cylinder also varies within certain limits. The medullary sheath faces interruptions at regular intervals, giving to the fiber the appearance of constriction at these points: these are known as the nodes of Ranvier.

The portion of nerve fiber between two nodes is called an internodal segment. The neurolemma or primitive sheath is not interrupted at the nodes, but passes over them as a continuous membrane. If the fiber be treated with silver nitrate the reagent penetrates the neurolemma at the nodes, and on exposure to light reduction takes place, giving rise to the appearance of black crosses, Ranvier's crosses, on the axis-cylinder.

Beyond the nodes termed Frommann's lines there may also be seen transverse lines; the significance of these is not understood. In addition to these interruptions oblique clefts may be seen in the medullary sheath, subdividing it into irregular portions, which are termed medullary segments, or segments of Lantermann ; there is reason to believe that these clefts are artificially produced in the preparation of the specimens.
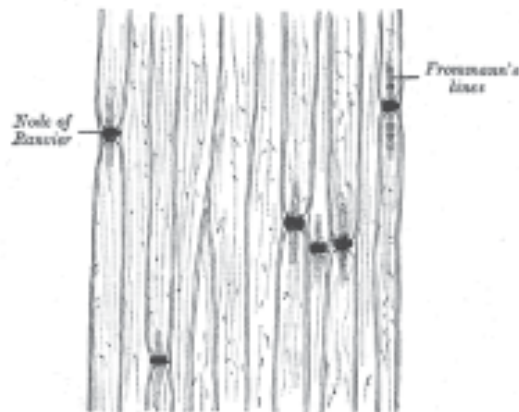
Fig. : Medullated nerve fibers stained with silver nitrate.

Fig. : A small nervous branch from the sympathetic of a mammal.
a.*Two medullated nerve fibers among a number of gray nerve fibers,* **b.**

Medullated nerve fibers, when examined in the fresh condition, frequently present a beaded or varicose appearance: this is due to manipulation and pressure causing the oily matter to collect into drops, and as result of the extreme delicacy of the primitive sheath, even slight pressure will cause the transudation of the fatty matter, which collects as drops of oil outside the membrane.

The neurolemma or primitive sheath is a delicate, structureless membrane. Here and there beneath it, and situated in depressions in the white matter of Schwann, are nuclei surrounded by a small amount of protoplasm. The nuclei is shape are oval and somewhat flattened, and bear a definite relation to the nodes of Ranvier, one nucleus generally lying in the center of each internode. In all medullated nerve fibers the primitive sheath is not present, being absent in those fibers which are found in the brain and medulla spinalis.

Wallerian Degeneration

If nerver fibres are cut across its central ends degenerate as far as the first node of Ranvier; but the peripheral ends degenerate

simultaneously throughout their whole length. The axons break up into fragments and become surrounded by drops of fatty substance which are formed from the breaking down of the medullary sheath.

The nuclei of the primitive sheath proliferate, and finally absorption of the axons and fatty substance occurs. If the cut ends of the nerve be sutured together regeneration of the nerve fibers takes place by the downgrowth of axons from the central end of the nerve. At one time it was believed that the regeneration was peripheral in origin, but this has been disproved, the proliferated nuclei in the peripheral portions taking part merely in the formation of the so-called scaffolding along which the new axons pass.

Non-medullated Fibers

Most of the fibers of the sympathetic system, and some of the cerebrospinal, consist of the gray or gelatinous nerve fibers (*fibers of Remak*). Each of these consists of an axis-cylinder to which nuclei are applied at intervals. These nuclei are believed to be in connection with a delicate sheath similar the neurolemma of the medullated nerve fiber. In external appearance the non-medullated nerve fibers are semitransparent and gray or yellowish gray. The individual fibers vary in size, generally averaging about half the size of the medullated fibers.

Peripheral Nerves and Ganglia: Structure

As far as the cerebrospinal nerves is concerned it consist of numerous nerve fibers collected together and enclosed in membranous sheaths. A small bundle of fibers, enclosed in a tubular sheath, is called a funiculus; if the nerve is of small size, it may consist only of a single funiculus; but if large, the funiculi are collected together into larger bundles or fasciculi, which are bound together in a common membranous investment. In structure the common membranous investment, or sheath of the whole nerve (epineurium), as well as the septa given off from it to separate the fasciculi, consist of connective tissue, composed of white and yellow elastic fibers, the latter existing in great

abundance. The tubular sheath of the funiculi (perineurium) is a fine, smooth, transparent membrane, which may be easily separated, in the form of a tube, from the fibers it encloses; in structure it is made up of connective tissue, which has a distinctly lamellar arrangement. The nerve fibers are held together and supported within the funiculus by delicate connective tissue, called the endoneurium. It is continuous with septa which pass inward from the innermost layer of the perineurium, and shows a ground substance in which are imbedded fine bundles of fibrous connective tissue running for the most part longitudinally. It serves to support capillary vessels, arranged so as to form a net-work with elongated meshes.

The cerebrospinal nerves consist almost exclusively of medullated nerve fibers, only a very small proportion of non-medullated being present. The bloodvessels supplying a nerve end in a minute capillary plexus, the vessels composing which pierce the perineurium, and run, for the most part, parallel with the fibers; they are connected together by short, transverse vessels, forming narrow, oblong meshes, corresponding to the capillary system of muscle. Fine non-medullated nerve fibers, vasomotor fibers, accompany these capillary vessels, and break up into elementary fibrils, which form a network around the vessels.

Horsley has demonstrated certain medullated fibers running in the epineurium and terminating in small spheroidal tactile corpuscles or end bulbs of Krause. These nerve fibers, which Marshall believes to be sensory, and which he has termed nervi nervorum, are considered by him to have a significant bearing upon certain neuralgic pains. The nerve fibers, so far as is at present known, do not coalesce, but pursue an uninterrupted course from the center to the periphery. In separating a nerve, however, into its component funiculi, it may be seen that these do not pursue a perfectly insulated course, but occasionally join at a very acute angle with other funiculi proceeding in the same direction; from this, branches are given off, to joint again in like manner with other funiculi.

It must be distinctly understood, however, that in these communications the individual nerve fibers do not coalesce, but only pass into the sheath of the adjacent nerve, become intermixed with its nerve fibers, and again pass on to intermingle with the nerve fibers in some adjoining funiculus. Nerves, in their course, subdivide into branches, and these frequently communicate with branches of a neighboring nerve. The communications which thus take place form what is called a plexus. Sometimes a plexus is formed by the primary branches of the trunks of the nerves—as the cervical, brachial, lumbar, and sacral plexuses—and occasionally by the terminal funiculi, as in the plexuses formed at the periphery of the body. In the formation of a plexus, the component nerves divide, then join, and again subdivide in such a complex manner that the individual funiculi become interlaced most intricate'y; so that each branch leaving a plexus may contain filaments from all the primary nervous trunks which form the plexus. In the formation also of smaller plexuses at the periphery of the body there is a free interchange of the funiculi and primitive fibers. In each case, however, the individual fibers remain separate and distinct.
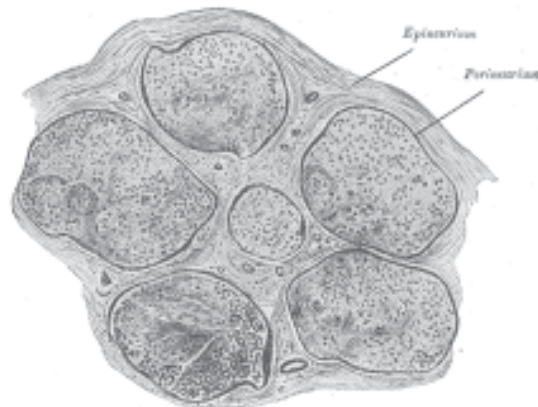
Fig. : Diagram of Transverse section of human tibial nerve.

There is a possibility that through this interchange of fibers, every branch passing off from a plexus has a more extensive

connection with the spinal cord than if it had proceeded to its distribution without forming connections with other nerves. Resultant by the parts supplied by these nerves have more extended relations with the nervous centers; by this means, also, groups of muscles may be associated for combined action. Very similar to cerebrospinal nerves the sympathetic nerves are constructed, but consist mainly of non-medullated fibers, collected in funiculi and enclosed in sheaths of connective tissue. There is, however, in these nerves a certain admixture of medullated fibers. The number of the latter varies in different nerves, and may be estimated by the color of the nerve.

Those branches of the sympathetic, which present a well-marked gray color, are composed chiefly of non-medullated nerve fibers, intermixed with a few medullated fibers; while those of a white color contain many of the latter fibers, and few of the former. Separate and diverse impressions are conveyed by the cerebrospinal and sympathetic nerve fibers. The sensory nerves, called also centripetal or afferent nerves, transmit to the nervous centers impressions made upon the peripheral extremities of the nerves, and in this way the mind, through the medium of the brain, becomes conscious of external objects. The centrifugal or efferent nerves transmit impressions from the nervous centers to the parts to which the nerves are distributed, these impressions either exciting muscular contraction or influencing the processes of nutrition, growth, and secretion.

Origins and Terminations of Nerves: Origins and TErminations

By the expression "the terminations of nerve fibers" is signified their connections with the nerve centers and with the parts they supply. The former are sometimes called their origins or central terminations; the latter their peripheral terminations.

Nerves: Its origination

In few cases the origin of nerves is single—that is to say, the whole nerve emerges from the nervous center by a single root; in

other instances the nerve arises by two or more roots which come off from various parts of the nerve center, sometimes widely apart from each other, and it often happens, when a nerve arises in this way by two roots, that the functions of these two roots are different; as, for example, in the spinal nerves, each of which arises by two roots, the anterior of which is motor, and the posterior sensory.

The point where the nerve root or roots emerge from the surface of the nervous center is named the superficial orapparent origin, but the fibers of the nerve can be traced for a certain distance into the substance of the nervous center to some portion of the gray matter, which constitutes the deep or real origin of the nerve.

The centrifugal or efferent nerve fibers originate in the nerve cells of the gray substance, the axis-cylinder processes of these cells being prolonged to form the fibers.

In the case of the centripetal or afferent nerves the fibers grow inward either from nerve cells in the organs of special sense, *e. g.*,the retina, or from nerve cells in the ganglia. Having entered the nerve center they branch and send their ultimate twigs among the cells, without, however, uniting with them.

Nerves' Peripheral Terminations

In various ways nerve fibers terminate peripherally, and these may be conveniently studied in the sensory and motor nerves respectively. The terminations of the sensory nerves are dealt with in the section on Sense Organs.

Motor nerves can be traced into either unstriped or striped muscular fibers. In the *unstriped* or *involuntary muscles* the nerves are derived from the sympathetic, and are composed mainly of non-medullated fibers.

Near their terminations they divide into numerous branches, which communicate and form intimate plexuses. At the junction of the branches small triangular nuclear bodies (ganglion cells) are situated. From these plexuses minute branches are given off which divide and break up into the ultimate fibrillæ of which the nerves

are composed. These fibrillæ course between the involuntary muscle cells, and, according to Elischer, terminate on the surfaces of the cells, opposite the nuclei, in minute swellings.

In the *striped* or *voluntary muscle* the nerves supplying the muscular fibers are derived from the cerebrospinal nerves, and are composed mainly of medullated fibers. The nerve, after entering the sheath of the muscle, breaks up into fibers or bundles of fibers, which form plexuses, and gradually divide until, as a rule, a single nerve fiber enters a single muscular fiber.

Sometimes, however, if the muscular fiber be long, more than one nerve fiber enters it. Within the muscular fiber the nerve terminates in a special expansion, called by Kühne, who first accurately described it, a motor end-plate .

On approaching the muscular fiber. The nerve fiber suddenly loses its medullary sheath, the neurolemma becomes continuous with the sarcolemma of the muscle, and only the axis-cylinder enters the muscular fiber. There it at once spreads out, ramifying like the roots of a tree, immediately beneath the sarcolemma, and becomes imbedded in a layer of granular matter, containing a number of clear, oblong nuclei, the whole constituting an end-plate from which the contractile wave of the muscular fiber is said to start.

Ganglia which are small aggregations of nerve cells found on the posterior roots of the spinal nerves; on the sensory roots of the trigeminal, facial, glossopharyngeal, and vagus nerves, and on the acoustic nerves. They are also found in connection with the sympathetic nerves. On section they are seen to consist of a reddish-gray substance, traversed by numerous white nerve fibers; they vary considerably in form and size; the largest are found in the cavity of the abdomen; the smallest, not visible to the naked eye, exist in considerable numbers upon the nerves distributed to the different viscera.

Each ganglion is invested by a smooth and firm, closely adhering, membranous envelope, consisting of dense areolar tissue;

this sheath is continuous with the perineurium of the nerves, and sends numerous processes into the interior to support the bloodvessels supplying the substance of the ganglion.
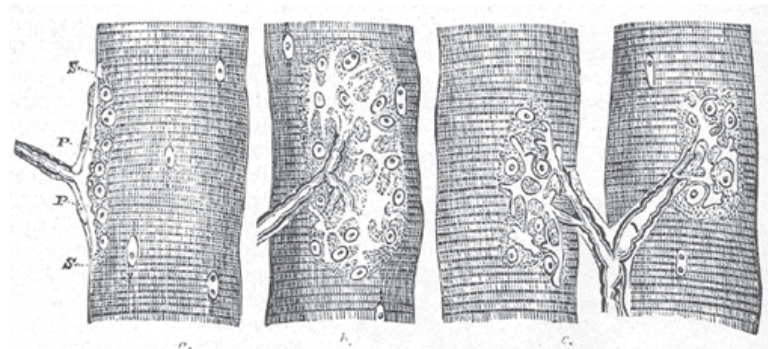
Fig. : Diagram of Muscular fibers of **Lacerta viridis** *with the terminations of nerves.* **a.** *Appeared in profile.* **P, P.** *The nerve end-plates.* **S, S.** *The base of the plate, consisting of a granular mass with nuclei.* **b.** *The same as seen in looking at a perfectly fresh fiber, the nervous ends being probably still excitable. (The forms of the variously divided plate can hardly be represented in a woodcut by sufficiently delicate and pale contours to reproduce correctly what is seen in nature.)* **c.** *The same as seen two hours after death from poisoning by curare.*

Fig. : Diagram of Transverse section of spinal ganglion of rabbit. **A.** *Ganglion. X 30.* **a.** *Large clear nerve cell.* **b.** *Small deeply staining nerve cell.* **c.** *Nuclei of capsule. X 250. The lines in the center point to the corresponding cells in the ganglion.*

As for as its structure is concerned all ganglia are essentially similar, consisting of the same structural elements—viz., nerve cells and nerve fibers. Each nerve cell has a nucleated sheath which is continuous with the neurolemma of the nerve fiber with which the cell is connected.

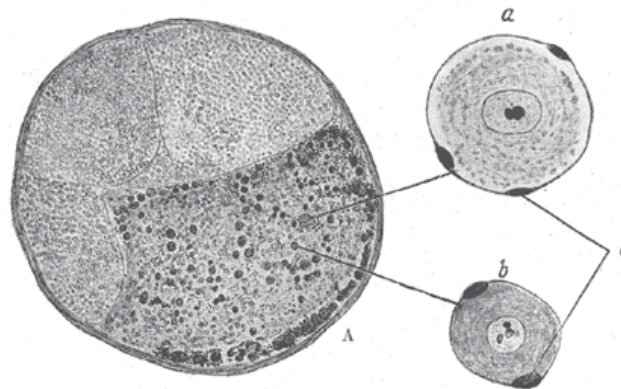The nerve cells in the ganglia of the spinal nerves are pyriform in shape, and have each a single process. A small distance from the cell and while still within the ganglion this process divides in a T-shaped manner, one limb of the cross-bar turning into the medulla spinalis, the other limb passing outward to the periphery. In the sympathetic ganglia the nerve cells are multipolar and each has one axis-cylinder process and several dendrons; the axon emerges from the ganglion as a non-medullated nerve fiber.

Similar cells are found in the ganglia connected with the trigeminal nerve, and these ganglia are therefore regarded as the cranial portions of the sympathetic system. The sympathetic nervous system comprises those portions of the nervous mechanism in which a medullated nerve fiber from the central system passes to a ganglion, sympathetic or peripheral, from which fibers, usually non-medullated, are distributed to such structures, *e. g.,* bloodvessels, as are not under voluntary control.
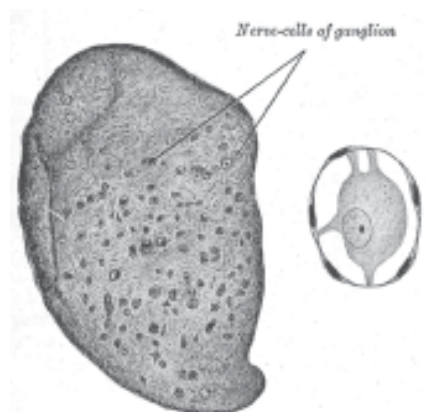

Fig. : Diagram of Transverse section of sympathetic ganglion of cat.
A. *Ganglion. X 50.* **a.** *A nerve cell. X 250.*

The spinal and sympathetic ganglia are not similar as far as their size and cell's disposition is concerned and in the number of nerve fibers entering and leaving them. In the spinal ganglia the nerve cells are much larger and for the most part collected in groups near the periphery, while the fibers, which are mostly medullated, traverse the central portion of the ganglion; whereas in the sympathetic ganglia the cells are smaller and distributed in irregular groups throughout the whole ganglion; the fibers also are irregularly scattered; some of the entering ones are medullated, while many of those leaving the ganglion are non-medullated.

Waldeyer's Neuron Theory

The nerve cell and its processes collectively constitute what is termed a neuron, and Waldeyer propounded a theory that said that the nervous system is built up of numerous neurons, "anatomically and genetically independent of one another." For this theory (*neuron theory*) the processes of one neuron only come into contact, and are never in direct continuity, with those of other neurons; while impulses are transmitted from one nerve cell to another through these points of contact, the synapses. The synapse or synaptic membrane appear to allow nervous impulses to pass in one direction only, namely, from the terminals of the axis-cylinder to the dendrons. This theory is based on the following facts, such as:

(1) embryonic nerve cells or neuroblasts are completely different from one another;

(2) when nervous tissues are stained by the Golgi method no continuity is seen even between neighboring neurons; and

(3) when degenerative changes take place in nervous tissue, either as the result of disease or experiment, they never spread from one neuron to another, but are limited to the individual neurons, or groups of neurons, primarily affected.

However, it must be added that within the past few years the validity of the neuron theory has been called in question by certain eminent histologists, who maintain that by the employment of

more delicate histological methods, minute fibrils can be followed from one nerve cell into another. Their existence, however, in the living is open to question.

Mott and Marinesco made careful examinations of living cells, using even the ultramicroscope and agree that neither Nissl bodies nor neurofibrils are present in the living state. For the present we may look upon the neurons as the units or structural elements of the nervous system. At birth all the neurons are present which are present in the adult, their division ceases before birth; they are not all functionally active at birth, but gradually assume functional activity. There is no indication of any regeneration after the destruction of the cell-body of any individual neuron.

Fasciculi, tracts or fiber systems are groups of axons having homologous origin and homologous distribution (as regards their collaterals, subdivisions and terminals) and are often named in accordance with their origin and termination, the name of the nucleus or the location of the cell body from which the axon or fiber arises preceding that of the nucleus or location of its termination. A given topographical area seldom represents a pure tract, as in most cases fibers of different systems are mixed.

HISTORY OF NERVOUS SYSTEM

The first known written record of a study of the anatomy of the human brain is the ancient Egyptian document the Edwin Smith Papyrus. The next major development in neuroanatomy came from the Greek Alcmaeon, who determined that the brain and not the heart ruled the body and that the senses were dependent on the brain.

After Alcmaeon's findings, many scientists, philosophers, and physicians from around the world continued to contribute to the understanding of neuroanatomy, notably: Galen, Herophilus, Rhazes and Erasistratus. Herophilus and Erasistratus of Alexandria were perhaps the most influential Greek neuroscientists with their studies involving dissecting the brains. For several hundred years afterward, with the cultural taboo of dissection, no major progress

occurred in neuroscience. However, Pope Sixtus IV effectively revitalized the study of neuroanatomy by altering the papal policy and allowing human dissection. This resulted in a boom of research in neuroanatomy by artists and scientists of the Renaissance.

In 1664, Thomas Willis, a physician and professor at Oxford University, coined the term neurology when he published his text Cerebri anatome which is considered the foundation of neuroanatomy.The subsequent three hundred and fifty some years has produced a great deal of documentation and study of the neural systems.

Composition

At the tissue level, the nervous system is composed of neurons, glial cells, and extracellular matrix. Both neurons and glial cells come in many types. Neurons are the information-processing cells of the nervous system: they sense our environment, communicate with each other via electrical signals and chemicals called neurotransmitters across synapses, and produce our memories, thoughts and movements. Glial cells maintain homeostasis, produce myelin, and provide support and protection for the brain's neurons. Some glial cells (astrocytes) can even propagate intercellular calcium waves over long distances in response to stimulation, and release gliotransmitters in response to changes in calcium concentration. The extracellular matrix also provides support on the molecular level for the brain's cells. At the organ level, the nervous system is composed of brain regions, such as the hippocampus in mammals or the mushroom bodies of thefruit fly. These regions are often modular and serve a particular role within the general pathways of the nervous system. For instance, the hippocampus is critical for forming memories. The nervous system also contains nerves, which are bundles of fibers that originate from the brain and spinal cord, and branch repeatedly to innervate every part of the body. Nerves are made mainly of the axons of neurons, along with a variety of membranes that wrap around and segregate them into nerve fascicles.

DIVISION OF VEEERTEBRATE NERVOUS SYSTEM

The vertebrate nervous system can be divided into the central and peripheral nervous systems. The central nervous system (CNS) consists of the brain, retina, and spinal cord, while the peripheral nervous system (PNS) is made up of all the nerves outside of the CNS that connect it to the rest of the body.

The PNS is further subdivided into the somatic and autonomic nervous systems. The somatic nervous system is made up of "afferent" neurons, which bring sensory information from the sense organs to the CNS, and "efferent" neurons, which carry motor instructions out to the muscles. The autonomic nervous system also has two subdivisions, the sympathetic and theparasympathetic, which are important for regulating the body's basic internal organ functions like heartbeat, breathing, digestion, and salivation. Autonomic nerves, like somatic nerves, contain afferent and efferent fibers.

Orientation in neuroanatomy

In anatomy in general and neuroanatomy in particular, many sets of topographic terms are used to denote orientation and location, which are generally referred to the body or brain axis. The pairs of terms used most commonly in neuroanatomy are as under:

- Dorsal and ventral: dorsal loosely meant the top or upper side, and ventral to the bottom or lower side. These descriptors originally referred to *dorsum* and *ventrum* - back and belly- of the body; the belly of most animals is oriented towards the ground; the erect posture of humans places our ventral aspect anteriorly, and the dorsal aspect becomes posterior. The case of the head and the brain is peculiar, since the belly does not extend into the head properly, unless we assume that the mouth represents an extended belly element.
- Therefore, in common use, those brain parts that lie close to the base of the cranium, and through it to the mouth

cavity, are known as ventral -i.e., at its bottom or lower side, as defined above)-, whereas dorsal parts are closer to the enclosing cranial vault.

- Rostral and caudal: *rostral* refers to the front of the body (towards the nose, or *rostrum* in Latin), and*caudal* to the tail end of the body (towards the tail; *cauda* in Latin). In Man, the directional terms "superior" and "inferior" inevitably refer to this rostrocaudal dimension, because our body axis is roughly oriented vertically in the erect position. However, all vertebrates develop a kink in the neural tube that is still detectable in the adult central nervous system, known as the cephalic flexure. The latter bends the rostral part of the CNS at a 90 degree angle relative to the caudal part, at the transition between the forebrain and the brainstem and spinal cord. This change in axial dimension is problematic when trying to describe relative position and sectioning planes in the brain.

- Medial and lateral: *medial* refers to being close, or relatively closer, to the midline (the descriptor *median* means a position precisely at the midline. *Lateral* is the opposite (a position separated away from the midline).

Note that such descriptors (dorsal/ventral, rostral/caudal; medial/lateral) are relative rather than absolute (e.g., a lateral structure may be said to lie medial to something else that lies even more laterally).

For planes of orientation or planes of section in neuroanatomy commonly used terms are "sagittal", "transverse" or "coronal", and "axial" or "horizontal". Again in this case, the situation is different for swimming, creeping or cuadrupedal (prone) animals than for Man, or other erect species, due to the changed position of the axis.

- By mid-sagittal plane the body and brain are divided into left and right halves; sagittal sections in general are parallel to this median plane, moving along the medial-lateral dimension. The term *sagittal* implies etymologically to the median suture between the right and left parietal bones

of the cranium, known classically as sagittal suture, as it looks roughly like an arrow by its confluence with other sutures (*sagitta*; arrow in Latin).

- A section plane across any elongated form in principle is held to be transverse if it is orthogonal to the axis (e.g., a transverse section of a finger; if there is no length axis, there is no way to define such sections, or there are infinite possibilities). Therefore, transverse body sections in vertebrates are parallel to the ribs, which are orthogonal to the vertebral column, that represents the body axis both in animals and man.

- The brain also has an intrinsic longitudinal axis -that of the primordial elongated neural tube-, which becomes largely vertical with the erect posture of Man, similarly as the body axis, except at its rostral end, as commented above. This explains that transverse spinal cord sections are roughly parallel to our ribs, or to the ground. However, this is only true for the spinal cord and the brainstem, since the forebrain end of the neural axis bends crook-like during early morphogenesis into the hypothalamus, where it ends; the orientation of true transverse sections accordingly changes, and is no longer parallel to the ribs and ground, but perpendicular to them; lack of awareness of this morphologic brain peculiarity (present in all vertebrate brains without exceptions) has caused and still causes erroneous thinking on forebrain brain parts.

- Acknowledging the singularity of rostral transverse sections, tradition has introduced a different descriptor for them, namely *coronal* sections. Coronal sections divide the forebrain from rostral (front) to caudal (back), forming a series orthogonal (transverse) to the local bent axis. The concept cannot be applied meaningfully to the brainstem and spinal cord, since there the coronal sections become horizontal to the axial dimension, being parallel to the axis.

- Across the head and brain a coronal plane is modernly conceived to be parallel to the face (the etymology refers

to *corona* or crown; the plane in which a king's crown sits on his head is not exactly parallel to the face, and exportation of the concept to less frontally endowed animals than us is obviously even more conflictive, but there is an implicit reference to the *coronal suture* of the cranium, which forms between the frontal and temporal/parietal bones, giving a sort of diadema configuration which is roughly parallel to the face). Coronal section planes thus essentially refer only to the head and brain, where a diadema makes sense, and not to the neck and body below.

- By definition horizontal sections are aligned with the horizon. In swimming, creeping and cuadrupedal animals the body axis itself is horizontal, and, thus, horizontal sections run along the length of the spinal cord, separating ventral from dorsal parts. Horizontal sections are orthogonal to both transverse and sagittal sections. Owing to the axial bend in the brain (forebrain), true horizontal sections in that region are orthogonal to coronal (transverse) sections (as is the horizon relative to the face).

According to these considerations, the three directions of space are represented precisely by the sagittal, transverse and horizontal planes, whereas coronal sections can be transverse, oblique or horizontal, depending on how they relate to the brain axis and its incurvations.

Various Kind of Tools

In neuroanatomy modern developments are directly correlated to the technologies used to perform research. Therefore it is necessary to discuss the various tools that are available. Several of the histological techniques used to study other tissues can be applied to the nervous system as well. However, there are some techniques that have been developed especially for the study of neuroanatomy.

Cell Staining

Under biological systems, cell staining is a technique used to enhance the contrast of particular features in microscopic images.

Nissl staining uses aniline basic dyes to intensely stain the acidic polyribosomes in the rough endoplasmic reticulum, which is abundant in neurons. This permits researchers to distinguish between different cell types (such as neurons and glia), and neuronal shapes and sizes, in various regions of the nervous system cytoarchitecture.

To fill selectively with a silver chromate precipitate a few neural cells (neurons or glia, but in principle any cells can react similarly) the classic Golgi stain uses potassium dichromate and silver nitrate . This so-called silver chromate impregnation procedure stains entirely or partially the cell bodies and neurites of some neurons -dendrites, axon- in brown and black, allowing researchers to trace their paths up to their thinnest terminal branches in a slice of nervous tissue, thanks to the transparency consequent to the lack of staining in the majority of surrounding cells. Modernly, Golgi-impregnated material has been adapted for electron-microscopic visualization of the unstained elements surrounding the stained processes and cell bodies, thus adding further resolutive power.

Significance of Histochemistry

Histochemistry uses knowledge about biochemical reaction properties of the chemical constituents of the brain (comprising notably enzymes) to apply selective methods of reaction to visualize where they occur in the brain and any functional or pathological changes. This applies importantly to molecules related to neurotransmitter production and metabolism, but applies likewise in many other directions chemoarchitecture, or chemical neuroanatomy.

IMMUNOCYTOCHEMISTRY

It is a special case of histochemistry that uses selective antibodies against a variety of chemical epitopes of the nervous system to selectively stain particular cell types, axonal fascicles, neuropiles, glial processes or blood vessels, or specific

intracytoplasmic or intranuclear proteins and other immunogenetic molecules, e.g., neurotransmitters.

Immunoreacted transcription factor proteins reveal genomic readout in terms of translated protein. This very increases the capacity of researchers to distinguish between different cell types (such as neurons and glia) in different regions of the nervous system.

In situ hybridization uses synthetic RNA probes that attach (hybridize) selectively to complementary mRNA transcripts of DNA exons in the cytoplasm, to visualize genomic readout, that is, distinguish active gene expression, in terms of mRNA rather than protein.

This permits to identify histologically (in situ) the cells involved in the production of genetically-coded molecules, which often represent differentiation or functional traits, as well as the molecular boundaries separating distinct brain domains or cell populations.

Genetically Encoded Markers

By expressing variable amounts of red, green, and blue fluorescent proteins in the brain, the so-called "brainbow" mutant mouse permits the combinatorial visualization of various different colors in neurons. This tags neurons with enough unique colors that they can often be distinguished from their neighbours with fluorescence microscopy, enabling researchers to map the local connections or mutual arrangement (tiling) between neurons.

Optogenetics uses transgenic constitutive and site-specific expression (normally in mice) of blocked markers that can be activated selectively by illumination with a light beam. This permits researchers to study axonal connectivity in the nervous system in a very discriminative way.

Non-Invasive Brain Imaging

With a view to investigate brain structure and function non-invasively in healthy human subjects magnetic resonance imaging has been used extensively. An important example is diffusion

tensor imaging, which relies on the restricted diffusion of water in tissue in order to produce axon images. In particular, water moves more quickly along the direction aligned with the axons, permitting the inference of their structure.

Viral-Based Methods

Some kind of viruses can replicate in brain cells and cross synapses. So, viruses modified to express markers (such as fluorescent proteins) can be brought to trace connectivity between brain regions across multiple synapses. Two tracer viruses which replicate and spread transneuronal/transsynaptic are the Herpes simplex virus type1 (HSV) and the Rhabdoviruses. Herpes simplex virus was utilise to trace the connections between the brain and the stomach, in order to examine the brain areas involved in viscero-sensory processing. Another study injected herpes simplex virus into the eye, thus allowing the visualization of the optical pathway from the retina into the visual system. An instance of a tracer virus which replicates from the synapse to the soma is the pseudorabies virus. By using pseudorabies viruses with different fluorescent reporters, dual infection models can parse complex synaptic architecture.

Dye-Based Methods

Various types of dyes (horseradish peroxidase variants, fluorescent or radioactive markers, lectins, dextrans) are used by Axonal transport methods that are more or less avidly absorbed by neurons or their processes. These molecules are selectively transported anterogradely (from soma to axon terminals) or retrogradely (from axon terminals to soma), thus providing evidence of primary and collateral connections in the brain. These 'physiologic' methods (because properties of living, unlesioned cells are used) can be combined with other procedures, and have essentially superseded the earlier procedures studying degeneration of lesioned neurons or axons. Detailed synaptic connections can be determined by correlative electron microscopy.

Connectomics

For the purpose use in studying nervous systems serial section electron microscopy has been extensively developed. For instance, the first application of serial block-face scanning electron microscopy was on rodent cortical tissue. Circuit reconstruction from data produced by this high-throughput method is challenging, and the Citizen science game EyeWire has been developed to aid research in that area.

Computational neuroanatomy

It is a field that uses various imaging modalities and computational techniques to model and quantify the spatiotemporal dynamics of neuroanatomical structures in both normal and clinical populations.

MODEL SYSTEMS

From the human brain, there are several other animals whose brains and nervous systems have received extensive study as model systems, comprising mice, zebrafish, fruit fly, and a species of roundworm called *C. elegans*. Each of these has its own advantages and disadvantages as a model system. For instance, the *C. elegans* nervous system is extremely stereotyped from one individual worm to the next. This has permitted researchers using electron microscopy to map the paths and connections of all of the approximately 300 neurons in this species. The fruit fly is widely studied in part because its genetics is very well understood and easily manipulated. The mouse is used since, as a mammal, its brain is more similar in structure to our own (e.g., it has a six-layered cortex, yet its genes can be easily modified and its reproductive cycle is relatively fast.

C. elegans

The brain is small and simple in some species, like the nematode worm, where the body plan is quite simple: a tube with a hollow gut cavity running from the mouth to the anus, and a nerve cord

with an enlargement (a ganglion) for each body segment, with an especially large ganglion at the front, known as the brain. The nematode *Caenorhabditis elegans* has been studied because of its importance in genetics.

In the early 1970s, Sydney Brenner chose it as a model system for studying the way that genes control development, including neuronal development. One advantage of working with this worm is that the nervous system of the hermaphrodite contains exactly 302 neurons, always in the same places, making corresponding synaptic connections in every worm. Brenner's team sliced worms into thousands of ultrathin sections and photographed every section under an electron microscope, then visually matched fibers from section to section, to map out every neuron and synapse in the entire body, to give a complete connectome of the nematode.

Nothing approaching this level of detail is available for any other organism, and the information has been used to enable a multitude of studies that would not have been possible without it.

Drosophila melanogaster

It is a popular experimental animal as it is easily cultured en masse from the wild, has a short generation time, and mutant animals are readily obtainable.

Arthropods have a central brain have three divisions and large optical lobes behind each eye for visual processing. The brain of a fruit fly contains several million synapses, compared to at least 100 billion in the human brain. Approximately two-thirds of the Drosophila brain is dedicated to visual processing.

Thomas Hunt Morgan began to work with Drosophila in 1906, and this work earned him the 1933 Nobel Prize in Medicine for identifying chromosomes as the vector of inheritance for genes. Because of the large array of tools available for studying Drosophila genetics, they have been a natural subject for studying the role of genes in the nervous system. The genome has been sequenced and

published in 2000. About 75% of known human disease genes have a recognizable match in the genome of fruit flies.

Drosophila is being used as a genetic model for several human neurological diseases comprising the neurodegenerative disorders Parkinson's, Huntington's, spinocerebellar ataxia and Alzheimer's disease. In spite of the large evolutionary distance between insects and mammals, various fundamental aspects of *Drosophila* neurogenetics have turned out to be relevant to humans. For example, the first biological clock genes were identified by examining *Drosophila* mutants that showed disrupted daily activity cycles.

Mouse

Mouse mutants: Rab23 is an essential negative regulator of the mouse Sonic hedgehog signaling pathway. The first understanding of biological processes requiring the Rab23 gene came from 2 independent mouse mutations in the gene and an epistasis analysis with mutations in the mouse shh gene. These studies exhibits that the gene is required for normal development of the brain and spinal cord and that the morphological defects seen in mutant embryos, such as failure to close dorsal regions of the neural tube during development, appeared secondary to expansion of ventral and reduction of dorsal identities in the developing neural tube.

These same mutations implicated the RAB23 gene in development of digits and eyes. The mouse open brain (opb) and Sonic hedgehog (Shh) genes have opposing roles in neural patterning: opb is required for dorsal cell types and Shh is required for ventral cell types in the spinal cord.In human, a regulator of rab: RabGDI alpha has been implicated in non-specific X-linked mental retardation.

NEUROANATOMY-A PRIMER

The structure of human brain is unique that boasts a complex three-dimensional architecture. Neuroscientists are only beginning to understand how the different parts of this intricate configuration

work together to produce behaviour. In the numerous neuroimaging studies that are published weekly, researchers use common neuroanatomical terms to denote location, organization, and, at times, implied function. Though a complete discussion of neuroanatomy is worthy of a thick textbook full of elaborate illustrations, common terminology used in neuroscientific research is highlighted below.

The basics

The brain perched on top of the spinal column is the epicenter of the human nervous system. It is the largest part of the central nervous system (CNS) and made up of three general areas: the brain stem, the cerebellum, and the cerebral cortex. The brain stem is involved with autonomic control of processes such as breathing and heart rate as well as conduction of information to and from the peripheral nervous system, the nerves and ganglia found outside the brain and spinal cord.

The cerebellum, adjacent to the brain stem, is accountable for balance and coordination of movement. Resting above these structures, the cerebral cortex quickly perceives, analyzes, and responds to information from the world around us. It handles sensory perception and processing as well as higher-level cognitive functions such as perception, memory, and decision-making. These three areas work together seamlessly in healthy individuals, allowing the brain to coordinate necessary functions and behaviors from breathing to spatial navigation. The cerebral cortex is divided into two hemispheres connected by the corpus callosum, a bridge of wide, flat neural fibers that act as communication relays between the two sides. While many popular books suggest this lateralization is important to function (i.e., the right side of the brain is the creative side while the left hemisphere dabbles more in analytical processing), most cognitive processes are represented by activation on both hemispheres. The exception is language—both Broca's Area, an area important to language syntax, and Wernicke's Area, a region critical to language content, reside on the left side of the

brain. Otherwise, the two hemispheres are nearly symmetrical and each one is further subdivided into four major lobes: the occipital, the temporal, the parietal, and the frontal.

These lobes are mainly used to denote general anatomical location. But they are also frequently spoken about in terms of function.

The occipital lobe, located at the back of the brain, is the seat of the primary visual cortex, the brain region responsible for processing and interpreting visual information. Reaching from the temple back towards the occipital lobe, the temporal lobe is a major processing center for language and memory. Above the temporal lobe and adjacent to the occipital lobe, the parietal lobe houses the somatosensory cortex and plays an important role in touch and spatial navigation. Lastly, the frontal lobe, extending from behind the forehead back to the parietal lobe, is the brain region that separates humans from our primate cousins. This large brain lobe is the seat of so-called executive function, with a hand in reasoning, decision-making, integration of sensory information, and the planning and execution of movement.

Folds and grooves

The cortex is, at its most basic, an extended pane of neural tissue that is gathered and pleated to fit inside the skull cavity. The bump in each pleat is called the gyrus, while the groove made by the fold is known as the sulcus. No two human brains are folded in the same exact way. Yet several of these folds are large and pronounced enough to merit specific names. They are used to specify location—but also may be referred to in discussions of function. For instance, the lateral sulcus is the inner fold that separates the temporal lobe from the frontal lobe. Adjacent to the lateral sulcus is the temporal gyrus. Both this groove and fold house the primary auditory cortex, where the brain processes sound information.

Wernicke's area, a brain region critical to understand language, also resides on the temporal gyrus. Similarly, different studies

may refer to specific activations in the superior frontal, middle frontal, and inferior frontal gyri in the frontal lobes. And, in studies of motor function, mentions of primary motor cortex may also refer to a location between the precentral gyrus and the central sulcus at the top of the brain.

Contrary to popular lay-press usage, the terms lobe and gyrus are not interchangeable. References to gyri and sulci can help give a more specific location on a particular lobe of the cortex.

Brodmann areas and Talairach coordinates

Sometimes researchers refer to specific locations on the human brain by a number, or Brodmann area. Korbinian Brodmann was a German neurologist who studied the brain in the early part of the twentieth century. He created maps of the brain based on cytoarchitecture, or how the cells were functionally organized. His classification system is still widely used today — though the borders of some areas have been refined over time. Although Brodmann areas are frequently cited in neuroscientific literature, it is not the only classification system available. The same brain area may be referred to by different names depending on the study. For instance, neuroscientists who study visual perception may refer to primary visual cortex as V1, Brodmann area 17, or simply as part of the occipital cortex.

Specific brain areas may also be denoted by Talairach coordinates, as defined by French neurosurgeon, Jean Talairach. Talairach used two key anatomical landmarks, the anterior commissure and the posterior commissure (parts of the corpus callosum) as the basis of his coordinate system. Today, several neuroimaging analysis programs spatially normalize the brains of each study participant to fit a standard reference brain based on Talairach's original brain atlas.

The Significance of White Matter

Neurons or brain cells, are made up of cell bodies, axons, and dendrites. The cells chiefly connect to one another through synapses

(small junctions between brain cells where neurotransmitters and other neurochemicals are passed). Synapses are often found between the axons and dendrites, which allows the cells to signal to one another. Current estimates suggest the brain has approximately 86 billion neurons.

The brain is made up of two types of matter: gray and white. Gray matter consists of the cell bodies and dendrites of the neurons, as well as supporting cells called astroglia and oligodendrocytes. White matter, however, is made up of mostly of axons sheathed in myelin, an insulating-type material that helps cells propagate signals more quickly. It's the myelin that gives the white matter its lighter color.

For many years, neuroscientists believed white matter was simply a support resource for gray matter. However, recent studies show that white matter architecture is important in processes like learning and memory.

It's all about connection

The frontal lobes are often referred to as the neocortex as they are the most recent parts of the brain to evolve—and their size and structure is unique to humans. But the neocortex works closely in concert with areas of the so-called reptilian brain, or subcortical brain areas residing close to the brain stem, to help us make sense of the world around us. Subcortical structures like the thalamus and basal ganglia (responsible for integrating sensory information and processing risk and rewards, respectively) are strongly connected to the neocortex and share information in both a bottom-up and top-down fashion. In fact, modern neuroimaging research is no longer focused on functional segregation, or the localization of function to a single area. Today, researchers are using new techniques to follow tracts of neurons that connect networks of brain areas to better understand how they work together to determine human behavior.

3

Behavioural Neurology

Behavioural neurology is that speciality of one, which deals with the study of neurological basis of behavior, memory, and cognition, and their impact of damage and disease and treatment.

Behavioural neurology is a subspecialty of neurology that studies the neurological basis of behaviour, memory, and cognition, the impact of neurological damage and disease upon these functions, and the treatment thereof. Two fields related to behavioural neurology are neuropsychiatry and neuropsychology.

A behavioural neurologist analyzes and treats cognitive and behavioural impairments resulting from a brain disorder or injury. Symptoms may comprise impaired memory, perception, cognition or emotional state. Because neuroendocrinology and behavioural neurology patients often share the same symptoms, finding the underlying basis for a disorder is key to managing it correctly. Many doctors fail to recognize this overlap between hormones and brain function, leading to incorrect diagnoses. Neuropsychiatry and Behavioural Neurology are disciplines among the clinical neurosciences that focus on the clinical and pathological aspects of neural processes associated with cognition, emotion, and behaviour. Current advances in structural and functional brain imaging, clinical electrophysiology, and experimental psychology fostered unprecedented growth in the clinical neurosciences, and have enlightened our understanding of both normal and disturbed

cognition, emotion, and behaviour. These technologies and the findings from them complement the clinical interview and examination and extend the core knowledge base and clinical skills that define modern neuropsychiatry and behavioural neurology. A principal goal of this integrative approach is to transcend the mind-brain duality reflected in the separation of psychiatry and neurology.

AGRAPHIA AN ACQUIRED NEUROLOGICAL DISORDER

Though able to read, some people cannot write because of a condition known as agraphia. Also known as dysgraphia, the writing deficiency is not an intellectual disability. It is instead a condition often based on lack of certain fine motor skills, usually due to congenital factors or neurological trauma. A writing disorder, dysgraphia is not simply messy handwriting or sloppy spelling. It is, rather, a medical disorder in which a person's writing skills are below their age level despite receiving an age-appropriate education. A person with dysgraphia has writing abilities well below his or her own measured intelligence level.

Dysgraphia usually becomes evident during early childhood when children are learning to write. While writing, children with dysgraphia may write with varied sizes, abnormal spacing between letters, or incorrect words. Though other learning disabilities can be present in a child with agraphia, social disorders and other academic issues are usually not a concern with these children. Children born with the disorder typically have many other dysgraphics in their families, usually including a close relative or parent.

Adults who suffer from dysgraphia who were not born with the disorder typically do so following a head injury. Brain disease or brain damage can also result in the condition. People with autism, Tourette syndrome, or Attention-Deficit Hyperactivity Disorder may also have agraphia.

Agraphia is an acquired neurological disorder causing a loss in the ability to communicate through writing, either due to some form of motor dysfunction or an inability to spell. The loss of writing ability may present with other language or neurological disorders; disorders appearing commonly with agraphia are alexia, aphasia, dysarthria,agnosia, and apraxia.

The study of individuals with agraphia may provide more information about the pathways involved in writing, both language related and motoric.Agraphia cannot be directly treated, but individuals can learn techniques to help regain and rehabilitate some of their previous writing abilities. These techniques differ depending on the type of agraphia.

Agraphia can be broadly divided into central and peripheral categories. Central agraphias typically involve language areas of the brain, causing difficulty spelling or with spontaneous communication, and are often accompanied by other language disorders. Peripheral agraphias usually target motor and visuospatial skills besides language and tend to involve motoric areas of the brain, causing difficulty in the movements associated with writing. Central agraphia may also be called aphasic agraphia as it involves areas of the brain whose major functions are connected to language and writing; peripheral agraphia may also be called nonaphasic agraphia as it involves areas of the brain whose functions are not directly connected to language and writing (typically motor areas).

The history of agraphia dates to the mid-fourteenth century, but it was not until the second half of the nineteenth century that it sparked significant clinical interest. Research in the twentieth century focused primary on aphasiology in patients with lesions from strokes.

THE NEUROLOGY OF WRITING

There are many brain areas which interact and which are responsible for various aspects of the ability to write. Likewise,

there are a number of theories which have been proposed to explain the ability to write, and the loss of writing ability. Broadly considered, the principle structures include the left frontal lobe (Exner's Writing Area and Broca's Expressive Speech area), the left temporal lobe (Wernicke's receptive speech area), and the superior and inferior parietal lobe.

Exner's and Broca's area are implicated in the expressive aspects of writing, whereas the temporal and parietal lobe are involved in the comprehension of written words. However, the parietal lobe is also believed to program the frontal motor areas and to supply the anterior region of the brain with the grapheme equivalents of auditory language; i.e. converting or visual images sounds into written symbols. Presumably the parietal lobe constructs the written-word images (probably via interaction with Wernicke's area) which and assists in converting these into graphemes. These motor-graphemes (or written word/letter images) are then transmitted to the left frontal convexity (i.e. Broca's and Exner's area) for grapheme conversion and motoric expression. It has also been proposed that there are at least two stages involved in the act of writing: a linguistic stage and a motor-expressive-praxic stage.

The linguistic stage involves the encoding of auditory and visual information into syntactical-lexical units—the symbols for letters and written words. This is mediated through the angular gyrus which thus provides the linguistic rules which subserve writing. The motor stage is the final step in which the expression of graphemes is subserved. This stage is mediated presumably by Exner's writing area (located in the left frontal convexity) in conjunction with the inferior parietal lobule. Because different regions of the brain contribute to the ability to write, damage to these different areas, therefore, affect different aspects of the ability to write. Thus, there are different subtypes of agaphia, depending on which areas of the brain have been damaged. These subtypes are referred to as Frontal Agraphia, Pure Agraphia, Alexic Agraphia, Apraxic Agraphia, and Spatial Agraphia.
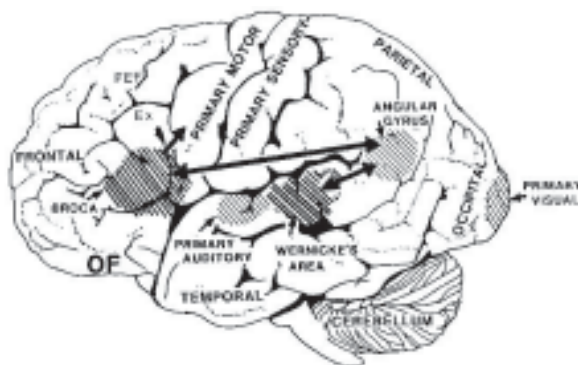
Exner's Writing Area

It is located within a small area along the lateral convexity of the left frontal lobe, and is adjacent to Broca's expressive speech area, and the primary and secondary areas controlling the movement of the hand and fine finger movements. Exner's area appears to be the final common pathway where linguistic impulses receive a final motoric stamp for the purposes of writing. That is, Exner's area translates auditory-images transferred from the posterior language areas, into those motor impulses that will form written words and sentences. Exner's area is very dependent on Broca's area with which is maintains extensive interconnections. That is, Broca's area also acts to organize impulses received from the posterior language zones and relays them to Exner's area for the purposes of written expression.

Frontal Lobe Agraphia

Lesions localized to the left frontal lobe and Exner's and Broca's area typically result in disturbances in the elementary motoric aspects of writing, i.e. Frontal Agraphia. Frontal lobe agraphia, however, is sometimes referred to as Pure Agraphia. On the other hand, pure Agraphia has also been attributed to left parietal lesions.

The similarity in symptoms is probably due to the fact that the inferior parietal lobe (IPL) transmits auditory-motor impulses to Broca's and Exner's area, and assists in programing sensory-

motor movements. Generally, with frontal agraphia, grapheme (letter) formation becomes labored, uncoordinated, and takes on a very sloppy appearance.

Cursive handwriting is usually more disturbed than printing, as cursive handwriting requires additional fine motor control. Cursive handwriting is also acquired at a later age, and is thus more likely to be more severely disrupted than printing which is (comparatively) an older and more ingrained skill. With frontal agraphia, the ability to spell is often affected. Patient's may not be able to spell correctly even if given block letters—particularly if the left IPL is also damaged.

However, with frontal agraphia, primarily, it is the ability to properly form letters and words that is disrupted. Predominantly, with frontal lesions, and thus frontal agraphia, there is a disturbances in grapheme selection. That is, the wrong letters may be chosen, and the patient may seem to have "forgotten" how to form certain letters. They may write the wrong letter—which in turn makes it appear that they have forgotten how to spell.

Those with frontal agraphia may also abnormally sequence or even add unnecessary letters when writing. In general, with a left frontal lesion, spelling and writing with both the right and left hand is severely affected, and the left hand may be even more profoundly affected.

Patients with frontal agraphia, particularly if Broca's area is damaged, are unable to write spontaneously or to dictation. Writing samples are contaminated with perseverations (such that they write the same letter over and over) or the addition of extra strokes to letters (e.g. such as when writing an "m"=mmm).

Patients with frontal agraphia may be unable to even write their name.

Pure (Parietal Lobe) Agrapha

Pure agraphia is related to frontal lesions, but is most commonly secondary to damage involving the superior and inferior parietal

lobe (IPL). The IPL sits and the junction of the frontal, parietal, occipital, and temporal lobe, and assimilates and integrates complex auditory, visual, motor and tactile sensations so as to form those multi-modal images and concepts which are integral to the comprehension and expression of human language. With IPL damage, patients have difficulty programming those movements necessary to form written words, such that there is a loss of the ability select, form, and express, in writing, words and sentences. Patients with pure (parietal lobe) agraphia frequently misspell words, and may insert the wrong letters or place them in the wrong order or sequence when attempting to write. In contrast, reading, oral speech and the ability to name objects or letters are generally unimpaired.

Very commonly, pure agraphia is related to lesions involving the superior and mid parietal regions of the left hemisphere; areas, 5 and 7 (Basso, et al. 2008; Vignolo, 2003), and/or the inferior parietal region (Strub & Geschwind, 1983).

Patients are unable to write because the area involved in organizing visual-letter organization (i.e. the inferior parietal lobe) is cut off from the region controlling hand movements in the frontal lobe (Strub & Geschwind, 1983). However, according to Vignolo (2003), the posterior superior left parietal lobule (area 7) is crucial for the sensorimotor linguistic integration needed for writing. It has also been argued that the sensory motor engrams necessary for the production and perception of written language are stored within the inferior parietal lobule of the left hemisphere.

When this region is damaged, patients sometimes have difficulty forming letters due to an inability to access these engrams (Strub & Geschwind, 1983). Writing samples, therefore, are characterized by mispellings, letter ommissions, distortions, temporal-sequential misplacements, and inversions.

Alexic-agraphia

Alexic agraphia is a disturbance involving the ability to read (alexia) and to write (agraphia). Thus alexic-agraphia is a

disturbance in the ability to decode and to encode written language. Reading and writing may not be equally affected. Some patients may be able to recognize written letters, but are unable to form them.

Some patients can form the letters, but are then unable to read them. However, even those who are able to read the letters or words they cannot write, began having difficulty as the words become longer or less familiar. Patients with alexic-agraphia have generally have difficulty with spelling, even when block letters are employed. Thus the ability to spell, per se, is disrupted. (Marcie & Heilman, 1979). Often alexia-agraphia is due to a lesion involving the left inferior parietal lobule and angular gyrus (Benson & Geschwind, 1969; Hecaen & Kremin, 1977). Because alexic-agrahia is associated with parietal lesions, it is also referred to as parietal lobe alexia. That is, rather than referred to as alexic agraphia, as patients who cannot spell are unable to write appropriately by definition, this condition could simply be referred to as alexia.

However, what distinguishes alexic agraphia from alexia, is the disturbance of motor control which is not characteristic of alexia per se. That is, alexia is a loss of the ability to read, and is not related to motor abnormalities, as is the case with agraphia and alexic-agraphia.

Apraxic Agraphia

When a patient has difficulty sequencing their movements or performing skilled movements involving a series of steps, the disorder is referred to as Apraxia. There are subtypes of apraxia, and different aspects of this disorder are seen with frontal vs parietal lobe lesions — in which case the ability to write may also be severely disrupted. This latter condition is referred to as apraxic agraphia.

Because the patient is also apraxic, the ability to make gestures or complex patterned movements becomes abnormal such as those involved in writing is also deficient. That is, the ability to correctly temporally sequence hand movements is affected which interferes

with the ability to write. The patient no longer knows how to correctly hold or manipulate a pen, or how to move their hand when writing. However, if given block letters, or if asked to spell out loud, they may be able to spell correctly.

Spatial Agraphia

Right cerebral injuries can secondarily disrupt writing skills becauses of to generalized spatial and constructional deficiencies. This is because the right half of the brain, although minimally involved in grammar and word selection, is dominant for almost all aspects of visual spatial functioning and orientation, including the ability to coordinate movements in space. This would include those fine motor movements involved in writing. Hence, with right hemisphere lesions, particularly right temporal-parietal injuries, words and letters will not be properly formed and aligned even when copying. Patients may have difficulty writing sentences in a straight line, and/or letters may be slanted at abnormal angles.

In some cases the writing may be reduced to a scrawl. In addition, patients may write only on the right half of the paper such that as they write, the left hand margin becomes progressively larger and the right side smaller (Hecaen & Marie, 1974). That is, they ignore the left half of visual space including the left half of the page they are writing on. If allowed to continue patients may end up writing only along the edge of the right hand margin of the paper. Patients with right hemisphere lesions may tend to abnormally introduce spaces between letters within the words they are writing, particularly when writing cursively (i.e. cu siv e ly). This is because of a failure to perform closure as well as a release over the left hemisphere (i.e. left hemisphere release). That is, whereas the right hemisphere performs closure, the left introduces sequences. If the right hemisphere is damaged, the left hemisphere acting unopposed begins to abnormally temporally-sequence and thus produce sequences separated by spaces, when writing. However, abnormal sequencing can also result from left hemisphere lesions

Aphasia & Agraphia

Aphasia is a disorder of receptive and expressive language, involving loss of comprehension, or loss of the ability to speak, or both. Although every patient with agraphia does not necessarily suffer from aphasic abnormalities, every patient who has aphasia has some degree of agraphia. Thus patients with aphasia always suffer from some degree of agraphia, though patients with agraphia do not always suffer from aphasic disturbances.

AGRAPHIA : ITS CHARACTERISITICS

Agraphia or impairment in producing written language can occur in several ways and various forms because writing involves many cognitive processes (language processing, spelling, visual perception, visuospatial orientation for graphic symbols, motor planning, and motor control of handwriting).

Agraphia has two chief subgroupings: central ("aphasic") agraphia and peripheral ("nonaphasic") agraphia. Central agraphias include lexical, phonological, deep, and semantic agraphia. Peripheral agraphias include allographic, apraxic, motor execution, hemianoptic and afferent agraphia. Central agraphia occurs when there are both impairments in spoken language and impairments to the various motor and visualization skills involved in writing. Individuals who have agraphia with fluent aphasia write a normal quantity of well-formed letters, but lack the ability to write meaningful words. Receptive aphasia is an instance of fluent aphasia. Those who have agraphia with nonfluent aphasia can write brief sentences but their writing is difficult to read. Their writing requires great physical effort but lacks proper syntax and often has poor spelling.

Expressive aphasia is an instance of nonfluent aphasia. Individuals who have Alexia with agraphia have difficulty with both the production and comprehension of written language. This form of agraphia does not impair spoken language. Deep agraphia affects an individuals' phonological ability and orthographic

memory. Deep agraphia is often the result of a lesion involving the left parietal region (supramarginal gyrus or insula). Individuals can neither remember how words look when spelled correctly, nor sound them out to determine spelling.

Individuals typically rely on their damaged orthographic memory to spell; this results in frequent errors, usually semantic in nature. Individuals have more difficulty with abstract concepts and uncommon words. Reading and spoken language are often impaired as well. Gerstmann syndrome agraphia is the impairment of written language production associated with the following structural symptoms: difficulty discriminating between one's own fingers, difficulty distinguishing left from right, and difficulty performing calculations.

All four of these symptoms result from pathway lesions. Gerstmann's syndrome may additionally be present with alexia and mild aphasia. Global agraphia also impairs an individuals' orthographic memory although to a greater extent than deep agraphia. In global apraxia, spelling knowledge is lost to such a degree that the individual can only write very few meaningful words, or cannot write any words at all. Reading and spoken language are also markedly impaired. Lexical and structural agraphia are caused by damage to the orthographic memory; these individuals cannot visualize the spelling of a word, though they do retain the ability to sound them out. This impaired spelling memory can imply the loss or degradation of the knowledge or just an inability to efficiently access it.

There is a regularity effect associated with lexical agraphia in that individuals are less likely to correctly spell words without regular, predictable spellings. Additionally, spelling ability tends to be less impaired for common words. Individuals also have difficulty with homophones. Language competence in terms of grammar and sentence writing tends to be preserved. Phonological agraphia is the opposite of lexical agraphia in that the ability to sound out words is impaired, but the orthographical memory of words may be intact. It is associated with a lexicality effect by a

difference in the ability to spell words versus nonwords; individuals with this form of agraphia are depending on their orthographic memory.

Additionally, it is generally harder for these individuals to access more abstract words without strong semantic representations (i.e., it is very difficult for them to spell prepositions than concrete nouns).

Pure agraphia is the impairment in written language production without any other language or cognitive disorder. Agraphia can occur separately or co-occur and can be caused by damage to the angular gyrus. Peripheral agraphias occurs when there is damage to the various motor and visualization skills involved in writing. Apraxic agraphia is the impairment in written language production related to disruption of the motor system. It results in distorted, slow, effortful, incomplete, and/or imprecise letter formation. Though written letters are often so poorly formed that they are almost illegible, the ability to spell aloud is often retained. This form of agraphia is caused specifically by a loss of specialized motor plans for the formation of letters and not by any dysfunction affecting the writing hand.

Apraxic agraphia may present with or without ideomotor apraxia. Paralysis, chorea, Parkinson's disease (micrographia), and dystonia (writer's cramp) are motor disorders commonly associated with agraphia. Hysterical agraphia is the impairment in written language production caused by a conversion disorder. Reiterative agraphia is found in individuals who repeat letters, words, or phrases in written language production an abnormal number of times. Preservation, paragraphia, and echographia are examples of reiterative agraphia. Visuospatial agraphia is the impairment in written language production defined by a tendency to neglect one portion (often an entire side) of the writing page, slanting lines upward or downward, and abnormal spacing between letters, syllables, and words.

The orientation and correct sequencing of the writing will also be impaired. Visuospatial agraphia is frequently related to left

hemispatial neglect, difficulty in building or assembling objects, and other spatial difficulties. Agraphia or impairment in producing written language can occur in many ways and many forms because writing involves many cognitive processes (language processing,spelling, visual perception, visuospatial orientation for graphic symbols, motor planning, and motor control of handwriting).

Agraphia has two main subgroupings: central ("aphasic") agraphia and peripheral ("nonaphasic") agraphia. Central agraphias include lexical, phonological, deep, and semanticagraphia. Peripheral agraphias include allographic, apraxic, motor execution, hemianoptic and afferent agraphia.

Central

Central agraphia takes place when there are both impairments in spoken language and impairments to the various motor and visualization skills involved in writing. Individuals who have agraphia with fluent aphasia write a normal quantity of well-formed letters, but lack the ability to write meaningful words. Receptive aphasia is an instance of fluent aphasia. Those who have agraphia with nonfluent aphasia can write brief sentences but their writing is difficult to read. Their writing requires great physical effort but lacks proper syntax and often has poor spelling.

Expressive aphasia is an instance of nonfluent aphasia. Individuals who have Alexia with agraphia have difficulty with both the production and comprehension of written language. This form of agraphia does not impair spoken language.

- Deep agraphia affects an individuals' phonological ability and orthographic memory. Deep agraphia is generally the result of a lesion involving the left parietal region (supramarginal gyrus or insula). Individuals can neither remember how words look when spelled correctly, nor sound them out to determine spelling. Individuals typically rely on their damaged orthographic memory to spell; this results in frequent errors, usually semantic in nature.

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- Lexical and structural agraphia are caused by damage to the orthographic memory; these individuals cannot visualize the spelling of a word, though they do retain the ability to sound them out. This impaired spelling memory can imply the loss or degradation of the knowledge or just an inability to efficiently access it. There is a regularity effect related to lexical agraphia in that individuals are less likely to correctly spell words without regular, predictable spellings. Additionally, spelling ability tends to be less impaired for common words. Individuals also have difficulty with homophones. Language competence in terms of grammar and sentence writing tends to be preserved.

- Phonological agraphia is the opposite of lexical agraphia in that the ability to sound out words is impaired, but the orthographical memory of words may be intact. It is associated with a lexicality effect by a difference in the ability to spell words versus nonwords; individuals with this form of agraphia are depending on their orthographic memory.

- Additionally, it is often harder for these individuals to access more abstract words without strong semantic representations (i.e., it is more difficult for them to spell prepositions than concrete nouns).
- Pure agraphia is the impairment in written language production without any other language or cognitive disorder.

Agraphia can occur separately or co-occur and can be caused by damage to the angular gyrus

Peripheral

Peripheral agraphias occurs when there is damage to the various motor and visualization skills involved in writing.

- Apraxic agraphia is the impairment in written language production associated with disruption of the motor system. It results in distorted, slow, effortful, incomplete, and/or imprecise letter formation. Though written letters are often so poorly formed that they are almost illegible, the ability to spell aloud is often retained. This form of agraphia is caused specifically by a loss of specialized motor plans for the formation of letters and not by any dysfunction affecting the writing hand. Apraxic agraphia may present with or without ideomotor apraxia. Paralysis, chorea, Parkinson's disease (micrographia), and dystonia (writer's cramp) are motor disorders commonly associated with agraphia.
- Hysterical agraphia is the impairment in written language production caused by a conversion disorder.
- Reiterative agraphia is found in individuals who repeat letters, words, or phrases in written language production an abnormal number of times. Preservation, paragraphia, and echographia are examples of reiterative agraphia.
- Visuospatial agraphia is the impairment in written language production defined by a tendency to neglect one portion (often an entire side) of the writing page, slanting lines upward or downward, and abnormal spacing between letters, syllables, and words. The orientation and correct

sequencing of the writing will also be impaired.Visuospatial agraphia is frequently associated with left hemispatial neglect, difficulty in building or assembling objects, and other spatial difficulties.

CAUSES OF AGRAPHIA

Agraphia has a number of causes ranging from strokes, lesions, traumatic brain injury, and dementia. Twelve regions of the brain are related to handwriting. The four distinct functional areas are the left superior frontal area composed of the middle frontal gyrus and the superior frontal sulcus, the left superior parietal area composed of theinferior parietal lobule, the superior parietal lobule and the intraparietal sulcus and lastly the primary motor cortex and the somatosensory cortex.

The eight other areas are considered associative areas and are the right anterior cerebellum, the left posterior nucleus of the thalamus, the left inferior frontal gyrus, the right posterior cerebellum, the right superior frontal cortex, the right inferior parietal lobule, the left fusiform gyrus and the left putamen. The specific type of agraphia resulting from brain damage will depend on which area of the brain was damaged.

Diagram of human brain showing surface gyri and the primary auditory cortex

- Angular gyrus
- Supramarginal gyrus
- Broca's area

- Wernicke's area
- Primary auditory cortex

Phonological agraphia is linked to damage in areas of the brain involved in phonological processing skills (sounding out words),specifically the language areas around the sylvian fissure, such as Broca's area, Wernicke's area, and the supramarginal gyrus.

Lexical agraphia is associated with damage to the left angular gyrus and/or posterior temporal cortex. The damage is typically posteriorand inferior to the perisylvian language areas. Deep agraphia involves damage to the same areas of the brain as lexical agraphia plus some damage to the perisylvian language areas as well. More extensive left hemisphere damage can lead to global agraphia. Gerstmann's syndrome is caused by a lesion of the dominant (usually the left) parietal lobe, usually an angular gyrus lesion. Apraxic agraphia with ideomotor apraxia is typically caused by damage to the superior parietal lobe (where graphomotor plans are stored) or the premotor cortex (where the plans are converted into motor commands).

Additionally, some individuals with cerebellar lesions (more typically associated with non-apraxic motor dysfunction) develop apraxic agraphia. Apraxic agraphia without ideomotor apraxia may be caused by damage to either of the parietal lobes, the dominant frontal lobe, or to the dominant thalamus. Visuospatial agraphia typically has a right hemisphere pathology. Damage to the right frontal area of the brain may cause more motor defects, whereas damage to the posterior part of the right hemisphere leads predominantly to spatial defects in writing.

Alzheimer's disease

Alzheimer's disease is the most common cause of dementia. The word dementia describes a set of symptoms that can include memory loss and difficulties with thinking, problem-solving or language. These symptoms occur when the brain is damaged by certain diseases, including Alzheimer's disease. This factsheet

describes the symptoms of Alzheimer's disease, how it is diagnosed, and the factors that can put someone at risk of developing it. It also describes the treatments and support that are currently available. Alzheimer's disease, named after the doctor who first described it (Alois Alzheimer), is a physical disease that affects the brain.

During the course of the disease, proteins build up in the brain to form structures called 'plaques' and 'tangles'. This leads to the loss of connections between nerve cells, and eventually to the death of nerve cells and loss of brain tissue.

People with Alzheimer's also have a shortage of some important chemicals in their brain. These chemical messengers help to transmit signals around the brain. When there is a shortage of them, the signals are not transmitted as effectively. Current treatments for Alzheimer's disease can help boost the levels of chemical messengers in the brain, which can help with some of the symptoms. Alzheimer's is a progressive disease. This means that gradually, over time, more parts of the brain are damaged. As this happens, more symptoms develop. They also become more severe.

Symptoms

The symptoms of Alzheimer's disease are generally mild to start with, but they get worse over time and start to interfere with daily life. There are some common symptoms of Alzheimer's disease, but it is significant to remember that everyone is unique. Two people with Alzheimer's are unlikely to experience the condition in exactly the same way. For most people with Alzheimer's, the earliest symptoms are memory lapses.

In particular, they may have difficulty recalling recent events and learning new information. These symptoms occur because the early damage in Alzheimer's is usually to a part of the brain called the hippocampus, which has a central role in day-to-day memory.

Memory for life events that happened a long time ago is often unaffected in the early stages of the disease. Memory loss due to

Alzheimer's disease increasingly interferes with daily life as the condition progresses. The person may:

- lose items (eg keys, glasses) around the house
- struggle to find the right word in a conversation or forget someone's name
- forget about recent conversations or events
- get lost in a familiar place or on a familiar journey
- forget appointments or anniversaries.

Although memory difficulties are generally the earliest symptoms of Alzheimer's, someone with the disease will also have – or go on to develop – problems with other aspects of thinking, reasoning, perception or communication. They might have difficulties with:

- language – struggling to follow a conversation or repeating themselves
- visuospatial skills – problems judging distance or seeing objects in three dimensions; navigating stairs or parking the car become much harder
- concentrating, planning or organising – difficulties making decisions, solving problems or carrying out a sequence of tasks (eg cooking a meal)
- orientation – becoming confused or losing track of the day or date.

A person in the earlier stages of Alzheimer's will often have changes in their mood. They may become anxious, irritable or depressed. Many people become withdrawn and lose interest in activities and hobbies.

Later stages

As Alzheimer's progresses, problems with memory loss, communication, reasoning and orientation become more severe. The person will need more day-to-day support from those who care for them. Some people start to believe things that are untrue (delusions) or – less often – see or hear things which are not really there (hallucinations).

Many people with Alzheimer's also develop behaviours that seem unusual or out of character. These include agitation (eg restlessness or pacing), calling out, repeating the same question, disturbed sleep patterns or reacting aggressively. Such behaviours can be distressing or challenging for the person and their carer. They may require separate treatment and management to memory problems. In the later stages of Alzheimer's disease someone may become much less aware of what is happening around them. They may have difficulties eating or walking without help, and become increasingly frail.

Eventually, the person will need help with all their daily activities. How quickly Alzheimer's disease progresses, and the life expectancy of someone with it, vary greatly. On average, people with Alzheimer's disease live for eight to ten years after the first symptoms. However, this varies a lot, depending particularly on how old the person was when they first developed Alzheimer's. For more information seefactsheet 458, The progression of Alzheimer's disease and other dementias andfactsheet 417, The later stages of dementia.

Mixed dementia

An estimated 10 per cent of people with dementia have more than one type at the same time. This is called mixed dementia. The most common combination is Alzheimer's disease with vascular dementia (caused by problems with the blood supply to the brain). The symptoms of this kind of mixed dementia are a mixture of the symptoms of Alzheimer's disease and vascular dementia.

Atypical Alzheimer's disease

In some people with Alzheimer's disease the earliest symptoms are not memory loss. This is called atypical Alzheimer's disease. The underlying damage (plaques and tangles) is the same, but the first part of the brain to be affected is not the hippocampus. Atypical Alzheimer's disease is uncommon in those diagnosed when they are over 65. It accounts for around five per cent of all Alzheimer's in this age group. It is, however, more common in

people diagnosed when they are under 65 (early-onset Alzheimer's disease). In this age group it represents up to one-third of cases.

The atypical forms of Alzheimer's disease are as under:

- Posterior cortical atrophy (PCA) occurs when there is damage to areas at the back and upper-rear of the brain. These are areas that process visual information and deal with spatial awareness. This means the early symptoms of PCA are often problems identifying objects or reading, even if the eyes are healthy. Someone may also struggle to judge distances when going down stairs, or seem uncoordinated (for example when dressing).
- Logopenic aphasia involves damage to the areas in the left side of the brain that produce language. The person's speech becomes laboured with long pauses.
- Frontal variant Alzheimer's disease involves damage to the lobes at the front of the brain. The symptoms are problems with planning and decision-making. The person may also behave in socially inappropriate ways or seem not to care about the feelings of others.

Who become subject to Alzheimer's disease?

Agraphia is generally seen in association with Alzheimer's Disease (AD). Writing disorders can be an early manifestation of AD. In individuals with AD, the first sign pertaining to writing skills is the selective syntactic simplification of their writing. Individuals will write with less description, detail and complexity, and other markers, such as grammatical errors, may emerge.

Different agraphias may develop as AD progresses. In the initial stages of AD, individuals show signs of allographic agraphia and apraxic agraphia. Allographic agraphia is represented in AD individuals by the mixing of lower and upper case letters in words; apraxic agraphia is represented in AD patients through poorly constructed or illegible letters and omission or over repetition of letter strokes. As their AD progresses, so does the severity of their agraphia; they may start to form spatial agraphia, which is the inability to write in a straight horizontal line, and

there are often unnecessary gaps between letters and words. A connection between AD and agraphia is the role of memory in normal writing ability. Normal spellers have access to a lexical spelling system that uses a whole-word; when functioning properly, it permits for recall of the spelling of a complete word, not as individual letters or sounds. This system further uses an internal memory store where the spellings of hundreds of words are kept. This is called the graphemic output lexicon and is aptly named in relation to the graphemic buffer, which is the short term memory loop for many of the functions involved in handwriting.

When the spelling system cannot be used, such as with unfamiliar words, non-words or words that we do not recognize the spelling for, some people are able to use the phonological process called the sub-lexical spelling system. This system is used to sound out a word and spell it. In AD individuals, memory stores that are used for everyday handwriting are lost as the disease progresses.

AGRAPHIA : ITS MANAGEMENT

Agraphia cannot be directly treated, but individuals can be rehabilitated to regain some of their previous writing abilities. For the management of phonological agraphia, individuals are trained to memorize key words, such as a familiar name or object, that can then help them form the grapheme for that phoneme. Management of allographic agraphia can be as simple as having alphabet cards so the individual can write legibly by copying the correct letter shapes.

There are few rehabilitation methods for apraxic agraphia; if the individual has considerably better hand control and movement with typing than they do with handwriting, then they can use technological devices.

Texting and typing do not require the same technical movements that handwriting does; for these technological methods, only spatial location of the fingers to type is required. If copying skills are preserved in an individual with apraxic agraphia, repeated

copying may help shift from the highly intentional and monitored hand movements indicative of apraxic agraphia to a more automated control.

Micrographia is a condition that can occur with the development of other disorders, such as Parkinson's disease, and is when handwriting becomes illegible because of small writing. For some individuals, a simple command to write bigger eliminates the issue.

- Anagram and Copy Treatment (ACT) uses the arrangement of component letters of target words and then repeated copying of the target word. This is similar to the CART; the chief difference is that the target words for ACT are specific to the individual. Target words that are important in the life of the individual are emphasized because people with deep or global agraphias do not typically have the same memory for the words as other people with agraphia may. Writing can be even very significance to these people as it can cue spoken language. ACT helps in this by facilitating the relearning of a set of personally relevant written words for use in communication.

- Copy and Recall Treatment (CART) method helps to reestablish the ability to spell specific words that are learned through repeated copying and recall of target words. CART is more likely to be successful in treating lexical agraphia when a few words are trained to mastery than when a large group of unrelated words is trained. Words chosen can be individualized to the patient, which makes treatment more personalized.

- Graphemic buffer uses the training of specific words to improve spelling. Cueing hierarchies and copy and recall method of specific words are used, to work the words into the short-term memory loop, or graphemic buffer. The segmentation of longer words into shorter syllables helps bring words into short-term memory.

- Problem solving approach is used as a self-correcting method for phonological errors. The individual sounds

out the word and attempts to spell it, typically using an electronic dictionary-type device that indicates correct spelling. This method takes advantage of the preserved sound-to-letter correspondences when they are intact. This approach may improve access to spelling memory, strengthen orthographic representations, or both.

AGNOSIA

Picture of the ventral and dorsal streams. The ventral stream is depicted in purple and the dorsal stream is depicted in green.

Agnosia is the inability to process sensory information. Often there is a loss of ability to recognize objects, persons, sounds, shapes, or smells while the specific sense is not defective nor is there any significant memory loss. It is usually related to brain injury or neurological illness, specially after damage to the occipitotemporal border, which is part of the ventral stream.Agnosia only affects a single modality, like as vision or hearing. Agnosia is the loss of the ability to recognize objects, faces, voices, or places. It is a rare disorder. People with agnosia can still think, speak, and interact with the world normally. Agnosia usually affects only a single information pathway in the brain. For, people with visual agnosia won't be able to name an object placed in front of them or describe its use. But they will still be able to reach for it and pick it up.

Once they are holding the object, they will be able to use their tactile information pathway — their sense of touch — to identify its use.

What Causes Agnosia?

Agnosia causes when the brain suffers damage along certain pathways. These pathways connect the primary sensory processing areas to the parts that store knowledge and information. Primary sensory processing areas include the visual and auditory cortices. Agnosia is usually caused by lesions on the parietal and temporal lobes of the brain. These lobes are where semantic information and language are stored. Lesions can be created by strokes, head traumas, or encephalitis. Other conditions that damage or impair the brain can also cause agnosia. These conditions include dementia, carbon monoxide poisoning, and anoxia.

Forms of Agnosia

There are three main forms of agnosia: visual, auditory, and tactile. Visual agnosia is the most common type of agnosia. This might be because humans' visual processing areas are so large and complex (Coslett, 2007).

Visual Agnosia

Visual agnosia occurs when there is brain damage along the pathways that connect the occipital lobe of the brain with the parietal and temporal lobes. The occipital lobe assembles incoming visual information. The parietal and temporal lobes understand the meaning of this information.

Apperceptive Visual Agnosia

Visual apperceptive agnosia is the difficulty in assembling parts of an image into an understandable whole. People with the condition may have difficulty understanding how objects are related to one another. When trying to copy a picture of a circle, an apperceptive agnosic might draw a series of concentric scribbles. People with this condition can still use vision to navigate their environment and pick up objects without trouble. Apperceptive visual agnosia is generally caused by lesions to the parietal or temporal lobes on both sides of the brain.

Associative Visual Agnosia

Associative visual agnosia is the inability to recall information associated with an object. This can include an object's name, use, or origin. Unlike an apperceptive agnosic, an associative agnosic can copy a picture without trouble. But he or she may not be able to name the object in the drawing. For instance, an associative agnosic who is shown a padlock will be able to recognize it and use it, but won't be able to say what it is.

Prosopagnosia

Prosopagnosia is the inability to recognize faces. It is caused when there is damage to the fusiform face area (FFA), a highly specific region of the brain that recognizes faces. Difficulty with facial recognition can also occur in Alzheimer's disease because brain deterioration damages this region. Individuals with autism often experience difficulty recognizing faces.

Autistic people do not use their FFA to see faces. Instead, each develops his or her own unique neural pattern for facial recognition (Pierce, et al., 2001).

Achromatopsia

Achromatopsia is the loss of colour vision. It is caused by lesions in the V4 region of the brain. When a lesion separates V4 from the language areas, the result is colour anomia. This is the inability to name colours despite being able to perceive them.

Agnosic Alexia (Pure Alexia)

Pure alexia is the inability to recognize words visually. People with pure alexia cannot read. They can still speak fluently and can usually write without difficulty.

Akinetopsia

Akinetopsia is the inability to perceive motion. People with this condition see moving objects as a series of stills, like an object moving under a strobe light.

Auditory Agnosia

Pure Word Deafness

Pure word deafness is the inability to repeat or understand spoken language. It develops when the A1 sound-processing region of the brain is disconnected from its language centers. People with pure word deafness can still recognize environmental sounds. They can also still read and write.

Phonagnosia

Phnonagnosia is the inability to recognize and identify familiar voices. It develops when the brain suffers damage to a definite part of the sound association region. This region is located in the right half of the brain. People with this condition can still understand the words being spoken. They can also recognize environmental sounds or sounds made by objects.

Tactile Agnosia

Astereognosis

Astereognosis is the inability to identify objects by touch. People with this condition cannot associate information regarding size, weight, and texture with the relevant words. They can still name objects by sight. They are also able to draw pictures of objects, as well as reach for them.

Autotopagnosia

Autotopagnosia is when a person loses the ability to orient the parts of his or her own body. It is caused by damage to the left parietal lobe of the brain. Normally, a person has an awareness of his or her limbs are in space at all times, even with closed eyes. This awareness gets distorted when the brain's internal representation of the body is damaged.

TYPES OF AGNOSIA

Agnosia is a cognitive disturbance caused by neurological damage that affects associating knowledge with an intact percept

within a single modality (vision, audition or somosthesis). Recently, neuroimaging research has led to a better understand of how the brain processes perceptual information and lesion loci that contribute to the various agnosias. It is now thought that agnosia, in the classical sense, represents a top-down disruption in processing of perceptual information. The late 1800s was a period when many neurologists were beginning to describe behavioural disturbances associated with brain injuries. At this point in medical history, little was known about the organization of the cerebral cortex. A prevailing view, connectionistic theory, posited that the brain processed in interconnected regions of specialization. However, a number of physicians of the time continued to reject the idea that specific brain regions were specialized for specific functions.

Accordingly, the first description of agnosia was provided in 1890 by Lissauer. His initial description was of a single modality recognition deficit. He described two types of agnoisa, apperceptive and associative agnosias, primarily distinguishing between disorders of perception and knowledge. This binary differentiation has persisted and is still used in neurobehavioural texts.

Lissauer stated that focal lesions and combinations of focal lesions could solely impair visual, auditory or somatosensory perception or recognition, leaving the other sensory modalities largely intact. The behaviour displayed in a visual associative agnosia, for example, would be an inability to recognize a key from an array of objects, name a key from a picture or object display, or match a picture of one kind of key with another. Yet the individual would not have lost the ability to "know" what a key was and could demonstrate that knowledge through other modalities: i.e., he or she could name the key if permitted to feel it or respond appropriately to a question like, "What do you use to open a lock?" In recent years, the development of sophisticated neuroimaging tools combined with careful cognitive-behavioural assessment has allowed revision of Lissauer's model, an elucidation of top-down (feed-back) and bottom-up (feed-forward) processing

systems, and an understanding of the complex ways in which processing networks can be disconnected (Mesulam) and disrupted (Mesaulam, 2000; Damasio et al., 2000; Riddoch and Humphreys, 2001). Although pure agnosias do exist, they are rare.

Furthermore, careful diagnostic investigation often reveals idiosyncratic patterns of behavioural deficits that differ from one patient to another despite the initial appearance of a similarity (Riddoch and Humphreys, 2001). Before to understanding the agnosias then, it is helpful to briefly describe the general cerebral organization of single modality processing. As a cautionary note, since neuroimaging technology is continuing to improve in its ability to provide a window into the human neurological processing, the description of human cerebral processing summarized in this chapter should be considered preliminary, at best.

Cerebral Organization of Visual, Somatosensory and Auditory Processing

The human brain is the organ of the body that allows us to adapt our internal body state to information and changes that occur in the environment (Mesaulam, 2000). When we are hungry, the brain directs us to find food in the world around us. When we are tired, we seek sleep.

To process information in the environment to meet our survival and personal needs, we need to process sensory information. This starts with a relay of visual, auditory, tactile and olfactory information from the sense organs (eye, ear, skin, nose) to primary sensory cells in the cortex (A1, V1 and S1 and the olfactory lobe respectively). Through early experience, the primary cortical cells become organized into a sensory map that represents salient stimulus qualities of the environment. For instance, cells in the primary auditory cortex form a "tonotopic" map during the critical period of brain development that matches the range of frequencies an infant hears. These sensory maps are not specific to the human brain. In animals, exposure to a variety of animal calls results in

an auditory map "tuned" to those calls while exposure to complex auditory signals like human speech result in a map that enables processing of speech stimuli (Chang and Merzenich, 2003).

During early development those maps can be distorted by noise within the environment or nervous system or sensory deprivation. Although the sensory maps of the primary sensory regions are malleable after this early set up period, refining distorted maps requires attention to specific stimuli and timed reinforcement. As the brain matures, perceptual refinement of environmental stimuli occurs by development. During human processing, the information encoded in the primary regions drive a feed forward organization of adjacent categorical perception. Like layers of an onion, perceptual organization of the brain develops based on the integrity and "fine tuning" of the sensory system (Mesaulam, 2000). For instance, the auditory regions adjacent to A1 in the left hemisphere process phonemic classifications of one's native language, while the visual modality regions adjacent to V1 process colour, form, and motion of visual stimuli (Mesaulam, 2000; Damasio et al., 2000). Thereafter, sensory information is processed by more complex unimodal associations and ultimately, transmodal projections to other modality associations, allow integration of stimuli into multimodal concepts, like words which can be processed auditorily and visually.

The Effects of Lesions on Single Modality Processing

Modality specific deficits can result from lesions that directly disrupt the unimodal perceptual regions. Thus, a lesion in V4, which processes colour perception, will cause acquired colour blindness, or a lesion in V5 (which processes perception of movement) will result in, an inability to perceive motion (Mesaulam, 2000).

In individuals with small, localized lesions, detailed assessment can demonstrate that these specific impairments can occur although there is intact visual perception. In this case, an individual with acquired colour blindness, who is shown a chair, would be able

to perceive the object's shape, size, orientation in space, but not the colour. She could match the chair to other similar and different chairs without difficulty. With larger lesions to the visual association cortex, several attributes of a stimulus might be misperceived. When lesions instead disconnect the sensory/perceptual regions from multimodal association areas, individuals can have more pervasive single modality "associative" disturbances. This is the classic agnosia and most contemporary neuroscientists reserve the term "agnosia" to refer to these types of associative deficits. When the lesions isolate a unimodal association area from other unimodal and heteromodal association areas, it results in an intact perception of the stimulus but inability to attach meaning to the perception.

The individual is characteristically able describe details of the object presented to him yet unable to name what she sees, hears or feels. Likewise, because the perception is intact, the individual should be able make a detailed drawing of the object or match two detailed drawings of the same object. But what will generally perplex an examiner is that after drawing or matching the stimulus, the individual will still be unable to tell the examiner what he has just drawn. The inability to associate past experience or knowledge to the stimulus is due to the disconnection from other modality input and conceptual processing (Mesaulam, 2000; Kandel et al., 2000).

Types of Associative Agnosias

Associative agnosias result from lesions that isolate in tact visual, auditory or somatosensory percepts from heteromodal processing networks, (associations) (Mesaulam, 2000; Riddoch and Humphreys, 2001; Kandel et al., 2000; Devinsky and D'Esposito, 2004). Since agnosias affect a single modality one can describe them in terms of the modality affected.

The Visual Agnosias

Adjacent and just anterior to the primary visual cortex in the posterior occipital lobe, is the visual association cortex. This region is still a unimodal visual region, and contains several specifically

mapped association areas. V4, and perhaps V8, are specialized for colour recognition. A unilateral lesion in V4 causes contralateral *hemi-achromatopsia*, loss of colour perception.

When a lesion spares V4 disconnects communication between V4 and the language cortex, the result is a colour anomia - the inability to name colours despite intact colour perception (Mesaulam, 2000; Damasio et al., 2000).

V5 and the middle temporal gyrus are visual association areas specialized for perception of movement. Damage to this region causes inability to perceive visual motion with relatively preserved acuity and colour perception, "*akinetopsia*" (Mesaulam, 2000). Motions appear as still shots, akin to the experience of a stroboscope, the perception of series of visual objects in different positions (Riddoch and Humphreys, 2001). A region in the fusiform cortex, called the fusiform facial area (FFA), is specialized for face and, to some extent, object recognition. When damaged the disturbance in facial recognition is termed *prosopagnosia*.

The "face" area of the brain is more strongly activated by faces than objects, with no differential responses for familiar vs. novel faces and more activated by upright and intact faces rather than upside down or scrambled faces.

Global impairment of object recognition, *pure object agnosia*, commonly results from lesions that isolate the visual association cortex from other unimodal and heteromodal association areas or a combination of broad based lesions in visual association areas (Mesaulam, 2000). Contemporary neuroscientists identify two separate areas specialized for encoding words and word-like strings of letters –a region lateral to the "face" area and an area in lateral occipito-temporal region Mesulam (2000) has said that it is likely words are handled as special forms of "objects." *Pure alexia* sometimes referred to as *alexia without agraphia*, is a visual word recognition deficit that results from damage to or isolation of this region from other association areas. The visual association pathways are often divided into ventral and dorsal pathways. Damage to dorsal visual areas or their connections cause visual

spatial processing disorders but these are not considered agnosias. These comprise *hemispatial visual neglect*,*dressing apraxia*, the inability to align body axis with garment, *simultagnosia*, the inability to integrate visual detail into a coherent whole, *optic ataxia*, deficit in reaching toward a visual object, and *optic apraxia*, occulomotor exploration deficit.

The former three may be seen as part of right hemisphere syndrome. The latter three are collectively know as Balint's syndrome (Mesaulam, 2000; Damasio et al., 2000; Devinsky and D'Esposito, 2004).

The Auditory agnosias

The primary auditory cortex (A1) is mapped for pitch and pure tone discrimination in all individuals who receive adequate auditory stimulation during early infancy. Bilateral damage to A1 has been termed central deafness, but generally results in problems with speech discrimination in noisy environments. The auditory association area adjacent to A1 in the left hemisphere responds to specific acoustic cues which allow for perception of phonetic parameters of spoken language. This region houses the following capacities, now often considered a prerequisite for phonemic awareness:

- Segmentation and sequencing of phonemes, perception of internal detail of syllable strings.
- Perception of polysyllabic and compound words.
- Presematic encoding of phonemes.

Damage to these areas results in auditory perceptual impairments and cortical deafness. Disconnection of these areas from other association regions results in *pure word deafness*, an agnosia characterized by the inability to repeat or understand spoken language despite good recognition of environmental sounds and no language deficit and *auditory agnosia* for environmental sounds. Often these agnosias have aperceptive and associative subtypes or components (Mesaulam, 2000). *Phonagnosia* results from damage to a right hemisphere auditory association area in

humans that is analogous to facial perception in the visual cortex, and is the inability to recognize familiar voices despite preserved word recognition in tact ability to perceive environmental sounds (Mesaulam, 2000; McCloskey, 2001).

The Somatosensory agnosias

S1 is the primary somatosensory (tactile perceptual) region of the parietal cortex. All primary sensory areas are mapped based on sensory experiences during early infancy. The mapping is similar to the homunculus mapping seen in the adjacent primary motor cortex in the left hemisphere. The adjacent association area S2 participates in pain perception and in some patients, lesions in S2 cause loss of pain perception. With additional damage to the insula and parietal operculum a painful contralateral disesthesia or "pain asymbolia" may result. The Somatosensory association areas Broadmann's areas (Kandel et al., 2000 ; McCloskey, 2001) and perhaps also area 40 in the posterior insula are essential to:

- Localization of touch
- Exploration manually,
- Somatosensory guidance and coordination of reaching and grasping
- Somatosensory imagery

Lesions to this region or that disconnect this region from other association areas may result in:

- Problems with spatial orientation, tactile search, and ability to align the body axis with other solid objects during dressing, sitting in a chair or getting in bed.
- Hemispatial neglect
- Dressing apraxia

Other kindstypes of posterior parietal/insular lesions cause *tactile agnosia* (Mesaulam, 2000).

Assessment of Agnosia

Assessment of agnosia necessitates determining that a disorder is limited to a single modality and does not affect other cognitive

domains. It requires ruling out basic disorders of attention, sensation, impaired intelligence and aphasia (word recall problems, grammatical disorder (agrammatism or paragrammatism), phonological problems or verbal comprehension). There should be no evidence of disorientation, short or long-term memory limitations (Damasio et al., 2000). Standardized testing may result in confusing findings, since standardized tests are usually designed to determine cognitive and linguistic deficits of neurological origin, not assess a single modality or contrast that modality with others using analogous tasks. For instance, a patient with a pure object agnosia will be unable to point to pictures on command on a picture pointing task on a standardized aphasia examination, inspite of the ability to follow commands and answer yes-no questions.

The same patient will be unable to name pictures or match pictures to words while responsive naming will be intact. If an agnosia is suspected or possible based on a lesion, it is preferable to determine two essential components of agnosia before conducting standardized tests. First is to determine whether all deficits exhibited are restricted to a single modality and if there is no evidence of a sensory deficit. The first step will be to obtain a substantial verbal description of what the individual sees (visual agnosia), hears (auditory agnosias), or feels (somosthetic agnosias) when presented with objects, pictures (visual agnosias) or sounds (auditory agnosias). Often when asked to name objects or sounds through the modality in question the patient will either misidentify the items or respond "I don't know."

However, when the same object or sound is presented through the other modality the patient has no problem with naming or identification. For instance, if the patient is unable to name a pen when seen, but names it easily when held, this is a sign that the problem does not have anaphasia but rather a problem with a single modality.

Similarly, if a patient is unable to identify an environmental sound like a cell phone ring, see if the patient's ability is normalized

when they are able to feel the vibration or see the phone light up. This type of dissociation task should be repeated with several stimuli to make sure that the pattern holds. Second, the clinician should attempt to distinguish between misperception, "aperceptive agnosia" versus the classical "associative agnosia". This can be done using copying and matching tasks. Individuals with aperceptive agnosias cannot match two identical visual stimuli (visual apperceptive agnosia), auditory stimuli (auditory apperceptive agnosia), or objects held in the hands (somatosensory apperceptive agnoisa).

The person will not be able to repeat a word or imitate a sound (auditory) or match an object to its drawing or copy it (visual agnosias).

In contrast, persons with associative agnosias will perform the above without error yet will not be able to match different instance of the stimuli. For instance, with visual agnosia a patient would not be able to match a pine tree to a maple, a green apple to a red one, or a cursive to a printed word. In the auditory modality, an individual would not be able to match two different horns blowing or dog barks, or even a girl and woman saying the same word. In the tactile modality the person might have trouble matching a large and small hand held glass, or spoon. With an associative agnosia an individual will also be unable to name the object seen, heard or touched (depending on modality affected) but they will be able to name it through the unaffected modality (i.e. from touch or from verbal description).

Finally, they will be unable to point the object or word (visual), identify the sound source representation (auditory) or find the object through manual exploration (somosthetic) to command (Mesaulam, 2000; Riddoch and Humphreys, 2001; Kandel et al., 2000). Prosopagnosia, the inability to recognize and name familiar human faces, may be assessed through colour or black and white photographs of family members, as well as contemporary politicians and celebrities taken from the internet and/or print media (Van Lanker and Canter, 1982). The examiner should use

a various types of photographs and ask the person to name one set., then, using a different set of photos ask the patient to point to each as the clinican names them.

Then, all photo(s) which the patient is unable to name or identify by name, check for knowledge by asking the patient a question pertaining to the individual,e.g., Who is our U.S. President now? Who starred in _____movie?

Other disorders of face processing such as facial emotion recognition deficits can occur with or without prosopagnosia. Such disturbances can be caused by bilateral damage to the amygdala or disconnection of the amygdala from other cortical regions (Damasio et al., 2000). Pure Alexia, (also called alexia without agraphia or pure word blindness), is a reading and letter naming deficit with intact ability to write. The patient will be able to copy and trace words, during which (because of the tactile cues) they may be able to recognize the letters and/or words. This is often due to lesions in the corpus collosum as well as the left visual association areas (Dehan, 2001).

Disorders of topographical orientation, sometimes called environmental agnosia, is the inability to locate a specific building in a city, find one's room in a home, or describe how to get to a specific location. The lesions are generally bilateral or in right hemisphere posterior regions.

There are generally also problems with route learning (Damasio et al., 2000). Environmental agnosia may occur with prosopagnosia and may also be seen in Parkinsonism.

Epstein and Kanwisher (1988) have identified a parahippocampal region (PPA) that might be critical in recognizing the geometry of a local environment and some recent research suggests the hippocampus might also be important in some place memory (Nature Reviews Neuroscience, 3.08). Disorders of colour perception that result from brain injury are called central achromatopsias. They are commonly caused by focal damage to the visual unimodal association cortex and involve all or part of

the visual field. The colour loss can be complete or partial. In individuals with achromatopsia form perception is usually presserved, although there may be an accompanying object agnosia and prosopagnosia (Mesaulam, 2000).

Simultagnosia is the inability to grasp the global view, focusing on one detail of a composition, then another. The patient with simultagnosia will attend to and describe details in the picture but often be unable to give a description of the scene as a whole.

The best way to identify it clinically is through picture description. A room scene may be described one piece of furniture at a time; rarely would the patient name the room. Because the patient has trouble attending to the gestalt, if the object pictured is a face, the individual will perceive the eyes and the nose, but fail to mention the face.

However, if the individual is viewing a human figure, they may perceive the head, the arms and the legs. Patients may complain that objects, or portions of objects may appear to move around. A patient may say the words or objects appear "jumpy" (Mesaulam, 2000). Pure word deafness is the inability to understand the spoken word or repeat words or sentences with preserved ability to read words. Sometimes it is described as "Wernicke's aphasia" without the aphasia. The lesions can be bilateral affecting Heschl's gyrus and its association tracts or a corpus colossal lesion occurring in conjunction with a lesion in the left auditory association region (Dehan, 2001).

The individual will not present as aphasic; they will not make grammatical or phonological errors in speaking and will not present with anomia. With pure word deafness an individual will understand and respond to prosodic contour and can recognize familiar voices (Mesaulam, 2000).

Phonagnosia, first described in depth by VanLanker and Canter in 1982 (McCloskey, 2001), is the inability to recognize familiar voices. It is characterized by inability to recognize familiar voices and, thus, considered the auditory analogue of prosopagnosia. It

may occur with pure sound agnosia, but it is rarely identified clinically because it is only a problem with recognition of familiar voices without a visual image, so it basically affects recognizing friends or well know persona by phone or on a radio.

Treatment

In acute stages the adult with agnosia may be intolerant of the therapeutic process because they are unaware of the problem. If there is additional involvement of the limbic system connections, generally occurring with posterior cerebral lesions or with very deep lesions, this may decrease motivation to improve even if aware of the problems. Before attempts at remediation the clinician will need to increase recognition of deficits. Since agnosia is restricted to one modality, one way to build awareness of the deficit is to alternate presenting a stimulus in the impaired modality, then through the unimpaired modality.

Over several repetitions the patient may gradually become aware of the difficulties experienced in the impaired modality. It might also be helpful to break down tasks into very small steps so that the patient can see each component of their problem. Once the patient is aware of his or her difficulties, treatment goals should focus on developing compensatory treatment approaches that quickly enable the individual to function independently in their living environment.

Visual agnosia

Visual agnosia is a broad category that refers to a deficiency in the ability to recognize visual objects. Visual agnosia can be further subdivided into two different subtypes:apperceptive visual agnosia and associative visual agnosia. Individuals with apperceptive visual agnosia display the ability to see contours and outlines when shown an object, but they experience difficulty if asked to categorize objects. Apperceptive visual agnosia is associated with damage to one hemisphere, specifically damage to the posterior sections of the right hemisphere. In contrast,

individuals with associative visual agnosia experience difficulty when asked to name objects. Associative agnosia is associated with damage to both the right and left hemispheres at the occipitotemporal border. A specific form of associative visual agnosia is known as prosopagnosia. Prosopagnosia is the inability to recognize faces.

For instance, these individuals have difficulty recognizing friends, family and coworkers. However, individuals with prosopagnosia can recognize all other types of visual stimuli.

Speech agnosia

Speech agnosia, or Auditory verbal agnosia, refers to "an inability to comprehend spoken words despite intact hearing, speech production and reading ability". Patients report that they do indeed hear sounds being produced, but that the sounds are fundamentally unrecognizable/untranslatable.

1. EXAMINER: What did you eat for breakfast?
2. PATIENT: Breakfast, breakfast, it sounds familiar but it doesn't speak to me. (Obler & Gjerlow 1999:45)

Despite an inability to process what the speaker is saying, some patients have been reported to recognize certain characteristic information about the speaker's voice (such as being a man or woman).

CAUSES OF AGNOSIA

Agnosia can result from strokes, dementia, or other neurological disorders. It may also be trauma-induced by a head injury, brain infection, or hereditary. Additionally, some forms of agnosia may be the result of developmental disorders. Damage causing agnosia usually occurs in either the occipital or parietal lobes of the brain. Although one modality may be affected, cognitive abilities in other areas are preserved. Patients who experience dramatic recovery from blindness experience significant to total Agnosia. The effect of damage to the superior temporal sulcus is consistent with various types of neurolinguistic deficiencies, and

some contend that agnosia is one of them. The superior temporal sulcus is vital for speech comprehension because the region is highly involved with the lexical interface.

According to the 1985 TRACE II Model, the lexical interface associates sound waves (phonemes) with morphological features to produce meaningful words. This association process is accomplished by lateral inhibition/excitement of certain words within an individual's lexicon (vocabulary). For example, if an experimenter were to say DOG aloud, the utterance would activate and inhibit various words within the subjects lexical interface:

- DOG activates 3, and inhibits 0 letters in DOG. — +3
- DOG activates 2, and inhibits 1 letters in FOG. — +2
- DOG activates 1, and inhibits 2 letters in DAN. — +1

The consistency of this model to agnosia is shown by evidence that bilateral lesions to the superior temporal sulcus produces 'pure word deafness' (Kussmaul, 1877), or as it's understood today — speech agnosia. Patients with pure word deafness demonstrate the inability to recognize and process speech sounds with normal auditory processing for non-speech sounds below the level of the cortex.

DIAGNOSIS

With a view to assess an individual for agnosia, it must be verified that the individual is not suffering from a loss of sensation, and that both their language abilities and intelligence are intact. In order for an individual to be diagnosed with agnosia, they must only be experiencing a sensory deficit in a single modality.

To make a diagnosis, the distinction between apperceptive and associative agnosia must be made. This distinction can be made by having the individual complete copying and matching tasks. If the individual is suffering from a form of apperceptive agnosia they will not be able to match two stimuli that are identical in appearance. In contrast, if an individual is suffering from a form of associative agnosia, they will not be able to match various

instances of a stimulus. For example, an individual who has been diagnosed with associative agnosia in the visual modality would not be able to match pictures of a laptop that is open with a laptop that is closed.

Pure alexia

Individuals with pure alexia generally have difficulty reading words as well as difficulty with identifying letters. In order to assess whether an individual has pure alexia, tests of copying and recognition must be performed. An individual with pure alexia should be able to copy a set of words, and should be able to recognize letters.

Prosopagnosia

Individuals are generally shown pictures of human faces that may be familiar to them such as famous actors, singers, politicians or family members. The pictures displayed to the patient are selected to be age and culture appropriate. The task involves the examiner asking the individual to name each face. If the individual cannot name whose face appears in the picture, the examiner may ask a question that would help to recognize the face in the picture.

TREATMENT OF AGNOSIA

For all practical purposes, there is no direct cure. Patients may improve if information is presented in other modalities than the damaged one. Various types of therapies can help to reverse the effects of Agnosia. In some cases, occupational therapy or speech therapy can improve agnosia, depending on its etiology. Initially many individuals with a form of agnosia are unaware of the extent to which they have either a perceptual or recognition deficit. This may be caused by anosognosia which is the lack of awareness of a deficit. This lack of awareness usually leads to a form of denial and resistance to any form of help or treatment. There are various methods that can be used which can help the individual recognize the impairment in perception or recognition that they may have. A patient can be presented with a stimulus to the impaired modality

only to help increase their awareness of their deficit. Alternatively, a task can be broken down into its component parts so that the individual can see each part of the problem caused by the deficit.

Once the individual acknowledges their perceptual or recognition deficit, a form of treatment may be recommended. There are different forms of treatment such as compensatory strategies with alternate modalities, verbal strategies, alternate cues and organizational strategies.

Verbal strategies

Using verbal descriptions may be helpful for individuals with certain types of agnosia. Individuals such as prosopagnosics may find it useful to listen to a description of their friend or family member and recognize them based on this description more easily than through visual cues.

Alternate cues

Alternate cues may be speciallyparticularly useful to an individual with environmental agnosia or prosopagnosia. Alternate cues for an individual with environmental agnosia may include colour cues or tactile markers to symbolize a new room or to remember an area by. Prosopagnosics may use alternate cues such as a scar on an individual's face or crooked teeth in order to recognize the individual.

Organizational strategies

Organizational strategies may be very helpful for an individual with visual agnosia. For instance organizing clothes according to different hangers provides tactile cues for the individual, making it easier to identify certain forms of clothing as opposed to relying solely on visual cues.

Alternative medicine

These strategies elicit the use of an unaffected modality. For instance visual agnosics can use tactile information in replacement of visual information. Alternatively, an individual with

prosopagnosia can use auditory information in order to replace visual information. For example, an individual with prosopagnosia can wait for someone to speak, and will usually recognize the individual from their speech.

SOCIAL-EMOTIONAL AGNOSIA

Social-emotional agnosia is because of to a right cerebral, or bilateral temporal and amygdala injury. Patients typically are unable to correctly perceive or comprehend social-emotional nuances conveyed through voice, gesture, or facial expression. Patients diagnosed with "schizophrenia" and children afflicted with autism, often appear to suffer from abnormalities involving social-emotional perceptual and expressive functioning, and amygdala and temporal lobe abnormalities have been found in these populations. If due to amygdala and temporal lobe injury, this may explain why these individuals appear to have extreme difficulty determining and identifying the motivational and emotional significance of externally occuring events, to discern social-emotional nuances conveyed by others, or to select what behaviour is appropriate given a specific social context. In consequence, in addition to their other afflictions, autistic children or schizophrenic adults may appear socially emotionally blunted or agnosic to varying degrees. Social-emotional agnosias are commonly observed following amygdala, and amygdala, and right cerebral lesions involving the temporal lobe in particular (Joseph 1988a, 1992a).

For example, with damage to the right temporal-occipital region, there can result a severe disturbance in the ability to recognize the faces of friends, loved ones, or pets or to discriminate and identify even facial affect (Braun et al. 1994); prosopagnosia. In fact, with gradual deterioration and degeneration of the right inferior temporal lobe, patients may suffer a progressive prosopagnosia (Evans et al. 2005). Some patients may in fact be unable to recognize their own face in the mirror. In large part these neocortical deficits are due to limbic system disconnection, and/

or destruction of specific limbic nuclei such as the amygdala. For example, lesions that destroy amygdala fibers of passage to the right or left temporal lobe, essentially disconnect the neocortex and amygdala such that they can no longer receive or transmit appropriate signals.

Besides, lesions to only the right or left amygdala (n primates) may induce social-emotional agnosic states, but only in regard to stimuli and persons in the contralateral half of auditory, visual, and tactile space (Downer 1961); e.g. only the right or left hemisphere may become severely effected. Hence, in humans, given right cerebral dominance for social and emotional stimuli, a right sided disconnection or destruction of the amygdala can exert profound influences regardless of which hemisphere is perceiving and responding to emotional stimuli. Among primates and mammals, bilateral destruction of the amygdala significantly disturbs the ability to determine and identify the motivational and emotional significance of externally occuring events, to discern social-emotional nuances conveyed by others, or to select what behaviour is appropriate given a specific social context.

Bilateral lesions lower responsiveness to aversive and social stimuli, reduce aggressiveness, fearfulness, competitiveness, dominance, and social interest (Rosvold et al. 1954). Indeed, this condition is so pervasive that subjects seem to have tremendous difficulty discerning the meaning or recognizing the significance of even common objects — a condition sometimes referred to as "psychic blindness", or, the "Kluver-Bucy syndrome".

Thus, animals with bilateral amygdaloid destruction, although able to see and interact with their environment, may respond in an emotionally blunted manner, and seem unable to recognize what they see, feel, and experience. Things seem stripped of meaning such that even the ability to appropriately interact with loved ones is impaired; similar, in some respects to what occurs in autism and with adults afflicted with schizophrenia. For instance, Terzian & Ore (2011) described a young man who following bilateral removal of the amygdala subsequently demonstrated an

inability to recognize anyone, including close friends, relatives and his mother. He ceased to respond in an emotional manner to his environment and seemed unable to recognize feelings expressed by others. In addition, he became extremely socially unresponsive such that he preferred to sit in isolation, well away from others.

Among primates who have undergone bilateral amygdaloid removal, once they are released from captivity and allowed to return to their social group, a social-emotional agnosia becomes readily apparent as they no longer respond to or seem able to appreciate or understand emotional or social nuances. Infact, they seen to have little or no interest in social activity and persistently attempt to avoid contact with others. If approached they withdraw, and if followed they flee.

Infact, they behave as if they have no understanding of what is expected of them or what others intend or are attempting to convey, even when the behaviour is quite friendly and concerned. Among adults with bilateral lesions, total isolation seems to be preferred.

Besides, they no longer display appropriate social or emotional behaviours, and if kept in captivity will fall in dominance in a group or competitive situation — even when formerly dominant. As might be expected, maternal behaviour is severly affected. According to Kling (1972), mothers will behave as if their "infant were a strange object be be mouthed, bitten and tossed around as though it were a rubber ball". Given the very similarities between amygdala destruction and the social-emotional agnosias demonstrated by certain subgroups of those classified as schizophrenic, as well as those diagnosed as autistic, it would thus appear that amygdala/temporal lobe dysfunction is implicated as a major source of psychopathology in these patient populations.

Finger Agnosia

Finger agnosia is not a form of finger blindness, as the name suggests. Nor is it an inability to recognize a finger as a finger. Rather, the difficulty involves naming and differentiating among

the fingers of either hand as well as the hands of others (Gerstmann, 1940). This includes pointing to fingers named by the examiner, or moving or indicating a particular finger on one hand when the same finger is stimulated on the opposite hand.

Besides, if you touch their finger while eyes are closed, and ask them to touch the same finger they may have difficulty. Generally patients who have difficulty identifying fingers by name or simply differentiating between them non-verbally also suffer from receptive language abnormalities (Sanquet, et al. 1971). However, disturbances differentiating between the different fingers can occur independent of language abnormalities or with right parietal injuries (in which case the problem is seen only with the patient's left hand).

Generally, however, finger agnosia is associated with left parietal (as well as temporal-occipital) lobe lesions in which case the agnosia is demonstrable in both hands. It is also part of the constellation of symptoms often referred to as Gerstmanns Syndrome, i.e. agraphia, acalculia, left-right disorientation, finger agnosia (Gerstmann, 1942). Gerstmann's symptom complex is most often associated with lesions in the area of the supramarginal gyrus and superior parietal lobule (Hrbek, 1977; Strub & Geschwind, 1983).

Simultanagnosia

Simultanagnosia is an inability to see more than one thing or one aspect of an object at a time, although individual details may be correctly perceived. However, the patient is unable to relate the different details so as to discern what is being viewed. For instance, if shown a picture of a man holding an umbrella and a suitcase, they may see the suitcase and the man, and the umbrella, but be unable to relate these items into a meaningfull whole.

In fact, by surrounding the object with other objects perceptual recognition may deteriorate even further. With severe damage the patient may be unable to even recognize individual objects. Indeed, one patient I examined with bilateral posterior parietal-occipital

damage (following a bilateral posterior artery stroke) could only identify parts of objects, but not the object itself.

In part, this is due to a breakdown in the ability to perform serial feature-by-feature visual analysis, and is sometimes accompanied by abnormal eye movements. Nevertheless, a variety of anatomical regions, when compromised can give rise to this abnormality. For example, simultanagnosia has been noted to occur with left, right and bilateral superior occipital lobe lesions, or injuries involving the frontal eye fields.

Category-specific Agnosia, And The Right & Left Temporal Lobe

Depending on the laterality and location of the injury, e.g., right vs left inferior/medial vs superior temporal lobe, patients may display category specific agnosias. For instance, a 27-year old man was examined who had sustained a massive right inferior-posterior temporal lobe injury that also involved surgical removal, was able to recognize pictures of tools (he had been a carpenter) but could not recognize or correctly name pictures of animals and he could not correctly remember facial stimuli that he had been shown five minutes earlier and could not differentiate them from faces he had not seen.

Contrarily, a 43 year old woman who had been a waitress, and had developed a left inferior temporal lobe glioma that required surgical removal (coupled with chemotherapy) was able to recognize and name pictures of animals and could remember different pictures of faces, but had considerable difficulty recognizing and naming common household objects. In this regard a 47-year old woman I examined who was subsequently found to have a calcium cyst growing from the skull into the right superior temporal lobe, was able to name pictures of animals, tools and household objects.

However, she was almost completely unable to recognize and correctly name animal and humans sounds (e.g. a baby crying, a crowd cheering, a lion roaring) which had been briefly presented,

but was better able to recognize non-living sounds such as a creaking door, or a hammer hammering—though these abilities were also compromised. These findings, which require independent confirmation, raises the possibility that the temporal lobes are not only able to distinguish between living and non-living things including tools and faces, but that the right temporal lobe is specialized for perceiving living creatures (and the sounds they make) whereas the left is specialized for perceiving and naming non-living things, such as tools and household objects.

The Temporal Lobe & The Neurology Of Form Recognition

The neocortex of the inferior temporla lobe is specialized for receiving, analyzing, discriminating, recognizing and recalling complex visual information and is involved in attention and visually guided behaviour, comprising the recollection and learning of visual discriminations (Gross, 1972) and memory for objects and spatial locations (Nunn et al., 2015; Ploner et al., 2015). If the temporal lobe is injured, these functions become compromised. For example, Kimura (1963) found that patients with right vs left temporal lobe injury were impaired when presented with overlapping nonsense shapes and then immediately tested for recognition. Similarly, Meier and French (1965), found that those with right vs left temporal lobe injuries were impaired when asked to make visual discriminations when presented with fragmented concentric circle patterns—skills which are also related to visual closure and gestalt formation.

More recently, Nunn et al., (2015) found that right vs left temporal lobectomy patients were more impaired when required to remember and recognize toys and recall their location. Cells in the ITL have very large, bilateral visual receptive fields which include the fovea, and many are sensitive to direction of stimulus movement, colour, contrast, size, shape, orientation and are involved in the perception of three dimensional objects and the supramodal analysis of information already processed in the association areas.

Thus inferior temporal (IT) neurons appear to take part in the last stages of visual analysis for form recognition and receive terminal fibers from the primary and association visual areas; that is, via the ventral visual stream. Indeed, a single neuron can respond to a combination of these features and many will fire selectively in response to particular shapes and faces. In fact, based on single cell recordings, some of these temporal lobe neurons have been found to become particularly excited when presented with two dimensional patterns or three dimensional objects such as hands, brushes, and in particular, faces (Deismone & Gross, 1979; Gross et al., 1972; Nakamura et al. 1994; Richmond et al., 1983; Richmond et al.2013).

A number of different feature detectors are found and the majority probably act collectively so as code and assemble a particular shape, including the formation of gestalts and thus the performance of visual closure, especially the right temporal region. Via closure an individual can detect a partial stimulus and determine if the stimulus is that of a human face vs a rabbit. Hence, if these areas are damaged, and these feature detecting neurons are destroyed, the patient will lose the ability to visually recognize a variety of visual stimuli, including the human face.

GRAPHESTHESIA

Graphesthesia is the ability to recognize writing on the skin purely by the sensation of touch. Its name derives from Greek *graphç* ("writing") and *aisthçsis* ("perception"). Graphesthesia tests combined cortical sensation; therefore, it is necessary that primary sensation be intact. During medical or neurological examination graphesthesia is tested in order to test for certain neurological conditions such as; lesions in brainstem, spinal cord, sensory cortexor thalamus.

An examiner writes single numbers or simple letters on the skin (usually the palm) with something that will provide a clear stimulus, such as a broken tongue depressor, pen cap etc. Prior to the start of testing, an agreement may be reached between the

examiner and the patient as to the orientation of the letters, although this is often unnecessary, since orientation and size of the figures are rarely an issue. The crucial aspect of testing graphesthesia, as with any sensory testing, is to establish that the patient understands the test, hence the test is commenced, in the hemiplegic patient, on the normal, intact hand. This also permits the examiner to establish the patient's numeracy, since semi-numerate patients may have difficulties performing the task. The patient provides a verbal response identifying the figure that was drawn. If the patient has a speech or language impairment that prevents them from verbalizing an answer, the answer can be selected from a series of images shown to them. Loss of graphesthesia indicates either parietal lobe damage on the side opposite the hand tested or damage to the dorsal columns pathway at any point between the tested point and the contralateral parietal lobe.

The major clinical utility of the test in the 21st century is in the condition,cortico-basal ganglionic degeneration, where, in addition to evidence of basal ganglia dysfunction, the presence of cortical sensory loss is likely to have reasonably high specificity for the diagnosis. Testing graphesthesia can be substituted for stereognosis if a patient is unable to grasp an object.

DYSLEXIA

Dyslexia has been around and has been defined in different ways. For example, in 1968, the World Federation of Neurologists defined dyslexia as "a disorder in children who, despite conventional classroom experience, fail to attain the language skills of reading, writing, and spelling commensurate with their intellectual abilities."

The International Dyslexia Association offers the following definition of dyslexia:

"*Dyslexia is a specific learning disability that is neurobiological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language*

that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede growth of vocabulary and background knowledge."

Dyslexia is the most common learning disability in children and persists throughout life. The severity of dyslexia can vary from mild to severe. The sooner dyslexia is treated, the more favorable the outcome. However, it is never too late for people with dyslexia to learn to improve their language skills.

Dyslexia, also called reading disorder, is characterized by trouble with reading despite normal intelligence. Different people are affected to varying degrees. Problems may include difficulties in spelling words, reading quickly, writing words, "sounding out" words in the head, pronouncing words when reading aloud and understanding what one reads. Generaly these difficulties are first noticed at school. When someone who previously could read loses their ability, it is known as alexia. The difficulties are involuntary and people with this disorder have normal desire to learn.

The cause of dyslexia is believed to involve both genetic and environmental factors. Some cases run in families. It often occurs in people with attention deficit hyperactivity disorder (ADHD) and is related to similar difficulties with numbers. It may begin in adulthood as the result of a traumatic brain injury, stroke, or dementia. The underlying mechanisms are problems within thebrain's language processing.

Dyslexia is diagnosed through a series of tests of memory, spelling, vision, and reading skills.Dyslexia is separate from reading difficulties caused by insufficient teaching; or either hearing or vision problems. Treatment involves adjusting teaching methods to meet the person's needs. While not curing the underlying problem, it may decrease the degree of symptoms. Treatments targeting vision are not effective. Dyslexia is the most common learning disability, affecting 3–7 % of the population; however, up to 20% may have some degree of symptoms. While dyslexia is

more often diagnosed in men, it has been suggested that it affects men and women equally.

Dyslexia occurs in all areas of the world. Some believe that dyslexia should be best considered as a different way of learning, with both benefits and downsides.

Classification of Dyslexia

Dyslexia is thought to have two types of cause, one pertaining to language processing and another to visual processing. It is considered a cognitive disorder, not a problem withintelligence. However, emotional problems often arise because of it. Some published definitions are purely descriptive, whereas others propose causes. The latter generally cover a variety of reading skills and deficits, and difficulties with distinct causes rather than a single condition.

The National Institute of Neurological Disorders and Strokedefinition describes dyslexia as "difficulty with spelling, phonological processing (the manipulation of sounds), or rapid visual-verbal responding". The British Dyslexia Association definition describes dyslexia as "a learning difficulty that primarily affects the skills involved in accurate and fluent word reading and spelling" and is characterized by "difficulties in phonological awareness, verbal memory and verbal processing speed". Acquired dyslexia or alexia may be caused by brain damage due to stroke or atrophy. Forms of alexia include pure alexia, surface dyslexia, semantic dyslexia,phonological dyslexia, and deep dyslexia.

Definition

In the definition of dyslexia there is some variability. Some sources, such as the U.S. National Institutes of Health, define it specifically as a learning disorder. Other sources, however, define it simply as inability to read in the context of normal intelligence, and distinguish between *developmental dyslexia* (a learning disorder) and *acquired dyslexia*(loss of the ability to read caused by brain damage). ICD 10, the manual of medical diagnosis used in much

of the world, comprises separate diagnoses for "developmental dyslexia" (81.0) and for "dyslexia and alexia" (48.0). DSM 5, the manual of psychiatric diagnosis used in the United States, does not specifically define dyslexia, justifying this decision by stating that "the many definitions of dyslexia and dyscalculia meant those terms would not be useful as disorder names or in the diagnostic criteria". Instead it includes dyslexia in a category called specific learning disorders.

Signs and symptoms of Dyslexia

In early childhood, symptoms that correlate with a later diagnosis of dyslexia include delayed onset of speech, difficulty distinguishing left from right, difficulty with direction, as well as being easily distracted by background noise. The reversal of letters or words and mirror writing are behaviours sometimes seen in people with dyslexia, but are not considered to be defining characteristics of the disorder. Dyslexia and attention deficit hyperactivity disorder (ADHD) commonly occur together; about 15% of people with dyslexia also have ADHD and 35% of those with ADHD have dyslexia.

School-age dyslexic children may exhibit signs of difficulty in identifying or generating rhyming words, or counting the number of syllables in words – both of which depend onphonological awareness. They may also show difficulty in segmenting words into individual sounds or may blend sounds when producing words, connoting reduced phonemic awareness. Difficulties with word retrieval or naming things is also related to dyslexia. Dyslexics are commonly poor spellers, a feature sometimes called dysorthographia or dysgraphia, which depends on orthographic coding. Problems persist into adolescence and adulthood and may accompany difficulties with summarizing stories, memorization, reading aloud, or learning foreign languages.

Adult dyslexics can often read with good comprehension, though they tend to read more slowly than non-dyslexics and perform worse in spelling tests or when reading nonsense words

– a measure of phonological awareness. A common myth about dyslexia is that its defining feature is reading or writing letters or words backwards, but this is true of many children as they learn to read and write.

Language

The orthographic complexity of a language directly impacts how difficult learning to read the language is. English and French have comparatively "deep" phonemic orthographies within the Latin alphabet writing system, with complex structures employing spelling patterns on several levels: letter-sound correspondence, syllables, andmorphemes.

Languages like Spanish, Italian and Finnish have mostly alphabetic orthographies, which primarily employ letter-sound correspondence – so-called shallow orthographies – which for dyslexics makes them easier to learn. Logographic writing systems, such as Chinese characters, have extensive symbol use, and pose problems for dyslexic learners.

Associated conditions

Dyslexia is often accompanied by several learning disabilities, but it is unclear whether they share underlying neurological causes. These associated disabilities include:

- Dysgraphia – A disorder which primarily expresses itself through difficulties with writing or typing, but in some cases through difficulties associated with eye–hand coordination and direction- or sequence-oriented processes such as tying knots or carrying out repetitive tasks. In dyslexia, dysgraphia is often multifactorial, due to impaired letter-writing automaticity, organizational and elaborative difficulties, and impaired visual word forming which makes it more difficult to retrieve the visual picture of words required for spelling.
- Attention deficit hyperactivity disorder – A significant degree of comorbidity has been reported between ADHD and reading disorders such as dyslexia. ADHD occurs in 12–24% of all individuals with dyslexia.

- Auditory processing disorder – A listening disability that affects the ability to process auditory information. This can lead to problems with auditory memory and auditorysequencing. Several people with dyslexia have auditory processing problems, and may develop their own logographic cues to compensate for this kind of deficit. Some research indicates that auditory processing skills could be the primary shortfall in dyslexia.
- Developmental coordination disorder – A neurological condition characterized by marked difficulty in carrying out routine tasks involving balance, fine-motor control,kinesthetic coordination, difficulty in the use of speech sounds, problems with short-term memory, and organization.

Causes of Dyslexia

Researchers have been trying to find the neurobiological basis of dyslexia since the condition was first identified in 1881. For instance, some have tried to associate the common problem among dyslexics of not being able to see letters clearly to abnormal development of their visual nerve cells.
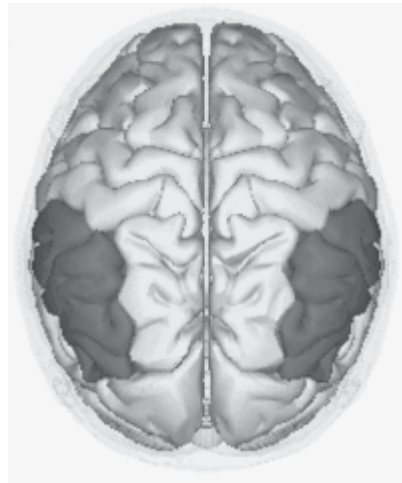
Inferior parietal lobule – (superior view animation)some dyslexics demonstrate less electrical activation in this area.

Neuroanatomy

Modern neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography(PET) have shown a correlation between both functional and structural differences in the brains of children with reading difficulties. Some dyslexics show less electrical activation in parts of the left hemisphere of the brain involved with reading, such as the inferior frontal gyrus, inferior parietal lobule, and the middle and ventral temporal cortex. Over the past decade, brain activation studies using PET to study language have produced a breakthrough in the understanding of the neural basis of language.

Neural bases for the visual lexicon and for auditory verbal short-term memory components have been proposed, with some implication that the observed neural manifestation of developmental dyslexia is task-specific (i.e. functional rather than structural). fMRIs in dyslexics have provided important data which point to the interactive role of the cerebellum and cerebral cortex as well as other brain structures. The cerebellar theory of dyslexia proposes that impairment of cerebellum-controlled muscle movement affects the formation of words by the tongue and facial muscles, resulting in the fluency problems that are characteristic of some dyslexics.

The cerebellum is also involved in the automatization of some tasks, such as reading. The fact that some dyslexic children have motor task and balance impairments has been used as evidence for a cerebellar role in their reading difficulties. However, the cerebellar theory is not supported by controlled research studies.

Genetics

Research into potential genetic causes of dyslexia has its roots in post-autopsy examination of the brains of people with dyslexia. Observed anatomical differences in thelanguage centers of such brains include microscopic cortical malformations called ectopias, more rarely, vascular micro-malformations, and microgyrus. The previously cited studies and others suggest that abnormal cortical

development presumed to occur before or during the sixth month of fetal brain development was the cause of the abnormalities. Abnormal cell formations in dyslexics have also been reported in non-language cerebral and subcortical brain structures. Several genes have been associated with dyslexia, including DCDC2 and KIAA0319 on chromosome 6, and DYX1C1 on chromosome 15.

Gene–environment interaction

The contribution of gene–environment interaction to reading disability has been intensely studied using twin studies, which estimate the proportion of variance associated with a person's environment and the proportion associated with their genes. Studies examining the influence of environmental factors like parental education and teacher quality have determined that genetics have greater influence in supportive, rather than less optimal, environments.

However, more optimal conditions may just allow those genetic risk factors to account for more of the variance in outcome because the environmental risk factors have been minimized.

As environment plays a large role in learning and memory, it is likely that epigenetic modifications play an important role in reading ability.

Animal experiments and measures of gene expression and methylation in the human periphery are used to study epigenetic processes; however, both types of study have several limitations in the extrapolation of results for application to the human brain.

Diagnosis of Dyslexia

There are tests that can indicate with high probability whether a person is a dyslexic. If diagnostic testing indicates that a person may be dyslexic, such tests are often followed up with a full diagnostic assessment to determine the extent and nature of the disorder. Tests can be administered by a teacher or computer. Some test results indicate how to carry out teaching strategies.

Central dyslexias

Central dyslexias include surface dyslexia, semantic dyslexia, phonological dyslexia, and deep dyslexia. ICD-10 reclassified the previous distinction between dyslexia (315.02 in ICD-9) and alexia (315.01 in ICD-9) into a single classification as R48.0. The terms are applied to developmental dyslexia and inherited dyslexia along with developmental aphasia and inherited alexia, which are considered synonymous.

Surface dyslexia

In surface dyslexia, words with regular pronunciations (highly consistent with their spelling, e.g. *mint*) are read more accurately than words with irregular pronunciation, such as *colonel*. Difficulty distinguishing homophones is a diagnostic used for some forms of surface dyslexia. This disorder is usually accompanied by surface agraphia and fluent aphasia. Acquired surface dyslexia arises when a previously literate person experiences brain damage, which results in pronunciation errors that indicate impairment of the lexical route.

Phonological dyslexia

Broca's area – (lateral view) dyslexics overuse this area which is associated with speech

In phonological dyslexia, sufferers can read familiar words but have difficulty with unfamiliar words, such as invented pseudo-

words.Phonological dyslexia is associated with lesions in the parts of the brain supplied with blood by the middle cerebral artery. The superior temporal lobe is often also involved.

Besides, dyslexics compensate by overusing a front-brain region called Broca's area, which is associated with aspects of language and speech.

The Lindamood Phoneme Sequencing Program (LiPS) is used to treat phonological dyslexia. This system is based on a three-way sensory feedback process, using auditory, visual, and oral skills to learn to recognize words and word patterns. Case studies with a total of three patients found a significant improvement in spelling and reading ability after using LiPS.

Deep dyslexia

Individuals with deep dyslexia experience both semantic paralexia (para-dyslexia) and phonological dyslexia, which causes the person to read a word and then say a related meaning instead of the denoted meaning. Deep alexia is associated with clear phonological processing impairments. Deep dyslexia is caused by widespread damage to the brain that often includes the left hemisphere. The "continuum" hypothesis claims that deep dyslexia develops from phonological dyslexia.

Peripheral dyslexias

Peripheral dyslexias have been described as affecting the visual analysis of letters as a result of brain injury. Hemianopsia, a visual field loss on the left/right side of the vertical midline, is associated with this condition.

Pure dyslexia

Pure, or phonologically-based, dyslexia, also known as agnosic dyslexia, dyslexia without agraphia, and pure word blindness, is dyslexia due to difficulty in recognizing written sequences of letters (such as words), or sometimes even letters. It is considered '"pure" because it is not accompanied by other significant language-related impairments. Pure dyslexia does not affect speech,

handwriting style, language or comprehension impairments. Pure dyslexia is caused by lesions on the visual word form area (VWFA).

The VWFA is composed of the left lateral occipital sulcus and is activated during reading. A lesion in the VWFA stops transmission between the visual cortex and the left angular gyrus. It can also be caused by a lesion involving the left occipital lobe or the splenium. It is usually accompanied by a homonymous hemianopsia in the right side of the visual field.

Multiple oral re-reading (MOR) is a treatment for pure dyslexia. It is considered a top-down processing technique in which affected individuals read and reread texts a predetermined number of times or until reading speed or accuracy improves a predetermined amount.

Hemianopic dyslexia

Hemianopic dyslexia is commonly considered to derive from visual field loss due to damage to the primary visual cortex. Sufferers may complain of abnormally slow reading but are able to read individual words normally. This is the most common form of peripheral alexia, and the form with the best evidence of effective treatments.

Neglect dyslexia

In neglect dyslexia, some letters, most commonly those at the beginning or left side of a word, are skipped or misread during reading. This alexia is associated with right parietal lesions. The use of prism glasses has been shown to substantially mitigate this condition.

Attentional dyslexia

People with attentional dyslexia complain of letter-crowding or migration, sometimes blending elements of two words into one. Sufferers read better when words are presented in isolation rather than flanked by other words and letters. Using a large magnifying glass may help mitigate this condition by reducing the effects of flanking from nearby words; however, no trials of this or indeed

any other therapy for left parietal syndromes have been published as of 2014.

Mechanisms of Dyslexia

The dual-route theory of reading aloud was first described in the early 1970s. This theory suggests that two separate mental mechanisms, or cognitive routes, are involved in reading aloud. One mechanism is the lexical route, which is the process whereby skilled readers can recognize known words by sight alone, through a "dictionary" lookup procedure. The other mechanism is the nonlexical or sublexical route, which is the process whereby the reader can "sound out" a written word. This is done by identifying the word's constituent parts (letters, phonemes, graphemes) and applying knowledge of how these parts are associated with each other, for instance, how a string of neighboring letters sound together.

The dual-route system could explain the different rates of dyslexia occurrence between different languages (e.g. the Spanish language dependence on phonological rules accounts for the fact that Spanish-speaking children show a higher level of performance in non-word reading, when compared to English-speakers).

Dyslexia disorder is not caused by mutation in one gene; in fact, it appears to involve the combined effects of several genes. Studying the cognitive problems associated with other disorders helps to better understand the genotype-phenotype link of dyslexia. Neurophysiological and imaging procedures are being used to ascertain phenotypic characteristics in dyslexics, thus identifying the effects of certain genes.

Prognosis

Dyslexic children require special instruction for word analysis and spelling from an early age. However, there are fonts that can help dyslexics better understand writing. The prognosis, generally speaking, is positive for individuals who are identified in childhood and receive support from friends and family.

Epidemiology

The percentage of people with dyslexia is unknown, but it has been estimated to be as low as 5% and as high as 17% of the population. While it is diagnosed more often in males, some believe that it affects males and females equally. There are many definitions of dyslexia used throughout the world, but despite significant differences in writing systems, dyslexia occurs in different populations. Dyslexia is not limited to difficulty in converting letters to sounds, and Chinese dyslexics may have difficulty converting Chinese characters into their meanings. The Chinese vocabulary uses logographic, monographic, non-alphabet writing where one character can represent an individual phoneme. The phonological-processing hypothesis attempts to explain why dyslexia occurs in a wide variety of languages. Furthermore, the relationship between phonological capacity and reading appears to be influenced by orthography.

ACQUISITION OF NEW MEMORIES

Patients with amnesia can learn new information, particularly non-declarative knowledge. However, some patients with dense anterograde amnesia do not remember the episodes during which they learned or observed the information previously.

Declarative information

Some patients with anterograde amnesia can still acquire some semantic information, even though it might be more difficult and might remain rather unrelated to more general knowledge. H.M. could accurately draw a floor plan of the home in which he lived after surgery, even though he had not lived there in years.

The reason patients could not form new episodic memories is likely because the CA1 region of the hippocampus was lesioned, and thus the hippocampus could not make connections to the cortex. After an ischemic episode following surgery, an MRI of patient R.B. showed his hippocampus to be intact except for a specific lesion restricted to the CA1 pyramidal cells.

Non-declarative information

Some retrograde and anterograde amnesics are capable of non-declarative memory, including implicit learning and procedural learning. For instance, some patients show improvement on the pseudorandom sequences experiment as healthy people do. Therefore, procedural learning can proceed independently of the brain system required for declarative memory.

According to fMRI studies, the acquisition of procedural memories activates the basal ganglia, the premotor cortex and the supplementary motor area, regions which are not normally associated with the formation of declarative memories. This kind of dissociation between declarative and procedural memory can also be found in patients with diencephalic amnesia such as Korsakoff's syndrome. Another instance demonstrated by some patients, such as K.C. and H.M, who have medial temporal damage and anterograde amnesia, still have perceptual priming. Those patients did well in the word fragment completion test.

Treatment

Various forms of amnesia fix themselves without being treated. However, there are a few ways to cope with memory loss if that is not the case. One of these ways is cognitive or occupational therapy. In therapy, amnesiacs will develop the memory skills they have and try to regain some they have lost by finding which techniques help retrieve memories or create new retrieval paths. This may also include strategies for organizing information to remember it more easily and for improving understanding of lengthy conversation. Another coping mechanism is taking advantage of technological assistance, such as a personal digital device to keep track of day-to-day tasks. Reminders can be set up for appointments, when to take medications, birthdays and other important events.

Many pictures can also be stored to help amnesiacs remember names of friends, family and co-workers. Notebooks, wall calendars, pill reminders and photographs of people and places

are low-tech memory aids that can help as well. While there are no medications available to treat amnesia, underlying medical conditions can be treated to improve memory. Such conditions include but are not limited to low thyroid function, liver or kidney disease, stroke, depression, bipolar disorder and blood clots in the brain.

Wernicke–Korsakoff syndrome involves a lack of thiamin and replacing this vitamin by consuming thiamin-rich foods such as whole-grain cereals, legumes (beans and lentils), nuts, lean pork, and yeast. Treating alcoholism and preventing alcohol and illicit drug use can prevent further damage, but in most cases will not recover lost memory.

Although improvements occur when patients receive certain treatments, there is still no actual cure remedy for amnesia so far. To what extent the patient recovers and how long the amnesia will continue depends on the type and severity of the lesion.

ANOSOGNOSIA

Anosognosia is an awkward term introduced by neurologists a century ago "to denote a complete or partial lack of awareness of different neurological…and/or cognitive dysfunctions." This definition comes from G.P. Prigatano, ed. The Study of Anosognosia, Oxford University Press, 2010, p.17. Anosognosia thus means dearth of awareness or lack of insight. It is not the same as denial of illness; anosognosia is caused by physical damage to the brain and is thus anatomical in origin whereas denial is psychological in origin. Anosognosia is very difficult to imagine or understand. Oliver Sacks, in The Man Who Mistook His Wife for a Hat, explained anosognosia as follows:

It is not only difficult, it is impossible for patients with certain right-hemisphere syndromes to know their own problems – a peculiar and specific 'anosognosia,' as Babinski called it. And it is singularly difficult, for even the most sensitive observer, to picture the inner state, the 'situation' of such patients, for this is almost unimaginably remote from anything he himself has ever known.

Among neurological patients, anosognosia is seen most commonly in Alzheimer's disease, Huntington's disease, and traumatic brain injury and occasionally in patients with stroke (especially those involving the right parietal lobe) and Parkinson's disease.

Most patients with Alzheimer's disease, for example, are aware that something is wrong early in the course of their illness but then lose all awareness of their illness as it progresses. Anosognosia is also very important in psychiatry since approximately 50 percent of individuals with schizophrenia and 40 percent of individuals with bipolar disorder have anosognosia. It is the most common cause why individuals with schizophrenia refuse to take medication; since they do not believe that there is anything wrong with them, why should they? Impaired awareness of illness is not a new idea for psychiatric patients; in 1604 playwright Thomas Dekker has a character in The Honest Whore say: "That proves you mad because you know it not."

Research on anosognosia in psychiatry in recent years has been led by Drs. Xavier Amador and Tony David; their 2004 book, Insight and Psychosis: Awareness of Illness in Schizophrenia and Related Disorders, is an excellent summary of the early research. Awareness of illness sometimes improves with treatment with antipsychotic medication, especially clozapine. Also very helpful is Dr. Amador's book: *I Am Not Sick: I Don't Need Help!* It is now clear that anosognosia in psychiatric patients, just as anosognosia in neurological patients, is caused by brain damage associated with the disease. Since 1992, there have been 22 studies comparing the brains of individuals with schizophrenia with and without anosognosia. In all except two studies, there were found to be great differences between the two in one or more anatomical structures.

Since anosognosia involves a broad brain network related to self-awareness, a variety of anatomical structures are involved, especially the anterior insula, anterior cingulate cortex, medial frontal cortex, and inferior parietal cortex. Three of the positive

studies included individuals with schizophrenia who had never been treated with medications so the observed brain changes cannot be attributed to the treatment.

Anosognosia for Hemiplegia

Probably the most striking instance of anosognosia can be found in brain-damaged patients, affected by a complete contralesional hemiplegia (for a review Bottini et al., 2010). These patients may deny that there is anything wrong with their contralesional limbs and claim of being able to perform any kind of action.

Besides, when asked to perform a purposeful movement with the paralysed limb they may appear convinced of having accomplished the requested action despite unambiguous proof to the contrary coming from different sensory channels. It is worth noticing that such "on line" confabulations, recently termed "illusory limb movements" (Feinberg, 2007), are not present in all anosognosic patients. The symptomatology of anosognosia for hemiplegia can vary between and within patients. This disturbance is frequent after damage to the right hemisphere, with a prevalence ranging from 20% to 50% of hemiplegic patients, depending on the studies, the differences being related to the time of evaluation (acute vs. chronic phase of the illness) and selection criteria (e.g., Pia et al. 2004). When explicitly questioned about the condition of their limbs, patients may show different degrees of denial ranging from emotional indifference (anosodiaphoria), in which the motor problems may be admitted but without any concerns, to resolute and intractable unawareness of the disease.

Additionally, productive symptoms, as verbal confabulations about the possibility of moving the plegic limb, and delusional beliefs may coexist. In this latter case, patients may experience their limb as not belonging to them (asomatognosia) or attribute their own body parts to other persons (somatoparaphrenia). The content of the confabulation can be very bizarre and patients may even claim that somebody else is lying on their beds or may show

violent attitude against those 'alien' limbs (misoplegia). The interpretation of anosognosia for hemiplegia is not straightforward. Theories that explain it either as a secondary consequence of sensory feedback deficits or as due to the co-occurrence of various kinds of neuropsychological disorders are not thought to be exhaustive explanations. Indeed, double dissociations have been shown between anosognosia for hemiplegia and sensory/cognitive deficits.

It is worth noticing, however, that the motivational factor account has been recently re-proposed in terms of abnormal affective regulation or altered emotional and attitudinal processes implicated in self-attribution of perceptual experiences (e.g., Turnbull et al., 2005). A lesion to a right-lateralized emotion-regulation system might crucially contribute to the emergence of anosognosia for hemiplegia. Consistently, some anatomical data show an overlap between areas underpinning motor awareness and those subserving emotions. Additionally, right brain-damaged patients often develop emotional changes and difficulty tolerating aversive emotional states (Turnbull et al., 2005). Thus, although the emotional theories do not explain the full-fledged syndrome of anosognosia for hemiplegia, it is possible that the complex interactions between individual predispositions and brain dysfunction would shape the way in which denial manifest itself in different patients. Recently, it has been proposed that anosognosia for hemiplegia might be explained as a domain specific disorder of motor control (Berti and Pia, 2006). Anatomo-clinical correlations and lesion analyses have shown that anosognosia for hemiplegia follows brain damages within lateral premotor and insular cortex. A possibility is that this damage would alter the monitoring of voluntary actions, thus preventing patients to distinguish between movement and no-movement states. Moreover, the (non-veridical) feeling of movement would arise from an intact motor intentionality subserved by a normal activity of the brain structures that implement the intention-programming system (Berti and Pia 2006). Evidence of preserved movement

intentionality in anosognosic patients comes from the fact that they may show normal proximal muscle electrical activity in the affected side when they believe they are moving the plegic limb (Berti et al., 2007).

Moreover, it has been shown that in bimanual action (Garbarini & Pia, 2013) the motor execution of the anosognosic patients' intact hand is affected by the intention to move the paretic hand. Interestingly, such an intentional stance dominates their subjective experience of willed actions because patients falsely detect movement of their plegic arm when they intend to move it, respect to when they do not (Fotopoulou et al., 2008).

Other forms of Anosognosia

Patients affected by hemianaesthesia (i.e., the loss of tactile/proprioceptive sensibility on one side of the body), can be completely unaware of their sensory impairment (e.g., Marcel et al., 2004; Spinazzola et al., 2008). Interestingly, unawareness for hemianaesthesia can be dissociated from anosognosia for hemiplegia, unilateral neglect, intellectual impairment and general self-monitoring on both functional and anatomical ground. This form of denial seems to be more frequently associated to lesions of those brain structures underpinning sensory-spatial processing (e.g., insular, temporal and subcortical lesions mainly affecting basal ganglia).

Hence, as for the cerebral circuits of self-monitoring processes for primary sensory functions are located in areas involved both in the execution of the primary functions and in the emergence of awareness related to the monitoring of the same functions. Current theories suggest that patients affected by anosognosia for hemianaestesia have a nonveridical sensory awareness generated as an illusory experience by the failure to distinguish between an imagined sensation and a real, physical one (Pia et al., 2014). The brain structures underpinning sensory-spatial processing would be the neural basis of sensory self-monitoring allowing the distinction between 'veridical' and 'non-veridical' sensory

awareness. Anosognosia may occur in cerebral achoromatopsia, a quite rare neurological disorder characterized by a complete or partial loss of colour vision after a bilateral cortical damage to the ventral occipito-temporal cortex. Patients affected by this disorder claim to see the world in black and white and are usually aware of their visual deficit. However, there are a few descriptions of patients who either did not notice their colour perception deficit or did so only some time after the brain damage, suggesting unawareness for the loss of colour vision.

Inspite of verbal and nonverbal/perceptual testing showing the presence of severe colour blindness, the patients may still claim a normal colour vision, even when faced with their errors in naming colours. It is worth noticing that colour vision may improve with time and a parallel improvement in awareness can be observed.

The simultaneous occurrence of achoromatopsia and anosognosia, their parallel recovery, and their lesion site in visual areas suggest that both deficits were due to dysfunction of the same brain region, implying again that normal perception and normal monitoring share common anatomical substrates.

As mentioned above, anosognosia may occur also within more complex cognitive disorders as, for instance, schizophrenia and Alzheimer's disease. In these pathologies, it is very hard to individuate a common core explaining the different denial behaviours. The fact that in many instances there is a severe intellectual impairment is of course a confounding factor. However, various data seems to support the idea that also in these cases unawareness can be selective and neurologically based.

In schizophrenia, it has been often used the term 'lack of insight' to indicate a broad construct encompassing unawareness of the disorder, of the effects of treatment, of social consequences, of the occurrence of psychiatric symptoms and difficulty in labeling them. Recently, however, numerous data suggest that unawareness in schizophrenia might have similarities with the concept of

anosognosia: persistence despite all contrary evidence, confabulations to explain the symptoms, frontal lobe impairments and domain specificity (e.g., Pia & Tamietto 2006).

For example, there can be dissociations between unawareness for negative and positive symptoms. Moreover, unawareness for pathological involuntary movement (i.e., tardive dyskenisia) can be present for some muscular group and not for others akin to what has been reported for patients with anosognosia for hemiplegia who may be aware of the motor deficit affecting the lower limb and not of the contemporary presence of the motor impairment of the upper limb and viceversa. Likewise, anosognosia in Alzheimer's disease has not been initially considered as a domain specific impairment Indeed, data from early/acute stages of the disease and from different aspects of functioning including cognition, mood, behaviour and daily activities have been often grouped in a single anosognosia index.

However, it has been recently suggested that also unawareness in Alzheimer's disease might be interpreted as a selective and neurologically based condition. It seems to be strictly connected to frontal lobe impairments (e.g., patients with anosognosia and Alzheimer's disease often show a reduction of cerebral haematic flow in the frontal regions, deficits of executive functions and extrapyramidal signs) and can be observed for some deficits and not for others.

Causes of Anosognosia

Relatively little has been discovered about the cause of the condition since its initial identification. Recent studies from the empirical data are prone to consider anosognosia a multi-componential syndrome or multi-faceted phenomenon. That is it can be manifested by failure to be aware of a number of specific deficits, including motor (hemiplegia), sensory (hemianaesthesia, hemianopia), spatial (unilateral neglect), memory (dementia), and language (receptive aphasia) due to impairment of anatomo-functionally discrete monitoring systems.

Anosognosia is relatively common following different etiologies of brain injury, such as stroke and traumatic brain injury (e.g. 10%–18% in the case of anosognosia for hemiparesis with onset of acute stroke), but can appear to occur in conjunction with virtually any neurological impairment. It is more frequent in the acute than in the chronic phase and more prominent for assessment in the cases with right hemispheric lesions than with the left kinds.

However, it is not related to global mental confusion, cognitive flexibility, other major intellectual disturbance, or mere sensory/perceptual deficits. Anosognosia can be selective in that an affected person with multiple impairments may seem unaware of only one handicap, while appearing to be fully aware of any others. For example, anosognosia for hemiplegia may occur with intact awareness of visuo-spatial unilateral neglect, or vice versa. This phenomenon of double dissociation can be an indicator of domain-specific disorders of awareness modules, meaning that brain damage can selectively impact the self-monitoring process of one specific physical or cognitive function.

The condition does not appear to be directly related to sensory loss and is thought to be caused by damage to higher level neurocognitive processes that are involved in integrating sensory information with processes that support spatial or bodily representations (including the somatosensory system). Anosognosia is thought to be related tounilateral neglect, a condition often found after damage to the non-dominant (usually the right) hemisphere of the cerebral cortex in which sufferers seem unable to attend to, or sometimes comprehend, anything on a particular side of their body (usually the left).

There are also studies showing that the maneuver of vestibular stimulation could temporarily improve both the syndrome of spatial unilateral neglect and of anosognosia for left hemiplegia. Combining the findings of hemispheric asymmetry to the right, association to spatial unilateral neglect, and the temporal improvement on both syndromes, it is suggested there can be a spatial component underlying the mechanism of anosognosia for

motor weakness and their neural processes could be modulated similarly. There were some cases of anosognosia for right hemiplegia after left hemisphere damage, but the frequency of this type of anosognosia has not been estimated. Those diagnosed with dementia of the Alzheimer's type, often display this dearth of awareness and insist that nothing is wrong with them.

Anosognosia may occur as part of receptive aphasia, a language disorder that causes poor comprehension of speech and the production of fluent but incomprehensible sentences. A patient with receptive aphasia cannot correct his own phonetic errors and shows "anger and disappointment with the person with whom s/he is speaking that person fails to understand her/him." This may be a result of brain damage to the posterior portion of the superior temporal gyrus, believed to contain representations of word sounds.

With those representations significantly distorted, patients with receptive aphasia are unable to monitor their mistakes. Other patients with receptive aphasia are fully aware of their condition and speech inhibitions, but cannot monitor their condition, which is not the same as anosognosia and therefore cannot explain the occurrence ofneologistic jargon.

ANOSOGNOSIA: THE MOST DEVASTATING SYMPTOM OF MENTAL ILLNESS

Mental illness comes in many forms. Depression, bipolar disorder, schizophrenia, and the anxiety disorders all have the potential to be crippling, and ruin lives. Yet as terrible as depression, mania, psychosis, and the other symptoms of these disorders can be, there is one that stands out as the most damaging of all:

Anosognosia

This obscure word, which is pronounced "uh-no-sog-no-zha," means "denial of illness," and is more serious than you might think.

Most of the people understand the psychological concept of denial, which is a refusal to believe an uncomfortable truth. Who

hasn't heard heard a heavy drinker, eater, smoker, or drug user say, "I can quite any time I want," or someone with a chronic cough (which may indicate a serious illness) say, "It's not important—It's just a cough." Pressing the denier on the obvious gap between reality and his belief typically yields a flurry of thin excuses that support his position, and can provoke an outburst of anger if continued long enough. Denial serves a useful purpose in helping people cope with sudden change, and is harmless as long as it is not maintained too long. Denial becomes harmful when it interferes with a person's ability to cope effectively with the challenges he faces. Fortunately, denial is temporary in most cases, and even chronic deniers can can learn better over time. Anosognosia different. It is not simply denial of a problem, but the genuine inability to recognize that the problem exists. It is a common consequence of brain injuries, and occurs to varying degrees in such disorders such as schizophrenia, bipolar disorder, and Alzheimer's disease. (I hasten to add that "common" does not mean "universal!" Most of the people who suffer from these illnesses are quite aware that they are sick.) Someone who has anosognosia isn't being difficult, or refusing to face the truth. He is literally unable to believe that his illness is, in fact, an illness. As a result, he does not see any reason to take medication that can control his illness.

Several people who have anosognosia will refuse to take medication for schizophrenia or bipolar disorder, because they do not believe they are ill. If pushed, they may give the appearance of cooperation, while secretly discarding their medication. In the case of paranoid schizophrenia, where the patient believes others are conspiring to harm him or control his life, the combination of anosognosia and paranoia can provoke the him to violent action in an attempt to escape his "persecutors." (Sadly, the often debilitating side effects of antipsychotic medication, which, unlike his illness, are all too apparent to the patient, provide supporting evidence for his beliefs.) For a symptom with such an obscure name, anosognosia plays a prominent role in both law and

medicine. Treatment for most illnesses is taken at the discretion of the patient, who is free to seek, select, or decline treatment, as he considers appropriate.

However, there are times when the individual's right to control his medical treatment conflicts with other important principles, namely, the sanctity of life, and the protection of others from harm. A person who is in the grip of a severe psychotic episode, who is judged likely to harm himself or someone else, may legally be committed to a psychiatric hospital for evaluation and treatment, on an involuntary basis.

Such treatment usually consists of antipsychotic or mood-stabilizer medications, observation, and possibly restraint. Most patients who are prone to psychosis (primarily, those with schizophrenia) do not have any particular desire to harm other people. The danger comes not from a desire to harm, but from hallucinations and delusions that can drive violent actions. (For instance, a patient may sincerely believe he is fighting for his life against an evil force, when in reality he is attacking an innocent person.) So it is not surprising that patients who are aware of the nature of their illness, and the risk of such harm, generally do prefer treatment to prevent violent incidents.

Similarly, patients who have anosognosia about their psychotic symptoms, but whose behaviour is harmless, may not have a need for medication that justifies removal of their right to make decisions about their treatment However, those psychotic patients who are at risk for committing violent acts, and also have anosognosia, are both dangerous, and unable to believe that anything is wrong with them. Because of this belief, they will refuse treatment, and remain dangerous. These are the patients whose right to control their own treatment conflicts with the right of others to safety.

Lastly, each case must be handled on its own merits, and someone must make the difficult calls—and be prepared to live with the consequences. It is because of anosognosia that such calls must be made.

Assessment of Anosognosia

Clinically, anosognosia is often assessed by giving patients an anosognosia questionnaire in order to assess their metacognitive knowledge of deficits. However, neither the existing questionnaires applied in the clinics are designed thoroughly for evaluating the multidimensional nature of this clinical phenomenon; nor are the responses obtained via offline questionnaire capable of revealing the discrepancy of awareness observed from their online task performance.

The discrepancy is noticed when patients showed no awareness of their deficits from the offline responses to the questionnaire but demonstrated reluctance or verbal circumlocution when asked to perform an online task. For instance, patients with anosognosia for hemiplegia may find excuses not to perform a bimanual task even though they do not admit it is because of their paralyzed arms.

Similar situation can happen on patients with anosognosia for cognitive deficits after traumatic brain injury when monitoring their errors during the tasks regarding their memory and attention (online emergent awareness) and when predicting their performance right before the same tasks (online anticipatory awareness). It can also takeplace among patients with dementia and anosognosia for memory deficit when prompted with dementia-related words, displaying possible pre-attentive processing and implicit knowledge of their memory problems. More interestingly, patients with anosognosia may overestimate their performance when asked in first-person formed questions but not from a third-person perspective when the questions referring to others. When assessing the causes of anosognosia within stroke patients, CT scans have been used to assess where the greatest amount of damage is found within the various areas of the brain. Stroke patients with mild and severe levels of anosognosia (determined by response to an anosognosia questionnaire) have been linked to lesions within the

temporoparietal and thalamic regions, when compared to those who experience moderate anosognosia, or none at all. In contrast, after suffering a stroke, people who have moderate anosognosia have a higher frequency of lesions involving the basal ganglia, compared to those with mild or severe anosognosia.

Psychiatry

Although largely used to describe unawareness of impairment after brain injury or stroke, the term 'anosognosia' is occasionally used to describe the dearth of insight shown by some people who suffer from anorexia nervosa. They do not seem to recognize that they suffer from a mental illness. There is proof that anosognosia related to schizophrenia may be the result of frontal lobe damage. E. Fuller Torrey, a psychiatrist and schizophrenia researcher, has stated that among those with schizophrenia and bipolar disorder, anosognosia is the most prevalent reason for not taking medications.

Anosognosia for Hemiplegia: A Window into Self-Awareness

You wake up in a hospital bed, scared, confused, and attached to a network of tubes and beeping equipment. After doctors assault you with a barrage of questions and tests, your family emerges from the sea of unfamiliar faces surrounding you and explains what has happened; you have had a stroke in the right half of your brain, and you are at least temporarily paralyzed on your left side. You wiggle your left toes to test yourself; everything seems normal. You lift your left arm to show your family that you are obviously not paralyzed.

However, this demonstration does not elicit the happy response you expect; it only causes your children to exchange worried glances with the doctors. No matter how many times you attempt to demonstrate movement in the left half of your body, the roomful of people insists that you are paralyzed. And you are, you just do not know it. How is this possible? You are suffering from anosognosia, a condition in which an ill patient is unaware of her own illness or the deficits resulting from her illness. Anosognosia

occurs at least temporarily in over 50% of stroke victims who suffer from paralysis on the side of the body opposite the stroke, a condition known as hemiplegia. Patients with anosognosia for hemiplegia insist they can do things like lift both legs, touch their doctor's nose with a finger on their paralyzed side, and walk normally. These patients are much less likely to regain independence after their stroke than patients without anosognosia, primarily because they overestimate their own abilities in unsafe situations.

However, the implications of the illness go far beyond those for patients who suffer from it; anosognosia brings questions of the origin of self-awareness to the forefront. How can someone lose the ability to know when she is or is not moving? Is this some type of elaborate Freudian defense mechanism, or is this person entirely unaware of her illness? How is self-awareness represented in the brain, and is this representation isolated from or attached to awareness of others? Though none of these questions are fully answerable at this time, research into anosognosia has provided scientists and philosophers with insight into some of these ancient questions of human consciousness. The question of "denial" versus "unawareness" is at the heart of debate between psychologists and neurologists about the origin of anosognosia. Proponents of a psychological explanation for the disorder insist that patients are aware on some level of their paralysis, but deny this information, as it would be traumatizing to the image of the self to admit to a lack of ability to control one's own body.

However, this theory is countered by the fact that anosognosia in stroke patients almost always occurs after a stroke in the right hemisphere of the brain; though a stroke in the left hemisphere is no less devastating to the body, patients with left hemisphere strokes nearly always fully recognize the impact of their strokes on their bodies. Another explanation of anosognosia draws on the fact that this disorder and hemiplegia are nearly always accompanied by hemispatial neglect, in which the patient does not recognize or attend to visual information on the side of the visual

field contralateral to the brain damage. Some researchers believe that since right-brain stroke patients can be inattentive to visual information on the left side, they may simply be displaying the same inattention to the left half of their bodies when they have anosognosia. In other words, if one pays no attention to the left arm, one would not notice if the left arm is doing something odd, like not moving.

However, one of the premier experts on anosognosia, Dr. Vilayanur Ramachandran, has pointed out a key flaw in this theory: though hemispatial neglect patients with right brain damage acknowledge seeing stimuli presented to the left visual field if it is brought to their attention, for example by being moved or set on fire, no amount of attention drawn to an anosognosiac's immobile limbs will make her acknowledge that her limb is paralyzed.

Generally the anosognosiac will insist that her limb is moving. If pressed, she will cite her arthritis or a lack of motivation as a reason for her immobility. When forced, the patient may even venture completely out of the realm of reality in defending her ability to move, stating that the immobile limb belongs to someone else, or is not a limb at all. Dr. Edoardo Bisiach, another expert in the field, once saw a patient who claimed that his paralyzed hand belonged to Bisiach himself. When Bisiach held his own two hands together with the patient's immobile hand, and asked how it was possible that he had three hands, the patient calmly replied, "A hand is the extremity of an arm.

Since you have three arms, it follows that you must have three hands". Ramachandran insists that this type of unrealistic rationalization is particular to patients with anosognosia; a patient suffering only from hemispatial neglect will not justify her beliefs with peculiar stories, but will accept a doctor's diagnosis. Ramachandran favors an explanation of anosognosia dependent on both psychology and neurology. He maintains that due to the vast amount of sensory information the brain regularly receives, it must have a filter of some sort that lets it process only important

information . Ramachandran's idea is that the left hemisphere of the brain contains a schema of the body in its entirety, which is updated as needed by a section of the right hemisphere. This right hemisphere function compares incoming sensory information to the left-brain schema, and decides which discrepancies are worth informing the left-brain about. For instance, while a few sneezes can be brushed off, a fever will bring the right brain to inform the left-brain that one is sick.

Not all discrepancies in information change the left-brain's schematic representation of the body, but the most important or startling ones do. Ramachandran believes that the right brain's ability to detect these discrepancies is damaged in patients with anosognosia . Thus, the left-brain receives no information about a change in the body's ability to move, and the current representation of the body as fully mobile is maintained . Current experiments have shown that if any information of a change in the body's abilities is present in anosognosiacs, it is extraordinarily inaccessible to the I-function. Ramachandran asked three hemiplegic anosognosiacs and two stroke victims with hemiplegia and no anosognosia to choose between winning a small prize for completing a task involving one hand (i.e., stacking blocks) and winning a large prize for completing a task involving two hands (i.e., tying a bow) . The hemiplegics with no anosognosia consistently opted for the smaller prize. However, the hemiplegic anosognosiacs chose repeatedly to attempt the two handed task, never learning from their failures, and never recognizing their limitations . Amazingly, many anosognosiacs also seem unable to recognize their own limitations in other people . In a recent experiment, Ramachandran found that two thirds of tested hemiplegic anosognosiacs were not able to recognize paralysis in another person . He suggests that this is because we have a schema for the bodies of others as well as ourselves, and that they are represented in close proximity in our brains . This idea was supported by recent research with monkeys, which exhibited that the same areas that were active when a monkey completed a

certain task were also active when he watched another monkey complete the same task . This information suggests that self-awareness is crucial in awareness of others. However, this research is in its early stages, and has not yet been used in the treatment of anosognosiacs.

Two methods of treatment, one primitive and one modern, are used currently to help bring a sense of awareness of failure to anosognosiacs. The first method, invented by Bisiach, involves pouring cold water in the ear of the patient on the side of the paralysis . Since nerves in the ear contribute information about the body's balance to the brain, Bisiach figured by shocking these nerves he might startle the part of the body liable for updating the body schema with new information . This appears to work astonishingly well; patients undergoing this treatment often fully realize their paralysis for several hours. The second method of treatment uses virtual reality programming to give patients repeated feedback about their failures in a safe setting . This kind of program helped I.S., a man with anosognosia for hemispatial neglect, without hemiplegia. I.S. was determined to drive, and saw no reason why he should not, until he was treated with a virtual reality program simulating street crossing.

Since I.S. did not pay attention to cars coming on his left side, he consistently had "accidents", which caused the program to make crashing noises and flash warnings. This type of confrontation with his limitations seemed to cause I.S. to start trusting his doctors over his own sense of self . Presumably, the shock of knowing that if he followed the information given to his I-function by the rest of his brain, he would die, caused him to realize that he needed to learn new ways to perceive himself and the world around him, perhaps even by trusting others over himself.

The issue of trust stands out as key in anosognosia, a disorder in which the patient can no longer trust her own information about herself. This seems almost unthinkable, hence the reason I chose to open this essay by addressing you, the reader. Could you possibly believe someone else's information about your body over

your own? And, if you ever learned to survive as someone who could no longer trust your brain (and, thus, yourself), could you ever again have any type of free will? Could you be creative or original without fully believing in your own mind? The fact that free will is so hard to imagine without an intact sense of self makes me appreciate the seemingly ridiculous lengths to which anosognosiacs will go to defend their perceptions.

Anosognosia : Its Treatment

In regard to anosognosia for neurological patients, no long-term treatments exist. As with unilateral neglect, caloric reflex testing (squirting ice cold water into the left ear) is known to temporarily ameliorate unawareness of impairment. It is not entirely clear how this works, although it is thought that the unconscious shift of attention or focus caused by the intense stimulation of the vestibular system temporarily influences awareness.

Most cases of anosognosia appear to simply disappear over time, while other cases can last indefinitely. Normally, long-term cases are treated with cognitive therapy to train the patient to adjust for their inoperable limbs (though it is believed that these patients still are not "aware" of their disability). Another commonly used method is the use of feedback – comparing clients' self-predicted performance with their actual performance on a task in an attempt to improve insight.

Neurorehabilitation is difficult because, as anosognosia impairs the patient's desire to seek medical aid, it may also impair their ability to seek rehabilitation. A lack of awareness of the deficit makes cooperative, mindful work with a therapist difficult. In the acute phase, very little can be done to improve their awareness, but during this time, it is important for the therapist to build a therapeutic alliance with patients by entering their phenomenological field and reducing their frustration and confusion. Since severity changes over time, no single method of treatment or rehabilitation has emerged or will likely emerge.

With regard to psychiatric patients, empirical studies verify that, for individuals with severe mental illnesses, lack of awareness of illness is significantly associated with both medication non-compliance and re-hospitalization. Fifteen percent of individuals with severe mental illnesses who refuse to take medication voluntarily under any circumstances may require some form of coercion to remain compliant because of anosognosia. Coercive psychiatric treatment is a delicate and complex legal and ethical issue. One study of voluntary and involuntary inpatients confirmed that committed patients require coercive treatment because they fail to recognize their need for care. The patients committed to the hospital had significantly lower measures of insight than the voluntary patients.

Anosognosia is also closely related to other cognitive dysfunctions that may impair the capacity of an individual to continuously participate in treatment. Other research has suggested that attitudes toward treatment can improve after involuntary treatment and that previously committed patients tend later to seek voluntary treatment.

APRAXIA

Apraxia is a poorly understood neurological condition. People who have it find it difficult or impossible to make certain motor movements, even though their muscles are normal. Milder forms of apraxia are known as dyspraxia. Apraxia can occur in a number of different forms.

One form is orofacial apraxia. People with orofacial apraxia are unable to voluntarily perform certain movements involving facial muscles. For example, they may not be able to lick their lips or wink. Another form of apraxia affects a person's ability to intentionally move arms and legs. With apraxia of speech a person finds it difficult or impossible to move his or her mouth and tongue to speak. This happens, even though the person has the desire to speak and the mouth and tongue muscles are physically able to form words.

Forms of Apraxia

There are various types of apraxia including:

- Ideomotor apraxia: These patients have deficits in their ability to plan or complete motor actions that rely on semantic memory. They are able to explain how to perform an action, but unable to "imagine" or act out a movement such as "pretend to brush your teeth" or "pucker as though you bit into a sour lemon."

- The ability to perform an action automatically when cued, however, remains intact. This is known as automatic-voluntary dissociation. For instance, they may not be able to pick up a phone when asked to do so, but can perform the action without thinking when the phone rings.

- Ideational/conceptual apraxia: Patients have an inability to conceptualize a task and impaired ability to complete multistep actions. Consists of an inability to select and carry out an appropriate motor program. For instance, the patient may complete actions in incorrect orders, such as buttering bread before putting it in the toaster, or putting on shoes before putting on socks. There is also a loss of ability to voluntarily perform a learned task when given the necessary objects or tools. For instance, if given a screwdriver, the patient may try to write with it as if it were a pen, or try to comb his hair with a toothbrush.

- Buccofacial or orofacial apraxia: Non-verbal oral or buccofacial ideomotor apraxia resulting in difficulty carrying out movements of the face on demand. For instance, an inability to lick one's lips or whistle. This is an ability to carry out any volitional movements of the tongue, cheeks, lips, pharynx, or larynx on command.

- Constructional apraxia: The inability to draw or construct simple configurations, such as intersecting shapes.

- Gait apraxia: The loss of ability to have normal function of the lower limbs such as walking. This is not due to loss of motor or sensory functions.

- Limb-kinetic apraxia: Difficulty making precise movements with an arm or leg.

- Oculomotor apraxia: Difficulty moving the eye, particularly with saccade movements that direct the gaze to targets. This is one of the 3 major components of Balint's syndrome.
- Apraxia of speech (AOS): Difficulty planning and coordinating the movements necessary for speech (e.g. Potato=Totapo,Topato.) AOS can independently occur without issues in areas such as verbal comprehension, reading comprehension, writing, articulation or prosody.

Each kind may be tested at decreasing levels of complexity; if the person tested fails to execute the commands, you can make the movement yourself and ask that the person mimic it, or you can even give them a real object (like a toothbrush) and ask them to use it.

Apraxia of speech

Apraxia of speech (AOS) is a neurologic speech disorder that reflects an impaired capacity to plan or program sensorimotor commands necessary for directing movements that result in phonetically and prosodically normal speech. It takes in both children (childhood apraxia of speech) and adults (acquired apraxia of speech) who have (prior to the onset of apraxia) acquired some level of speaking ability. AOS affects an individual's volitional speech and is typically the result of a stroke, tumor, or other known neurological illness or injury. Apraxia may be accompanied by a language disorder called aphasia. Symptoms of AOS include inconsistent articulatory errors, groping oral movements to locate the correct articulatory position, and increasing errors with increasing word and phrase length. Individuals with apraxia of speech know what words they want to say, but their brains have difficulty coordinating the muscle movements necessary to say all the sounds in the words.

Patients with apraxia find that vowels are easier to produce than consonants. Single consonants are easier than blends. As in stuttering, final consonants are easier than those in the initial position. This may occur because initial consonants are affected by anticipatory errors. Also, perhaps once a person with apraxia

begins speech with the production of a vowel, production continues in a more automatic fashion. Fricative and affricates are the most difficult phonemes for apraxics to produce. AOS often co-occurs with Oral Apraxia, which is the inability to perform volitional tasks with the oral structures not involving speech. Some of these tasks might include coughing, puckering the lips, and smiling. AOS also often co-occurs with Limb Apraxia. Developmental verbal dyspraxia presents in children who have no evidence of difficulty with strength or range of motion of the articulators, but are unable to execute speech movements because of motor planning and coordination problems.

Causes

Apraxia is caused by damage to the brain. When apraxia develops in a person who was previously able to perform the tasks or abilities, it is called acquired apraxia.

The very common causes of acquired apraxia are:
- Brain tumor
- Condition that causes gradual worsening of the brain and nervous system (neurodegenerative illness)
- Dementia
- Stroke
- Traumatic brain injury

Apraxia may also be seen at birth. Symptoms appear as the child grows and develops. The cause is unknown. Apraxia of speech is often present along with another speech disorder called aphasia. Depending on the cause of apraxia, a number of other brain or nervous system problems may be present.

Apraxia is most often due to a lesion located in the left hemisphere of the brain, typically in the frontal and parietal lobes. Lesions may be because of stroke, acquired brain injuries, or neurodegenerative diseases such as Alzheimer's disease or other dementias, Parkinson's disease, or Huntington's disease. It is also possible for apraxia to be caused by lesions in other areas of the brain including the right hemisphere. Ideomotor apraxia is typically

due to a decrease in blood flow to the left hemisphere of the brain and particularly the parietal and premotor areas. It is frequently seen in patients with corticobasal degeneration.

Ideational apraxia often results in functional impairments in activities of daily living (ADLs) similar to those seen with late stage dementia. In very recent past, it has been observed in patients with lesions in the left hemisphere near areas associated with aphasia; however, more research is needed on ideational apraxia due to brain lesions. The localization of lesions in areas of the frontal and temporal lobes would provide explanation for the difficulty in motor planning seen in ideational apraxia as well as its difficulty to distinguish it from certain aphasias.

Constructional apraxia is generally caused by lesions of the inferior right parietal lobe, and can be caused by brain injury, illness, tumor or other condition that can result in a brain lesion.

Diagnosis

Although qualitative and quantitative studies exist, there is little consensus on the proper method to assess for apraxia. The criticisms of past methods include failure to meet standard psychometric properties as well as research-specific designs that translate poorly to non-research use. The Test to Measure Upper Limb Apraxia (TULIA) is one method of determining upper limb apraxia through the qualitative and quantitative assessment of gesture production. In contrast to previous publications on apraxic assessment, the reliability and validity of TULIA was thoroughly investigated.

The TULIA consists of subtests for the imitation and pantomime of non-symbolic ("put your index finger on top of your nose"), intransitive ("wave goodbye") and transitive ("show me how to use a hammer") gestures.Discrimination (differentiating between well- and poorly performed tasks) and recognition (indicating which object corresponds to a pantomimed gesture) tasks are also often tested for a full apraxia evaluation. However, there may not be a strong correlation between formal test results and actual

performance in everyday functioning or activities of daily living (ADLs).

A comprehensive assessment of apraxia should include formal testing, standardized measurements of ADLs, observation of daily routines, self-report questionnaires and targeted interviews with the patients and their relatives. As said above, apraxia should not be confused with aphasia, however they are frequently accompanied with each other. It has been said that apraxia is so often accompanied by aphasia that many believe that if a person displays AOS; it should be assumed that the patient also has some level of aphasia.

Treatment

People with apraxia may benefit from treatment by a health care team. The team should also include family members. Occupational and speech therapists may help both patients and their caregivers learn ways to deal with the apraxia. Because patients with apraxia have trouble following instructions, therapists who are experienced in treating this disorder may have better results.

Speech and language treatment may include:
- Repeating sounds over and over to teach mouth movements
- Slowing down the person's speech
- Teaching different techniques to help with communication

Recognition and treatment of depression is important for people with severe speech and language disorders.

Other tips:
- Maintain a relaxed, calm environment.
- Take time to show someone with apraxia how to do a task, and allow enough time for them to do so. Do not ask them to repeat the task if they are clearly struggling with it and doing so will increase frustration.
- Suggest alternative ways to do the same things. For example, try a hook and loop closure instead of laces for shoes.

When speech apraxia is present:
- Avoid giving complex directions.
- Use simple phrases to avoid misunderstandings.
- Speak in a normal tone of voice. Speech apraxia is not a hearing problem.
- Do not assume that the person understands.
- Provide communication aids, if possible, depending on the person and condition.

Treatment for individuals with apraxia includes speech therapy, occupational therapy, and physical therapy. Yet, treatments for apraxia have received little attention for several reasons, including the tendency for the condition to resolve spontaneously in acute cases. Besides, the very nature of the automatic-voluntary dissociation of motor abilities that defines apraxia means that patients may still be able to automatically perform activities if cued to do so in daily life. Nevertheless, research shows that patients experiencing apraxia have less functional independence in their daily lives, and that evidence for the treatment of apraxia is scarce. However, a literature review of apraxia treatment to date reveals that although the field is in its early stages of treatment design, certain aspects can be included to treat apraxia.

One method is through rehabilitative treatment, which has been found to positively impact apraxia, as well as activities of daily living. In this review, rehabilitative treatment consisted of 12 different contextual cues, which were used in order to teach patients how to produce the same gesture under different contextual situations. Extra studies have also recommended varying forms of gesture therapy, whereby the patient is instructed to make gestures (either using objects or symbolically meaningful and non-meaningful gestures) with progressively less cuing from the therapist. It may be necessary for patients with apraxia to use a form of alternative and augmentative communication depending on the severity of the disorder. Beside to using gestures as mentioned, patients can also use communication boards or more

sophisticated electronic devices if needed. No single type of therapy or approach has been proven as the best way to treat a patient with apraxia, since each patient's case varies. However, one-on-one sessions usually work the best, with the support of family members and friends. Since everyone responds to therapy differently, some patients will make significant improvements, while others will make less progress. The overall aim for treatment of apraxia is to treat the motor plans for speech, not treating at the phoneme (sound) level.

DEMENTIA

Dementia is not a specific disease. It's an overall term that describes a wide range of symptomsassociated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities.Alzheimer's disease accounts for 60 to 80 percent of cases.Vascular dementia, which occurs after a stroke, is the second most common dementia type. But there are several other conditions that can cause symptoms of dementia, including some that are reversible, like thyroid problems and vitamin deficiencies. Dementia is often incorrectly referred to as "senility" or "senile dementia," which reflects the formerly widespread but incorrect belief that serious mental decline is a normal part of aging.

Dementia, also known as senility, is a broad category of brain diseases that cause a long term and often gradual decrease in the ability to think and remember that is great enough to affect a person's daily functioning. Other common symptoms include emotional problems, problems with language, and a decrease in motivation. A person's consciousness is not affected. A dementia diagnosis needs a change from a person's usual mental functioning and a greater decline than one would expect due to aging. These diseases also have a significant effect on a person's caregivers. The most common type of dementia is Alzheimer's disease, which makes up 50% to 70% of cases. Other common types includevascular dementia (25%), Lewy body dementia (15%), and

frontotemporal dementia. Less common causes needs normal pressure hydrocephalus, Parkinson's disease, syphilis, and Creutzfeldt–Jakob disease among others.

More than one type of dementia may exist in the same person. A small proportion of cases run in families. In the DSM-5, dementia was reclassified as a neurocognitive disorder, with various degrees of severity. Diagnosis is generally based on history of the illness and cognitive testing with medical imaging and blood work used to rule out other possible causes. The mini mental state examination is one commonly used cognitive test.

Efforts to prevent dementia include trying to decrease risk factors such as high blood pressure, smoking, diabetes, and obesity. Screening the general population for the disease is not recommended. There is no cure for dementia. Cholinesterase inhibitors such as donepezil are often used and may be beneficial in mild to moderate disease. Overall benefit, however, may be minor. For people with dementia and those who care for them many measures can improve their lives. Cognitive and behavioural interventions may be appropriate.

Educating and providing emotional support to the caregiver is important. Exercise programs are beneficial with respect to activities of daily living and potentially improve outcomes. Treatment of behavioural problems or psychosis due to dementia with antipsychotics is common but not usually recommended due to there often being little benefit and an increased risk of death. Globally, dementia affects 36 million people. About 10% of people develop the disease at some point in their lives. It becomes more common with age. About 3% of people between the ages of 65–74 have dementia, 19% between 75 and 84 and nearly half of those over 85 years of age. In 2013 dementia resulted in about 1.7 million deaths up from 0.8 million in 1990. As more people are living longer, dementia is becoming more common in the population as a whole. For people of a specific age, however, it may be becoming less frequent, at least in the developed world, due to a decrease in risk factors. It is one of the most common causes of disability

among the old. It is believed to result in economic costs of 604 billion USD a year. People with dementia are often physically or chemically restrained to a greater degree than necessary, raising issues of human rights. Social stigma against those affected is common.

Signs and symptoms

The symptoms of dementia are of different types and stages of the diagnosis. The most common affected areas include memory, visual-spatial, language, attention and problem solving. Most types of dementia are slow and progressive.

By the time the person shows signs of the disease, the process in the brain has been happening for a long time. It is possible for a patient to have two types of dementia at the same time. About 10% of people with dementia have what is known as *mixed dementia*, which is usually a combination of Alzheimer's disease and another type of dementia such as frontotemporal dementia or vascular dementia. Additional psychological and behavioural problems that often affect people who have dementia comprise:

- Balance problems
- Tremor
- Speech and language difficulty
- Trouble eating or swallowing
- Memory distortions (believing that a memory has already happened when it has not, thinking an old memory is a new one, combining two memories, or confusing the people in a memory)
- Wandering or restlessness
- Perception and visual problems
- *Behavioural and psychological symptoms of dementia* (BPSD) almost always occur in all types of dementia. BPSDs may manifest as:
- Agitation
- Depression
- Anxiety

- Abnormal motor behaviour
- Elated mood
- Irritability
- Apathy
- Disinhibition and impulsivity
- Delusions (often believing people are stealing from them) or hallucinations
- Changes in sleep or appetite.

When people with dementia are put in circumstances beyond their abilities, there may be a sudden change to crying or anger (a *"catastrophic reaction"*). Depression affects 20–30% of people who have dementia, and about 20% have anxiety. Psychosis (often delusions of persecution) and agitation/aggression also often accompany dementia. Each of these must be assessed and treated independently of the underlying dementia.

Mild cognitive impairment

In the first stages of dementia, the signs and symptoms of the disease may be subtle. Often, the early signs of dementia only become apparent when looking back in time. The earliest stage of dementia is called mild cognitive impairment (MCI). 70% of those diagnosed with MCI progress to dementia at some point. In MCI, changes in the person's brain have been happening for a long time, but the symptoms of the disease are just beginning to show. These problems, however, are not yet severe enough to affect the person's daily function. If they do, it is considered dementia. A

person with MCI scores between 27 and 30 on the Mini-Mental State Examination (MMSE), which is a normal score. They may have some memory trouble and trouble finding words, but they solve everyday problems and handle their own life affairs well.

Early stages

In the early stage of dementia, the person begins to show symptoms noticeable to the people around them. In addition, the

symptoms begin to interfere with daily activities. The person usually scores between a 20 and 25 on the MMSE. The symptoms are dependent on the type of dementia a person has. The person may initiate to have difficulty with more complicated chores and tasks around the house. The person can usually still take care of him or herself but may forget things like taking pills or doing laundry and may need prompting or reminders. The symptoms of early dementia usually include memory difficulty, but can also include some word-finding problems (anomia) and problems with planning and organizational skills (executive function).

One very good way of assessing a person's impairment is by asking if he or she is still able to handle his/her finances independently. This is often one of the first things to become problematic. Other signs might be getting lost in new places, repeating things, personality changes, social withdrawal and difficulties at work. When evaluating a person for dementia, it is important to consider how the person was able to function five or ten years earlier. It is also important to consider a person's level of education when assessing for loss of function. For instance, an accountant who can no longer balance a checkbook would be more concerning than a person who had not finished high school or had never taken care of his/her own finances.

In Alzheimer's dementia the most prominent early symptom is memory difficulty. Others include word-finding problems and getting lost. In other kinds of dementia, like dementia with Lewy bodies and fronto-temporal dementia, personality changes and difficulty with organization and planning may be the first signs.

Middle stages

As dementia progresses, the symptoms first experienced in the early stages of the dementia generally worsen. The rate of decline is different for each person. A person with moderate dementia scores between 6-17 on the MMSE. For instance, people with Alzheimer's dementia in the moderate stages lose almost all new information very quickly. Dementia sufferers may be severely

impaired in solving problems, and their social judgment is generally also impaired. They cannot generally function outside their own home, and generally should not be left alone. They may be able to do simple chores around the house but not much else, and begin to require assistance for personal care and hygiene other than simple reminders.

Late stages

People with late-stage dementia typically turn increasingly inward and need assistance with most or all of their personal care. Persons with dementia in the late stages generally need 24-hour supervision to ensure personal safety, as well as to ensure that basic needs are being met. If left unsupervised, a person with late-stage dementia may wander and fall, may not recognize common dangers around them such as a hot stove, may not realize that they need to use the bathroom or become unable to control their bladder or bowels (incontinent).

Changes in eating frequently occur, and those with late-stage dementia often need pureed diets, thickened liquids, and assistance in eating. Their appetite may decline to the point that the person does not want to eat at all. He or she may not want to get out of bed, or may need complete assistance doing so. They may no longer recognize familiar people. He or she may have significant changes in sleeping habits or have trouble sleeping at all.

Causes

Dementia is caused by damage to brain cells. This damage interferes with the ability of brain cells to communicate with each other. When brain cells cannot communicate normally, thinking, behaviour and feelings can be affected. The brain has many distinct regions, each of which is responsible for different functions (for example, memory, judgment and movement). When cells in a particular region are damaged, that region cannot carry out its functions normally.

Various kinds of dementia are associated with particular types of brain cell damage in particular regions of the brain. For example,

in Alzheimer's disease, high levels of certain proteins inside and outside brain cells make it hard for brain cells to stay healthy and to communicate with each other.

The brain region called the hippocampus is the center of learning and memory in the brain, and the brain cells in this region are often the first to be damaged.

That's why memory loss is generally one of the earliest symptoms of Alzheimer's. While most changes in the brain that cause dementia are permanent and worsen over time, thinking and memory problems caused by the following conditions may improve when the condition is treated or addressed:

- Depression
- Medication side effects
- Excess use of alcohol
- Thyroid problems
- Vitamin deficiencies

Reversible causes

There are four main causes of easily reversible dementia: hypothyroidism, vitamin B12 deficiency, Lyme disease, and neurosyphillis. All people with memory difficulty should be checked for hypothyroidism and B12 deficiency.

For Lyme disease and neurosyphilis, testing should be done if there are risk factors for those diseases in the person.

Alzheimer's disease

Alzheimer's disease accounts for up to 50% to 70% of cases of dementia. The most common symptoms of Alzheimer's disease are short-term memory loss and word-finding difficulties.

People with Alzheimer's also have trouble with visual-spatial areas (for instance they may begin to get lost often), reasoning, judgment, and insight. Insight refers to whether or not the person realizes he/she has memory problems. Common early symptoms of Alzheimer's include repetition, getting lost, difficulties keeping

track of bills, problems with cooking especially new or complicated meals, forgetting to take medication, and word-finding problems.
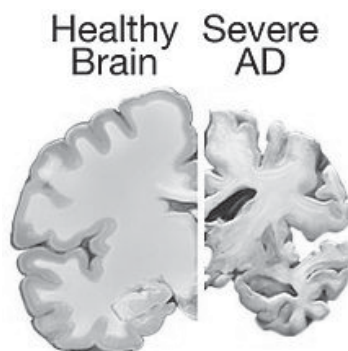
Fig. Brain atrophy in severe Alzheimer's

The part of the brain most affected by Alzheimer's is the hippocampus. Other parts of the brain that show shrinking (atrophy) comprise thetemporal and parietal lobes. Although this pattern suggests Alzheimer's, the brain shrinkage in Alzheimer's disease is very variable, and a scan of the brain cannot actually make the diagnosis. The relationship between undergoing anesthesia and AD is unclear.

Vascular dementia

Vascular dementia is the cause of at least 20% of dementia cases, making it the second most common cause of dementia. It is caused by disease or injury to blood vessels that damage the brain, including strokes. The symptoms of this dementia depend on where in the brain the strokes have occurred and whether the vessels are large or small.

Multiple injuries can cause progressive dementia over time, while a single injury located in an area critical for cognition (i.e. hippocampus, thalamus) can lead to sudden cognitive decline.

On scans of the brain, a person with vascular dementia may show evidence of multiple different strokes of different sizes. They tend to have risk factors for artery disease such as tobacco smoking, high blood pressure, atrial fibrillation, high cholesterol

or diabetes, or other signs of blood vessel disease such as a previous heart attack or angina.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is a dementia that has the main symptoms of visual hallucinations and "Parkinsonism." Parkinsonism is a term that describes a person with features of Parkinson's disease. This comprises tremor, rigid muscles, and a face without emotion.

The visual hallucinations in DLB are generally very vivid hallucinations of people and/or animals and they often occur when someone is about to fall asleep or just waking up. Other prominent symptoms include problems with attention, organization, problem solving and planning (executive function), and difficulty with visual-spatial function. Again, imaging studies cannot necessarily make the diagnosis of DLB, but some signs are particularly common. A person with DLB oftens show occipital hypoperfusion onSPECT scan or occipital hypometabolism on a PET scan.

Generally, a diagnosis of DLB is straightforward and unless it is complicated, a brain scan is not always necessary.

Frontotemporal dementia

Frontotemporal dementia (FTD) is a dementia that is characterized by drastic personality changes and language difficulties. In all FTD, the person has a relatively early social withdrawal and early lack of insight into the disease. Memory problems are not a main feature of this disease. There are three main types of FTD. The first has significant symptoms in the area of personality and behaviour. This is called behavioural variant FTD (bv-FTD) and is the most common. In bv-FTD, the person shows a change in personal hygiene, becomes rigid in their thinking, and rarely recognize that there is a problem, they are socially withdrawn, and often have a drastic increase in appetite. They may also be socially inappropriate. For instance, they may make

inappropriate sexual comments, or may begin using pornography openly when they had not before. One of the most common signs is apathy, or not caring about anything. Apathy, however, is a common symptom in many different dementias.

The other two types of FTD feature language problems as the main symptom. The second type is called semantic dementia or temporal variant dementia (TV-FTD). The main feature of this is the loss of the meaning of words. It may begin with difficulty naming things. The person eventually may also lose the meaning of objects as well. For instance, a drawing of a bird, dog, and an airplane in someone with FTD may all appear just about the same. In a classic test for this, a patient is shown a picture of a pyramid and below there is a picture of both a palm tree and a pine tree. The person is asked to say which one goes best with the pyramid. In TV-FTD the person would not be able to answer that question. The last type of FTD is called progressive non-fluent aphasia (PNFA). This is mainly a problem with producing speech. They have trouble finding the right words, but mostly they have a difficulty coordinating the muscles they need to speak. Eventually, someone with PNFA only uses one-syllable words or may become totally mute. With both TV-FTD and PNFA the symptoms of behaviour may be present, but milder and later than in bv-FTD. imaging studies show shrinking of the frontal and temporal lobes of the brain.

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is a form of dementia that is characterized by problems with eye movements. Generally the problems begin with difficulty moving the eyes up and/or down (vertical gaze palsy). Since difficulty moving the eyes upward can sometimes happen in normal aging, problems with downward eye movements are the key in PSP.

Other key symptoms of PSP include falls backwards, balance problems, slow movements, rigid muscles, irritability, apathy, social withdrawal, and depression. The person may also have

certain "frontal lobe signs" such as perseveration, a grasp reflex and utilization behaviour (the need to use an object once you see it). People with PSP often have progressive difficulty eating and swallowing, and eventually with talking as well.

Because of the rigidity and slow movements, PSP is sometimes misdiagnosed as Parkinson's disease. On scans of the brain, the midbrain of people with PSP is generally shrunken (atrophied), but there are no other common brain abnormalities visible on images of the person's brain.

Corticobasal Degeneration

Corticobasal degeneration is a rare form of dementia that is characterized by many different types of neurological problems that get progressively worse over time. This is because the disease affects the brain in many different places, but at different rates. One common sign is difficulty with using only one limb. One symptom that is extremely rare in any condition other than corticobasal degeneration is the "alien limb." The alien limb is a limb of the person that seems to have a mind of its own, it moves without control of the person's brain.

Other common symptoms include jerky movements of one or more limbs (myoclonus), symptoms that are different in different limbs (asymmetric), difficulty with speech that is due to not being able to move the mouth muscles in a coordinated way, numbness and tingling of the limbs and neglecting one side of the person's vision or senses. In neglect, a person ignores the opposite side of the body from the one that has the problem. For example, a person may not feel pain on one side, or may only draw half of a picture when asked. Besides, the person's affected limbs may be rigid or have muscle contractions causing strange repetitive movements (dystonia).

The area of the brain most often affected in corticobasal degeneration is the posterior frontal lobe and parietal lobe. Still, several other part of the brain can be affected.

Rapidly progressive

Creutzfeldt-Jakob disease typically causes a dementia that worsens over weeks to months, being caused by prions. The common causes of slowly progressive dementia also sometimes present with rapid progression: Alzheimer's disease, dementia with Lewy bodies, frontotemporal lobar degeneration (including corticobasal degeneration andprogressive supranuclear palsy). On the other hand, encephalopathy or delirium may develop relatively slowly and resemble dementia.

Possible causes include brain infection (viral encephalitis, subacute sclerosing panencephalitis, Whipple's disease) or inflammation (limbic encephalitis, Hashimoto's encephalopathy, cerebral vasculitis); tumors such as lymphoma or glioma; drug toxicity (e.g., anticonvulsant drugs); metabolic causes such as liver failure or kidney failure; and chronic subdural hematoma.

Other conditions

There are many other medical and neurological conditions in which dementia only occurs late in the illness. For example, a proportion of patients with Parkinson's diseasedevelop dementia, though widely varying figures are quoted for this proportion. When dementia occurs in Parkinson's disease, the underlying cause may bedementia with Lewy bodies or Alzheimer's disease, or both.

Cognitive impairment also occurs in the Parkinson-plus syndromes of progressive supranuclear palsy andcorticobasal degeneration (and the same underlying pathology may cause the clinical syndromes of frontotemporal lobar degeneration). Chronic inflammatory conditions of the brain may affect cognition in the long term, including Behçet's disease, multiple sclerosis, sarcoidosis, Sjögren's syndrome, and systemic lupus erythematosus.

Although the acute porphyrias may cause episodes of confusion and psychiatric disturbance, dementia is a rare feature of these rare diseases.

Apart from those mentioned above, inherited conditions that can cause dementia (alongside other symptoms) include:

- Alexander disease
- Canavan disease
- Cerebrotendinous xanthomatosis
- Dentatorubral-pallidoluysian atrophy
- Epilepsy
- Fatal familial insomnia
- Fragile X-associated tremor/ataxia syndrome
- Glutaric aciduria type 1
- Krabbe's disease
- Maple syrup urine disease
- Niemann Pick disease type C
- Neuronal ceroid lipofuscinosis
- Neuroacanthocytosis
- Organic acidemias
- Pelizaeus-Merzbacher disease
- Urea cycle disorders
- Sanfilippo syndrome type B
- Spinocerebellar ataxia type 2

Mild Cognitive Impairment

Mild cognitive impairment basically means that the person exhibits memory or thinking difficulties, but not severe enough yet for a dementia diagnoses. He or she should score between 25-30 on the MMSE. Around 70% of people with MCI go on to develop some form of dementia. MCI is generally divided into two categories. The first is one that is primarily memory loss (amnestic MCI). The second category is anything that is not primarily memory difficulties (non-amnestic MCI). People with primarily memory problems generally go on to develop Alzheimer's disease. People with the other type of MCI may go on to develop other types of dementia. Diagnosis of MCI is often difficult, as cognitive testing may be normal. Often, more in-depth neuropsychological testing is necessary to make the diagnosis. the

most commonly used criteria are called the Peterson criteria and include:

- Memory or other cognitive (thought-processing) complaint by the person or a person who knows the patient well.
- The person must have a memory or other cognitive problem as compared to a person of the same age and level of education.
- The problem must not be severe enough to affect the person's daily function.
- The person must not have dementia.

Fixed Cognitive Impairment

Different types of brain injury may cause irreversible cognitive impairment that do not get worse over time. Traumatic brain injury may cause generalized damage to the white matter of the brain (diffuse axonal injury), or more localized damage (as also may neurosurgery). A temporary reduction in the brain's supply of blood or oxygen may lead tohypoxic-ischemic injury. Strokes (ischemic stroke, or intracerebral, subarachnoid, subdural or extradural hemorrhage) or infections (meningitis and/or encephalitis) affecting the brain, prolonged epileptic seizures, and acute hydrocephalus may also have long-term effects on cognition. Excessive alcohol use may cause alcohol dementia, Wernicke's encephalopathy, and/or Korsakoff's psychosis.

Slowly Progressive

Dementia that begins gradually and worsens progressively over many years is generally caused by neurodegenerative disease—that is, by conditions that affect only or primarily the neurons of the brain and cause gradual but irreversible loss of function of these cells. Less commonly, a non-degenerative condition may have secondary effects on brain cells, which may or may not be reversible if the condition is treated.

Causes of dementia depend on the age when symptoms begin. In the elderly population (usually defined in this context as over 65 years of age), a large majority of dementia cases are caused by

Alzheimer's disease, vascular dementia, or both. Dementia with Lewy bodies is another commonly exhibited form, which again may occur alongside either or both of the other causes.

Hypothyroidism sometimes causes slowly progressive cognitive impairment as the main symptom, and this may be fully reversible with treatment. Normal pressure hydrocephalus, though relatively rare, is important to recognize since treatment may prevent progression and improve other symptoms of the condition. However, significant cognitive improvement is unusual. Dementia is much less common under 65 years of age. Alzheimer's disease is still the most frequent cause, but inherited forms of the disease account for a higher proportion of cases in this age group. Frontotemporal lobar degeneration and Huntington's disease account for most of the remaining cases. Vascular dementia also occurs, but this in turn may be due to underlying conditions (including antiphospholipid syndrome, CADASIL, MELAS, homocystinuria, moyamoya, and Binswanger's disease). People who receive frequent head trauma, such as boxers or football players, are at risk of chronic traumatic encephalopathy (also called dementia pugilistica in boxers). In young adults (up to 40 years of age) who were previously of normal intelligence, it is very rare to develop dementia without other features of neurological disease, or without features of disease elsewhere in the body.

Most cases of progressive cognitive disturbance in this age group are caused by psychiatric illness, alcohol or other drugs, or metabolic disturbance. However, certain genetic disorders can cause true neurodegenerative dementia at this age. These include familial Alzheimer's disease, SCA17 (dominantinheritance); adrenoleukodystrophy (X-linked); Gaucher's disease type 3, metachromatic leukodystrophy, Niemann-Pick disease type C, pantothenate kinase-associated neurodegeneration, Tay-Sachs disease, and Wilson's disease (all recessive). Wilson's disease is particularly important since cognition can improve with treatment. At all ages, a substantial proportion of patients who complain of memory difficulty or other cognitive symptoms have depression

rather than a neurodegenerative disease. Vitamin deficiencies and chronic infections may also occur at any age; they usually cause other symptoms before dementia occurs, but occasionally mimic degenerative dementia. These include deficiencies of vitamin B_{12}, folate, or niacin, and infective causes including cryptococcal meningitis, HIV, Lyme disease, progressive multifocal leukoencephalopathy, subacute sclerosing panencephalitis, syphilis, and Whipple's disease.

DIAGNOSIS

There is no one test to determine if someone has dementia. Doctors diagnose Alzheimer's and other types of dementia based on a careful medical history, a physical examination, laboratory tests, and the characteristic changes in thinking, day-to-day function and behaviour associated with each type. Doctors can determine that a person has dementia with a high level of certainty. But it's harder to determine the exact type of dementia because the symptoms and brain changes of different dementias can overlap. In some cases, a doctor may diagnose "dementia" and not specify a type. If this occurs it may be necessary to see a specialist such as a neurologist or gero-psychologist. There are many specific types and causes of dementia, generaly showing slightly different symptoms. However, the symptoms are very similar and it is usually difficult to diagnose the type of dementia by symptoms alone.

Diagnosis may be aided by brain scanning techniques. In many cases, the diagnosis cannot be absolutely sure except with a brain biopsy, but this is very rarely recommended (though it can be performed at autopsy). In those who are getting older, general screening for cognitive impairment using cognitive testing or early diagnosis of dementia has not been shown to improve outcomes. However, it has been shown that screening exams are useful in those people over the age of 65 with memory complaints. Normally, symptoms must be present for at least six months to support a diagnosis. Cognitive dysfunction of shorter duration is called

delirium. Delirium can be easily confused with dementia due to similar symptoms.

Delirium is characterized by a sudden onset, fluctuating course, a short duration (often lasting from hours to weeks), and is primarily related to a somatic (or medical) disturbance. In comparison, dementia has typically a long, slow onset (except in the cases of a stroke or trauma), slow decline of mental functioning, as well as a longer duration (from months to years). Some mental illnesses, including depression and psychosis, may produce symptoms that must be differentiated from both delirium and dementia. Therefore, any dementia evaluation should include a depression screening such as the Neuropsychiatric Inventory or the Geriatric Depression Scale. Physicians used to think that anyone who came in with memory complaints had depression and not dementia (because they thought that those with dementia are generally unaware of their memory problems). This is called pseudodementia.

However, in recent past researchers have realized that many older people with memory complaints in fact have MCI, the earliest stage of dementia. Depression should always remain high on the list of possibilities, however, for an elderly person with memory trouble.

Cognitive Testing

There are some brief tests (5–15 minutes) that have reasonable reliability to screen for dementia. While many tests have been studied, presently the mini mental state examination (MMSE) is the best studied and most commonly used, albeit some may emerge as better alternatives. Other instances include the abbreviated mental test score (AMTS), the,*Modified Mini-Mental State Examination* (3MS), the *Cognitive Abilities Screening Instrument* (CASI), the Trail-making test, and the clock drawing test.

The MOCA (Montreal Cognitive Assessment) is a very reliable screening test and is available online for free in 35 different languages. The MOCA has also been shown somewhat better at detecting mild cognitive impairment than the MMSE. Another

approach to screening for dementia is to ask an informant (relative or other supporter) to fill out a questionnaire about the person's everyday cognitive functioning. Informant questionnaires provide complementary information to brief cognitive tests. Probably the best known questionnaire of this sort is the *Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)*.

The Alzheimer's Disease Caregiver Questionnaire is another tool. It is about 90% accurate for Alzheimer's and can be completed online or in the office by a caregiver. On the other hand, the *General Practitioner Assessment Of Cognition* combines both, a patient assessment and an informant interview. It was specifically designed for the use in the primary care setting. Clinical neuropsychologists provide diagnostic consultation following administration of a full battery of cognitive testing, often lasting several hours, to determine functional patterns of decline associated with varying types of dementia.

Tests of memory, executive function, processing speed, attention, and language skills are relevant, as well as tests of emotional and psychological adjustment. These tests assist with ruling out other etiologies and determining relative cognitive decline over time or from estimates of prior cognitive abilities.

Laboratory tests

Routine blood tests are also generally performed to rule out treatable causes. These tests include vitamin B_{12}, folic acid, thyroid-stimulating hormone (TSH), C-reactive protein, full blood count, electrolytes, calcium, renal function, and liver enzymes.

Abnormalities may suggest vitamin deficiency, infection, or other problems that commonly cause confusion or disorientation in the elderly. The problem is complicated by the fact that these cause confusion more often in persons who have early dementia, so that "reversal" of such problems may ultimately only be temporary.

Testing for alcohol and other known dementia-inducing drugs may be indicated.

MRI (Scan) or Imaging

A CT scan or magnetic resonance imaging (MRI scan) is commonly performed, although these tests do not pick up diffuse metabolic changes associated with dementia in a person that shows no gross neurological problems (like paralysis or weakness) on neurological exam. CT or MRI may suggest normal pressure hydrocephalus, a potentially reversible cause of dementia, and can yield information relevant to other types of dementia, such as infarction (stroke) that would point at a vascular type of dementia. The functional neuroimaging modalities of SPECT and PET are more useful in assessing long-standing cognitive dysfunction, since they have shown similar ability to diagnose dementia as a clinical exam and cognitive testing.

The ability of SPECT to differentiate the vascular cause (i.e., multi-infarct dementia) from Alzheimer's disease dementias, appears superior to differentiation by clinical exam. Recent research has established the value of PET imaging using carbon-11 Pittsburgh Compound B as a radiotracer (PIB-PET) in predictive diagnosis of different kinds of dementia, in particular Alzheimer's disease. Studies from Australia have found PIB-PET 86% accurate in predicting which patients with mild cognitive impairment will develop Alzheimer's disease within two years.

In another study, carried out using 66 patients seen at the University of Michigan, PET studies using either PIB or another radiotracer, carbon-11 dihydrotetrabenazine (DTBZ), led to more accurate diagnosis for more than one-fourth of patients with mild cognitive impairment or mild dementia.

PREVENTION

Many prevention measures have been proposed, including lifestyle changes and medication, though none has been reliably shown effective. Among otherwise healthy older people, computerized cognitive training may improve memory. However it is not known if it prevents dementia.

Management

Except for the treatable types listed above, there is no cure. Cholinesterase inhibitors are generaly used early in the disease course; however, benefit is usually small.Cognitive and behavioural interventions may be appropriate. Educating and providing emotional support to the caregiver is of importance as well. Exercise programs are beneficial with respect to activities of daily living and potentially improve dementia.

Psychological therapies

Psychological therapies for dementia include music therapy with unclear evidence, temporary evidence for reminiscence therapy, some benefit for cognitive reframing for caretakers, unclear evidence for validation therapy, and tentative evidence for mental exercise. Adult daycare centers as well as special care units in nursing homes often provide specialized care for dementia patients.

Adult daycare centers offer supervision, recreation, meals, and limited health care to participants, as well as providing respite for caregivers. Besides, home care can provide one-on-one support and care in the home allowing for more individualized attention that is needed as the disease progresses.

Psychiatric nurses can make a distinctive contribution to people's mental health. Since dementia impairs normal communication due to changes in receptive and expressive language, as well as the ability to plan and problem solve, agitated behaviour is often a form of communication for the person with dementia. Actively searching for a potential cause, such as pain, physical illness, or overstimulation can be helpful in reducing agitation.

Besides, using an "ABC analysis of behaviour" can be a useful tool for understanding behaviour in people with dementia. It involves looking at the antecedents (A), behaviour (B), and consequences (C) associated with an event to help define the problem and prevent further incidents that may arise if the person's needs are misunderstood.

Medications

At present, no medications have been shown to prevent or cure dementia. Medications may be used to treat the behavioural and cognitive symptoms but have no effect on the underlying disease process. Acetylcholinesterase inhibitors, such as donepezil, may be useful for Alzheimer disease and dementia in Parkinson's, DLB, or vascular dementia. The quality of the evidence however is poor and the benefit is small. No difference has been shown between the agents in this family. In a minority of people side effects includebradycardia and syncope. As assessment for an underlying cause of the behaviour is a needed before prescribing antipsychotic medication for symptoms of dementia.

Antipsychotic drugs should be used to treat dementia only if non-drug therapies have not worked, and the person's actions threaten themselves or others. Aggressive behaviour changes are sometimes the result of other solvable problems, that could make treatment with antipsychotics unnecessary. Because people with dementia can be aggressive, resistant to their treatment, and otherwise disruptive, sometimes antipsychotic drugs are considered as a therapy in response. These drugs have risky adverse effects, including increasing the patient's chance of stroke and death. Generally, stopping antipsychotics for people with dementia does not cause problems, even in those who have been on them a long time. N-methyl-D-aspartate (NMDA) receptor blockers such as memantine may be of benefit but the evidence is less conclusive than for AChEIs. Becauses of their differing mechanisms of action memantine and acetylcholinesterase inhibitors can be used in combination however the benefit is slight.

Antidepressant drugs: Depression is frequently related to dementia and generally worsens the degree of cognitive and behavioural impairment. Antidepressants effectively treat the cognitive and behavioural symptoms of depression in patients with Alzheimer's disease, but evidence for their use in other forms of dementia is weak. It is recommended that benzodiazepines such as diazepam be avoided in dementia due to the risks of

increased cognitive impairment and falls. There is little evidence for the effectiveness in this population. There is no solid proof that folate or vitamin B12 improves outcomes in those with cognitive problems. Statins also have no benefit in dementia.

Pain

As people age, they experience more health problems, and most health problems associated with aging carry a substantial burden of pain; therefore, between 25% and 50% of older adults experience persistent pain. Seniors with dementia experience the same prevalence of conditions likely to cause pain as seniors without dementia. Pain is generally overlooked in older adults and, when screened for, often poorly assessed, especially among those with dementia since they become incapable of informing others that they're in pain. Beyond the issue of humane care, unrelieved pain has functional implications.

Persistent pain can lead to decreased ambulation, depressed mood, sleep disturbances, impaired appetite, and exacerbation of cognitive impairment, and pain-related interference with activity is a factor contributing to falls in the elderly. Although persistent pain in the person with dementia is difficult to communicate, diagnose, and treat, failure to address persistent pain has profound functional, psychosocial, and quality of life implications for this vulnerable population. Health professionals generally lack the skills and generally lack the time needed to recognize, accurately assess, and adequately monitor pain in people with dementia. Family members and friends can make a valuable contribution to the care of a person with dementia by learning to recognize and assess their pain. Educational resources (such as the Understand Pain and Dementia tutorial) and observational assessment tools are available.

Eating difficulties

Persons with dementia may have difficulty eating. Whenever it is available as an option, the recommended response to eating problems is having a caretaker do assisted feeding for the person.

A secondary option for people who cannot swallow effectively is to consider gastrostomy feeding tube placement as a way to give nutrition. However, in bringing person comfort and keeping functional status while lowering risk of aspiration pneumonia and death, assistance with oral feeding is at least as good as tube feeding. Tube-feeding is related to agitation, increased use of physical and chemical restraints, and worsening pressure ulcers. Tube feedings may also cause fluid overload, diarrhea, abdominal pain, local complications, less human interaction, and may increase the risk of aspiration. Benefits of this procedure in those with advanced dementia has not been shown. The risks of using tube feeding include agitation, the person pulling out the tube or otherwise being physically or chemically immobilized to prevent them from doing this, or getting pressure ulcers. There is about a 1% fatality rate directly related to the procedurewith a 3% major complication rate.

Alternative medicine

Other therapies that have been studied for effectiveness comprise aromatherapy with slight evidence, massage with unclear evidence.

Palliative care

Given the progressive and terminal nature of dementia, palliative care can be helpful to patients and their caregivers by helping both people with the disease and their caregivers understand what to expect, deal with loss of physical and mental abilities, plan out a patient's wishes and goals comprising surrogate decision making, and discuss wishes for or against CPR and life support. Because the decline can be rapid, and because most people prefer to allow the person with dementia to make his or her own decisions, palliative care involvement before the late stages of dementia is recommended.

4

Neurophysiology

The subject has been studied for thousands of years. For example, Hippocrates studied it, in part in conjunction with epilepsy. He correctly determined that epilepsy had its origin in the brain. He also theorized that the brain was involved in all kinds of bodily sensation. Jumping ahead several thousand years, Galen theorized that human thought occurred in the brain. He was right, too. Thereafter, many other scientists conjectured and determined that the brain was the prime mover in virtually all aspects of the human condition.

Neurophysiology is a medical specialty that focuses on the relationship between the brain and the peripheral nervous system. As its name implies, neurophysiology is in various ways a melding of neurology, which is the study of the human brain and its functions, and physiology, which is the study of the sum of the body's parts and how they interrelate. Neurophysiologists examine the many ways in which brain activities impact nervous system activities.

Much of the field's work is investigative, with doctors seeking to understand the origins of and best treatments for a variety of neurological disorders. There are two parts to the human nervous system: the central nervous system, which is the brain and spinal cord, and the peripheral nervous system, which is the network of nerves that extends throughout the entire body. Nerves are

responsible for sensitivity and feeling, but also muscle health and control. Neurophysiology examines the relationship between the two systems in causing degenerative diseases like multiple sclerosis and Parkinson's disease, as well as neurological disorders like epilepsy.

Neurophysiology is a branch of physiology that focuses on the study of the central nervous system (CNS). While physiology is the broad study of the mechanisms of how cells, muscles and organs work together and how they interact, neurophysiology is much narrower.

One of the main diagnostic tools used in neurophysiology is electroencephalography (EEG). The original tool, while later refined and augmented by other tools, was originally developed in 1929 by German psychiatrist, Hans Berger. It was a milestone in the development of neuroscience and in the practice of neurology, specially related to epilepsy.

Generally, the EEG is a direct measure of electrical energies in the brain. It is generally recorded at the scalp surface and reflects the moment-to-moment electrical activity of the brain.

The electrical activity is produced by the synaptic currents that arise on the dendrites and cell bodies of billions of cortical cells that are usually only a few centimeters below the scalp.

It can also be a measure of damage of electrical networks in the brain that are disturbed by traumatic brain injuries (TBI). The most consistent findings in this regard are:

- Reduced power in the higher frequency bands (8-49 Hz) which is directly related to the degree of injury to cortical gray matter of the brain. The gray matter routes sensory or motor stimuli to the central nervous system to create a response to the stimulus through chemical synaptic activity;
- Increased slow waves in the delta frequency bands (1-4 Hz) occurs in the more severe cases of TBI. This is directly related to the magnitude of damage to the cerebral white

matter as the increase in delta waves are often associated with, inter alia, certain neurological disorders;

- Changes in delta frequency bands and EEG phase delays that are directly related to both the gray and the white matter, especially when the temporal and frontal lobes are involved.

Clinical and validation studies performed on EEG results have shown a high correlation between them and clinical measures such as neuropsychological test performance, Glasgow coma scores, length of coma and MRI biophysical measures.

There are several other tests that are associated with the field of neurophysiology. These comp0rise:

- Nerve conduction study: Measures electrical signals in the nerves, primarily in the arms and legs. Small electrical shocks are administered to the skin over the nerve. It is typically done to determine if there is damage to the peripheral nervous system, that includes all nerves that lead away from the brain and spinal cord and the smaller nerves that branch out from the main nerves;

- Electromyogram (EMG): Measures the activity of muscles while at rest and while contracted and in so doing, measured how fast the nerves send electrical messages to the brain. While the test does not show brain or spinal cord disease, it is useful in finding the cause of paralysis or weakness, or diseases of muscles, nerves or the junction of them.

When the brain, its constituent parts and those parts of the body that directly and indirectly interact with it work and connect properly, usually all is well. However, when traumatic brain injuries, spinal cord injuries, strokes and various other difficult and challenging diagnoses arise after acute intervention, neurobehavioural and specialized neurorehabilitative services and other clinically relevant types of care are needed to restore the independence of the client. These can include post-acute care, residential services or assistance with supported living.

HISTORICAL BACKGROUND

Neurophysiology has been a subject of study since as early as 4,000 B.C. In the early B.C. years, most studies were of different natural sedatives like alcohol and poppy plants. In 1700 B.C., the Edwin Smith surgical papyrus was written. This papyrus was crucial in understanding how the ancient Egyptians understood the nervous system. This papyrus looked at different case studies about injuries to various parts of the body, most notably the head.

Beginning around 460 B.C., Hippocrates began to study epilepsy, and theorized that it had its origins in the brain. Hippocrates also theorized that the brain was involved in sensation, and that it was where intelligence was derived from. Hippocrates, as well as most ancient Greeks, believed that relaxation and a stress free environment was crucial in helping treat neurological disorders. In 280 B.C., Erasistratus of Chios theorized that there were divisions in the vestibular processing the brain, as well as deducing from observation that sensation was located there.

In 177 Galen theorized that human thought occurred in the brain, as opposed to the heart as Aristotle had theorized. The optic chiasm, which is crucial to the visual system, was discovered around 100 C.E. by Marinus. Circa 1000, Al-Zahrawi, living in Spain, started to write about different surgical treatments for neurological disorders. In 1216, the firstanatomy textbook in Europe, which included a description of the brain, was written by Mondino de'Luzzi. In 1402, St Mary of Bethlehem Hospital (later known as Bedlam in Britain) was the first hospital used exclusively for the mentally ill.

Leonardo da Vinci In 1504 continued his study of the human body with a wax cast of the human ventricle system. In 1536, Nicolo Massa described the effects of various diseases, such as syphilis on the nervous system. He also noticed that the ventricular cavities were filled with cerebrospinal fluid. In 1542, the term physiology was used for the first time by a French physician named Jean Fernal, to explain bodily function in relation to the

brain. In 1543, Andreas Vesalius wrote On the Workings of the Human Body, which revolutionized the study of anatomy. In this book, he described the pineal gland and what he believed the function was, and was able to draw the corpus striatum which is made up of the basal ganglia and the internal capsule.

In 1549, Jason Pratensis published De Cerebri Morbis. This book was devoted to neurological diseases, and discussed symptoms, as well as ideas from Galen and other Greek, Roman and Arabic authors. It also looked into the anatomy and specific functions of different areas. In 1550, Andreas Vesalius worked on a case of hydrocephalus, or fluid filling the brain. In the same year, Bartolomeo Eustachio studied the optic nerves, mainly focusing on their origins in the brain. In 1564, Giulio Cesare Aranzio discovered the hippocampus, naming it such due to its shape resemblance to a sea horse. In 1621, Robert Burton published The Anatomy of Melancholy, which looked at the loss of important characters in one's life as leading to depression. In 1649, René Descartesstudied the pineal gland. He mistakenly believed that it was the "soul" of the brain, and believed it was where thoughts formed.

In 1658, Johann Jakob Wepfer studied a patient in which he believed that a broken blood vessel had caused apoplexy, or a stroke. In 1749, David Hartley published Observations of Man, which focused on frame (neurology), duty (moral psychology) and expectations (spirituality) and how these integrated within one another. This text was also the first to use the English term "psychology". In 1752, the Society of Friends created an asylum in Philadelphia, Pennsylvania. This asylum was intended to give not only medical treatment to those mentally ill individuals, but also to provide them with caretakers and comfortable living conditions.

In 1755, J.B. Le Roy began using electroconvulsive therapy for the mentally ill, a treatment still used today in specific cases. In 1760, Arne-Charles studied how different lesions in thecerebellum could affect motor movements. In 1776, M.V.G. Malacarne studied

the cerebellum intensely, and published a book solely based on its function and appearance. In 1784, Félix Vicq-d'Azyr, discovered a black coloured structure in the midbrain. In 1791 Samuel Thomas von Sömmerring alluded to this structure, calling it the substantia nigra.

In 1808, Franz Joseph Gall studied and published work on phrenology. Phrenology was the faulty science of looking at head shape to determine various aspects of personality and brain function. In 1811, Julien Jean Legallois studied respiration in animal dissection and lesions and found the center of respiration in the medulla oblongata. In the same year, Charles Bell finished work on what would later become known as the Bell-Magendie law, which compared functional differences between dorsal and ventral roots of the spinal cord. In 1822, Friedrich Burdach distinguished between the lateral and medial geniculate bodies, as well as named the cingular gyrus. In 1824, F. Magendie studied and produced the first evidence of the cerebellum's role in equilibration to complete the Bell-Magendie law.

In 1838, Theodor Schwann began studying white and grey matter in the brain, and discovered the myelin sheath. These cells, which cover the axons of the neurons in the brain, are named Schwann cells after him. In 1848, Phineas Gage, the classical neurophysiology patient, had his brain pierced by an iron tamping rod in a blasting accident. He became an excellent case study in the connection between the prefrontal cortex and behaviour, decision making and consequences. In 1849, Hermann von Helmholtz studied the speed of frog nerve impulses while studying electricity in the body. While these are certainly not all the developments in neurophysiology before 1849, these developments were significant to the study of the brain and body.

NEURAL CORRELATES OF CONSCIOUSNESS

The Neuronal Correlates of Consciousness (NCC) constitute the smallest set of neural events and structures sufficient for a given conscious percept or explicit memory. This case involves

synchronized action potentials in neocortical pyramidal neurons. The neural correlates of consciousness (NCC) constitute the minimal set of neuronal events and mechanisms sufficient for a specific conscious percept. Neuroscientists use empirical approaches to discover neural correlates of subjective phenomena. The set should be *minimal* because, under the assumption that the brain is sufficient to give rise to any given conscious experience, the question is which of its components is necessary to produce it.

Neurobiological Approach to Consciousness

A science of consciousness must explain the proper relationship between subjective mental states and brain states, the nature of the relationship between the conscious mind and the electro-chemical interactions in the body. Progress in neurophilosophy has come from focusing on the body rather than the mind. In this perspective the neuronal correlates of consciousness may be viewed as its causes, and consciousness may be thought of as a state-dependent property of some undefined complex, adaptive, and highly interconnected biological system.Discovering and characterizing neural correlates does not offer a theory of consciousness that can explain how particular systems experience anything at all, or how and why they are associated with consciousness, the so-called hard problem of consciousness, but understanding the NCC may be a step toward such a theory.

Most neurobiologists assume that the variables giving rise to consciousness are to be found at the neuronal level, governed by classical physics, though a few scholars have proposed theories ofquantum consciousness based on quantum mechanics.

There is great explicit redundancy and parallelism in neural networks so, while activity in one group of neurons may correlate with a percept in one case, a different population might mediate a related percept if the former population is lost or inactivated. It may be that every phenomenal, subjective state has a neural correlate. Where the NCC can be induced artificially the subject will experience the associated percept, while perturbing or

inactivating the region of correlation for a specific percept will affect the percept or cause it to disappear, giving a cause-effect relationship from the neural region to the nature of the percept. What characterizes the NCC? What are the commonalities between the NCC for seeing and for hearing? Will the NCC involve all the pyramidal neurons in the cortex at any given point in time? Or only a subset of long-range projection cells in the frontal lobes that project to the sensory cortices in the back? Neurons that fire in a rhythmic manner? Neurons that fire in a synchronous manner? These are some of the proposals that have been advanced over the years. The growing ability of neuroscientists to manipulate neurons using methods from molecular biology in combination with optical tools (e.g., Adamantidis et al. 2007) depends on the simultaneous development of appropriate behavioural assays and model organisms amenable to large-scale genomic analysis and manipulation. It is the combination of such fine-grained neuronal analysis in animals with ever more sensitive psychophysical and brain imaging techniques in humans, complemented by the development of a robust theoretical predictive framework, that will hopefully lead to a rational understanding of consciousness, one of the central mysteries of life.

Level of Arousal and Content of Consciousness

There are two common but distinct dimensions of the term *consciousness*, one involving *arousal* and *states of consciousness* and the other involving *content of consciousness*and *conscious states*. To be conscious *of* anything the brain must be in a relatively high state of arousal (sometimes called *vigilance*), whether in wakefulness or REM sleep, vividly experienced in dreams although usually not remembered. Brain arousal level fluctuates in a circadian rhythm but may be influenced by lack of sleep, drugs and alcohol, physical exertion, etc.

Arousal can be measured behaviourally by the signal amplitude that triggers some criterion reaction (for example, the sound level necessary to evoke an eye movement or a head turn toward the sound source). Clinicians use scoring systems such as the Glasgow

Coma Scale to assess the level of arousal in patients. High arousal states are associated with conscious states that have specific content, seeing, hearing, remembering, planning or fantasizing about something. Different levels or states of consciousness are associated with different kinds of conscious experiences. The "awake" state is quite different from the "dreaming" state (for instance, the latter has little or no self-reflection) and from the state of deep sleep.

In all three cases the basic physiology of the brain is affected, as it also is in *altered states of consciousness*, for example after taking drugs or during meditation when conscious perception and insight may be enhanced compared to the normal waking state. Clinicians talk about *impaired states of consciousness* as in "the comatose state", "the persistent vegetative state" (PVS), and "the minimally conscious state" (MCS). Here, "state" refers to different "amounts" of external/physical consciousness, from a total absence in coma, persistent vegetative state and general anesthesia, to a fluctuating and limited form of conscious sensation in a minimally conscious state such as sleep walking or during a complex partial epileptic seizure. The repertoire of conscious states or experiences accessible to a patient in a minimally conscious state is comparatively limited. In brain death there is no arousal, but it is unknown whether the subjectivity of experience has been interrupted, rather than its observable link with the organism.

The potential *richness of conscious experience* appears to increase from deep sleep to drowsiness to full wakefulness, as might be quantified using notions from complexity theory that incorporate both the dimensionality as well as the granularity of conscious experience to give an integrated-information-theoretical account of consciousness. As behavioural arousal increases so does the range and complexity of possible behaviour. Yet in REM sleep there is a characteristic atonia, low motor arousal and the person is difficult to wake up, but there is still high metabolic and electric brain activity and vivid perception. Many nuclei with distinct chemical signatures in the thalamus, midbrain and pons must function for a subject to be in a sufficient state of brain arousal

to experience anything at all. These nuclei therefore belong to the enabling factors for consciousness. Conversely it is likely that the specific content of any particular conscious sensation is mediated by particular neurons in cortex and their associated satellite structures, including the amygdala, thalamus, claustrum and the basal ganglia.

The Neuronal Basis of Perception

The possibility of precisely manipulating visual percepts in time and space has made vision a preferred modality in the quest for the NCC. Psychologists have perfected a number of techniques – masking, binocular rivalry, continuous flash suppression, motion induced blindness, change blindness, inattentional blindness – in which the seemingly simple and unambiguous relationship between a physical stimulus in the world and its associated percept in the privacy of the subject's mind is disrupted. In particular a stimulus can be perceptually suppressed for seconds or even minutes at a time: the image is projected into one of the observer's eyes but is invisible, not seen. In this manner the neural mechanisms that respond to the subjective percept rather than the physical stimulus can be isolated, permitting visual consciousness to be tracked in the brain. In a *perceptual illusion*, the physical stimulus remains fixed while the percept fluctuates. The best known example is the *Necker cube* whose 12 lines can be perceived in one of two different ways in depth.
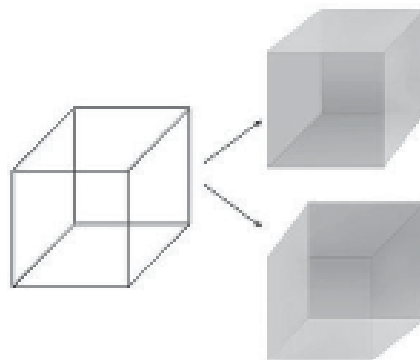
The Necker Cube: The left line drawing can be perceived in one of two distinct depth configurations shown on the right. Without any other cue, the visual system flips back and forth between these two interpretations.A perceptual illusion that can be precisely controlled is *binocular rivalry.*

Here, a small image, e.g., a horizontal grating, is presented to the left eye, and another image, e.g., a vertical grating, is shown to the corresponding location in the right eye. In spite of the constant visual stimulus, observers consciously see the horizontal grating alternate every few seconds with the vertical one. The brain does not allow for the simultaneous perception of both images.

Logothetis and colleagues recorded a number of visual cortical areas in awake macaque monkeys performing a binocular rivalry task. Macaque monkeys can be trained to report whether they see the left or the right image. The distribution of the switching times and the way in which changing the contrast in one eye affects these leaves little doubt that monkeys and humans experience the same basic phenomenon.

In the primary visual cortex (V1) only a small fraction of cells weakly modulated their response as a function of the percept of the monkey while most cells responded to one or the other retinal stimulus with little regard to what the animal perceived at the time. But in a high-level cortical area such as the inferior temporal cortex along the ventral stream almost all neurons responded only to the perceptually dominant stimulus, so that a "face" cell only fired when the animal indicated that it saw the face and not the pattern presented to the other eye.

This means that NCC involve neurons active in the inferior temporal cortex: it is likely that specific reciprocal actions of neurons in the inferior temporal and parts of the prefrontal cortex are necessary. Many of fMRI experiments that have exploited binocular rivalry and related illusions to identify the hemodynamic activity underlying visual consciousness in humans demonstrate quite

conclusively that BOLD activity in the upper stages of the ventral pathway (e.g., the fusiform face area and the parahippocampal place area) as well as in early regions, including V1 and the lateral geniculate nucleus (LGN), follow the percept and not the retinal stimulus. Further, a number of fMRI and DTI experiments suggest V1 is necessary but not sufficient for visual consciousness.

In a related perceptual phenomenon, *flash suppression*, the percept associated with an image projected into one eye is suppressed by flashing another image into the other eye while the original image remains. Its methodological benefit over binocular rivalry is that the timing of the perceptual transition is determined by an external trigger rather than by an internal event.

The majority of cells in the inferior temporal cortex and the superior temporal sulcus of monkeys trained to report their percept during flash suppression follow the animal's percept: when the cell's preferred stimulus is perceived, the cell responds.

If the picture is still present on the retina but is perceptually suppressed, the cell falls silent, even though primary visual cortex neurons fire. Single-neuron recordings in the medial temporal lobe of epilepsy patients during flash suppression likewise demonstrate abolishment of response when the preferred stimulus is present but perceptually masked.

Global Disorders of Consciousness

Given the absence of any accepted criterion of the minimal neuronal correlates necessary for consciousness, the distinction between a persistently vegetative patient who shows regular sleep-wave transitions and may be able to move or smile, and a minimally conscious patient who can communicate (on occasion) in a meaningful manner (for instance, by differential eye movements) and who shows some signs of consciousness, is often difficult.

In global anesthesia the patient should not experience psychological trauma but the level of arousal should be compatible with clinical exigencies.
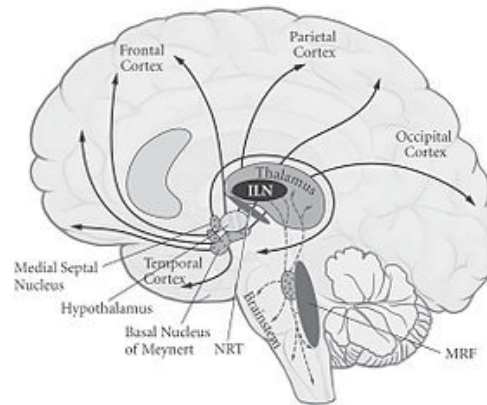
Midline structures in the brainstem and thalamus necessary to regulate the level of brain arousal. Small, bilateral lesions in many of these nuclei cause a global loss of consciousness.

Blood-oxygen-level-dependent fMRI (BOLD fMRI) have demonstrated normal patterns of brain activity in a patient in a vegetative state following a severe traumatic brain injury when asked to imagine playing tennis or visiting rooms in his/her house. Differential brain imaging of patients with such global disturbances of consciousness (including akinetic mutism) reveal that dysfunction in a widespread cortical network including medial and lateral prefrontal and parietal associative areas is associated with a global loss of awareness.

Impaired consciousness in epileptic seizures of the temporal lobe was likewise accompanied by a decrease in cerebral blood flow in frontal and parietal association cortex and an increase in midline structures such as the mediodorsal thalamus. Relatively local bilateral injuries to midline (paramedian) subcortical structures can also cause a complete loss of awareness. These structures therefore *enable* and control brain arousal (as determined by metabolic or electrical activity) and are necessary neural correlates.

One such example is the heterogeneous collection of more than two dozen nuclei on each side of the upper brainstem (pons,

midbrain and in the posterior hypothalamus), collectively referred to as the reticular activating system (RAS). Their axons project widely throughout the brain. These nuclei – three-dimensional collections of neurons with their own cyto-architecture and neurochemical identity – release distinct neuromodulators such as acetylcholine, noradrenaline/norepinephrine, serotonin, histamine and orexin/hypocretin to control the excitability of the thalamus and forebrain, mediating alternation between wakefulness and sleep as well as general level of behavioural and brain arousal. After such trauma, however, ultimately the excitability of the thalamus and forebrain can recover and consciousness can return. Another enabling factor for consciousness are the five or more intralaminar nuclei (ILN) of the thalamus. These receive input from many brainstem nuclei and project strongly, directly to the basal ganglia and, in a more distributed manner, into layer I of much of the neocortex. Comparatively small (1 cm³ or less) bilateral lesions in the thalamic ILN completely knock out all awareness.

Forward versus Feedback Projections

Many actions in response to sensory inputs are rapid, transient, stereotyped, and unconscious. They could be thought of as cortical reflexes and are characterized by rapid and somewhat stereotyped responses that can take the form of rather complex automated behaviour as seen, e.g., in complex partial epileptic seizures. These automated responses, sometimes called *zombie behaviours*, could be contrasted by a slower, all-purpose conscious mode that deals more slowly with broader, less stereotyped aspects of the sensory inputs (or a reflection of these, as in imagery) and takes time to decide on appropriate thoughts and responses. Without such a consciousness mode, a vast number of different zombie modes would be required to react to unusual events. A feature that distinguishes humans from most animals is that we are not born with an extensive repertoire of behavioural programs that would enable us to survive on our own ("physiological prematurity").

To compensate for this, we have an unmatched ability to learn, i.e., to consciously acquire such programs by imitation or

exploration. Once consciously acquired and sufficiently exercised, these programs can become automated to the extent that their execution happens beyond the realms of our awareness. Take, as an example, the incredible fine motor skills exerted in playing a Beethoven piano sonata or the sensorimotor coordination required to ride a motorcycle along a curvy mountain road.

Such complex behaviours are possible only because a an adequate number of the subprograms involved can be executed with minimal or even suspended conscious control. In fact, the conscious system may actually interfere somewhat with these automated programs.From an evolutionary standpoint it clearly makes sense to have both automated behavioural programs that can be executed rapidly in a stereotyped and automated manner, and a slightly slower system that allows time for thinking and planning more complex behaviour. This latter aspect may be one of the principal functions of consciousness.

It appears feasible that visual zombie modes in the cortex mainly use the dorsal stream in the parietal region. However, parietal activity can affect consciousness by producing attentional effects on the ventral stream, at least under some circumstances. The conscious mode for vision depends largely on the early visual areas (beyond V1) and especially on the ventral stream. Seemingly complex visual processing (such as detecting animals in natural, cluttered scenes) can be accomplished by the human cortex within 130–150 ms, far too brief for eye movements and conscious perception to occur. Furthermore, reflexes such as the oculovestibular reflex take place at even more rapid time-scales.

It is quite plausible that such behaviours are mediated by a purely feed-forward moving wave of spiking activity that passes from the retina through V1, into V4, IT and prefrontal cortex, until it affects motorneurons in the spinal cord that control the finger press (as in a typical laboratory experiment).

The hypothesis that the basic processing of information is feedforward is supported most directly by the short times (approx. 100 ms) required for a selective response to appear in IT cells.

Conversely, conscious perception is believed to require more sustained, reverberatory neural activity, most likely via global feedback from frontal regions of neocortex back to sensory cortical areas that builds up over time until it exceeds a critical threshold. At this point, the sustained neural activity rapidly propagates to parietal, prefrontal and anterior cingulate cortical regions, thalamus, claustrum and related structures that support short-term memory, multi-modality integration, planning, speech, and other processes intimately related to consciousness.

Competition prevents more than one or a very small number of percepts to be simultaneously and actively represented. This is the core hypothesis of the global workspace theory of consciousness.

In a nutshell, while rapid but transient neural activity in the thalamo-cortical system can mediate complex behaviour without conscious sensation, it is surmised that consciousness requires sustained but well-organized neural activity dependent on long-range cortico-cortical feedback.

NEUROPHYSIOLOGY AND MENTAL FUNCTION

The objective of this series has been to try to identify the neurological structures within which mind/identity/self exists for the purpose of ensuring that biostasis does not irreparably destroy those structures. Since this could be a matter of life or death, it has been sought to maintain focus on neuroscientific fact and to limit speculation. Nonetheless, the time for speculation has come. Sheer factual data by itself does not yield insight, but factual data can strengthen speculation leading to better factual data and insight. Neuroscience cannot, at present, tell us the anatomical basis of mind with certainty, but it gives a great many clues.

The Locus of the Mind in the Brain

There is no "little person" in some small area of the brain who puts together the colour, motion, orientation and depth information to "see" the image. This "little person" is technically known as a homunculus and this model of how the brain works is known as

"the fallacy of the homunculus". If we imagine a tiny center in our brains (a little person) who sees the information coming from our eyes, hears the information coming from our ears, smells the information coming from our nostrils, etc., we are begging the question of how the brain works. We are also left with a silly infinite regression of homunculi, since each homunculus would need a tiny homunculus in his or her head.

FALLACY OF THE HOMUNCULI
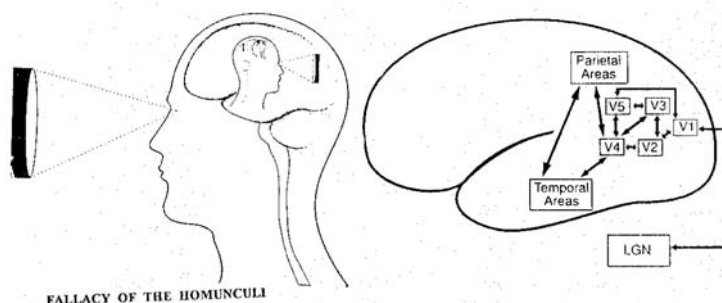
A bee colony is more than just a collection of bees, and a brain is more than just a collection of neurons. It appears mysterious that a mind could be distributed and only exist through the operation of billions of neurons. Some neurons have specialized operations (like queen bees and drones), but the analogy breaksdown when you begin to talk about the localized functioning of collections of neurons in nuclei and regions of the cerebral cortex. Visual perception does have some hierarchical character insofar as the recognition of visual objects takes place in the temporal lobe. The majority of these temporal lobe neurons participate in facial recognition. (Inputs to the temporal lobe are primarily from V4 because V4 is specialized for form & stereopsis as well as for colour — essential features for object recognition.)

The determination of location in space takes place in the parietal lobe of the cortex. But specialization of function does not necessarily mean hierarchy. Destroy the V5 region and the subject will see life as a series of still pictures — motion is absent although recognition can still occur. The full experience of a recognized object in motion in a general location requires the activation of neurons in all the

relevant centers (and the flow of information is bidirectional in every case).

Memory

Immediate (scratch-pad) memory is active in the working-memory areas of the frontal lobes. Recent memory is processed by the hippocampus. Long-term memory for information (such as the date of your birthday) is likely stored in the parietal lobe, whereas long-term memories of events in your life (such as a birthday party) is likely to be stored in the temporal lobe. Recalling a memory, however, will also activate the frontal lobe.

Nonetheless, memory in the brain does not function like memory in a computer. Recalling the image of a banana does not simply mean retrieving an item from disk (temporal or parietal) into active RAM (frontal lobe active memory). In the brain, recalling a memory means activation of neurons at the sites of memory storage. (Sites is plural, because memory storage is undoubtedly coded as synaptic strengths for many synapses distributed among many neurons.)

A person with a lesion in the V4 (colour) area who does not see colours fails to see colour in memory. A remembered banana will be "remembered" as gray, even if the memory of the banana was formed prior to the lesion. The search for the engram (single memory storage site) probably failed because there is no engram — memory is distributed, not localized. Our identity, our active consciousness, is not simply the sum of our memories. The vast majority of our memories are lying latent in our minds most of the time. While we are remembering that we must renew our driver's license, we are not remembering the name of the capitol of France, or the number of planets in the solar system or meaning of the word "holography".

Memory must be organized in such a way that we can know what we know and have a way of retrieving the memories we want, when we want them.

Attention

The phenomenon of attention seems central to a notion localizing consciousness in the brain. When we pay attention to a thought, a sound, an itching toe, a memory, etc. our consciousness seems to willfully concentrate on a few amongst many possible inputs. What we experience is not simply what our environment subjects us to, but what we pay attention to in our environment.

At a social gathering where many conversations are in progress simultaneously, we can follow one conversation and "tune out" all the others by an act of will. Nonetheless, if our name is spoken in one of the "tuned-out" conversations, our attention may suddenly shift even to a conversation which we thought was outside our awareness. The most global control of attention apparently comes from the prefrontal cortex. Distractibility is often observed in animals with prefrontal lesions. The prefrontal cortex sends inputs to the reticular nucleus of the thalamus, which is able to gate transmission from the thalamus to the rest of the cortex.

Finer control of attention in peripheral discrimination requires involvement of the pulvinar nucleus of the thalamus. We concentrate attention on each action required for driving a car until mastery of the actions allows them to be performed without much attention. A child learning to read must concentrate on how letters form words.

A mature reader pays attention not to the reading process, but to the meanings the reading conveys — and to the thoughts those meanings stimulate. Attention is like a mental magnifying glass which we hold up to our experience. How do we do it? About one-quarter of the cerebral cortex in humans is dedicated to processing visual information. Attention, especially to visual objects in space, is best done by the right hemisphere. So-called "unilateral neglect", wherein a patient appears to lose awareness of half of his/her perceptual hemisphere, is most frequent & severe after lesions to the right hemisphere. Visual attention need not be at the center of the visual field. For instance, young monkeys rarely look at a

dominant male because eye contact is a threatening gesture, but the dominant male is nonetheless a focus of attention.

PET scans of a brain performing an attention-requiring task give a good idea of which brain areas are functionally active. In one such task, a subject may be flashed one of the 3 sequences 585858S585858, 5858588585858 or 5858585585858 — and asked to identify whether the center letter is a "5", an "8" or an "S". A series of such flashes occurs, so the subject knows the approximate expected location of the sequence. Recognition of the target letter requires much attention because of the similarity of "detractor" letters to the target letter, and because of the closeness of the detractors to the target letter. A PET scan not only shows the expected activity in the visual cortex, Inferior Temporal (IT) cortex and Posterior Parietal Cortex (PPC), but also exhibits activity in the DorsoLateral PreFrontal Cortex (DLPFC) and the VentroLateral PreFrontal Cortex (VLPFC). The activity of the DLPFC reflects working memory expectation of the location of the target letter. The activity of the VLPFC represents working memory expectation of the target letter shape to be recognized. These working memory areas are in close communication with the PPC and IT, respectively.
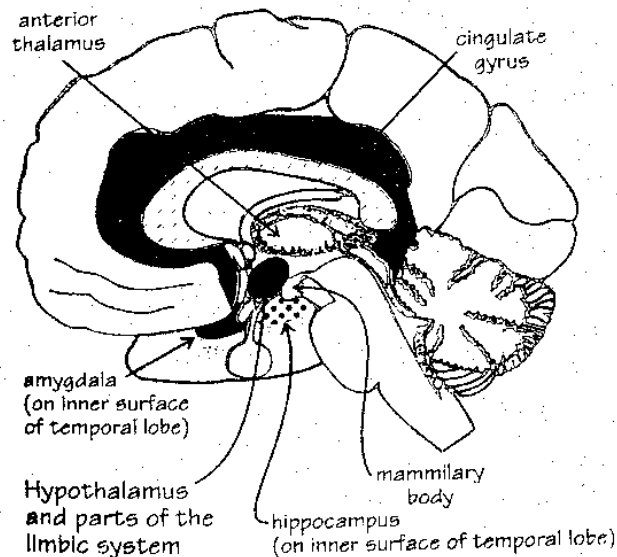
The pulvinar is the largest nucleus in the thalamus, occupying two-fifths of the thalamic volume. The pulvinar plays a crucial role in attention, by contributing to the activation of neurons for the object which is at the center of visual attention, and by contributing to the deactivation of other neurons, especially those similar to the visual field of the detractor letters. Although the pulvinar might seem to be controlling attention, it is not much more in control than a light-switch is in control of whether a light comes on. A more complete picture would include the anterior cingulate gyrus (which conjoins motivation with physical action) and the superior colliculus of the tectum (which controls eye movement). As the PET scan shows, the experience of attention correlates with neuron activity in all of the areas illustrated. Attention permits us to increase the speed, accuracy and efficiency of our actions. By attending to a stoplight, we can more rapidly respond when the light turns green. My assessment of the way this occurs would be to say that working memory and the pulvinar activate neurons for the recognition of the green stoplight (IT) and the location of the stoplight (PPC) so that less additional activation is required when the light actually does turn green. In the case of waiting for a stoplight, attention is also directed to the footpedal so that the subject can rapidly step on the gas. The pulvinar serves a "gating" function — directing which neurons responding to our sensory experience are to be most activated. But this does not make the pulvinar the center of our consciousness. We are most conscious of what we are attending-to.

Consciousness

We can direct our attention to ruminate upon a memory or to recognize an object or to solve a problem. PET scans, monitoring individual neurons show that the conscious experience is unquestionably associated with the activation of neurons.

A person who is unconscious has no active memories and (if unconscious enough) no activated (depolarizing) neurons. Yet regaining consciousness, memories can again be recalled. Memory

may be essential for consciousness, but it is not identical with consciousness.

Likewise, the Reticular Activating System (RAS) in the upper pons is essential for arousal and consciousness, but the RAS is not identical with consciousness, nor is it the center of consciousness. The RAS is itself subject to control by exterior stimuli — and is even subject to inputs from the cerebral cortex through a "bootstrapping" process whereby the awakening cortex sends more signals to the RAS. The cortex requires the RAS for arousal much as the cortex requires the heart for blood — but the heart is not a center of consciousness.

Memories — passively stored synaptic connection strengths — influence patterns of activated neurons in the cerebral cortex. But patterns of activated neurons represent consciousness, not passive synaptic connections strengths. If it is not the ultimate mystery of consciousness, it is nonetheless somewhat astounding and incomprehensible that patterns of activated neurons represent a consciousness. How does this result in unity of mind? How does it represent mind at all?

The prefrontal cortex, specially the dorsolateral cortex, contains much of the functionality often associated with the word "consciousness". Patients with frontal lobe lesions have difficulty making estimates or inferences, such as estimating prices, weights, etc. In association with working memory is the capacity to imagine the consequences of hypothetical actions or events.

This kind of "if-then" reasoning or simulation is a crucial part of planning for action — although the orbitofrontal cortex is probably required for a decision and the anterior cingulate cortex probably generates emotional states based on reward expectancy to help put a plan into action though influence on executive centers.

If PET or MRI scans are an indication of consciousness — if neuron depolarizations are the essence of consciousness — then there is no one center of consciousness in the brain. Rather, consciousness shifts from brain region to brain region — in the

parietal lobe when doing a calculation, in the temporal lobe when trying to "place a face", and in the frontal lobe when trying to decide whether to carry an umbrella. It would be a mistake, however, to equate PET or MRI scan activity with consciousness.

The cerebellum may be very active in calculating the anticipated expected position of a rapidly-moving limb, but it seems likely that only the results of cerebellar activity enter consciousness. Is the cerebellum simply a co-processor of the brain which does not participate in the essence of consciousness? Can the same be said of the pulvinar, which may "gate" attention but, being subject to outside influence, neither controls consciousness nor is included in consciousness. Is consciousness only an attribute of the cerebral cortex? Is hunger experienced in the hypothalamus or in the cortical regions with which the hypothalamus communicates? (Cats with no cerebral cortex are able to feed and function, though with far less evidence of "consciousness".) Consciousness may well be the sum of various cortical and subcortical regions acting in conjunction.

Moreover, it seems unlikely that we are aware of all cortical activity since V1 in the visual cortex, for example, seems to be more of a pre-processing area than an area participating in conscious awareness. Motivation needn't be conscious. Sigmund Freud was fond of finding hidden "unconscious" motives for seemingly accidental mental events.

The idea that painful experiences can be repressed from conscious memory was significant part of the "theory of the unconscious mind". It may be that consciousness is only the tip of the iceberg of mental activity. But it appears more likely that co-processors, rather than a hidden mental manipulator, are primarily what is "behind the scenes" of consciousness. The nuclei of the thalamus have distinctive (usually reciprocal) connections with different areas of the cortex. The basal ganglia are strongly connected to the frontal lobes, and their participation in cognitive functions make them prime candidates for sub-cortical participation in consciousness.

Motivation

The hypothalamus is the source of significant of the most elemental emotions: hunger, thirst, chills, etc. — ultimately pleasure & pain. Painful stimulation of a limb can lead to the withdrawal reflex, mediated directly in the spinal cord. Pain receptors from the skin & organs project directly to the somatosensory cortex, although many of these ascending fibres terminate in the reticular formation (increasing arousal) and the periaqueductal gray. Yet all these sub-cortical drives can often be over-ridden by higher centers of motivation in the cerebral cortex. A person on a hunger strike can resist eating even to the point of death. The anterior cingulate gyrus (Brodmann Area 24) is that part of the cortex (and limbic system) often mentioned as the ultimate locus of motivation control. Francis Crick, in THE ASTONISHING HYPOTHESIS, speculates that the anterior cingulate gyrus is the seat of the will. Sitting adjacent to the motor cortex it seems well-situated for this role — and it is well-connected with the frontal cortex and with the rest of the limbic system. A motive need not result in action. A person may want to buy a new car, but refrain from purchase because of the expense. An ex-alcoholic may want to drink alcohol, but resist doings so out of fear of the consequences. Do such conflicts exist in a single motivation-center, or are there different centers in the brain for different types of motivation? If the latter, is there a single center for conflict-resolution? It seems likely that, just as consciousness can apparently migrate from place to place in the brain, motivation can arise from various parts of the brain at different times.

A "competition" may exist for eventualy control of the will, rather than an ultimate arbiter, and the baton may pass from hand to hand (brain area to brain area) like a "token ring" in a Local Area Network (LAN) of Personal Computers (PCs).

Emotion

Pain can be described as a signal directly from the body to the cerebral cortex, which warns of injurious environmental

conditions. Fear has also been described as a warning signal, which comes from the body to the cortex — but the environmental stimulus generally first enters through the eyes and ears. Thus, a threatening condition appears in the environment, the cortex becomes aware of the condition, signals are sent from the cortex to subcortical structures & body organs, and then the cortex receives "fear" signals back from the physiological turbulence of the body.

The center of the fight/flight response is in the periaqueductal gray (also known as the central gray) which surrounds the cerebral aqueduct of the midbrain (just below the tectum). The central gray is under tonic inhibition from the medial hypothalamus, which receives input from the central nucleus of the amygdala, which receives signals from the orbitofrontal cortex.

The central gray activates the autonomic nervous system elevating heart rate, raising blood glucose&adrenalin, etc. Endorphin-containing neurons in the central gray probably play a significant role in pain modulation.

The sympathetic nervous system is dedicated to what might be called emotional responses, whereas the parasympathetic nervous system is more concerned with localized regulation of organ function. Nonetheless, parasympathetic involvement is seen in emotion when, for instance, a fearful person involuntarily urinates or defecates. It has not been possible to differentiate the anatomical responses of fear from those of anger at the level of the central gray or below — so it is common to speak of the "fight/flight" response.

Electrical stimulation of the amygdala can produce fear or anger, depending on the spot stimulated. Stimulation of the septum usually results in delight&sexual-arousal. Stimulation of the globus pallidus and the midcenter of the thalamus can produce a feeling of joy. Fear might be described as a "reflex" of a peculiar sort — a reflex of the autonomic system to an environmental situation which the cerebral cortex regards to be threatening. It is often a conditioned reflex (ie, a learned reflex), but not always — e.g., the

"startle reflex" to a sudden loud sound. Although fear may be a deeply conditioned reflex — a phobia of snakes, for example — it can also have highly cognitive associations.

A person may be very afraid of pit bull terriers, and yet have much of that fear disappear instantly upon learning that the dog in the old "Little Rascals" film-series was a pit bull terrier. Fear is motivating because it places the organism in a physiological state in which to effectively fight or flee — and in a psychological state to want to relieve the "stress" through fight or flight. Fear and other emotions can also contribute to learning — the close association of the amygdala and the hippocampus is no accident. Emotion means meaningfulness — and we most readily learn & remember those things which are most personally meaningful to us.

Fear is the emotion that has been most studied & thought-about by philosophers, psychologists and physiologists. Attempts to exhaustively and distinctively categorize emotions are a source of dispute among experts.

Anger, Love, Enthusiasm, Lust, Sadness, Boredom, Hate, Hope, Jealousy, and many other emotions can be named, but they do not all seem entirely distinct. Jealousy is a kind of anger. Hate seems to be anger in a more hardened form. Anxiety is certainly a kind of fear — and modifiers can further refine the emotion, as in "performance anxiety" or "free-floating anxiety". Fear appears to be the most widely evident emotion in the animal kingdom, although the emotional repertoire of other species may be as distinct as their physiologies.

Dogs seem to show Shame, but it is hard to imagine this emotion in a frog. Shame, Embarrassment, Jealousy and Envy are emotions that are directly connected to human relations. Love and Anger can involve other species. Unlike Anger or Fear, Grief is an emotion that does not appear to motivate. Perhaps, however, it motivates thought, rather than action, thereby leading the subject to re-examine and re-organize his/her life so as to prevent future

tragedy. If so, this emotion should be distinctively found in species with a well-developed cerebral cortex — as is the case with the aforementioned "social emotions". Patients with damage to areas of the right cortex corresponding to the language areas of the left cortex have difficulty conveying emotion in speech and have difficulty understanding the emotional overtones in the language they see and hear. The right temporal lobe is specialized for recognizing the emotional content of facial expression.

A patient with damage to the left motor cortex cannot voluntarily smile, but will involuntarily smile in a normal manner in response to positive emotion. A patient with damage to the left anterior cingulate gyrus shows the opposite effect — not smiling involuntarily in response to emotion, but able to mechanically produce an artificial smile under voluntary control. Experiments have demonstrated faster reaction times to warning stimuli sent to the right brain, leading some experimentalists to conclude that the right brain is the source of intention.

Personality

A significant aspect of personality is the tendency to experience certain emotions. Drugs and surgery have effectively been used against extreme forms of these "personality" manifestations. Lobotomy has been used as a treatment for phobias. Removal of portions of the amygdala has been effective for violent criminals prone to dangerous states of rage. Drugs such as tranquilizers and antidepressants are well-known for their mood-altering abilities. Physiological correlates have been found that accompany the personality dichotomy "Introvert/Extrovert". Introverts display more cortical blood flow (more arousal) with lower levels of stimulation than Extroverts. A few drops of lemon juice on the tongue of an Extrovert will produce little saliva, but extreme Introverts will salivate profusely.

Introverts require a much higher dose of sedative to put them to sleep than Extroverts. Introverts are naturally more aroused than Extroverts (who are driven to seek sensation & stimulation).

At the root of these differences are higher levels of norepinephrine (noradrenalin) in the brains of Introverts. Obsessive-Compulsive Disorder (OCD) is characterized by obsessive thoughts and compulsive behaviours, which can be accompanied by great fear or, at least, anxiety. PET scans show high levels of activity in the orbitofrontal cortex of OCD patients. Atrophy of the head of the caudate nucleus of the basal ganglia (and decreased caudate metabolism) are a frequent finding, although this is less consistent. One of the most effective treatments for OCD is a drug that inhibits serotonin uptake, such as the antidepressant Prozac. Increased serotonin in the orbitofrontal cortex and in the amygdala reduces aggression and favors "social behaviour".

Self-awareness

Bilateral damage to the orbitofrontal cortex (Brodmann areas 11, 12, 13 and 47) has a notable effect on "moral character". Such patients show a loss of deference for others and a lessened concern for themselves. Their actions show less concern for social accountability or convention — while at the same time failing to take account of their own best interests. They lose a sense of "right & wrong", behave in a manner that is "crass & vulgar" and may have a difficult time making many kinds of decisions.

The anterior orbitofrontal cortex (areas 11&47) receives inputs from the parvenocellular dorsomedial thalamic nucleus, and it exerts tonic inhibitory control over the amygdala. The posterior orbitofrontal cortex (area 13) receives inputs from the magnocellular dorsomedial thalamic nucleus (which receives inputs from the amygdala and inferior temporal cortex. There are also direct inputs to the orbitofrontal cortex from the temporal lobe, the hypothalamus, the caudate nucleus and the amygdala. (The main cortical inputs to the amygdala, however, are from areas 38&20).

The interpretation of this evidence is that there is an intimate connection between self-awareness and self-image. Much of the basis for deference to others is the protection of self and protection of the image of the self. H.L.Mencken once said, "Conscience is

that wee inner voice that says 'somebody might be looking'". Genuine empathy perhaps involves connections between the orbitofrontal and dorsolateral cortex — the ability to imagine and feel oneself as being inside another person. With such close connections to the hypothalamus and the limbic system, it makes sense that the orbitofrontal cortex would be so implicated in decision-making (linking facts and values). Although the orbitofrontal cortex may be a center for morality & self-valuation, we must again be careful about over-localization and the homunculus fallacy. The temporal lobe may play a role in "self-recognition" or self-image, and the dorsolateral cortex, while simulating reality & potential reality, must include a model of the self (self-image) — including a model of image of the self held in the minds of others.

The Split Brain

There is controversy over whether cutting the corpus callosum produces two distinct "selfs", each with a complete personal identity — one in the left cerebral hemisphere and one in the right. Nobel laureate Roger Sperry has contended that this is true, whereas Nobel laureate Sir John Eccles maintained that the right hemisphere is a mere "automaton". The left and right hands of a split-brain monkey have been observed to seemingly fight over a peanut. Human patients with a severed corpus callosum demonstrate an awareness with left hand/right cortex which differs from that of the right hand/left cortex. This occasionally even leads to conflicting behaviour between the right hand and left hand.

There is a few observations here. If the left arm were connected to the thirst center of the hypothalamus and the right arm were connected to the hunger center, we can imagine that the left arm might reach for water and the right arm might reach for food. If there is no homunculus in the brain there may be many different control centers or, at least, control centers may compete for control of action on the basis of competing inputs from various areas of the brain. Using the analogy of the visual cortex V1, V2, V3, etc.

areas, control centers C1, C2, C3, etc. could receive inputs from motivation centers M1, M2, M3, etc. and decision inputs from cognitive judgement centers J1, J2, J3, etc. The control center with the strongest inputs may result in action. Severing many of these areas and giving them control of limb L1, L2, L3, etc. could result in actions by the different limbs which are at variance with each other.

Split-brain patients are notable for their loss of creativity. The patients generally complain that they no longer dream (or, rather, that is the report from the left hemisphere). Having two hemispheres gives us many of the benefits of double-entry bookkeeping — a certain redundancy allows for the detection and correction of errors. Much of our creativity and decision-making involves resolving conflicting desires and perspectives arising from different brain centers and different cortical hemispheres. Even if cutting the corpus callosum does produce two distinct personal identities, they are both probably impoverished vestiges of the original singular identity. It cannot be believed that the unity of conscious experienced by a person with an intact corpus callosum is an illusion.

SURVIVAL AND THE BRAIN

The purpose of this at series has been to learn & explain what is known about how neurophysiology results in the phenomena of mind & self. Further, to understand which brain/neuronal structures must be preserved to preserve mind&self. And still further, to be able to use that knowledge to suggest & evaluate cryonics and other preservation methods. What brain structures must not be destroyed in order for our personal identity to survive? It may be that the survival of our selfhood is dependent on multiple brain areas just as our capacity to be alive is dependent on multiple body organs — heart, kidney, lungs, etc. — even though the heart, the kidneys and the lungs perform very different functions. The cerebral cortex certainly seems essential for our consciousness, but the destruction of any one of the 30 billion or so neurons in that

structure probably could not destroy a person's identity. If 900 cortical neurons were destroyed per second, in random order, after a full year there would be no more neurons (no Self) — but at what point is the Self lost? The implication here is that personal identity is all-or-nothing, rather than capable of partial survival. But if identity is distributed in the brain, rather than localized, it cannot be "all-or-nothing".

Several cortical sites of lesions, strokes and tumors have been mentioned in this series without any one site being associated with a loss of "identity". Even "Elliot", an orbitofrontal-lobe damage patient described in Antonio Damasio's book DESCARTE'S ERROR, is not deemed to have lost his "Self" — inspite of a loss of feeling, personal involvement with life and decision-making ability. Patients with Alzheimer's Disease and other forms of progressive senile dementia, which may not be localized in any one brain area, do not demonstrate sudden mental death — they just "fade away". The philosopher David Hume claimed that true self-awareness does not exist — that what we imagine to be self-awareness is just an abstraction rather than a true perception. In fact, he went so far as to say that self-awareness is really just an illusion:

"For my part, when I enter most intimately into what I call myself, I always stumble upon some particular perception or other, of heat or cold, light or shade, love or hatred, pain or pleasure. I can never catch myself at any time without a perception, and never can observe any thing but the perception... Pain and pleasure, grief and joy, passions and sensations succeed each other, and never all exist at the same time. It cannot therefore be from any of these impressions, or from any other, that the idea of self is derived; and consequently there is no such idea."

— David Hume, TREATISE OF HUMAN NATURE, Book I,Part IV,Section 6

Hume had a notable talent for using skepticism as a tool for incapacitating himself and anyone else he could influence.

Nonetheless, there may be truth to the idea that I am not the same person when I am listening to music as when I am preparing a shopping list. Moreover, I may have little or no self-awareness during either activity. If there is a center of the "Self" in the brain, would the neurons in that area be active at all times? Does identifying Selfhood with emotion imply that one is surviving less when one is solving a physics problem than when one is crying during a film?

Do mood-altering drugs — or even personality-altering drugs — change a person's identity? If Self is regarded as the entity that feels rather than the feeling itself, then this criterion begs the question. One could as readily define the Self as the entity which sees the colour green, remembers a telephone number or solves a cross-word puzzle. A problem with the "information" criterion of identity (related to the "memory" criterion) is that a book — even an encyclopedia — is a storage place for information, but is not an active consciousness.

The average cortical neuron is idle 99.8% of the time, and a similar statement could be made about the average synapse. Conscious awareness, whether self-conscious at any particular moment or not, involves many activated neurons, usually in diverse parts of the brain. Consciousness, therefore, seems to be associated with several activated experiential neurons in communication with each other. Does the connectedness of a neuron define whether it is "experiential" or not?

In our present knowledge of the brain, we cannot describe the neural functioning that happens when 7 is divided by 4, or a birthday is remembered. And the daunting task of decoding these operations seems trivial compared to determining how neural activity results in consciousness, Self and — above all — our own subjective experience. Nonetheless, as mysterious as it seems, there is no tenable alternative to the idea that personal identity is embedded in synapses and active neurons, distributed throughout the brain and with different aspects of "Self" manifested in different brain areas. The basic to preserving personal identity

is to preserve the structural and functional integrity (or repairability) of neurons & synapses (neural networks). Some people worry that the cessation of electrical activity during cryopreservation would mean a loss of personal identity & memory.

Although immediate (short-term) memories would perhaps be lost, there is ample reason to believe that identity & long-term memory is encoded in synapses and in the connections between neurons — which would be cryopreserved. Dogs have been cooled to low temperature in a bloodless state with no evident electrical activity, yet have demonstrated memory upon recovery.

Similarly, humans reduced to a state of no detectable electrical activity by drugs have demonstrated recovery of memory & identity. If you light a candle, the nature of the flame is a product of the nature of the wax and the wick.

Snuff-out the candle, re-light it and the flame will be the same. Likewise, if the heart stops and is restarted (and has not been damaged) the heart will resume operation, contracting in response to the waves of electrical impulses in precisely the same manner as it did before and producing the exact same result because the patterns of electrical activity and the effects of electrical activity are entirely determined by the structure of the fibers carrying the electrical impulses and their connections.

Similarly, if the axons, dendrites and synapses — including the strength of synaptic connections — in the brain are not destroyed, then memory and personal identity should be maintained. There is ample evidence that memory is encoded by modification of synaptic strengths — although the physical connections by the cables (axons and dendrites) are obviously an important part of this.

Thus, re-starting the electical signals should re-activate our memories. During non-REM (non-dreaming) portions of our sleep-cycle there is diminished electrical activity of the brain due to reduced input from the reticular activating system (RAS). The RAS is analogous to the pacemaker of the heart — generating

electrical signals to activate brain function, just as the heart pacemaker generates electrical signals to activate heart function.

To repeat, what those functions are depend upon the connections in the heart & brain, not the instigation of signals. The RAS is even less active in unconsciousness and coma — and if coma is deep enough there may not even be enough electrical activity in the medulla to keep the heart functioning, much less the brain, and death will ensue. To imagine that the RAS is a source of identity is to confuse the nature of consciousness with the distinction between being conscious or unconsious.

NEUROPHYSIOLOGY OF CENTRAL AND PERIPHERAL NERVOUS SYSTEM AND MUSCLES

The central nervous system comprises the brain and spinal cord. The brain and spinal cord are protected by bony structures, membranes, and fluid. The brain is held in the cranial cavity of the skull and it consists of the cerebrum, cerebellum, and the brain stem. The nerves involved are cranial nerves and spinal nerves.

Overview of the Entire Nervous System

The nervous system performs three chief functions: sensory input, integration of data and motor output. Sensory input is when the body gathers information or data, by way of neurons, glia and synapses. The nervous system is composed of excitable nerve cells (neurons) and synapses that form between the neurons and connect them to centers throughout the body or to other neurons. These neurons operate on excitation or inhibition, and although nerve cells can vary in size and location, their communication with one another determines their function. These nerves conduct impulses from sensory receptors to the brain and spinal cord.

The data is then processed by way of integration of data, which occurs only in the brain. After the brain has processed the information, impulses are then conducted from the brain and spinal cord to muscles and glands, which is called motor output.

Glia cells are found within tissues and are not excitable but help with myelination, ionic regulation and extracellular fluid. The nervous system is comprised of two major parts, or subdivisions, the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and spinal cord.

The brain is the body's "control center". The CNS has various centers located within it that carry out the sensory, motor and integration of data. These centers can be subdivided to Lower Centers (including the spinal cord and brain stem) and Higher centers communicating with the brain via effectors.

The PNS is a vast network of spinal and cranial nerves that are linked to the brain and the spinal cord. It contains sensory receptors which help in processing changes in the internal and external environment. This information is sent to the CNS via afferent sensory nerves.

The PNS is then subdivided into the autonomic nervous system and the somatic nervous system. The autonomic has involuntary control of internal organs, blood vessels, smooth and cardiac muscles. The somatic has voluntary control of skin, bones, joints, and skeletal muscle. The two systems function together, by way of nerves from the PNS entering and becoming part of the CNS, and vice versa.

General functions of the CNS

When the central nervous system becomes damaged or peripheral nerves become trapped, it can increase or decrease your internal organs functionality, it can even affect your facial expressions, i.e. make you frown a lot, your smile becomes lop sided, your lungs can overwork, or underwork, the lung capacity is increased or decreased, your bladder can fill, but you are notable to urinate, your bowels become lapsed and you are unable to completely clear them upon each bowel movement, the muscles in your arms, legs and torso can become weaker and more fatty, not from lack of use, but from the nerves that run from your spine

into them being restricted from working properly, you can suffer headaches, earaches, sore throats, blocked sinuses. Even your ability to orgasm can be affected.
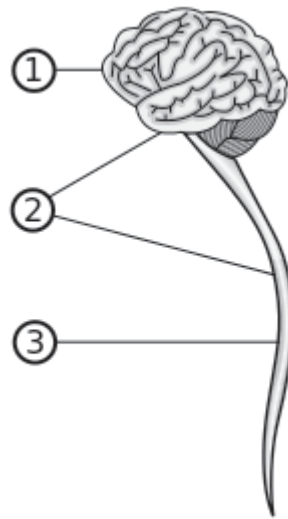
Fig. Brain, brain stem, and spinal cord.

CNS: The "Central Nervous System", comprised of brain, brain stem, and spinal cord.

The central nervous system (CNS) represents the largest part of the nervous system, including the brain and the spinal cord. Together with the peripheral nervous system (PNS), it has a fundamental role in the control of behaviour.

The CNS is conceived as a system devoted to information processing, where an appropriate motor output is computed as a response to a sensory input.

Various threads of research suggest that motor activity exists well before the maturation of the sensory systems, and senses only influence behaviour without dictating it. This has brought the conception of the CNS as an autonomous system. Structure and function of neurons

Structure

Neurons are highly specialized for the processing and transmission of cellular signals. Given the diversity of functions performed by neurons in different parts of the nervous system, there is, as expected, a wide variety in the shape, size, and electrochemical properties of neurons.

For instance, the soma of a neuron can vary in size from 4 to 100 micrometers in diameter. The soma (cell body) is the central part of the neuron. It contains the nucleus of the cell, and therefore is where most protein synthesis occurs. The nucleus ranges from 3 to 18 micrometers in diameter.

The dendrites of a neuron are cellular extensions with many branches, and metaphorically this overall shape and structure is referred to as a dendritic tree. This is where the much of input to the neuron occurs. However, information outflow (i.e. from dendrites to other neurons) can also occur (except in chemical synapse in which backflow of impulse is inhibited by the fact that axon do not possess chemoreceptors and dendrites cannot secrete neurotransmitter chemical). This explains one way conduction of nerve impulse. The axon is a finer, cable-like projection which can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length.

The axon carries nerve signals away from the soma (and also carry some types of information back to it). Many neurons have only one axon, but this axon may - and usually will - undergo extensive branching, enabling communication with many target cells. The part of the axon where it emerges from the soma is called the 'axon hillock'. In addition to being an anatomical structure, the axon hillock is also the part of the neuron that has the greatest density of voltage-dependent sodium channels. This makes it the most easily-excited part of the neuron and the spike initiation zone for the axon: in neurological terms it has the greatest hyperpolarized action potential threshold. While the axon and axon hillock are generally involved in information outflow, this region can also receive input from other neurons as well.

The axon terminal is a specialized structure at the end of the axon that is used to release neurotransmitter chemicals and communicate with target neurons. Although the canonical view of the neuron attributes dedicated functions to its various anatomical components, dendrites and axons often act in ways contrary to their so-called main function. Axons and dendrites in the central nervous system are typically only about a micrometer thick, while some in the peripheral nervous system are much thicker. The soma is generally about 10–25 micrometers in diameter and often is not much larger than the cell nucleus it contains. The longest axon of a human motor neuron can be over a meter long, reaching from the base of the spine to the toes. Sensory neurons have axons that run from the toes to the dorsal columns, over 1.5 meters in adults.

Giraffes have single axons several meters in length running along the entire length of their necks. Much of what is known about axonal function comes from studying the squids giant axon, an ideal experimental preparation because of its relatively immense size (0.5–1 millimeters thick, many centimeters long).

Function

Sensory afferent neurons convey information from tissues and organs into the central nervous system. Efferent neurons transmit signals from the central nervous system to the effector cells and are sometimes called motor neurons. Interneurons connect neurons within specific regions of the central nervous system. Afferent and efferent can also refer generally to neurons which, respectively, bring information to or send information from brain region.

Classification by action on other neurons

Excitatory neurons excite their target postsynaptic neurons or target cells causing it to function. Motor neurons and somatic neurons are all excitatory neurons. Excitatory neurons in the brain are often glutamatergic. Spinal motor neurons, which synapse on muscle cells, use acetylcholine as their neurotransmitter. Inhibitory neurons inhibit their target neurons. Inhibitory neurons are also

known as short axon neurons, interneurons or microneurons. The output of some brain structures (neostriatum, globus pallidus, cerebellum) are inhibitory.

The primary inhibitory neurotransmitters are GABA and glycine. Modulatory neurons evoke more complex effects termed neuromodulation. These neurons use such neurotransmitters as dopamine, acetylcholine, serotonin and others. Each synapses can receive both excitatory and inhibitory signals and the outcome is determined by the adding up of summation.

Excitatory and inhibitory process

The release of an excitatory neurotransmitter (e.g. glutamate) at the synapses will cause an inflow of positively charged sodium ions (Na+) making a localized depolarization of the membrane. The current then flows to the resting (polarized) segment of the axon. Inhibitory synapse causes an inflow of Cl- (chlorine) or outflow of K+ (potassium) making the synaptic membrane hyperpolarized. This increase prevents depolarization, causing a decrease in the possibility of an axon discharge. If they are both equal to their charges, then the operation will cancel itself out. This effect is referred to as summation.

There are two kinds of summation: spatial and temporal. Spatial summation requires several excitatory synapses (firing various times) to add up, thus causing an axon discharge.

It also occurs within inhibitory synapses, where just the opposite will occur. In temporal summation, it causes an increase of the frequency at the same synapses until it is large enough to cause a discharge.

Spatial and temporal summation can occur at the same time as well. The neurons of the brain release inhibitory neurotransmitters far more than excitatory neurotransmitters, which helps explain why we are not aware of all memories and all sensory stimuli simultaneously. The various kinds of information stored in the brain is inhibited most of the time.

Summation

When excitatory synapses exceed the amount of inhibitory synapses there are, then the excitatory synapses will prevail over the other. The same goes with inhibitory synapses, if there are more inhibitory synapses than excitatory, the synapses will be inhibited. To determine all of this is called summation.

Classification by Discharge Patterns

Neurons can be classified according to their electrophysiological characteristics (note that a single action potential is not enough to move a large muscle, and instead will cause a twitch).

Tonic or regular spiking: Some neurons are typically constantly (or tonically) active. Example: interneurons in neurostriatum.

Phasic or bursting: Neurons that fire in bursts are called phasic.

Fast spiking: Some neurons are notable for their fast firing rates. For example, some types of cortical inhibitory interneurons, cells in globus pallidus.

Thin-spike: Action potentials of some neurons are more narrow compared to the others. For example, interneurons in prefrontal cortex are thin-spike neurons.

Classification by neurotransmitter released:

Some examples are cholinergic, GABAergic, glutamatergic and dopaminergic neurons.

Central Nervous System (CNS)

The central nervous system is the control center for the body. It regulates organ function, higher thought, and movement of the body. The central nervous system consists of the brain and spinal cord.

Action Potential: Its Generaton and Propagation

The Nerve Impulse

When a nerve is stimulated the resting potential changes.

Examples of such stimuli are pressure, electricity, chemicals, etc. Different neurons are sensitive to different stimuli(although most can register pain). The stimulus causes sodium ion channels to open.

The rapid change in polarity that moves along the nerve fiber is known as the "action potential." In order for an action potential to occur, it must reach threshold. If threshold does not occur, then no action potential can occur. This moving change in polarity has many stages:

Depolarization

The upswing is caused when positively charged sodium ions (Na+) suddenly rush through open sodium gates into a nerve cell. The membrane potential of the stimulated cell undergoes a localized change from -55 millivolts to 0 in a limited area. As additional sodium rushes in, the membrane potential actually reverses its polarity so that the outside of the membrane is negative relative to the inside.

During this change of polarity the membrane actually develops a positive value for a moment(+30 millivolts). The change in voltage stimulates the opening of additional sodium channels (called a voltage-gated ion channel). This is an instance of a positive feedback loop.

Repolarization

The downswing is caused by the closing of sodium ion channels and the opening of potassium ion channels. Release of positively charged potassium ions (K+) from the nerve cell when potassium gates open. Again, these are opened in response to the positive voltage—they are voltage gated. This expulsion acts to restore the localized negative membrane potential of the cell (about -65 or -70 mV is typical for nerves).

Hyperpolarization

When the potassium ions are below resting potential (-90 mV). Since the cell is hyper polarized, it goes to a refractory phrase.

Refractory phase

The refractory period is a short period of time after the depolarization stage. Shortly after the sodium gates open, they close and go into an inactive conformation. The sodium gates cannot be opened again until the membrane is repolarized to its normal resting potential.

The sodium-potassium pump returns sodium ions to the outside and potassium ions to the inside. During the refractory phase this particular area of the nerve cell membrane cannot be depolarized. This refractory area explains why action potentials can only move forward from the point of stimulation.

Factors that affect sensitivity and speed

Sensitivity

Increased permeability of the sodium channel occurs when there is a deficit of calcium ions. When there is a deficit of calcium ions ($Ca+2$) in the interstitial fluid, the sodium channels are activated (opened) by very little increase of the membrane potential above the normal resting level.

The nerve fiber can therefore fire off action potentials spontaneously, resulting in tetany. This could be caused by the lack of hormone from parathyroid glands. It could also be caused by hyperventilation, which leads to a higher pH, which causes calcium to bind and become unavailable.

Speed of Conduction

This area of depolarization/repolarization/recovery moves along a nerve fiber like a very fast wave. In myelinated fibers, conduction is hundreds of times faster because the action potential only occurs at the nodes of Ranvier (pictured below in 'types of neurons') by jumping from node to node. This is known as "saltatory" conduction. Damage to the myelin sheath by the disease can cause severe impairment of nerve cell function. Some poisons and drugs interfere with nerve impulses by blocking sodium channels in nerves.

Brain
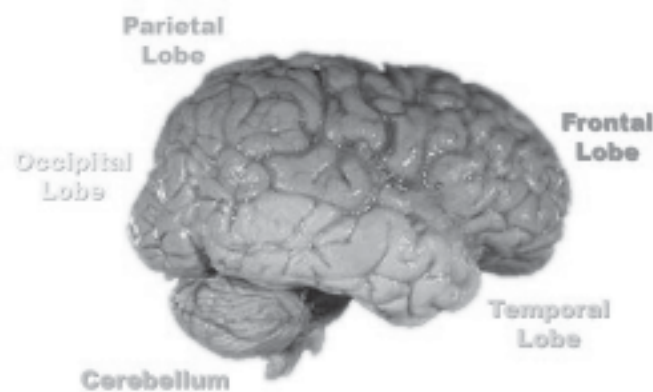
Fig. : A colour-coded image of the brain, showing the main sections.

The brain is found in the cranial cavity. Within it are found the higher nerve centers responsible for coordinating the sensory and motor systems of the body (forebrain). The brain stem houses the lower nerve centers (consisting of midbrain, pons, and medulla),

Medulla

The medulla is the control center for respiratory, cardiovascular and digestive functions.

Pons

The pons houses the control centers for respiration and inhibitory functions. Here it will interact with the cerebellum.

Cerebrum

The cerebrum, or top portion of the brain, is divided by a deep crevice, called the longitudinal sulcus. The longitudinal sulcus separates the cerebrum in to the right and left hemispheres. In the hemispheres you will find the cerebral cortex, basal ganglia and the limbic system. The two hemispheres are connected by a bundle of nerve fibers called the corpus callosum.

The right hemisphere is responsible for the left side of the body while the opposite is true of the left hemisphere. Each of the

two hemispheres are divided into four separated lobes: the frontal in control of specialized motor control, learning, planning and speech; parietal in control of somatic sensory functions; occipital in control of vision; and temporal lobes which consists of hearing centers and some speech. Located deep to the temporal lobe of the cerebrum is the insula.

Cerebellum

The cerebellum is the part of the brain that is located posterior to the medulla oblongata and pons. It coordinates skeletal muscles to produce smooth, graceful motions. The cerebellum receives information from our eyes, ears, muscles, and joints about what position our body is currently in (proprioception). It also receives output from the cerebral cortex about where these parts should be. After processing this information, the cerebellum sends motor impulses from the brain stem to the skeletal muscles.

The main function of the cerebellum is coordination. The cerebellum is also responsible for balance and posture. It also assists us when we are learning a new motor skill, such as playing a sport or musical instrument. Recent research shows that apart from motor functions cerebellum also has some emotional role.

The Limbic System and Higher Mental Functions

The Limbic System

The Limbic System is a complex set of structures found just beneath the cerebrum and on both sides of the thalamus. It combines higher mental functions, and primitive emotion, into one system. It is often referred to as the emotional nervous system. It is not only responsible for our emotional lives, but also our higher mental functions, such as learning and formation of memories. The Limbic system explains why some things seem so pleasurable to us, such as eating and why some medical conditions are caused by mental stress, such as high blood pressure. There are two most important structures within the limbic system and several smaller structures that are important as well. They are:

1. The Hippocampus
2. The Amygdala
3. The Thalamus
4. The Hypothalamus
5. The Fornix and Parahippocampus
6. The Cingulate Gyrus

Limbic System: Its Structure

Hippocampus

The Hippocampus is found deep in the temporal lobe, shaped like a seahorse. It consists of two horns that curve back from the amygdala. It is situated in the brain so as to make the prefrontal area aware of our past experiences stored in that area. The prefrontal area of the brain consults this structure to use memories to modify our behaviour. The hippocampus is a primary contributor to memory.

Amygdala

The Amygdala is a little almond shaped structure, deep inside the anteroinferior region of the temporal lobe, that connects with the hippocampus, the septi nuclei, the prefrontal area and the medial dorsal nucleus of the thalamus. These connections make it possible for the amygdala to play its significant role on the mediation and control of such activities and feelings as love, friendship, affection, and expression of mood. The amygdala is the center for identification of danger and is fundamental for self preservation. The amygdala is the nucleus responsible for fear.

Thalamus

Lesions or stimulation of the medial, dorsal, and anterior nuclei of the thalamus are associated with changes in emotional reactivity. However, the significane of these nuclei on the regulation of emotional behaviour is not due to the thalamus itself, but to the connections of these nuclei with other limbic system structures.

The medial dorsal nucleus makes connections with cortical zones of the prefrontal area and with the hypothalamus. The

anterior nuclei connect with the mamillary bodies and through them, via fornix, with the hippocampus and the cingulated gyrus, thus taking part in what is known as the Papez's circuit.

Hypothalamus

The Hypothalamus is a small part of the brain located just below the thalamus on both sides of the third ventricle. Lesions of the hypothalamus interfere with various vegetative functions and some so called motivated behaviours like sexuality, combativeness, and hunger. The hypothalamus also plays a role in emotion.

Specifically, the lateral parts seem to be involved with pleasure and rage, while the medial part is linked to aversion, displeasure, and a tendency to uncontrollable and loud laughing. However, in general the hypothalamus has more to do with the expression of emotions. When the physical symptoms of emotion appear, the threat they pose returns, via the hypothalamus, to the limbic centers and then the prefrontal nuclei, increasing anxiety.

The Fornix and Parahippocampal

These small structures are important connecting pathways for the limbic system.

The Cingulate Gyrus

The Cingulate Gyrus is located in the medial side of the brain between the cingulated sulcus and the corpus callosum. There is still much to be learned about this gyrus, but it is already known that its frontal part coordinates smells and sights, with pleasant memories of previous emotions. The region participates in the emotional reaction to pain and in the regulation of aggressive behaviour.

Memory and Learning

Memory is defined as : The mental faculty of retaining and recalling past experiences, the act or instance of remembering recollection. Learning takes place when we retain and utilize past memories. Overall, the mechanisms of memory are not completely

understood. Brain areas such as the hippocampus, the amygdala, the striatum, or the mammillary bodies are thought to be involved in specific types of memory. For instance, the hippocampus is believed to be involved in spatial learning and declarative learning (learning information such as what you're reading now), while the amygdala is thought to be involved in emotional memory. Damage to certain areas in patients and animal models and subsequent memory deficits is a primary source of information.

However, rather than implicating a specific area, it could be that damage to adjacent areas, or to a pathway traveling through the area is actually responsible for the observed deficit. Further, it is insufficient to describe memory, and its counterpart, learning, as solely dependent on specific brain regions. Learning and memory are attributed to changes in neuronal synapses, thought to be mediated by long-term potentiation and long-term depression.

There are three basic types of memory:
1. Sensory Memory
2. Short Term Memory
3. Long Term Memory

Sensory Memory

The sensory memories act as a buffer for stimuli through senses. A sensory memory retains an exact copy of what is seen or heard: *iconic memory for visual, echoic memory for aural and haptic memory for touch.* Information is passed from sensory memory into short term memory. Some believe it lasts only 300 milliseconds, it has unlimited capacity. Selective attention determines what information moves from sensory memory to short term memory.

Short Term Memory

Short Term Memory acts as a scratch pad for temporary recall of the information under process. For instance, in order to understand this sentence you need to hold in your mind the beginning of the sentence as you read the rest. Short term memory decays fastly and also has a limited capacity.

Chunking of information can lead to an increase in the short term memory capacity, this is the reason why a hyphenated phone number is easier to remember than a single long number. The successful formation of a chunk is known as *closure.* Interference often causes disturbance in short term memory retention. This accounts for the desire to complete a task held in short term memory as soon as possible.

Within short term memory there are three basic operations:

1. Iconic memory - the ability to hold visual images
2. Acoustic memory - the ability to hold sounds. Can be held longer than iconic.
3. Working memory - an active attentional process to keep it until it is put to use. Note that the goal is not really to move the information from short term memory to long term memory, but merely to put it to immediate use.

The process of transferring information from short term to long term memory involves the encoding or consolidation of information. This is not a function of time, that is, the longer the memory stays in the short term the more likely it is to be placed in the long term memory.

On organizing complex information in short term before it can be encoded into the long term memory, in this process the meaningfulness or emotional content of an item may play a greater role in its retention in the long term memory. The limbic system sets up local reverberating circuits such as the Papez's Circuit.

Long Term Memory

Long Term Memory is used for storage of information over a long time. Information from short to long term memory is transferred after a short period. Unlike short term memory, long term memory has little decay.

Long term potential is an enhanced response at the synapse within the hippocampus. It is inneviable to memory storage. The limbic system isn't directly involved in long term memory necessarily but it selects them from short term memory, consolidates

these memories by playing them like a continuous tape, and involves the hippocampus and amygdala.

There are two kinds of long term memory:
1. Episodic Memory
2. Semantic Memory

Episodic memory represents our memory of events and experiences in a serial form. It is from this memory that we can reconstruct the actual events that took place at a given point in our lives. Semantic memory, on the other hand, is a structured record of facts, concepts, and skills that we have acquired. The information in the semantic memory is derived from our own episode memory, such as that we can learn new facts or concepts from experiences.

There are three chief activities that are related to long term memory:
1. Storage
2. Deletion
3. Retrieval

Information for short term memory is stored in long term memory by rehearsal. The repeated exposure to a stimulus or the rehearsal of a piece of information transfers it into long term memory. Experiments also suggest that learning is most effective if it is distributed over time.

Deletion is mainly caused by decay and interference. Emotional factors also affect long term memory. However, it is debatable whether we actually ever forget anything or whether it just sometimes becomes increasingly difficult to retrieve it. Information may not be recalled sometimes but may be recognized, or may be recalled only with prompting. This leads us to the third operation of memory, information retrieval.

There are two sorts of information retrieval:
1. Recall
2. Recognition

In recall, the information is reproduced from memory. In recognition the presentation of the information provides the knowledge that the information has been seen before. Recognition is of lesser complexity, as the information is provided as a cue. However, the recall may be assisted by the provision of retrieval cues which enable the subject to quickly access the information in memory.

Long-term Potentiation

Long-term potentiation (LTP) is the lasting enhancement of connections between two neurons that results from stimulating them simultaneously. Since neurons communicate via chemical synapses, and because memories are believed to be stored by virtue of patterns of activation of these synapses, LTP and its opposing process, long-term depression, are widely considered the major cellular mechanisms that underlie learning and memory. This has been proven by lab experiments. When one of the chemicals involved is inhibited in rats, it causes retrograde amnesia with short term memory left intact (meaning they can't recall events from before the inhibitor was given).

Having enhanced synaptic transmission, LTP improves the ability of two neurons, one presynaptic and the other postsynaptic, to communicate with one another across a synapse. The precise mechanism for this enhancement isn't known, but it varies based on things like brain region, age and species. This will focus on LTP in the CA1 section of the hippocampus, because that's what is well known.

The end result of LTP is a well established neural circuit that can be called upon later for memory.

LTP in the CA1 hippocampus is called NMDA receptor-dependent LTP. It has four main properties.

Rapid induction

LTP can be rapidly induced by applying one or more brief, high-frequency, stimulus to a presynaptic cell.

Input specificity

Once induced, LTP at one synapse does not spread to other synapses; rather LTP is input specific. LTP is only propagated to those synapses according to the rules of associativity and cooperativity.

Associativity

Associativity refers to the observation that when weak stimulation of a single pathway is insufficient for the induction of LTP, simultaneous strong stimulation of another pathway will induce LTP at both pathways.

Cooperativity

LTP can be induced either by strong tetanic stimulation of a single pathway to a synapse, or cooperatively via the weaker stimulation of many. When one pathway into a synapse is stimulated weakly, it produces insufficient postsynaptic depolarization to induce LTP. In contrast, when weak stimuli are applied to many pathways that converge on a single patch of postsynaptic membrane, the individual postsynaptic depolarizations generated may collectively depolarize the postsynaptic cell enough to induce LTP cooperatively. Synaptic tagging, discussed later, may be a common mechanism underlying associativity and cooperativity. LTP is generally divided into three parts that occur sequentially: Short-term potentiation, early LTP (E-LTP) and late LTP (L-LTP). Short-term potentiation isn't well understood and will not be discussed.

E-LTP and L-LTP phases of LTP are each characterized by a series of three events: induction, maintenance and expression. Induction happens when a short-lived signal triggers that phase to begin.

Maintenance corresponds to the persistent biochemical changes that occur in response to the induction of that phase. Expression entails the long-lasting cellular changes that result from activation of the maintenance signal.

Each phase of LTP has a set of mediator molecules that dictate the events of that phase. These molecules include protein receptors, enzymes, and signaling molecules that allow progression from one phase to the next. Besides to mediators, there are modulator molecules that interact with mediators to fine tune the LTP. Modulators are a bit beyond the scope of this introductory book, and won't be discussed here.

ANATOMY AND FUNCTION OF NERVOUS SYSTEM

Read this page and discover how the nervous system controls everything we do - with significant implications for exercise instruction.

Nervous system terms

Firstly, with the nervous system there are many new terms you will likely come across, whether its in this section, in other anatomy text books and in the fitness industry. To help you understand some of these new terms we have defined them in the following table (bear in mind that you may need to read on for some of these definitions to make sense!):

Term	Definition
CNS	CNS stands for central nervous system and includes the brain and spinal cord.
PNS	PNS stands for peripheral nervous system and includes all nerves outside of the CNS
Neuron	Neurons (nerve cells) are the building blocks of all nerves. Individual nerves are made up of thousands of neurons.
Action potential	Action potentials are the electrical impulses (messages) that travel throughout the nervous system
EPSP	EPSP stands for excitory post-synaptic potential. It is a positive change that makes a nerve more likely to fire an action potential

IPSP	IPSP stands for inhibitory post-synaptic potential. It is a negative change that makes a nerve less likely to fire an action potential
Depolarisation	This refers to the charge within a neuron becoming positive and reaching threshold. Resulting in an action potential being fired.
Hyperpolarisation	This refers to the charge within a neuron becoming more negative and an action potential being blocked from firing.
Re-polarisation	This means the neuron returning to its resting/relaxed state after it has depolarised at sent an action potential.
Temporal summation	This m two or more action potentials arriving in quick succession from one neuron.
Spatial summation	This means two or more action potentials arriving at the same time from two or more different neurons.

Nervous system: What it is?

The nervous system is a control system of the body and is a bit like a computer. The brain is similar to the software and is responsible for making decisions and the nerves are like the hardware or wiring that communicates those decisions with the rest of the body.

What does the nervous system do?

The nervous system along with the endocrine (hormonal) system works to control all activities within the human body. It does this by communicating messages between the brain and the body very quickly using nerve impulses (action potentials).

The four chief functions of the nervous system are:

1. Control of body's internal environment to maintain 'homeostasis': An example of this is the regulation of body temperature. As we exercise we create heat, in order to maintain a relatively constant core temperature the nervous system sends messages to the blood vessels to dilate

(expand), increasing blood flow to the skin, and increasing sweating to help disperse the accumulating heat.

2. Programming of spinal cord reflexes: An instance of this is the stretch reflex. This reflex functions to protect us from injury. If we were out jogging and accidentally ran into a pot-hole and rolled our ankle, the stretch reflex would instantly sense the stretch in the muscles around the ankle and send messages to those muscles telling them to contract and resist the stretch. This reflex serves to protect the ankle from breaking and results in a minor sprain rather than a severe break.

3. Memory and learning: You didn't learn to read or write overnight did you? A certain amount of repetition was required to learn and memorise these key functions. The same applies with exercise. New movements, especially complex ones, take time for the nervous system to learn. Remember this when teaching new exercises to people – a certain amount of repetition will need to occur before their nervous system gets it right!

4. Voluntary control of movement: Every voluntary movement that a person performs is under the direct control of the nervous system as the nervous system sends the messages to the particular body parts to move. If the movement has been repeated numerous times (walking for most of us…) the movement will be very efficient. If however the movement is new and still requires some repetition then we would expect the movement to be less efficient and in some cases look awkward and ungainly (such as a person learning the squat for the first time).

Significance of Nervous System

The nervous system is integral to our ability to function in everyway. As we know muscle creates movement by contracting and pulling on our bones. However it is the nervous system that is responsible for stimulating the muscles and causing them to contract. Without the neural impulses of the nervous system, muscle would simply not work. When someone experiences a

severe trauma to their spinal cord, it will often result in paralysis of their body below the point of trauma. For example if the spinal cord is damaged above the nerves that stimulate their lower body (legs etc), then they will not be able to walk again. This is because the messages which are intended for the legs can no longer reach them.

In essence it is like the power cable to your house being cut and the lights going out.

The nervous system is not just responsible for stimulating muscle; it stimulates every tissue and organ within the body. It is therefore important that you understand the nervous system so that you can train clients safely and effectively.

The nervous system and fitness

The nervous system and fitness go hand in hand. Completing an activity that you have done thousands of times like running, learning a new skill such as squatting or simply thinking about the activity you are about to do all utilise the nervous system.

For instance when a client learns a new exercise, like the dumbbell bench press, you may find that the movement is quite awkward and difficult for them. This is because their nervous system is trying to learn something new. However the more they repeat and refine the same movement the more efficient and

smooth it becomes, until it is second nature. When working with clients, a lot of the initial gains come from improvements in the nervous system as it learns new movement patterns and becomes more efficient at doing its job.

It is also worth noting however, that if you give a client an exercise that is too advanced for them they may be deterred from exercising. This is because the experience of not being able to do the exercise, feeling vulnerable while lifting weights or being excessively sore the next day may put them off.

Ensuring your client is challenged sufficiently and appropriately to achieve their goals is fundamental when working in fitness. To help you do this understanding the nervous system and your clients ability is important. This is because it will help you pick the correct types of exercise and intensities for clients, as well as know when to progress or regress an exercise.

Organisation of Nervous System

The nervous system has many divisions, each division has their own distinct objective. The diagram that follows represents the nervous system and its various divisions, followed by a explanation of each division.

Central Nervous System (CNS)

The structures of the CNS are the brain and spinal cord. Their job is to integrate information coming back from the peripheral nervous system and to respond automatically or make decisions on actions that should be taken. You can think of the CNS as the 'head office' of the body, it works consciously and subconsciously to control all activities within the body.

Peripheral Nervous System (PNS)

The structures of the PNS include the cranial nerves (nerves of the head) and spinal nerves.

Their job is to communicate information between the CNS and the rest of the body.

Sensory (afferent) Division

The sensory (also known as afferent) division of the nervous system contains nerves that come from the viscera (internal organs) and the somatic areas (muscles, tendons, ligaments, ears, eyes and skin).

These nerves conduct impulses to the PNS/CNS providing information on what is happening within and outside the body. The senses include; hearing, sight, touch, and proprioception (the awareness of where you are in space and what position you're in).

Motor (efferent) Division

The motor (also known as efferent) division of the nervous system contains motor nerves.

These nerves conduct impulses from the CNS and PNS to the muscles, organs and glands' effecting what happens in those tissues.

Somatic Nervous System

The somatic division of the nervous system contains nerves which end in the skeletal muscles.

These nerves conduct impulses which control the skeletal muscles in response to a directive that comes from the brain. This conscious control means we call the activity of this division 'voluntary'.

Autonomic Nervous System

The autonomic division of the nervous system contains nerves which end in the viscera (internal organs). They are therefore called visceral motor nerves.

These nerves conduct impulses which control the heart, lungs, smooth muscle in blood vessels, digestive tract and glands. These nerves are active without conscious input from the brain so are said to be 'involuntary'.

Sympathetic Division

The sympathetic division of the nervous system is part of the autonomic nervous system. It works 'automatically' to mobilise

the body's systems during activity (for example the fight or flight response).

If you have ever had a fright and afterward realise your heart is still beating rapidly, you're tense and your palms are sweating, then you have experienced the activity of the sympathetic portion of the autonomic nervous system.

Parasympathetic Division

The parasympathetic division of the nervous system is part of the autonomic nervous system as well. It works 'automatically' to inhibit or relax the body's systems. It promotes digestion and other 'housekeeping' functions when the body is at rest.

The following diagram highlights how the sympathetic and parasympathetic divisions have different effects on different organs.

Central Nervous System – what does the brain and Spinal cord Do?

The Brain

The brain is organised into areas responsible for processing information, making decisions and then carrying out the appropriate task. As you know from the previous section it can do this consciously and subconsciously. Instances of some of these tasks are:

1. maintaining homeostasis
2. interpreting sensory information
3. creating motor responses (movement)
4. learning
5. thinking
6. talking.

By looking at the following diagram you can see that the brain has distinguishable anatomical divisions that operate simultaneously. Inevitably the brain is modular by design, with each module responsible for a particular function, but the brain also has the ability to integrate information in a split second between modules.
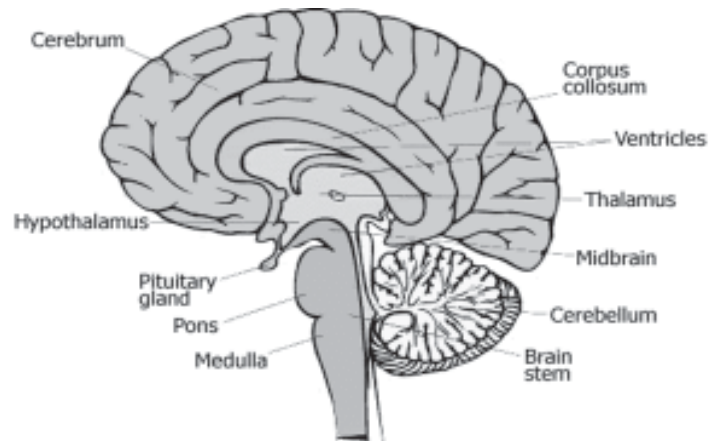
The spinal cord

The spinal cord provides an ASCENDING pathway for sensory information travelling from sensory receptors in the body up to the brain and a DESCENDING pathway for motor information travelling down from the brain to the motor units.
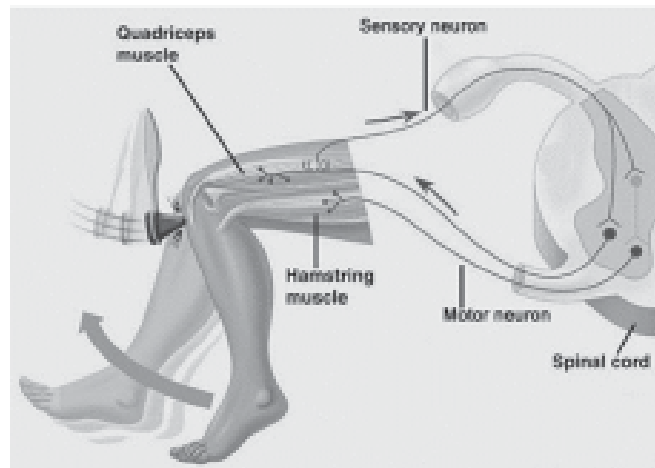
The spinal cord also acts like a switchboard for reflexes or movements requiring speed. With reflexes, motor responses (movements) are initiated at the spinal cord rather than the brain. This is because with reflexes speed is the absolute key – precious

time would be lost if the message had to travel to and from the brain.

Withdrawal and jerk are the most common types of reflexes. An instance of a withdrawal reflex is putting your hand on a hot element and moving it away before the sensation of pain is registered. In this reflex sensory information is relayed to the spinal cord through a sensory neuron. The spinal cord then sends a command via a motor neuron back to the motor unit telling it to contract the muscle and move the hand off the element.

An instance of the jerk reflex is the kick of the leg resulting from a tap on the patella tendon. This usually happens at the doctors when they are testing function. As shown on the adjacent diagram a stretch receptor in the muscle senses the tap on the patella and sends this information to the spinal cord via a sensory nerve.

The spinal cord sends a command via a motor nerve to the motor unit in the muscle (in this case the quadriceps) to contract, causing a rapid contraction or 'jerk'.

Connection different Nervous System Divisions to Work Together

Understanding what each of the nervous system divisions are and their individual roles is important, but it's also vital to know how they are wired in to work together in order to function as a whole. This is because it is the nervous system divisions working together that allow it to function and effectively carryout it's various tasks. The Central Nervous System (CNS) is connected to the rest of the body by the sensory and motor nerves of the Peripheral Nervous System (PNS). Sensory nerves relay information to the CNS; motor nerves execute motor commands from the CNS. The nerves of the PNS are split into the Cranial and Spinal nerves.

Cranial nerves branch out of the brains ending information and commands directly between the brain and structures in the head, neck, thoracic and abdominal cavities including eyes, ears,

nose, mouth throat, heart, lungs, liver and all the other abdominal and thoracic organs, as well as some muscles of the shoulder and neck. Spinal nerves branch out from the spinal cord then branch off to make all the nerves of the trunk, arms and legs.

The spinal nerves are classified according to the region in which they branch off the spinal cord; the cervical spinal nerves branch off from the neck region, the thoracic nerves branch off from the mid torso region and the lumbar and sacral spinal nerves branch off from the lower back and hip regions. Spinal nerves carry information and commands to and from the spinal cord, trunk, arms and legs. The motor and sensory tracts of the spinal cord carry information and commands between the spinal nerves and the brain.

NERVOUS SYSTEM: STRUCTURE AND FUNCTION

Muscle contraction is initiated by the nervous system which together with the endocrine system controls the human organism. They are responsible for the steadiness of the inner environment and coordination of all the bodily functions. The nerve cell, a neuron, is the basic unit of the nervous system. Cells attending to muscles are called motoneurons. A neuron is composed of the body and projections. The shorter ones are called dendrites, the long one is axon. Through the dendrite the neuron is able to obtain information from other neurons. The axon then passes the processed information to other cells (e.g. muscle cells).

The information is further spread along the neuron through changes in the voltage in the cell membrane, the so called action potential. The transfer of information between individual nerve cells is then secured by chemical agents. Once the action potential has reached the end of an axon, the mediator is released.

Neuromuscular junction is a place where the last motoneuron and the muscle cell meet. The binding of the mediator (acetylcholine) to the receptor brings about another action potential which spreads along the muscle cell membranes.

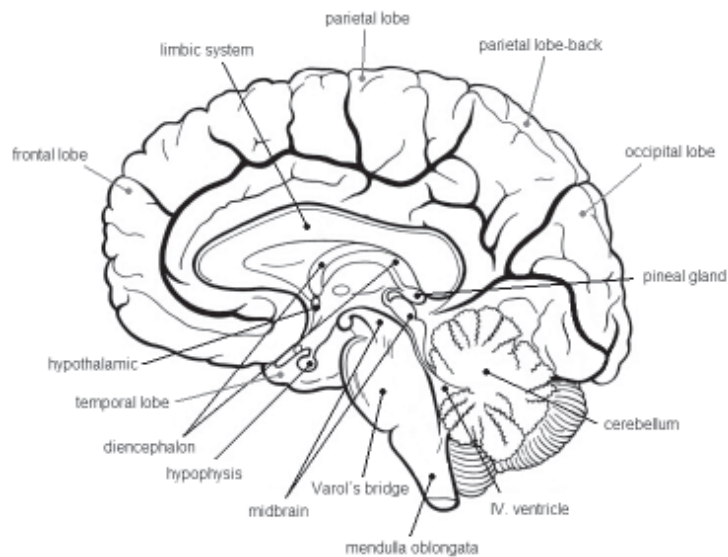## Central and peripheral nervous system

The nervous system is made up of the central and peripheral nervous systems.

The central nervous system (CNS) is composed of the brain and the spinal cord.

The brain is made up of:
- medulla oblongata
- pons Varolii
- midbrain or mesencephalon
- little brain or cerebellum
- interbrain or diencephalon: thalamus and hypothalamus
- basal ganglia
- limbic system
- cerebral cortex

Different parts of the CNS are interconnected through ascending and descending pathways creating functional wholes.

Figure : Structure of the brain

The peripheral nervous system is composed of 12 pairs of head nerves connected to the brain and of 31 pairs of spinal nerves attached to the spinal cord. Sensoric nerves transfer information from body receptors to the CNS. Motoric nerves transport information from the CNS to muscle fibres.

Autonomic nervous system: Functions and Activities

The autonomic nervous system functions to control the activities of the inner organs (heart, glands, smooth muscles). It is involuntary. It is made up of sympathetic and parasympathetic systems which both try to keep the functional balance of the human body with the possibility of either of the systems taking prevalence in certain situations. In athletes the sympathetic system becomes dominant during movement activities while the parasympathetic system prevails under resting conditions.

The sympathetic nervous system enhances organ activity (increase in HR, increase in BP, etc.) while the parasympathetic nervous system produces the opposite effect, i.e. reduces organ activity (decrease in HR).

5

Neurogenetics: Origin, Development and Research

The Neurogenetics Unit at the National Hospital for Neurology and Neurosurgery offers a fully integrated service encompassing clinical assessment, diagnosis, molecular genetic testing and counselling for neurogenetic conditions. In particular, we have clinical and scientific expertise in inherited movement disorders including Huntington's disease, ataxia and familial Parkinsonian diseases, neuromuscular disorders including peripheral neuropathies, channelopathies and mitochondrial disorders. A comprehensive User Manual is available from the laboratory on request. The laboratory is CPA accredited and a member of the UK Genetic Testing Network and is situated within the Department of Molecular Neuroscience at the NHNN/UCL. Close ties with clinical colleagues mean that the service is regularly developing in line with clinical need and so provides users (both patients and medical professionals) with an up-to-date and comprehensive service.

Our scientists are well trained and professionally regulated (all participate in a CPD programme aimed at ensuring that scientists are both technically and theoretically up-to-date with new developments in the field) and have many years experience in analysis and interpretation of molecular genetic results. The Neurogenetics Laboratory provides a regional service for inherited

neurological disease and a national and international diagnostic service for rare neurogenetic disorders. The Laboratory is based at the Institute of Neurology and laboratory staff actively contribute to and supervise research projects. The focus of much of the research is the molecular basis of neurogenetic disorders and these include channelopathies, neuropathies and mitochondrial disease as well as common diseases such as epilepsy and Parkinson Disease. The laboratory is well placed to perform these studies as we have some of the largest clinically characterised cohorts of patients nationally and worldwide. The Neurogenetics Laboratory forms an integral part of the clinical, research and teaching team.

Origin

The field of neurogenetics emerged from advances made in molecular biology, genetics and a desire to understand the link between genes, behaviour, the brain, and neurological disorders and diseases. The field started to expand in the 1960s through the research of Seymour Benzer, considered by some to be the father of neurogenetics.His pioneering work with *Drosophila* helped to elucidate the link between circadian rhythms and genes, which led to further investigations into other behaviour traits. He also began conducting research in neurodegeneration in fruit flies in an attempt to discover ways to suppress neurological diseases in humans. Several of the techniques he used and conclusions he drew would drive the field forward.Early analysis relied on statistical interpretation through processes such as LOD (logarithm of odds) scores of pedigrees and other observational methods such as affected sib-pairs, which looks at phenotype and IBD (identity by descent) configuration. Several of the disorders studied early on including Alzheimer's, Huntington's and amyotrophic lateral sclerosis (ALS) are still at the center of much research to this day. By the late 1980s new advances in genetics such as recombinant DNA technology and reverse genetics allowed for the broader use of DNA polymorphisms to test for linkage between DNA and gene defects. This process is referred to sometimes as linkage analysis.

By the 1990s ever advancing technology had made genetic analysis more feasible and available. This decade saw a marked increase in identifying the specific role genes played in relation to neurological disorders. Advancements were made in but not limited to:Fragile X syndrome, Alzheimer's, Parkinson's, epilepsy and ALS.

Neurological disorders

While the genetic basis of simple diseases and disorders has been accurately pinpointed, the genetics behind more complex, neurological disorders is still a source of ongoing research. New developments such as the genome wide association studies (GWAS) have brought vast new resources within grasp. With this new information genetic variability within the human population and possibly linked diseases can be more readily discerned.

Neurodegenerative diseases are a more common subset of neurological disorders, with examples beingAlzheimer's disease and Parkinson's disease. Presently no viable treatments exist that actually reverse the progression of neurodegenerative diseases; however, neurogenetics is emerging as one field that might yield a causative connection. The discovery of linkages could then lead to therapeutic drugs, which could reverse brain degeneration.

Gene sequencing

One of the most noticeable results of further research into neurogenetics is a greater knowledge of gene loci that show linkage to neurological diseases. The table below represents a sampling of specific gene locations identified to play a role in selected neurological diseases.

Gene Loci	Neurological Disease
APOE å4, *PICALM*	Alzheimer's Disease
DR15, *DQ6*	Multiple Sclerosis
LRRK2, *PARK2*, *PARK7*	Parkinson's Disease
HTT	Huntington's Disease

METHODS OF RESEARCH

Statistical Analysis

Logarithm of odds (LOD) is a statistical technique used to estimate the probability of gene linkage between traits. LOD is often used in conjunction with pedigrees, maps of a family's genetic make-up, in order to yield more accurate estimations. The main advantage of this technique is its ability to give reliable results in both large and small sample sizes, which is a marked advantage in laboratory research.Quantitative trait loci (QTL) mapping is another statistical method used to determine the chromosomal positions of a set of genes responsible for a given trait. By identifying specific genetic markers for the genes of interest in a recombinant inbred strain, the amount of interaction between these genes and their relation to the observed phenotype can be determined through complex statistical analysis.

In a neurogenetics laboratory, the phenotype of a model organisms is observed by assessing the morphology of their brain through thin slices. QTL mapping can also be carried out in humans, though brain morphologies are examined using nuclear magnetic resonance imaging (MRI) rather than brain slices. Human beings pose a greater challenge for QTL analysis because the genetic population cannot be as carefully controlled as that of an inbred recombinant population, which can result in sources of statistical error.

Recombinant DNA

Recombinant DNA is an important method of research in various fields, comprising neurogenetics. It is used to make alterations to an organism's genome, usually causing it to over- or under-express a certain gene of interest, or express a mutated form of it. The results of these experiments can provide information on that gene's role in the organism's body, and it importance in survival and fitness. The hosts are then screened with the aid of a toxic drug that the selectable marker is resistant to.

The use of recombinant DNA is an example of a reverse genetics, where researchers create a mutant genotype and analyze the resulting phenotype. In forward genetics, an organism with a particular phenotype is identified first, and its genotype is then analyzed.

Animal Research

Model organisms are an important tool in many areas of research, comprising the field of neurogenetics. By studying creatures with simpler nervous systems and with smaller genomes, scientists can better understand their biological processes and apply them to more complex organisms, like humans. Due to their low-maintenance and highly mapped genomes, mice,*Drosophila*, and *C. elegans* are very common. Zebrafish and prairie voles have also become more common, especially in the social and behavioural scopes of neurogenetics.

Besides examining how genetic mutations affect the actual structure of the brain, researchers in neurogenetics also examine how these mutations affect cognition and behaviour. One method of examining this involves purposely engineering model organisms with mutations of certain genes of interest. These animals are then classically conditioned to perform certain types of tasks, like pulling a lever in order to gain a reward. The speed of their learning, the retention of the learned behaviour, and other factors are then compared to the results of healthy organisms to determine what kind of an effect – if any – the mutation has had on these higher processes. The results of this research can help identify genes that may be associated with conditions involving cognitive and learning deficiencies.

Human Research

Several research facilities seek out volunteers with certain conditions or illnesses to participate in studies. Model organisms, while important, cannot completely model the complexity of the human body, making volunteers a key part to the progression of research. Along with gathering some basic information about

medical history and the extent of their symptoms, samples are taken from the participants, including blood, cerebrospinal fluid, and/or muscle tissue. These tissue samples are then genetically sequenced, and the genomes are added to current database collections.

The growth of these data bases will ultimately permit researchers to better understand the genetic nuances of these conditions and bring therapy treatments closer to reality. Prebent areas of interest in this field have a wide range, spanning anywhere from the maintenance of circadian rhythms, the progression of neurodegenerative disorders, the persistence of periodic disorders, and the effects of mitochondrial decay on metabolism.

Behavioural Neurogenetics

Advances in molecular biology techniques and the species-wide genome project have made it possible to map out an individual's entire genome. Whether genetic or environmental factors are primarily responsible for an individual's personality has long been a topic of debate. Thanks to the advances being made in the field of neurogenetics, researchers have begun to tackle this question by beginning to map out genes and correlate them to different personality traits. There is little to no evidence to suggest that the presence of a *single* gene indicates that an individual will express one style of behaviour over another; rather, having a specific gene could make one more predisposed to displaying this kind of behaviour. It is starting to become clear that most genetically influenced behaviours are due to the effects of *multiple* genes, besides other neurological regulating factors like neurotransmitter levels. Aggression, for example, has been linked to at least 16 different genes, many of which have been shown to have different influences on levels of serotonin and dopamine, neurotransmitter density, and other aspects of brain structure and chemistry.

Similar findings have been found in studies of impulsivity and alcoholism. Because of to fact that many behavioural

characteristics have been conserved across species for generations, researchers are able to use animal subjects such as mice and rats, but also fruit flies, worms, and zebrafish, to try to determine specific genes that correlate to behaviour and attempt to match these with human genes.

Cross-species Gene Conservation

While it is true that variation between species can appear to be pronounced, at their most basic they share many similar behaviour traits which are necessary for survival. Such traits include mating, aggression, foraging, social behaviour and sleep patterns. This conservation of behaviour across species has led biologists to hypothesize that these traits could possibly have similar, if not the same, genetic causes and pathways.

Studies conducted on the genomes of a plethora of organisms have revealed that many organisms have homologous genes, meaning that some genetic material has been conserved between species. If these organisms shared a common evolutionary ancestor, then this might imply that aspects of behaviour can be inherited from previous generations, lending support to the genetic causes – as opposed to the environmental causes - of behaviour. Variations in personalities and behavioural traits seen amongst individuals of the same species could be explained by differing levels of expression of these genes and their corresponding proteins.

Impulse Control

Impulsivity is the inclination of an individual to initiate behaviour without adequate forethought. An individual with high impulsivity will be more likely to act in ways that are not generally beneficial or are outside the normal range of action one would expect to see. Through the use of such techniques as fMRI and PET scans, differences in impulsivity have been seen to be directly influenced by a right lateralized neural circuit.

In addition, impulsivity levels have been linked to brain density levels, specifically the density of white and grey matter and levels of myelination. This suggests that there are specific areas of the

brain that play a direct role in the regulation of behaviour. This indicates a possible genetic correlation since all human brains have the same general anatomical make up. A 2008 study found a significant correlation between gene expression and brain structure in both model organisms and humans. The levels of expression of dopamine and serotonin in particular have been found to be very influential on brain structure. *DAT* and *DRD4* genes, both of which code for proteins that contribute to the density of the prefrontal gray matter, also have been found to be particularly significant. Individuals with ADHD, specifically those with a *DRD* 4/4 genotype, were found to have smaller prefrontal gray matter volume than those without the 4/4 genotype, indicating that their level of impulse control would be lower than normal. There are several other genes that can contribute to either brain density or its composition, and further studies are being conducted to determine the significance of each.

Higher Cognitive Function

Corresponding to impulsivity, varying levels of cognition have been linked to various different genes, several of which are related to dopamine genes expression in frontostriatal circuitry. These genes have been seen to play a role in higher cognitive functions such as learning and motivation, possibly by acting on the reward system in the dopamine pathway. It has been shown that these factors, along with many others not related to dopamine, such as *CHRM2*, are highly heritable. While several executive functions can be learned through experience and environmental factors, individuals with these specific genes, particularly those with high expression levels, were shown to possess higher cognitive function than those without them.

One possible explanation for this is that these genes act as high motivational factor, making these individuals more likely to either develop better cognitive function naturally or participate in activities that result in higher cognitive function by means of experience. Much of this motivation may arise from reward based learning. In this type of learning, a particular outcome is more

positive than anticipated, resulting in a higher level of dopamine being released in the brain.

Dopamine release was for a long time thought to result in a feeling of pleasure, causing an increase in this behaviour. However, recent advances in our understanding of reward prediction and learning are leading researchers to view dopamine simply as a reward-error signal, rather than being responsible for inducing the feeling of pleasure. Over time this reward-seeking behaviour will increase synaptic plasticity, resulting in an increase in neuronal connections and faster response times.

Aggression

There is also research being conducted on how an individual's genes can cause varying levels of aggression and aggression control. Throughout the animal kingdom, varying styles, types and levels of aggression can be observed leading scientists to believe that there might be a genetic contribution that has conserved this particular behavioural trait. For some species varying levels of aggression have indeed exhibited direct correlation to a higher level of Darwinian fitness. The effect serotonin (5-HT) and the varying genes, proteins and enzymes have on aggression is the focus of studies currently. This pathway has been linked to aggression through its influences on early brain development and morphology, as well as directly regulating an individual's level of impulsive aggression. One enzyme that researchers believe plays a direct role in aggression control is the enzyme MAO, which is partially liable for the degradation of serotonin and thus aggression control. The genes, as well as the proteins themselves, for the 5-HT receptor, as well as the 5-HT transporter, SERT, also have a direct effect on the level of aggression seen in test subjects. The up regulation of a specific 5-HT receptor, 5-HT1A, and the down regulation of SERT, both contribute to lowering an individual's level of aggression.

While studies have been conducted on humans, such as Han Brunner's experiment with a MAO-A deficient Dutch family, which

first hinted at the possible linkage between MAO A and aggression, and was later confirmed by Isabelle Seif's mouse experiment, much of the current research is being conducted on zebrafish to identify the underlying genetic and morphological aspects that lead to aggression as well as many other behavioural traits.

Alcohol dependency

The study of alcoholism and the neurogenetic factors that increase one's susceptibility is a budding field of study. A multitude of genes associated with the condition have been found which can act as indicators for an individual's predisposition to alcoholism. Improper expression of *ALDH2* and *ADH1B* leads to polymorphism and causes these two enzymes to function improperly, making it difficult to digest alcohol. This kind of expression has been found to be a strong indicator of alcoholism, along with the presence of *GABRA2*, a gene which codes for a specific GABA receptor. How GABRA2 leads to alcohol dependence is still unclear, but it is thought to interact negatively with alcohol, altering the behavioural effect and resulting in dependency. In general, these genes code for receptor or digestive proteins, and while having these particular genes does indicate a predisposition towards alcoholism, it is not a definitive determining factor. Like all behavioural traits, genes alone do not determine an individual's personality or behaviour, for the influence of the environment is just as important.

Development

A great deal of research has been done on the effects of genes and the formation of the brain and the central nervous system. The following wiki links may prove helpful:

- Neural development
- Neurogenesis
- The Brain
- Neural tube.

There are several genes and proteins that contribute to the formation and development of the CNS, many of which can be

found in the aforementioned links. Of particular importance are those that code for BMPs, BMP inhibitors and *SHH*. When expressed during early development, BMP's are responsible for the differentiation of epidermal cells from the ventral ectoderm. Inhibitors of BMPs, like *NOG* and *CHRD*, promote differentiation of ectoderm cells into prospective neural tissue on the dorsal side. If any of these genes are improperly regulated, then proper formation and differentiation will not occur. BMP also plays a very important role in the patterning that occurs after the formation of the neural tube. Because of the graded response the cells of the neural tube have to BMP and Shh signaling, these pathways are in competition to determine the fate of preneural cells. BMP promotes dorsal differentiation of pre-neural cells into sensory neurons and Shh promotes ventral differentiation into motor neurons. There are several other genes that help to determine neural fate and proper development include, *RELN*, *SOX9*, *WNT*, Notch and Delta coding genes, *HOX*, and various cadherin coding genes like *CDH1* and *CDH2*.

Some present research has shown that the level of gene expression changes drastically in the brain at different periods throughout the life cycle. For instance, during prenatal development the amount of mRNA in the brain (an indicator of gene expression) is exceptionally high, and drops to a significantly lower level not long after birth. The only other point of the life cycle during which expression is this high is during the mid- to late-life period, during 50–70 years of age. While the increased expression during the prenatal period can be explained by the rapid growth and formation of the brain tissue, the reason behind the surge of late-life expression remains a topic of ongoing research.

Current research

Neurogenetics is a field that is rapidly expanding and growing. The current areas of research are very diverse in their focuses. One area deals with molecular processes and the function of certain proteins, often in conjunction with cell signaling and

neurotransmitter release, cell development and repair, or neuronal plasticity. Behavioural and cognitive areas of research continue to expand in an effort to pinpoint contributing genetic factors. As a result of the expanding neorogenetics field a better understanding of specific neurological disorders and phenotypes has arisen with direct correlation to genetic mutations. With severe disorders such as epilepsy, brain malformations, or mental retardation a single gene or causative condition has been identified 60% of the time; however, the milder the intellectual handicap the lower chance a specific genetic cause has been pinpointed.

Autism for instance is only linked to a specific, mutated gene about 15-20% of the time while the mildest forms of mental handicaps are only being accounted for genetically less than 5% of the time. Research in neurogenetics has yielded some promising results, though, in that mutations at specific gene loci have been linked to harmful phenotypes and their resulting disorders. For example a frameshift mutation or a missense mutation at the *DCX* gene location causes a neuronal migration defect also known as lissencephaly. Another example is the *ROBO3* gene where a mutation alters axon length negatively impacting neuronal connections. Horizontal gaze palsy with progressive scoliosis (HGPPS) accompanies a mutation here. These are just a few examples of what current research in the field of neurogenetics has achieved.

DEFINITION

Neurogenetics is a branch of genetics that analyzes the impact of genes on the structure and function of the brain and peripheral nervous system. Because studies of neurogenetics pertain to genes that determine our individuality, as well as diseases and dysfunctions, exploration of normal and disordered genes in the nervous system requires further knowledge and thoughtful consideration.

One aspect of neurogenetics identifies the genetic basis for diseases and pathologies of the brain and nervous system. This

information could be used to identify factors that cause or increase risk for those conditions.

Subsequent steps could be taken to prevent or mitigate the onset of symptoms, or at least enable genetic counseling that could protect the gene-bearer's offspring from the condition. A second aspect of neurogenetics identifies the genes associated with various positive personality traits and abilities (musical talent, intellect, athletic ability), as well as negative traits such as violence and aggression.

There is a moral imperative not to confuse science with metaphysics. Likewise, neuroscience is not neuroethics. A scientific discovery does not answer all the questions about its role in society. We require to take the discoveries of science out of the laboratory and into our lives to determine the implications regarding how the discoveries will be interpreted, applied, and assimilated into current schools of thought.

Reasons for ethical Consideration

All new technologies deserve reasoned, thoughtful debate before large-scale introduction, whether the technologies or the debates are biomedical in nature, legal, political, even environmental. If an innovation has the potential to change the ways in which we live and work, it is important that we consider the ethical, social, and legal implications and decide if, on balance, the positive outcomes outweigh the negative.

Are the potential benefits worth the potential costs, efforts, or harms?

DIAGNOSTIC USES OF NEUROGENETICS

Finding Disease Markers

The National Institute of Neurological Disorders and Stroke (NINDS) estimates that twenty percent of the United States population, about 50 million people, suffer from at least one of more than 600 neurological diseases. Several of these disorders

have been linked to genetic factors, while for others the etiologies and whether or not they are genetically determined are still unknown. The same points can be made regarding psychiatric disorders which are among the most prevalent disorders world wide. Indeed, advances in genetics have brought the fields of neurology and psychiatry closer together than ever before.

Genes can be switched on and off, and even regulated in a graded way. Some inherited genetic mutations may well be in the operation of these switches, and genetic anomalies may act on more than one gene.

There is great interest in the role of genetics in neurological diseases. In some cases, we only know that a correlation exists between a region on a chromosome and a disease. In other cases, specific mutations have been identified that cause the disease in question (e.g., Huntington's disease, Fragile X syndrome). In several examples, mutations have been identified that increase the risk for a disease even though they have not been proven to be a direct cause of the disease (e.g., APOE4 in Alzheimer 's disease).

Even in conditions where we know of specific genetic mutations (e.g., in Parkinson's disease, amyotrophic lateral sclerosis (ALS), muscular dystrophy, and various forms of epilepsy), it has become clear in recent years that the genetics of many of these common disorders is complex in that many genes contribute to the disease phenotype. It is significant to emphasize that we are dealing with brain disorders. As we learn more about genetic determinants, traditional distinctions between neurological and psychiatric diseases may fade or disappear. Genes may determine traits in addition to defined clinical disorders. The depression of Parkinson's disease may have the same determinants as the depression observed in bipolar disorder. In this module, we present a brief overview of the genetics of some common neurological disorders and the ethical implications for the individual and society that this fast moving field holds. The objective is to encourage thoughtful debate about the positive as well as negative uses and implications of neurogenetics.

Huntington's Disease

Through the field of neurogenetics, we can test for genetic markers and mutations for pathologies in the brain. The classic example is Huntington's disease (HD), a neurodegenerative brain disorder that is both monogenetic and has complete penetrance. At the present time, it is very essential that those who carry the HD mutation will develop this disease if they live long enough, and a parent who carries the HD mutation (excessive CAG repeats) has a 50:50 chance of passing the HD mutation to each of his or her children. A genetic test for Huntington's disease (HD) is currently available to at-risk persons with affected family members. Because the test is for a single gene mutation with high penetrance, those who test positive for the HD mutation will inevitably exhibit degeneration of nerve cells in the basal ganglia.

People at risk for HD may choose to be tested, but many choose not to be tested. Even among those who do undergo testing for the HD mutation, many then choose not to learn their results if they feel they cannot face the burden of knowing their genetic status.

Autism

Autism provides a stark contrast to Huntington's disease. It is explicitly a genetic disorder in families, but no single gene has emerged that can portend this devastating developmental disorder. The emphasis on genetics comes from the simple fact that the concordance rate for autism among identical twins is extraordinarily high—between 70% and 90% in different studies. The complexity of the genetics is indicated by the fact that the phenotypes of concordant identical twins may vary widely—from mildly to severely affected.

Current efforts are focused on early diagnosis, even though it is difficult to be certain of an autism diagnosis before the age of 3, as verbal IQ and mild language delays may complicate routine clinical evaluations. In working with toddlers, evaluators use measures that are independent of verbal interaction such as

tracking eye movements and on estimates of brain volume obtained by non-invasive Magnetic Resonance Imaging (MRI).

Attention is made on infants (6-12 months of age) who have older siblings with a clear diagnosis of autism. The likelihood of developing autism is higher in such "infant siblings" than in the general population. The significance of early diagnosis lies in the fact that prognosis may improve with early intervention. Although a genetic test might enable early diagnosis of autism, genome scans of families (linkage analyses) or populations of unrelated individuals (association analyses) have been inconclusive. Suspicious regions have been identified on many of the 23 pairs of chromosomes, but few of these "hot spots" have been seen in more than one study.

Thus, definitive, reproducible molecular targets have yet to emerge in autism. We do not yet have a reliable diagnostic, biochemical or molecular test for the majority of cases of autism.

One reason for the lack of definitive genetic findings lies in the complexity of the clinical phenotype. The DSM IV and other diagnostic manuals now place classic autism among a larger class of Progressive Developmental Disorders. There may be several forms of autism.

Classic autism is characterized by deficits in three principle areas: social cognition, language development, and repetitive, restrictive movements. Each of these categories shows wide variation. Social cognition deficits, for instance, can vary from infrequent eye contact to total lack of interpersonal play and empathy, as well as total inability to engage in tasks that require joint attention.

Another reason behind lack of genetic answers may lie in the complexity of the human genome. In recent years, we have learned that there is variation in the numbers of many different genes. We presumed that individuals have two copies of each gene, one on each chromosome, but recent data have uncovered "copy number variants" (CNVs). Small (sub-microscopic) regions of a

chromosome may be duplicated one or more times, and others may be deleted leaving one copy, or none at all. Genetic mutations may be due to CNVs as well as to "mis-spellings" or changes in the nucleotide sequence.

Techniques for detecting CNVs have evolved rapidly, and we can expect detection tests to become more routine in the near future. Children diagnosed with Fragile X syndrome or Rett Syndrome often exhibit features of autism. It is therefore recommended that children diagnosed with autism also be tested for the Fragile X and Rett syndrome mutations. The presence or absence of a genetic mutation may affect the types of care and treatment an individual receives.

Most clinicians agree that intervention with behavioural therapy for children with autism is most effective when started early; therefore, if doctors learn of the presence of a Fragile X mutation, they may begin more tailored interventions. Other co-morbidities have been identified, and they may be added to the list of recommended tests in the future. Of interest, such "syndromic" autism may be associated with single gene defects that may shed light on other cases of "essential" (no co-morbidity) autism.

Alzheimer's disease

In Alzheimer's disease (AD) genes play key roles but the roles are different for early onset AD and late onset AD. Early onset disease usually begins between age 45 and 60, and certainly before age 65 if there is a strong family history of the condition. Indeed, early onset AD is often referred to as Familial Alzheimer's disease (FAD). FAD is relatively rare, definitely much less common than late onset AD. It is inherited in an autosomal dominant fashion. That is, the disease will occur if one mutant gene is inherited from either parent. Mutations in the Aß amyloid gene have attracted a great deal of attention. A fragment of this transmembrane protein called AB42 accumulates in plaques (dense clumps of abnormal proteins) that form throughout the brain. Plaques in the

hippocampus and in the frontal lobes are especially devastating for functions related to learning and memory. Ordinarily a shorter fragment, AB40, is produced that does not accumulate in plaques. A mutation in the AB gene, discovered in many families, leads to altered cleavage of the AB protein and accumulation of the dangerous AB42 fragment. Other genes can alter the processing of the parent AB protein.

Two enzymes, beta and gamma secretase, regulate the cleavage of AB, and alterations in these enzymes can produce the toxic 43 amino acid cleavage product. Mutations in these enzymes have, indeed, been implicated in FAD.

None of these genes has been implicated in the more common late onset form of the disease. The prevalence of late onset AD increases with each decade of life after age 65. Some estimates suggest that 50% of the population over 85 suffers from AD.

Thus there is a dire need to identify late onset AD risk factors. Despite the enthusiastic search for such identifiers, the complexity of the AD phenotype may be a confounding factor, just as the complexity of autism and other mental disorders is for genetic analyses of those conditions. We simply do not know how many biochemical mechanisms contribute to the various facets of the syndrome now called AD. No genes have been identified that cause late onset AD. However, an allele of the APOE gene, located on chromosome 19, has been implicated as an important risk factor.

Four alleles (#1 — 4) of the APOE gene have been identified. They are all involved in the transport of cholesterol in the blood and in the metabolism of triglycerides. But something is different about the APOE4 protein. APOE4 is a risk factor, but it is not a certain predictor of the disease. Individuals who are homozygous for the E4 isoform may show no cognitive decline. Conversely, individuals with the E3 isoform which some consider to be protective for AD, may be severely demented. APOE4 presents special problems for genetic counseling. It is not difficult to identify the various gene alleles of protein isoforms, but what does one

advise a young couple who are both homozygous for the APOE4 isoform? As we have no effective treatment and no effective preventive measure that might delay the onset of AD, is the information useful? Should this be a consideration in their childbearing?

Epilepsy

Genes have been identified that are related to various rare forms of epilepsy. However, the most common forms of epilepsy such as febrile seizures, post-traumatic epilepsy, and generalized absence seizures undoubtedly reflect the interplay of multiple genetic factors and the environment.

Common forms of epilepsy do not follow a pattern of simple Mendelian inheritance. As with Alzheimer's disease, it appears that each risk conferring gene provides only a small additive effect to increase susceptibility.Many epilepsy genes encode components of membrane ion channels that regulate neuronal excitability. Indeed the different epilepsies are among a growing class of disorders now called "channelopathies." While such discoveries offer insights into underlying mechanisms, without more definitive causal links, there is limited utility to genetic testing of asymptomatic persons. This is the case even if the proband has a family history of the condition.

GENETIC TESTING

Minors : Its Genetic Testing

Majority are agreed that presymptomatic, predictive testing of minors below the age of 18 for genetically-linked neurological conditions is not recommended for adult onset neurological disorders for which there is no prevention because the children and adolescents lack the capacity for truly informed consent. Since several adults with family histories that put them at risk for genetic-linked diseases choose not to avail themselves of these tests, or they choose to have the genetic test and later decide not to receive the test results, it seems inappropriate to test children before they,

too, have the opportunity to choose for themselves whether they want to know their genetic status with all the benefits and harms of this information.

While there may be consensus not to test asymptomatic individuals before they reach an appropriate age of consent, there are exceptions to this rule — notably with some forms of epilepsy where knowledge of the child's genetic status can be important in planning medication and treatment protocols.

Genetic testing of symptomatic children is appropriate to obtain a definitive diagnosis. Lesch-Nyhan Syndrome, for instance, is a particularly violent self-destructive disorder that often requires restraints and constant observation; genetic testing may distinguish it from other disorders associated with mental retardation to optimize therapy and predict prognosis.

Pre-natal testing and Pre-implantation Genetic Diagnosis (PGD)

In Greek mythology, Pygmalion is a sculptor who sculpts a woman out of ivory, and falls in love with this statue, endowing her with gifts.
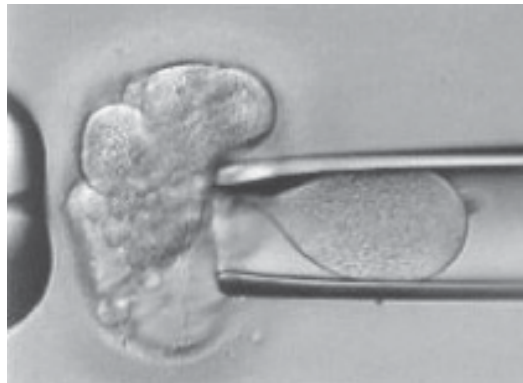
Removing a cell from a blastocyst for pre-implantation genetic diagnosis (PGD)

After a time, he asks the gods to imbue the statue with life, which they do. The myth is generally seen as the quintessential

transformation of fantasy into reality, where the reality perfectly mirrors the fantasy that has been designed.

A pygmalion effect in this case would involve parents shaping their child's behaviour to reflect the expectations based on the child's genotype, almost as a self-fulfilling prophesy.

Pregnant women and couples undergoing in vitro fertilization (IVF) procedures, especially those with a personal or family history of monogenic highly penetrant diseases, are genrally encouraged to undergo tests that reveal genetic information about the fetus or even the pre-implanted embryo. In cases where the tests show a genetic abnormality, but the parents decide to continue the pregnancy, what are the parents' responsibilities to the child in disclosing its genetic susceptibility to disease? Will they treat the child as if there were no genetic mutation, or rather, will they be overly cautious and overly protective with this child, a pattern that can lead to a Pygmalion effect, or even will they give up on the child prematurely?

Accuracy and Predictability of Results

Interpreting the results of genetic testing for several neurological diseases can be challenging, even for trained geneticists who are best prepared to interpret complex test results. Appropriate interpretation is challenged by varying knowledge of disease susceptibility, given certain genetic variants of unknown generally and gene interactions. One notable exception to this conundrum, of course, is Huntington's disease. To date, anyone having the grossly expanded CAG sequence will inevitably develop disease symptoms. The likelihood of developing a neurological condition based on one's genetic profile or make-up is hardly a straightforward prediction. Researchers perform complex mapping of the many genes and many different alleles. A gene may indicate a 70% susceptibility for a trait or disease in one example, but the presence of an accompanying gene may increase or decrease the likelihood of disease, offering an additive, a synergistic, or multiplicative effect. There are also complex environmental and

psychological factors that can influence the likelihood of developing a disease or condition based on the genetic profile.

Perceived Risk

The imprecision of genetic screening for several neurological conditions and diseases is complicated by a fundamental misunderstanding of statistics on the part of the general population, or a refusal to accept statistical arguments — even among the intellectually sophisticated.

There is the concept of "perceived" risk as opposed to "actual" risk. As an instance of this misunderstanding, take the well-established fact that car crashes result in more fatalities than airplane disasters. While the actual risk of riding in a car is much greater than in a plane, much of the public ignores this fact, and focuses more attention and anxiety on the perceived risks of air travel.

Fig. Human Chromosomes

Likewise, if a person has a gene that has a 20% chance of resulting in illness, will he or she emphasize that 20% chance of disease, or the 80% chance of health? Studies have also shown that

genes operate in complex networks rather than with simple, direct relationships. Instead of each sequence of DNA having a distinct and discrete function, it is now believed that genes and their effects interact and overlap. Predicting disease outcomes based on genetic profiles is therefore a complex matter, especially when one considers the environmental factors that contribute to disease etiology.

Neurologists order several of the available genetic tests for neurological conditions. While knowledgeable and savvy about neurology, disease syndromes, and treatment modalities, the interpretation of genetic tests may be best done in partnership with trained geneticists and genetic counselors. Interpretation of various kinds of the tests depends on a detailed knowledge of family history, on phenotypes associated with homozygous (both gene alleles are mutant) and heterozygous (one of the two gene alleles is mutant) states. Differentiating between benign normal genetic variants and disease-associated mutations can at times be difficult and may not be intuitively obvious to most neurologists.

The manifestation of the same mutation may vary among individuals. It takes considerable experience to recognize all of the various forms that a given mutation might take. With enhanced understanding of the genetic data, the neurologist will be better positioned to work with the patients, provide additional testing when necessary, and to recommend and offer the most appropriate intervention or treatment.

Home Testing Kits

The availability of home testing kits permits individuals to screen themselves for particular genes and gauge their susceptibility for certain diseases. This type of direct-to-consumer testing should be discouraged by physicians and geneticists. In addition to some tests not being valid, without proper interpretation or understanding of genetics and disease, a home test could result in needless confusion, panic, and erroneous contingency planning. Inaccurate or incorrectly interpreted home testing may also make

people less vigilant about their other health maintenance issues (e.g., cardiovascular disease, diabetes, hypertension, etc.) that are more likely to cause morbidity or even mortality.

The availability of direct-to-consumer genetic testing kits has alarmed some physicians and genetic counselors. Just because something's available does not mean it's safe or effective or worth your money.

Informed Consent

Informed consent to conduct a specific genetic test should acknowledge "the potential social and family implications, including the potential for discrimination on the basis of genetic-risk status."When clinicians provide informed consent procedures for genetic testing for heritable neurological diseases, especially those for which there is no treatment or cure, they should consider the benefits and harms of the resulting information for the individual. In the case of a neurological disorder such as Huntington's disease, physicians should counsel patients on the utility of undergoing such a genetic test.

For some, knowing that they will inevitably undergo a type of brain degeneration for which there is currently no cure, treatment, or effective prevention, may empower them to prepare for the future in terms of career choice, child bearing decisions, etc. For others, it would be too great a burden to bear this knowledge. For yet another subset of individuals, it can induce a sense of fatalism and futility in present and future endeavors, knowing one day they will become incapacitated.

Model requirements for informed consent

New York State law calls for eight statements that MUST be included in the informed consent process for patients undergoing clinical genetic testing. These eight required statements can serve as a model for an informed consent form. The statements comprise:

1. A general description of the genetic test
2. A statement of the purpose of the genetic test

3. A description of diseases and conditions being tested for

4. The likelihood of getting the condition given a positive genetic test result

5. Recommendations for further clinical tests if the genetic test is positive

6. A suggestion to seek genetic counseling before consenting to the test

7. Individuals to whom the genetic test results may be disclosed

8. Plans for destruction of the sample after a certain length of time so no other genetic tests may be done on the sample.

Additional suggestions for proper informed consent for genetic testing would include check-boxes that require research subjects/ participants to actively select the uses they will allow for their tissue sample.

Privacy and Confidentiality

In recommending genetic tests for brain disorders, one must appreciate the implications and broad reaches of the resulting information and consider the possibility of a loss of privacy because of a breach of confidentiality in the cases of heritable diseases (as opposed to spontaneous genetic mutations). By recommending that an individual be tested for an inherited condition, you must suggest that a parent or a sibling may have the gene, and therefore this parent or sibling either may or will get the disease.

Thus, these tests are only recommended for those who have a family history of or predisposition for contracting the disorder. There are also implications for the children of tested individuals, since a positive result for an inherited gene exposes the susceptibility of a child who may not want to know his or her genetic status or risk factors.

Protecting privacy and maintaining confidentiality are critically important in neurogenetics. Information resulting from genetic tests reveals much about an individual and the individual's family.

Besides, tests that reveal elements of a person's genetic code can, and often will, uncover unintended information with result that may affect more than just the individual. In about ten percent of a test group, truths about paternity are revealed that were not previously known.
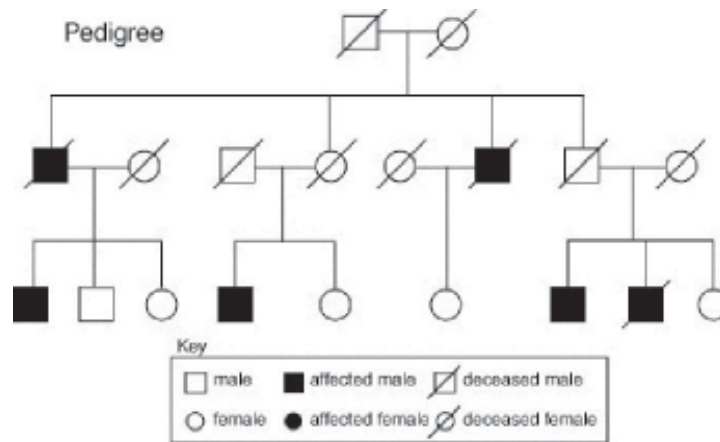

Fig. Sample pedigree chart

This information would be devastating information, indeed, were it released to inappropriate people (employers, insurance companies, etc.) through sloppy or careless privacy and confidentiality procedures. The emergence of more easily-accessed genetic codes requires a full-scale revision of our current codes of privacy and confidentiality. There are questions about who, eventually, owns the information displayed on an individual's genetic code. Is this information the property of the testing lab, the physician who ordered the test, the patient, the patient's family, etc.? Among these entities, whose responsibility is it to ensure that the information does not fall into the hands of insurers, employers, government agencies, and others who could use the information to discriminate against the individual? We must also consider the possibility of such information being used in the criminal justice system. The physician and the genetic counselor have a special obligation to protect the patient's right to privacy and to maintain strict confidentiality of private information.

Further, we must ensure that people do not undergo genetic testing without their knowledge. A patient's consent to a particular blood test is not an open-ended consent for every genetic test that can be done with a blood sample. For this reason, the informed consent process should require that the patient consent to specific tests or give permission for unspecified testing under certain circumstances, as well as the destruction and disposal of samples after a specified period of time.

Genetic Exceptionalism
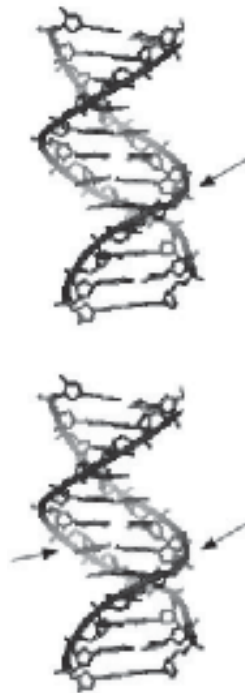
Fig. Damaged Strand of DNA

The notion of genetic exceptionalism recognizes the increased sensitivity of the results of genetic tests, as contrasted with other medical test results such as an X-ray or EKG. In the example of neurogenetics, as with other genetic testing, the results of testing

can contribute to negative labeling, and discrimination in insurance or employment. For this reason, many believe that the results of genetic testing hold a more privileged status regarding privacy and confidentiality. The results of genetic tests can have far-reaching effects both for the individual and for first-degree relatives.

Richard Ashcroft, in the British Medical Journal, discusses the need for genetic exceptionalism pertaining to disclosure of genetic profiles to insurance companies, and further cites the possibility of discrimination based on actuarial misunderstanding of increased risk for certain diseases once a gene is identified. He also explains how actuarial computation may be scientifically sound but socially unjust. If the purpose of insurance is to protect the insured against ill luck, the insured should also be protected against the ill-luck of genetic predispositions.

A counter argument presented by Soren Holm in the same issues suggests that if the individual seeking insurance knows that he or she is at a higher risk for a genetic disorder, then failure to disclose this information prevents the insurance industry from being able to make decisions that would create the most favorable risk-pool for the rest of their client population. Holm further points out that genetic information is already available and easily accessible through means such as family histories.

Certificate of confidentiality

When performing research of a sensitive nature, like genetic testing, where the results could have adverse results for participants, researchers should apply for a Certificate of Confidentiality from the National Institutes of Health (NIH). These certificates are designed to protect researchers, who may be served with a subpoena, from having to disclose identifying information about the research participants and test results for any civil, criminal, legislative, administrative, or other federal, state, or local court proceedings unless the participant consents. While these certificates have never been tested in court, it is assumed that the researcher cannot be compelled to reveal any information about

the participants in his or her study. If the participant, on the other hand, reveals personal information to anyone, the certificate is no longer valid for that person.

As a further protection, several research organizations explain to their study participants in the informed consent process that the results of the genetic tests will not be released to the participants in the research study, generally because testing was not done by a CLIA approved lab and thus, if questioned in the future, the study participants are instructed to say that they have never undergone the genetic test.

Behavioural uses of Neurogenetics

Research is at present exploring whether it is possible to identify genes for specific behaviours or characteristics e.g., intelligence, athletic ability, violence. It is important to recognize that genes with behavioural or personality implications would neither be monogenic, nor would they have complete penetrance. Inspite of the mathematically precise results demonstrated by Gregor Mendel in the 1800s, even within the sphere and understandings of dominant and recessive genes, characteristics would not be predictably expressed. Additionally, there is a large human factor to consider in personality and behavioural traits, which brings up the familiar debate of nature vs. nurture. To some extent, people have the ability to mold their character traits, sometimes in spite of genetic predispositions.

Genetic Determinism

Persons who know their genetic make-up — whether this make-up results from natural variation or is genetically planned at conception — may allow greater expression of identified traits.

A parent, knowing a child has the genotype (genetic propensity) for a trait may act on the expectation of that trait being exhibited, creating a self-fulfilling prophesy that the trait will be expressed much like the Pygmalion response. Those who believe in genetic determinism expect that characteristics manifest in their genetic

profiles will be their destiny. This sense of inevitability ignores the very important role played by environmental factors in shaping individuals and their personalities.

Behavioural choices and decision-making are complex processes of which genetics is only one element. Part of being human is overcoming impulses and behaviour traits, and making independent intellectual decisions based on rational evaluations of the situation at hand.

Revealing one's neurogenetic makeup can have deleterious effects by undermining personal enhancement and self-determination in favour of saying, "This is just how I was meant to be." A tragic exception is the Lesch-Nyhan Syndrome in which the individual (usually a child) is unable to control impulses to self-mutilate.

GENETIC ENHANCEMENT

For the purposes of this section, enhancement can be defined as using technology to fundamentally change who we are for a socially-defined "better" state. This could include pharmacological preparations to make us sharper or smarter, or to enable us to require less sleep. It could comprise implants to improve otherwise normal hearing or vision. Relevant to neurogenetics, it could also include the alteration or selection of particular genes to make normal brains better. According to the National Human Genome Research Institute, this could one day be accomplished using injectable forms of the genes.Genetic enhancement experiments through the injection of specific genes or DNA sequences either into an adult organism or into an embryo have had limited success to date. This is because of the current lack of control once the genetic material enters the donor's cell nuclei and integrates into the host's DNA.

There is often little control of the number of gene copies inserted, or the specific site of integration of the donor DNA. Although these technologies may not be available for human experimentation and use for a long time, even at this early stage

we should contemplate their meaning and future potential implications for society.

Genobility

There are concerns that genetic enhancement will likely be available only to the privileged classes. We must be wary of creating a "genobility," a class of people privileged precisely because of its genetic code. A kind of natural genobility already exists to a certain extent: individuals choose partners and mates based on physical, intellectual, and behavioural attributes, and these traits are often class-related. The upper classes pass on their genes — along with shape social privileges — in the form of opportunity, access to better health care and education, as well as access to life's better rewards.

A truer genobility, created from deliberate rather than random DNA sequences, could preclude people from lower classes from ascending the social or economic ladder, despite personal dedication and successes.

Do we practice Eugenics?

While genetic enhancement refers to the injection or selection of genes for the purpose of improving the likelihood of good attributes, there are applications for genetic research and technology to remove negative attributes from society. Eugenics, literally meaning "well born," is a genetic and social theory whereby the human race is improved by selective reproduction in which desirable characteristics are propagated and undesirable traits are eliminated.

As an instance, parents who carry genes related to disorders with high levels of penetrance may choose to undergo pre-implantation genetic diagnosis (PGD) to select an embryo without these genes so the resulting child would be unlikely to develop the disorder. Similarly, prospective parents may use amniocentesis to determine the fetus' genotype and choose not to continue a pregnancy if there is a high probability of a neurological disorder.

The use of these technologies to reduce the likelihood of a person being born with a severe neurological deficiency is relatively uncontroversial (e.g., Tay Sachs). The controversy arises when we decide what kinds of disorders or deficiencies are considered "severe." Many members of certain "disease" or disability communities may disapprove of parents who choose to use genetic screening technologies to eliminate their diseases or disorders in future generations (e.g., deafness, achondroplasia). These supports assert that this choice de-values and de-legitimizes their own lives and the lives of their children who are born either with these disorders or with the increased possibility for developing them.

MEDICAL VS. SOCIAL DEFINITIONS OF PROBLEMS AND SOLUTIONS

Neurogenetics may result in the medicalization or pathologization of natural human variation. Various traits that, in the extreme, are considered pathological can be detected in milder forms in the "normal" population, and there may not be a distinct dividing line between the two. Once science offers people the ability to control whether we have or we express a given gene, those who choose not to suppress it may be seen as additionally flawed. This could reinforce social prejudices and stereotypes to the detriment of people already in those stigmatized groups, as well as those for whom neurogenetic manipulation was not an option.

Designer Babies

Questions of socially versus medically defined problems and deficiencies are important to consider in the growing world of pre-implantation genetic diagnosis (PGD). PGD technology is presently used to:

1. find euploid embryos for implantation, or
2. screen out known fatal or serious disorders and deficiencies for which one or both parents are carriers or the couple's earlier child(ren) has(have) been diagnosed to have.

In the future, the ability to identify many more genes for different neurological, psychiatric, and behavioural traits and disorders before uterine implantation may present opportunities for parents to "design" their children, selecting in or out the desired physical, intellectual, and temperament traits they desire. What is not certain, though, is if selecting the child's genetic make-up based on parental preferences is the right decision. It is possible that the world into which these designed children grow changes its values, leaving these genetically-designed children at a new disadvantage.

Parents who have a socially undesirable trait, like deafness, may choose to reify their own existence by not sparing their children this trait, or even selecting for it, but the children may grow to resent their parents for it, wanting to be more like the norm. Other children may be "designed" to be genetically similar at the HLA locus to a sibling with a condition that can be "cured" with a bone marrow transplant. Once people "special-order" their "designer children," they will have different expectations of them. No longer will children be prized for their unique contributions to the world.

In some cases, they may prove to be grave disappointments to their parents when they turn out to be different from what their parents "ordered" from their genetic menu. We also should remain cognizant of the differences between genotype and phenotype, remembering that just because someone has a gene for a particular trait, it does not mean that the trait will be expressed.

Some Final Considerations

The various uses of neurogenetics, both current and future, make the field an exciting one to study. Whether we use the findings to alleviate human suffering from neurodegenerative diseases, or use these findings to enhance the status of individuals and future generations, we can expect significant innovation in this area in the years to come. This module intends to encourage thoughtful debate about the positive as well as negative uses and

implications of neurogenetics, with the goal of minimizing any of the harms while maximizing all of the benefits.

NEUROGENETICS IN POPULAR CULTURE AND IN THE POPULAR IMAGINATION

Popular culture frequently jumps to the wildest extremes when depicting potential uses of emerging technology. Below are instances from "pop-culture" that stimulate popular imagination in neurogenetics. When considering these and others, we require to question if "the fantasy technologies... serve to dull the public's ability to be critical and thoughtful of actual new developments."

The Boys from Brazil

The Boys from Brazil, by Ira Levin, is an example of how people conceive of genetic determinism and what it means. In the book, as the Nazis are losing the war, party officials decide to clone Adolph Hitler.

The assumption is that it was Hitler's genetic make-up that made him, in their minds, the greatest ruler and visionary, and that by cloning him, they could create another great leader who could learn from the mistakes of the current regime and successfully carry out the mission of the Nazi party.

The collaborators recognized that they needed more than just Hitler's genetic code to produce a new fuehrer, so they created several clones and set up each boy in a home situation mimicking the one in which Hitler was raised. When the Nazi hunters obtained the list of these boys, their ethical quandary was whether to take action against these still innocent pre-adolescents, or recognize that human and social factors can trump genetic codes in determining how people think and behave.

In the end, they decided that destroying these boys on the basis of their genes and DNA would be akin to what the Nazis had done to six million Jews, so they permitted the boys to live their lives, rather than condemning them in advance for their genetic make-ups and for crimes they likely would never commit.

Gattaca

In the 1997 sci-fi movie thriller Gattaca, prospective parents are able to pre-select traits for their children. One couple decides to go the old-fashioned, natural, surprise route for their first son, at whose birth the doctors spew out the probabilities of his contracting a myriad of diseases and conditions that could have been prevented easily. Due to of his genetics, and his related physical limitations, he is discriminated against in all aspects of his life, forcing him to assume someone else's identity in order to have more chances in life. He scrupulously avoids leaving behind any of his own DNA, requiring extreme exfoliation, keeping his hair very short, etc.

Under this assumed identity and using his alias's blood, urine, and skin in his daily genetic ID tests, he is able to succeed in an aerospace career that would have been closed to him based on his own genetic make-up.

ADVANCES IN NEUROGENETICS, NEUROMICS AID UNDERSTANDING OF NEUROLOGIC DISORDERS

Genetics and Risk for Alzheimer's Disease

If both parents have a clinical diagnosis of Alzheimer's disease, are their children at increased risk? That was the question Suman Jayadev, MD, and colleagues attempted to answer in a retrospective study of 111 conjugal couples who had 297 children surviving to adulthood. Of the 297 offspring, 22.6% had developed Alzheimer's disease, with the risk increasing as they aged. Among those older than 60, 31% (58 of 137) had Alzheimer's disease; among those older than 70, 41.8% (41 of 98) had the disease.

Dr. Jayadev, Assistant Professor of Neurology, University of Washington, Seattle, pointed out that because 79% of the offspring are younger than 70, the risk of occurrence will only increase. This work confirmed results of a small pilot study involving the offspring of 31 of the couples, which found a higher rate of Alzheimer's

disease than would be expected in the general population. "A family history of Alzheimer's disease beyond the parents did not change the risk of Alzheimer's disease in the children but did reduce the median age at onset in affected children," Dr. Jayadev and colleagues said. Besides, although the apolipoprotein E å4 allele has an important role, it "did not account for all Alzheimer's disease cases in offspring, supporting the hypothesis that this is a complex polygenic phenomenon" and calling for a better definition of the role of family history and specific genes involved, they concluded.

Genome-wide association studies are being used as a tool for identifying genetic contributions to complex diseases and have shown success, for instance, in helping to identify risk for age-related macular generation and diabetes mellitus. "Whether this will hold true for a genetically complex and heterogeneous disease such as Alzheimer's disease is not known, although early reports are encouraging," noted Dr. Rosenberg and -Stephen C. Waring, DVM, PhD, Assistant Professor in the Department of Epidemiology at the University of Texas School of Public Health at Houston and a researcher with the Texas Alz-heimer's Research Consortium.

Drs. Rosenberg and Waring reported on results of genome-wide association studies to date that combine high-throughput arrays, bioinformatics, and advances in software to investigate significant markers related to the risk of Alzheimer's disease.

Examining Single-Gene Neurogenetic Disorders

In another study, Thomas D. Bird, MD, and colleagues conducted a retrospective review to describe the occurrence of single-gene neurogenetic disorders in eight elderly patients. Seven patients were men—two had Huntington's disease (ages 85 and 87), three had spinocerebellar ataxia types 5, 6, and 14 (ages 86, 78, 78, respectively), one had presenilin 1 familial Alzheimer's disease mutation (age 85), and one had autosomal dominant hereditary neuropathy (age 87). An 84-year-old woman had limb-girdle muscular dystrophy type 2A. "Three patients had no family

history of neurologic disease," said Dr. Bird, a Professor of Neurology at the University of Washington, Seattle, and colleagues. "Their median age of 83 years is remarkable because genetic diseases are generally assumed to be relegated to much younger populations." Five patients had late symptom onset; the other three "had onset of symptoms at much younger ages but survived several decades and did not receive specific genetic diagnoses until relevant genetics tests became available in their senior years." The researchers noted that recognition of single-gene diseases in elderly patients can be explained by the aging of the population, increased awareness of symptom onset, and DNA-based genetic testing. "The specific diagnosis of genetic diseases is soon available to a degree completely unknown a few years ago," they said. "Patients in this study would have been considered to have senile chorea, senile dementia, and unexplained myopathy before the advent of such testing."

Parent-of-Origin Effect

Ilse A. Hoppenbrouwers, MD, from the Department of Neurology, MS Centre Erasmus, Rotterdam, the Netherlands, and colleagues investigated parental relationships among patients with MS using extensive genealogic information from the Genetic Research in Isolated Populations program. Fewer than 400 individuals comprised the mid-18th-century founding population of a region located in the southwest Netherlands.

To date, approximately 20,000 descendants live in eight adjacent communities and are generally related. More than 90,000 people spanning 23 generations are included in a genealogic database. Of these, 24 patients (19 women) with MS "could be linked to the most recent common ancestor in 14 generations." Reconstruction of a pedigree of these 24 patients with common clinical phenotypes of MS found that "the shortest connection to a common ancestor between two individuals with MS was significantly more often through their nonaffected mother than through their nonaffected father, suggesting a maternal parent-of-

origin effect" that was specific for MS, noted Dr. Hoppenbrouwers and colleagues. "Mothers of the 24 MS patients were also more closely related to each other than their fathers." Maternal transmission of MS can be a result of genetic factors, environmental factors, or both. These data suggest that "the most likely explanation is a gene-environment effect that takes place in utero," the researchers concluded. "Dense genotyping in this pedigree can help to unravel the genetic combination, thus aiding in resolving the nature-nurture dilemma in MS."

Malformations of Cortical Development

In another study from the Erasmus Medical Center–Sophia Children's Hospital, Rotterdam, Marie Claire Yvette de Wit, MD, of the Department of Pediatric Neurology, and colleagues evaluated the etiology of malformations of cortical development in children to determine whether a combined radiologic, clinical, and syndrome classification could provide a molecularly confirmed diagnosis. A case series of 113 children who had a radiologic diagnosis of malformations of cortical development from 1992 to 2006 was included in the study. Each child had a complete radiologic, clinical, and neurologic assessment and was tested for phenotypically appropriate genes known to be involved in the pathogenesis of malformations of cortical development. An etiologic diagnosis was established in 45 of the 113 children (40%). Diagnoses included molecular and/or genetic confirmation in 21 patients (19%) of -Miller---Dieker syndrome; LIS1, DCX, FLNA, -EIF2AK3, or KIAA1279 mutations; or an inborn error of metabolism. A syndrome with an unknown genetic defect was diagnosed in 17 children (15%), and evidence of gestational insult was found in seven (6%). "Of the remaining 68 patients, 34 probably have a yet-unknown genetic disorder based on the presence of multiple congenital anomalies (15 patients), a family history of multiple affected persons (12 patients), or consanguineous parents (seven patients)," the investigators wrote.

Most patients were diagnosed as having malformations of cortical development when they developed seizures; 26 of 63

patients (41%) were previously misdiagnosed, demonstrating that "a quality MRI of the brain and a skilled neuroradiologist are essential for a correct classification and the choice of diagnostic tests." Dr. de Wit's group concluded that "classification based on radiological, clinical genetic, and neurological examinations combined with genetic testing can yield important information about monogenetic, syndromal, and metabolic causes and can lead to improvement of patient care and genetic counseling. This needs a multidisciplinary team specialized in neuroradiology, pediatric neurology, and genetics. Even then, the underlying cause remains elusive in more than 50% of patients, and the suspicion of an underlying genetic cause remains in many of our unclassified cases. This encourages exploitation of new genome-wide techniques." Additional articles in the theme issues also focused on stem cells, the human HapMap, primary and amyotrophic lateral sclerosis, Huntington's disease, frontotemporal disease, Parkinson's disease, cryptogenic epileptic syndromes, fragile X, spinocerebellar ataxia, Machado-Joseph disease, Troyer syndrome, MELAS, Leigh syndrome, and hereditary spastic paraplegia.

GENETIC TESTING

Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. More than 1,000 genetic tests are currently in use, and more are being developed.

Various methods can be used for genetic testing:
- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.
- Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.

- Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Genetic testing is voluntary. Because testing has benefits as well as limitations and risks, the decision about whether to be tested is a personal and complex one. A geneticist or genetic counselor can help by providing information about the pros and cons of the test and discussing the social and emotional aspects of testing.

What is Genetic Testing?

Genetic testing looks for specific inherited changes (mutations) in a person's chromosomes, genes, or proteins. Genetic mutations can have harmful, beneficial, neutral (no effect), or uncertain effects on health. Mutations that are harmful may increase a person's chance, or risk, of developing a disease such as cancer. Overall, inherited mutations are thought to play a role in about 5 to 10 percent of all cancers. Cancer can sometimes appear to "run in families" even if it is not caused by an inherited mutation. For instance, a shared environment or lifestyle, such as tobacco use, can cause similar cancers to develop among family members. However, certain patterns—such as the types of cancer that develop, other non-cancer conditions that are seen, and the ages at which cancer typically develops—may suggest the presence of a hereditary cancer syndrome. The genetic mutations that cause many of the known hereditary cancer syndromes have been identified, and genetic testing can confirm whether a condition is, indeed, the result of an inherited syndrome. Genetic testing is also done to determine whether family members without obvious illness have inherited the same mutation as a family member who is known to carry a cancer-associated mutation.

Inherited genetic mutations can increase a person's risk of developing cancer through a variety of mechanisms, depending on the function of the gene. Mutations in genes that control cell growth and the repair of damaged DNA are likely to be related

to increased cancer risk. Genetic testing of tumor samples can also be performed, but this Fact Sheet does not cover such testing.

Does someone who inherits a cancer-predisposing mutation always get cancer?

No. Even if a cancer-predisposing mutation is present in a family, it does not essentially mean that everyone who inherits the mutation will develop cancer. Several factors influence the outcome in a given person with the mutation. One factor is the pattern of inheritance of the cancer syndrome. To understand how hereditary cancer syndromes may be inherited, it is helpful to keep in mind that every person has two copies of most genes, with one copy inherited from each parent.

Most mutations involved in hereditary cancer syndromes are inherited in one of two main patterns: autosomal dominant and autosomal recessive. With autosomal dominant inheritance, a single altered copy of the gene is enough to increase a person's chances of developing cancer. In this case, the parent from whom the mutation was inherited may also show the effects of the gene mutation. The parent may also be referred to as a carrier. With autosomal recessive inheritance, a person has an increased risk of cancer only if he or she inherits a mutant (altered) copy of the gene from each parent.

The parents, who each carry one copy of the altered gene along with a normal (unaltered) copy, do not usually have an increased risk of cancer themselves. However, because they can pass the altered gene to their children, they are called carriers.

A third form of inheritance of cancer-predisposing mutations is X-linked recessive inheritance. Males have a single X chromosome, which they inherit from their mothers, and females have two X chromosomes (one from each parent). A female with a recessive cancer-predisposing mutation on one of her X chromosomes and a normal copy of the gene on her other X chromosome is a carrier but will not have an increased risk of cancer. Her sons, however, will have only the altered copy of the gene and will therefore have

an increased risk of cancer. Even when people have one copy of a dominant cancer-predisposing mutation, two copies of a recessive mutation, or, for males, one copy of an X-linked recessive mutation, they may not develop cancer.

Some mutations are "incompletely penetrant," which means that only some people will show the effects of these mutations. Mutations can also "vary in their expressivity," which means that the severity of the symptoms may vary from person to person.

Genetic tests available for cancer risk

More than 50 hereditary cancer syndromes have been described.

The majority of these are caused by highly penetrantmutations that are inherited in a dominant fashion. The list below includes some of the more common inherited cancer syndromes for which genetic testing is available, the gene(s) that are mutated in each syndrome, and the cancer types most often associated with these syndromes.

Hereditary breast cancer and ovarian cancer syndrome
- Genes: *BRCA1*, *BRCA2*
- Related cancer types: Female breast, ovarian, and other cancers, including prostate, pancreatic, and male breast cancer

Li-Fraumeni syndrome
- Gene: *TP53*
- Related cancer types: Breast cancer, soft tissue sarcoma, osteosarcoma (bone cancer), leukemia, brain tumors, adrenocortical carcinoma (cancer of the adrenal glands), and other cancers

Cowden syndrome (*PTEN* hamartoma tumor syndrome)
- Gene: *PTEN*
- Related cancer types: Breast, thyroid, endometrial (uterine lining), and other cancers

Lynch syndrome (hereditary nonpolyposis colourectal cancer)
- Genes: *MSH2, MLH1, MSH6, PMS2, EPCAM*
- Related cancer types: Colorectal, endometrial, ovarian, renal pelvis, pancreatic, small intestine, liver and biliary tract, stomach, brain, and breast cancers

Familial adenomatous polyposis
- Gene: *APC*
- Related cancer types: Colorectal cancer, multiple non-malignant colon polyps, and both non-cancerous (benign) and cancerous tumors in the small intestine, brain, stomach, bone, skin, and other tissues

Retinoblastoma
- Gene: *RB1*
- Related cancer types: Eye cancer (cancer of the retina), pinealoma (cancer of the pineal gland), osteosarcoma, melanoma, and soft tissue sarcoma

Multiple endocrine neoplasia type 1 (Wermer syndrome)
- Gene: *MEN1*
- Related cancer types: Pancreatic endocrine tumors and (usually benign) parathyroid and pituitary gland tumors

Multiple endocrine neoplasia type 2
- Gene: *RET*
- Related cancer types: Medullary thyroid cancer and pheochromocytoma (benign adrenal gland tumor)

Von Hippel-Lindau syndrome
- Gene: *VHL*
- Related cancer types: Kidney cancer and multiple noncancerous tumors, including pheochromocytoma

Consideration of Genetic Testing for Cancer Risk

Many experts recommend that genetic testing for cancer risk should be strongly considered when all three of the following criteria are met:
- The person being tested has a personal or family history that suggests an inherited cancer risk condition

- The test results can be adequately interpreted (that is, they can clearly tell whether a specific genetic change is present or absent)
- The results provide information that will help guide a person's future medical care

The features of a person's personal or family medical history that, particularly in combination, may suggest a hereditary cancer syndrome include:

- Cancer that was diagnosed at an unusually young age
- Several different types of cancer that have occurred independently in the same person
- Cancer that has developed in both organs in a set of paired organs, such as both kidneys or both breasts
- Several close blood relatives that have the same type of cancer (for example, a mother, daughter, and sisters with breast cancer)
- Unusual cases of a specific cancer type (for example, breast cancer in a man)
- The presence of birth defects, such as certain noncancerous (benign) skin growths or skeletal abnormalities, that are known to be associated with inherited cancer syndromes
- Being a member of a racial/ethnic group that is known to have an increased chance of having a certain hereditary cancer syndrome and having one or more of the above features as well

It is strongly recommended that a person who is considering genetic testing speak with a professional trained in genetics before deciding whether to be tested. These professionals can include doctors, genetic counselors, and other health care providers (such as nurses, psychologists, or social workers). Genetic counseling can help people consider the risks, benefits, and limitations of genetic testing in their particular situation. Sometimes the genetic professional finds that testing is not needed.

Genetic counseling includes a detailed review of the individual's personal and family medical history related to possible

cancer risk. Counseling also includes discussions about such issues as:

- Whether genetic testing is appropriate, which specific test(s) might be used, and the technical accuracy of the test(s)
- The medical implications of a positive or a negative test result
- The possibility that a test result might not be informative—that is, that the information may not be useful in making health care decisions
- The psychological risks and benefits of learning one's genetic test results
- The risk of passing a genetic mutation (if one is present in a parent) to children

Learning about these issues is a key part of the informed consent process. Written informed consent is strongly recommended before a genetic test is ordered. People give their consent by signing a form saying that they have been told about, and understand, the purpose of the test, its medical implications, the risks and benefits of the test, possible alternatives to the test, and their privacy rights. Unlike most other medical tests, genetic tests can reveal information not only about the person being tested but also about that person's relatives.

The presence of a harmful genetic mutation in one family member makes it more likely that other blood relatives may also carry the same mutation. Family relationships can be affected when one member of a family discloses genetic test results that may have implications for other family members.

Family members may have diverse opinions about how useful it is to learn whether they do or do not have a disease-related genetic mutation. Health discussions may get complicated when some family members know their genetic status while other family members do not choose to know their test results. A conversation with genetics professionals may help family members better understand the complicated choices they may face.

How to do Genetic Testing?

Genetic tests are generally requested by a person's doctor or other health care provider. Although it may be possible to obtain some genetic tests without a health care provider's order, this approach is not recommended because it does not give the patient the valuable opportunity to discuss this complicated decision with a knowledgeable professional. Testing is done on a small sample of body fluid or tissue—usually blood, but sometimes saliva, cells from inside the cheek, skin cells, or amniotic fluid (the fluid surrounding a developing fetus).

The sample is then sent to a laboratory that specializes in genetic testing. The laboratory returns the test results to the doctor or genetic counselor who requested the test.

In some cases, the laboratory may send the results to the patient directly. It usually takes several weeks or longer to get the test results. Genetic counseling is recommended both before and after genetic testing to make sure that patients have accurate information about what a particular genetic test means for their health and care.

Meaning of the Results of Genetic Testing

Genetic testing can have several possible results: positive, negative, true negative, uninformative negative, false negative, variant of unknown significance, or benign polymorphism. These results are described below.

A "positive test result" means that the laboratory found a specific genetic alteration (or mutation) that is associated with ahereditary cancer syndrome. A positive result may:

- Confirm the diagnosis of a hereditary cancer syndrome
- Indicate an increased risk of developing certain cancer(s) in the future
- Show that someone carries a particular genetic change that does not increase their own risk of cancer but that may increase the risk in their children if they also inherit an

altered copy from their other parent (that is, if the child inherits two copies of the abnormal gene, one from their mother and one from their father).

- Suggest a need for further testing
- Provide important information that can help other family members make decisions about their own health care.

Also, people who have a positive test result that indicates that they have an increased risk of developing cancer in the future may be able to take steps to lower their risk of developing cancer or to find cancer earlier, including:

- Being checked at a younger age or more often for signs of cancer
- Reducing their cancer risk by taking medications or having surgery to remove "at-risk" tissue (These approaches to risk reduction are options for only a few inherited cancer syndromes.)
- Changing personal behaviours (such as quitting smoking, getting more exercise, and eating a healthier diet) to reduce the risk of certain cancers

A positive outcome on a prenatal genetic test for cancer risk may influence a decision about whether to continue a pregnancy. The results of pre-implantation testing (performed on embryos created by in vitro fertilization) can guide a doctor in deciding which embryo (or embryos) to implant in a woman's uterus. Finally, in patients who have already been diagnosed with cancer, a positive result for a mutation associated with certain hereditary cancer syndromes can influence how the cancer is treated. For instance, some hereditary cancer disorders interfere with the body's ability to repair damage that occurs to cellular DNA. If someone with one of these conditions receives a standard dose of radiation or chemotherapy to treat their cancer, they may experience severe, potentially life-threatening treatment side effects.

Knowing about the genetic disorder before treatment begins allows doctors to modify the treatment and reduce the severity of the side effects.

A "negative test result" means that the laboratory did not find the specific alteration that the test was designed to detect. This result is most useful when working with a family in which the specific, disease-causing genetic alteration is already known to be present. In such a case, a negative result can show that the tested family member has not inherited the mutation that is present in their family and that this person therefore does not have the inherited cancer syndrome tested for, does not have an increased genetic risk of developing cancer, or is not a carrier of a mutation that increases cancer risk.

Such a test result is called a "true negative." A true negative result does not mean that there is no cancer risk, but rather that the risk is perhaps the same as the cancer risk in the general population.

When a person has a strong family history of cancer but the family has not been found to have a known mutation associated with a hereditary cancer syndrome, a negative test result is classified as an "uninformative negative" (that is, does not provide useful information). It is not possible to tell whether someone has a harmful gene mutation that was not detected by the particular test used (a "false negative") or whether the person truly has no cancer-predisposing genetic alterations in that gene.

It is also possible for a person to have a mutation in a gene other than the gene that was tested.

If genetic testing shows a change that has not been previously related to cancer in other people, the person's test result may report "variant of unknown significance," or VUS. This result may be interpreted as "ambiguous" (uncertain), which is to say that the information does not help in making health care decisions. If the test reveals a genetic change that is common in the general population among people without cancer, the change is called a polymorphism. Everyone has commonly occurring genetic variations (polymorphisms) that are not associated with any increased risk of disease.

Who help people to understand their test results?

A genetic counselor, doctor, or other health care professional trained in genetics can help an individual or family understand their test results. Such counseling may include discussing recommendations for preventive care and screening with the patient, referring the patient to support groups and other information resources, and providing emotional support to the person receiving the results. In some cases, a genetic counselor or doctor may recommend that other family members consider being tested for specific gene changes that indicate an increased risk of cancer. The decision to test other family members is complicated. It requires a careful evaluation of family history and other factors as well as advice from a genetic counselor or other professional trained in genetics.

In general, physicians rely on the family member who has been tested to share the genetic information with their relatives so that family members will know that a genetic condition has been identified in their family. Then, each family member will need to make their own decision regarding whether or not to be tested themselves.

Access to a person's genetic test Results

Medical test results are generally included in a person's medical records, particularly if a doctor or other health care provider has ordered the test or has been consulted about the test results. Therefore, people considering genetic testing must understand that their results may become known to other people or organizations that have legitimate, legal access to their medical records, such as their insurance company or employer, if their employer provides the patient's health insurance as a benefit. However, legal protections are in place to prevent genetic discrimination, which would occur if insurance companies or employers were to treat people differently because they have a gene mutation that increases their risk of a disease such as cancer or because they have a strong family history of a disease such as

cancer. In 2008, the Genetic Information Nondiscrimination Act (GINA) became federal law for all U.S. residents. GINA prohibits discrimination based on genetic information in determining health insurance eligibility or rates and suitability for employment. However, GINA does not cover members of the military, and it does not apply to life insurance, disability insurance, or long-term care insurance. Some states have additional genetic nondiscrimination legislation that addresses the possibility of discrimination in those contexts.

Besides, because a person's genetic information is considered one kind of health information, it is covered by the Privacy Rule of the Health Information Portability and Accountability Act (HIPAA) of 1996. The Privacy Rule requires that health care providers and others with medical record access protect the privacy of health information, sets limits on the use and release of health records, and empowers people to control certain uses and sharing of their health-related information.

Many states also have laws to protect patient privacy and limit the release of genetic and other health information. The National Human Genome Research Institute Genetic Discrimination page includes links to more information about GINA, HIPAA, and other legislation related to genetic discrimination in insurance or employment.

At-home or direct-to-consumer genetic Tests

Some companies offer at-home genetic testing, also called as direct-to-consumer (DTC) genetic testing. People collect a tissue sample themselves and submit the sample through the mail. They learn about the test results online, by mail, or over the phone. DTC genetic testing is often done without a doctor's order or guidance from a doctor or genetic counselor before the test. Some states in the United States do not allow DTC genetic testing. Whereas the genetic testing for cancer that is typically ordered by a doctor involves testing for rare major hereditary cancer syndromes, most DTC genetic testing for cancer risk involves the analysis of common

inherited genetic variants, called single-nucleotide polymorphisms, that have been shown to be statistically associated with a certain type of cancer. Each individual variant is generally related to only a minor increase in risk, and even when added together all the known variants for a particular cancer type account for only a small portion of a person's risk of that cancer. Although the identification and study of such variants is an active area of research, genetic tests based on these variants have not yet been found to help patients and their care providers make health care decisions and, therefore, they are not a part of recommended clinical practice. Even when people have DTC genetic tests for known mutations in genes associated with hereditary cancer syndrome, there are potential risks and drawbacks to the use of DTC testing. In particular, without guidance about genetic test results from an informed, genetically knowledgeable health care provider, people may experience unneeded anxiety or false reassurance, or they may make important decisions about medical treatment or care based on incomplete information. Also, although some people may view DTC genetic testing as a way to ensure the privacy of their genetic test results, companies that offer DTC genetic testing do not always tell the consumer the details of their privacy policies. In addition, if people consult their doctor or other health care provider about the test results obtained from a DTC testing vendor, the results may become part of the patient's medical record anyway. Also, companies that provide DTC testing may not be subject to current state and federal privacy laws and regulations. It is often recommended that people considering DTC genetic testing make sure that they have chosen a reputable company.

The U.S. Federal Trade Commission (FTC) has a fact sheet about at-home genetic tests which offers advice for people who are considering such a test. As part of its mission, the FTC investigates complaints about false or misleading health claims in advertisements. The American Society of Human Genetics, a membership organization of genetics professionals, has issued a

statement about DTC genetic tests that recommends transparency in such testing, provider education about the testing, and the development of appropriate regulations to ensure test and laboratory quality.

Regulation of Genetic Tests

U.S. laboratories that perform health-related testing, including genetic testing, are regulated under the Clinical Laboratory Improvement Amendments (CLIA) program. Laboratories that are certified under CLIA are required to meet federal standards for quality, accuracy, and reliability of tests. All laboratories that do genetic testing and share results must be CLIA certified.

However, CLIA certification only indicates that appropriate laboratory quality control standards are being followed; it does not guarantee that a genetic test being done by a laboratory is medically useful. The Centers for Medicare and Medicaid Services has more information about CLIA programs. The National Library of Medicine also has information about how genetic testing is regulated and how to judge the quality of a genetic test. This information is available in the Genetics Home Reference.

Research to improve genetic testing for Cancer

Research to find newer and better ways of detecting, treating, and preventing cancer in people who carry genetic mutationsthat increase the risk of certain cancers is ongoing. Scientists are also doing studies to find additional genetic changes that can increase a person's risk of cancer.

NCI's Cancer Genetic Markers of Susceptibility project, launched in 2005, is identifying common inherited genetic variations that are associated with an increased risk of breast cancer, prostate cancer, and other cancer types.

This research may lead to new ways to prevent, diagnose, and treat cancer. However, none of the genetic variants identified through that type of research has yet proven useful for clinical management, so this remains a research effort.

NCI also funds the Cancer Genetics NetworkExit Disclaimer. This network is a resource for researchers studying inherited cancer risk, the integration of this information into medical practice, and behavioural, ethical, and public health issues pertaining to human genetics.

Additional NCI research is focused on improving genetic counseling methods and outcomes, the risks and benefits of at-home genetic testing, and the effects of advertising of these tests on patients, providers, and the health care system. Researchers are also working to improve the laboratory methods available for genetic testing.

NEUROLOGICAL DISORDERS

The basic unit of the nervous system is the nerve cell, also called as a neuron. These cells contain fibres called axons which send electrical impulses, and dendrites that branch out from the cell to receive these impulses. The nervous system has two distinct parts: the central nervous system (CNS) consisting of the brain and spinal cord, and the peripheral nervous system describing the nerves outside the brain and spinal cord.

Neuropathies describe disorders involving the peripheral nerves. If motor nerves (neurons transmit signals from the CNS to stimulate effector cells such as muscles) are damaged, muscles may weaken or become paralysed, and if sensory nerves (neurons that convey information, in the opposite direction, from tissues to the CNS) are damaged, sensation may be lost or abnormal sensations may be felt. The most common hereditary motor and sensory neuropathy is Charcot-Marie-Tooth disease.

Various diseases result from the degradation of myelin sheaths. These are the membranes surrounding neuronal axons which enables nerve impulses to travel quickly. Composed of fatty substances called lipids, myelin can be likened to the insulation around an electrical wire, acting as an insulator to electrical signals. In demyelinating diseases myelin sheaths become degraded impeding the transport of impulses.

The most common demyelinating disease is multiple sclerosis where the myelin is destroyed by the body's own immune system possibly in response to some environmental trigger, and possibly in combination some level of genetic susceptibility. One of the most common inherited demyelination diseases isadrenoleukodystrophy.

A degeneration of neurons in the cerebellum and nerve tissue in the spinal cord, important for controlling muscle movement in the arms and legs can result in a progressive loss in coordination called ataxia, while another major group of diseases resulting from degeneration of neurons in the spine are hereditary spastic paraplegia. Some neuropathies affect the autonomic system which regulates functions not under conscious control, such as heart rate or breathing.

For example the heart rate can increase for no apparent reason, or the kidneys suddenly fail to properly retain water. Several disorders associate with dysautonomia like chronic fatigue system, the autoimmune multiple system atrophy and the inherited familial dysautonomia.

One of the most severe dysautonomic diseases is known as Ondine's Curse in which there is no autonomic control of breathing. Degeneration of neurons or areas in the brain can cause characteristic clinical syndromes.Amyloidlateral sclerosis (also known as Motor neuron disease) causes paralysis, due to death of motor neurons in the motor cortex, brain stem and spinal cord while Huntington's diseasedamages regions of the brain that control movement, emotion, and cognitive ability. Parkinson's disease results from loss of neurons in regions of the brain controlling movement and is characterised by unusual clumps of protein, called Lewy bodies, building up in brain cells. Further types of young onset Parkinson's disease include Parkin disease. A further disease characterised by these aggregations is Lewy body dementia, that shows degradation in cognition as well as motor control. The most common neurodegenerative disease and the most common cause of dementia (Lat.*de*; away; *mentis*; mind) is Alzheimer's

disease. This disease also related to the accumulation of clumps of amyloid protein, called plaques or tau protein as tangles.

The aggregation of tau in different regions of the brain such as in the frontal and temporal lobes, causes frontotemporal dementia leading behavioural abnormalities rather than memory loss while progressive supranuclear palsy results from such aggregations in the midbrain. Prion degenerative diseases result from an infectious agent that is neither bacterial, fungal, viral and in fact contains no genetic material at all but an altered protein.

Mental retardation is present in around 2 - 3% percent of the population; defined as cognitive ability that is markedly below average. A number of environmental, genetic or multiple factors can cause mental retardation. Many single-gene disorders include fragile X syndrome,neurofibromatosis, tuberous sclerosis, Noonan's syndrome and as many as 25% of persons with mental retardation have a detectable chromosome abnormality such as Down syndrome, DiGeorge, Prader-Willi, Angelman and Williams syndromes.

6

Neuro Pathology: Introduction, Methodology and Progress

Neuropathology is the study of disease of nervous system tissue, generally in the form of either small surgical biopsies or whole autopsies. It is a subspecialty of anatomic pathology, neurology, and neurosurgery. It should not be confused with neuro*pathy*, which refers to disorders of the nerves (usually in the peripheral nervous system).

Methodology

Its main function largely consists of examining biopsy tissue from the brain and spinal cord to aid in diagnosis of disease. The biopsy is usually requested after a mass is detected by radiologic imaging. As for autopsies, the principal work of the neuropathologist is to help in the post-mortem diagnosis of various forms of dementia and other conditions that affect the central nervous system. Biopsies can also consist of the skin. Epidermal nerve fiber density testing (ENFD) is a more recently developed neuropathology test in which a punch skin biopsy is taken to identify small fiber neuropathies by analyzing the nerve fibers of the skin. This pathology test is becoming available in select labs as well as many universities; it replaces the traditional sural nerve

biopsy test as less invasive. It is used to identify painful small fiber neuropathies.

FOCUS OF SPECIALIZATION

In several English speaking countries neuropathology is considered a subfield of anatomical pathology. In contrast, there are a number of independent university chairs in neuropathology and even institutes of neuropathology in German speaking countries due to a different historical background.

A physician who specializes in neuropathology, generally by completing a fellowship after a residency in anatomical or general pathology, is called a neuropathologist. In day-to-day clinical practice, a neuropathologist is a consultant for other physicians. If a disease of the nervous system is suspected, and the diagnosis cannot be made by less invasive methods, a biopsy of nervous tissue is taken and sent to the neuropathologist, who examines it using a microscope or certain molecular methods to make a definitive diagnosis. A number neuropathologists in Europe have a background in the clinical neurosciences (neurology, psychiatry) as well as pathology.

Neuropathology in the US System

Neuropathologists are physicians with MD (Doctor of Medicine) degrees. They must finish either 2 or 3 years of an anatomical pathology residency followed by 2 years of a neuropathology fellowship and be certified by the American Board of Pathology in both anatomical and neuropathology. This is less specialized neuropathology training than in most other countries. It is also quite common for neuropathologists to have a Ph.D. in a related field.

Neuropathology in the UK/Canadian/Commonwealth System

Neuropathologists are medically qualified practitioners who are registered with the General Medical Council in the UK. A

postgraduate qualification in neuropathology is obtained through training and an examination overseen by the Royal College of Pathologists UK. A neuropathologist has training in anatomic pathology followed by training in relation to diagnosis of diseases of the nervous system and muscle.

The training in other European and commonwealth countries is similar. In Canada, Neuropathologists complete a 5-year Royal College of Physicians and Surgeons of Canada Neuropathology residency including a year of clinical medicine and a year of anatomical pathology. It is quite common for neuropathologists to have PhDs in a related field.

Besides to examining central nervous system tissue, the neuropathologist usually is assigned the task of examining muscle and peripheral nerve biopsies. Muscle biopsies are taken to aid in the diagnosis of muscle diseases (such as polymyositis, mitochondrial myopathy, etc.). Peripheral nerve is assessed to help work up patients with suspected peripheral neuropathies secondary to such conditions as vasculitis and amyloidosis.

Neuropathology is a heavily research-oriented field.

Prominent historical and current figures in neuropathology

Santiago Ramon y Cajal is considered one of the founders of modern neuroanatomy. Alois Alzheimer, the person after whom Alzheimer's disease is named, is considered an important early contributor to the field. There are several neuropathologists around the world who have made important clinical and research contributions toward our understanding of diseases that specifically affect the brain (degenerative diseases, multiple sclerosis, stroke, brain tumors, trauma and neuromuscular diseases).

The majority are members of the International Society of Neuropathology (ISN). For neuropathologists practicing within the United States of America please refer to the Membership Directory available through the American Association of Neuropathologists (AANP) website. There are also Membership Directories available for many of the neuropathology societies

that exist in other specific countries and/or regions of the world (British, European, Canadian... etc.).

Progress

A European Board Examination in Neuropathology which focuses the importance of proper training in the neurosciences is currently being established (www.euro-cns.org). The most recent international meeting of neuropathologists occurred in September 2014 in Rio de Janeiro, Brazil.

NUCLEAR ACCUMULATION OF MUTANT POLYGLUTAMINE PROTEINS

In all polyQ diseases, the disease proteins are ubiquitously expressed; however, cell loss is restricted to the brain cells of polyQ disease patients. The context of the polyQ proteins and their interacting proteins may determine the selective neuronal loss seen in distinct brain regions in the different polyQ diseases. Also, the selective neuropathology appears to be associated with the preferential accumulation of expanded polyQ proteins in neuronal cells, as the presence of nuclear polyQ proteins is clear evident in all polyQ disease brains.

A prime example of this is that htt, which is normally distributed in the cytoplasm, can accumulate in the nucleus when its polyQ tract is expanded. Immunohistochemical data from the brains of HD patients reveal the presence of nuclear htt inclusions in the affected brain regions of both juvenile and adult patients. Patients with other polyQ diseases, like as SCA1, SCA3, SCA7, SCA17, DPRLA, and SBMA, also show nuclear polyQ inclusions in the affected brain regions. Even in the brains of patients with SCA2 and SCA6, which are caused by a polyQ expansion in the cytoplasmic proteins ataxin-2 and ataxin-6, respectively, there is evidence for the presence of polyQ inclusions in the nuclei of neuronal cells.

Moreover, linking an expanded polyQ repeat to the cytoplasmic protein Hprt results in the formation of nuclear polyQ inclusions

in the brains of transgenic mice [7]. Thus, inspile of different subcellular localizations of the normal polyQ proteins, mutant proteins with their expanded polyQ repeats commonly form nuclear inclusions or accumulate in the nucleus; such a common feature could be related towith the selective neuropathology of polyQ diseases.

PolyQ inclusions in the nucleus are colocalized with ubiquitin, proteasome components, and heat shock proteins [3, 8–10]. These findings suggest that polyQ protein deposits are targeted by cellular clearing systems. PolyQ inclusions are likely to be compact structures consisting primarily of the polyQ protein itself, since expanded polyQ repeats can cause self-association of polyQ peptides, leading to various forms of the proteins with different conformations.

Examination of the brains of HD patients indicates that only truncated N-terminal htt fragments with an expanded polyQ tract are capable of forming nuclear inclusions, as these nuclear inclusions can only be labeled by antibodies against the N-terminal, but not the internal or C-terminal, region of htt. Western blot analysis of HD mouse models that express full-length mutant htt reveals the presence of a number of N-terminal fragments of various sizes. Cellular models of HD have revealed a number of htt fragments containing the polyQ tract and various proteolytic cleavage sites, including those for caspase-3, caspase-6, and calpains.

Nonetheless, which fragments can accumulate in the nucleus and how they contribute to neuropathology remain to be investigated. Inspite of these unanswered questions, we know that the presence of N-terminal htt fragments in HD mouse brains can be detected as early as two months prior to the obvious neurological phenotype, which does not appear until the age of four to five months, indicating that the generation and accumulation of N-terminal htt precede neurological symptoms.

The fact that small htt fragments form nuclear inclusions suggests that a shorter peptide with a larger polyQ tract tends to

misfold and aggregate more rapidly. In other polyQ diseases, it is also evident that shorter polyQ proteins are prone to misfolding and aggregation. For example, western blot analysis of a transgenic mouse model of DRPLA showed the presence of a small N-terminal fragment of atrophin-1. Similarly, brain samples from SCA3 patients as well as mice transgenic for full-length ataxin-3 with 71Q showed the production of a C-terminal truncated fragment with the expanded polyQ domain. Furthermore, the production of small polyQ protein fragments is found to be required for aggregation, indicating that proteolytic processing of polyQ proteins is critical for the generation of toxic and misfolded polyQ proteins. Although the role of nuclear inclusions remains controversial, the formation of these nuclear inclusions clearly results from the nuclear accumulation of misfolded and toxic forms of mutant polyQ proteins. The toxicity of small N-terminal htt fragments with an expanded polyQ repeat is evidenced by the severe neuropathological phenotypes of transgenic mice expressing truncated and polyQ-expanded htt. For instance, the ubiquitous expression of exon 1 of mutant htt in the transgenic R6/2 model of HD is sufficient to produce a progressive and severe neurological phenotype. These mice display the abundant nuclear inclusions, motor abnormalities, weight loss, and brain atrophy indicative of early neurodegeneration. The neuronal toxicity of mutant htt can be enhanced by its nuclear accumulation, as the addition of a nuclear localization sequence (NLS) to exon 1 of mutant htt increases toxicity in neuroblastoma cells and also results in an accelerated neurological phenotype in transgenic mice.

Nuclear effects of mutant polyQ proteins

When localized to the nucleus, polyQ-expanded proteins aberrantly interact with a diversse transcription factors, many of which contain a polyQ or glutamine-rich domain. Certain transcription pathways, including those involving the cAMP response element (CRE)-binding protein (CREB), Sp1, and PGC-1alpha, have been implicated in the pathogenesis of multiple polyQ diseases. Soluble mutant htt seems to be able to abnormally bind

transcription factors to affect their transcriptional activity. In SCA17 mouse brains, aggregated polyQ proteins could also sequester the transcription factor TF-IIB, though it has been reported that there is not a direct correlation between the presence of nuclear polyQ inclusions and neurodegeneration in other polyQ disease models. It seems that protein context determines specific protein interactions and their consequences in polyQ diseases. It is evident that mutant polyQ proteins can affect transcriptional activities. Microarray experiments using brain mRNAs from various polyQ mouse models have revealed some overlap in the expression changes induced by the different polyQ disease proteins. For instance, comparing gene expression profiles of HD mouse models that express exon 1 mutant htt (R6/2) and full-length mutant htt shows no discernable differences between the full-length and fragment models, despite the delayed changes in full-length htt mouse brains, suggesting that N-terminal fragments of mutant htt are the major pathogenic form to induce altered gene transcription. Although it is expected that mutant polyQ proteins in the nucleus can affect gene expression, whether and how transcriptional dysregulation can lead to neuronal dysfunction or cell death in the brain is not entirely clear.

Preferential accumulation of polyQ-expanded proteins in the Nucleus

Although immunocytochemistry studies show that some normal htt can localize to the nucleus, nuclear fractionation of HD mouse brains clearly indicates that the majority of full-length mutant htt is cytoplasmic and that smaller N-terminal htt fragments are enriched in the nucleus. Understanding how a polyQ protein that is normally distributed in the cytoplasm can accumulate in the nucleus when its polyQ tract is expanded is critical for gaining insight into the pathogenic mechanisms of polyQ repeat disorders. This is especially significant for understanding the pathogenesis of HD, as N-terminal htt does not carry the conserved nuclear import sequences. Several putative nuclear localization signals have been found in htt; however, they are not localized in N-

terminal htt fragments that are able to accumulate in the nucleus. Because only small N-terminal htt fragments are able to accumulate in the nucleus, the belief is that these htt fragments enter the nucleus via a passive diffusion mechanism.

We know that proteins <40 kDa can diffuse freely through the nuclear pore, whereas proteins >40 kDa normally rely on active transport. N-terminal htt fragments localize to the nucleus, while the large fragments (>60 kDa) showed perinuclear and cytoplasmic but no nuclear localization, suggesting that smaller fragments are prone to passive diffusion.

Indeed, the transgenic mouse model of HD expressing the short exon 1 or N171 fragment of mutant htt consistently showed more abundant nuclear aggregates and a more severe neurological phenotype than HD mice expressing full-length mutant htt. The delayed nuclear accumulation of mutant htt and the late onset of neurological phenotypes in HD knock-in mice are consistent with a time-dependent accumulation of N-terminal htt fragments. If small polyQ proteins can be freely translocated between the nucleus and cytoplasm, why do they preferentially accumulate in the nucleus to form nuclear inclusions? Cornett *et al* have demonstrated that a polyQ expansion can prevent mutant htt from being exported from the nucleus.

The presence of an expanded polyQ tract reduces the association of N-terminal htt with the translocated promoter region protein (Tpr). Tpr is a nuclear pore protein that localizes to the nucleoplasmic side of the nuclear pore complex and exports molecules from the nucleus. Expanded htt exhibits decreased interaction with Tpr compared with wild-type htt and thereby shows reduced nuclear export and increased nuclear accumulation. Thus their study suggests that polyQ-expanded htt is prone to misfolding in the nucleus, which subsequently reduces its ability to exit the nucleus. This study also raises the interesting issue of whether the nuclear environment itself favors the misfolding of polyQ proteins.

Nuclear Accumulation of polyQ proteins: Its Regulation

Since polyQ expansions cause proteins to misfold and aggregate, clearing misfolded polyQ proteins is crucial to prevent their accumulation. Protein degradation via the ubiquitin-proteasome system (UPS) and autophagy are the major mechanisms to remove polyQ proteins in the cytoplasm. Because autophagy is not seen in the nucleus, it is the nuclear UPS that plays a major role in clearing mutant polyQ proteins in the nucleus. *In vitro* experiments using cultured cells have shown that overexpressed polyQ proteins can impair the function of the UPS; however, the real question is whether this impairment occurs in the brains of mouse models expressing transgenic mutant polyQ proteins. Various groups using different mouse models of polyQ diseases have found no decrease in UPS activity in the brain tissues of mutant mice. Hence the accumulation of mutant polyQ proteins in the nucleus is likely due to an intrinsic difference in the neuronal nuclear UPS activity.

One important issue in this regard is whether the nuclear UPS has a lower activity than the cytoplasmic UPS, such that the nuclear UPS cannot efficiently degrade polyQ proteins, leading to the preferential accumulation of mutant polyQ proteins in the nucleus. Using fractionation and biochemical assays of the UPS activity, Zhou *et al* demonstrated that nuclear UPS activity is indeed lower than in the cytoplasm. The difference between nuclear and cytoplasmic UPS activities was also demonstrated by targeting a fluorescent UPS reporter to the cytoplasm and nucleus, which again shows that UPS activity is lower in the nucleus than in the cytoplasm. Another relevant question is why mutant polyQ proteins accumulate and form inclusions in the nucleus in an age-dependent manner. Aging is reported to increase cellular oxidative stress, which can damage the UPS and may cause an age-dependent decline in UPS activity. Biochemical and fluorescent UPS reporter assays have in fact revealed an age-dependent decline in mouse brain UPS activity. Besides, this decline is correlated with the observed age-dependent increase in nuclear htt accumulation and

aggregation. Further buttressing this correlation, increased nuclear accumulation of transfected mutant htt was found in cultured cells that were treated with proteasome inhibitors. Thus, an age-dependent decrease in the clearance of misfolded polyQ proteins explains the late onset of nuclear polyQ protein accumulation and the associated neurological phenotypes. Heat shock proteins are molecular chaperones that recognize and refold misfolded proteins, such as polyQ protein fragments, and the expression of endogenous chaperones, such as Hsp70, is decreased in mouse models of polyQ diseases.

Conversely, overexpression of heat shock proteins decreases the half-life of mutant polyQ proteins expressed in cell culture. Although we have yet to establish whether Hsp activity is reduced in the nucleus by aging or mutant polyQ proteins, it is likely that enhancing nuclear Hsp activity or increasing the clearance of nuclear mutant polyQ proteins via the UPS should decrease the nuclear accumulation of polyQ proteins and ameliorate polyQ-mediated neuropathology.

Indications of muscle disease

Muscular atrophy and weakness are among the most common indications of muscular disease. Though the degree of weakness is not necessarily proportional to the amount of wasting, it usually is so if there is specific involvement of nerve or muscle. Persistent weakness exacerbated by exercise is the primary characteristic of myasthenia gravis.

Pain may be present in muscle disease because of defects in blood circulation, injury, or inflammation of the muscle. Pain is rare, barring as a result of abnormal posture or fatigue in muscular dystrophy — a hereditary disease characterized by progressive wasting of the muscles. Cramps may occur with disease of the motor or sensory neurons, with certain biochemical disorders (e.g., hypocalcemia, a condition in which the blood level of calcium is abnormally low), when the muscle tissues are affected by some form of poisoning, with disease of the blood vessels, and with

exercise, particularly when cold. Muscle enlargement (muscular hypertrophy) occurs naturally in athletes. Hypertrophy not associated with exercise occurs in an unusual form of muscular dystrophy known asmyotonia congenita, which combines increased muscle size with strength and stiffness.Pseudohypertrophy, muscular enlargement through deposition of fat rather than muscle fibre, occurs in other forms of muscular dystrophy, particularly the Duchenne type. Tetany is the occurrence of intermittent spasms, or involuntary contractions, of muscles, particularly in the arms and legs and in the larynx, or voice box; it results from low levels ofcalcium in the blood and from alkalosis, an increased alkalinity of the blood and tissues.

Tetanus, also called lockjaw, is a state of continued muscle spasm, particularly of the jaw muscles, caused by toxins produced by the bacillus *Clostridium tetani*. The twitching of muscle fibres controlled by a single motor nerve cell, called fasciculation, may occur in a healthy person, but it generally indicates that the muscular atrophy is due to disease of motor nerve cells in the spinal cord. Fasciculation is seen most clearly in muscles close to the surface of the skin.

Glycogen is a storage form of carbohydrate, and its breakdown is a source of energy. Muscle weakness is found in a rare group of hereditary diseases, the glycogen-storage diseases, in which various enzyme defects prevent the release of energy by the normal breakdown of glycogen in muscles. As a result, abnormal amounts of glycogen are stored in the muscles and other organs.

The best-known glycogen-storage disease affecting muscles is McArdle disease, in which the muscles are unable to degrade glycogen to lactic acid on exertion due to absence of the enzyme phosphorylase. Abnormal accumulations of glycogen are distributed within muscle cells. Symptoms of the condition include pain, stiffness, and weakness in the muscles on exertion. McArdle disease generally starts in childhood. No particular treatment is available, and persons affected are usually required to restrict exertion to tolerable limits. The condition does not seem to become

steadily worse, but serious complications may occur when the muscle protein myoglobin is excreted in the urine. Other glycogen-storage diseases result from deficiency of the enzymes phosphofructokinase or acid maltase. With acid maltase deficiency, both heart and voluntary muscles are affected, and death usually occurs within a year of birth.

Muscle Weakness

Signs and Symptoms

Weakness is a failure of the muscle to develop an expected force. Weakness may affect all muscles or only a few, and the pattern of muscle weakness is an indication of the type of muscle disease. Often associated with muscle weakness is the wasting of affected muscle groups.

A muscle may not be fully activated in weakness because of a less than maximal voluntary effort; a disease of the brain, spinal cord, or peripheral nerves that interferes with proper electrical stimulation of the muscle fibres; or a defect in the muscle itself. Only when all causes have been considered can weakness be attributed to failure of the contractile machinery (i.e., the anatomy) of the muscle cell.

The effect of weakness in a particular muscle group depends on the normal functional role of the muscle and the degree to which force fails to develop.

A weakness in muscles that are near the ends of the limbs usually results in a tendency to drop things if the upper limb is affected or in "foot drop" if the lower limbs are affected. The overall disability is not as great as weakness of more proximal (closer to the body) muscles controlling the pelvic or shoulder girdles, which hold large components of the total body mass against the force of gravity. Weakness of the proximal muscles that control the shoulder blade (scapula), for instance, results in "winging" (i.e., when the sharp inner border protrudes backward) as the arms are held outstretched. If the weakness is severe, the arms cannot be raised at all.

Assessment

Muscle disease may be detected by assessing whether the muscle groups can withhold or overcome the efforts of the physician to pull or push or by observing the individual carrying out isolated voluntary movements against gravity or more complex and integrated activities, such as walking. The weakness of individual muscles or groups of muscles can be quantified by using a myometer, which measures force based on a hydraulic or electronic principle. Recordings of contraction force over a period of time are valuable in determining whether the weakness is improving or worsening.

The assessment of muscle weakness (and wasting) is directed toward discovering evidence of muscle inflammation or damage. These changes are discerned by blood tests or by measuring alterations of the electrical properties of contracting muscles. Another investigative tool is the muscle biopsy, which provides muscle specimens for pathological diagnosis and biochemical analysis. Muscle biopsies can be taken with a needle or during a surgical procedure.

Muscle Weakness : Its Classification

Muscle contraction results from a chain of events that begins with a nerve impulse traveling in the upper motor neuron from the cerebral cortex in the brain to the spinal cord. The nerve impulse then travels in the lower motor neuron from the spinal cord to the neuromuscular junction, where the neurotransmitter acetylcholine is released.

Acetylcholine diffuses across the neuromuscular junction, stimulating acetylcholine receptors to depolarize the muscle membrane. The result is the contraction of the muscle fibre. Contraction depends on the integrity of each of these parts; disease or disorder in any part causes muscle weakness.

Upper Motor Neuron Disease

Muscle weakness typical of upper motor neuron disease is seen in stroke, producing weakness of one side of the body. The

arm is typically flexed, the leg is extended, and the limbs have increased tone. Some movement may be preserved, although the use of the hand is specially limited. In comparison with muscle weakness due to disease of the lower motor neuron or muscle, in the upper motor neuron weakness the muscle bulk is generally well preserved. Other causes of upper motor neuron disorders multiple sclerosis, tumours, and spinal cord injury.

Lower Motor Neuron Disease

Degeneration of the lower neuron produces a flaccid muscle weakness. Muscle wasting is a prominent feature because the shrinkage and eventual death of neurons lead to denervation of the muscle. Diseases of the motor neurons lying in the spinal cord are called motor neuron diseases. The most common is motor neuron disease itself, also calledamyotrophic lateral sclerosis and Lou Gehrig disease. Affected individuals are generally between 50 and 70 years of age and have upper and lower motor neuron weakness.

Paralysis progresses rapidly, and death often results within three years. The spinal muscular atrophies are a group of disorders affecting infants, children, and young adults, often with an autosomal recessive mode of inheritance (i.e., requiring the gene from both parents for expression). The infantile type of amyotrophic lateral sclerosis is fatal within one year, but the older cases tend to be less severe. No cause is yet known for any of these diseases, and no cure is available. Diseases of the peripheral nerves (peripheral neuropathies, or polyneuropathies) can produce symptoms similar to the motor neuron diseases. Sensory disturbance due to involvement of the nerve fibres carrying sensory impulses is usually also involved. Symptoms usually begin in the hands and feet and progress toward the body. Peripheral neuropathies can cause degeneration of the axons, the core of the nerve fibres. The axons can regenerate but only at a rate of one to two millimetres per day.

Thus, after injury to a nerve at the elbow, the hand will not recover for six to nine months. Toxins and damage to blood vessels

tend to cause axonal types of neuropathy. Peripheral neuropathy also can be caused by degeneration of the myelin sheaths, the insulation around the axons. These are termed demyelinating neuropathies. Symptoms are similar to neuropathies with axonal degeneration, but since the axons remain intact, the muscles rarely atrophy. Recovery from demyelinating neuropathies can be rapid.Diphtheria and autoimmune diseases such as Guillain-Barré syndrome cause demyelinating neuropathies. Other causes of peripheral neuropathy include diabetes mellitus, nerve trauma, inherited factors, and chronic renal failure.

Neuromuscular Junction Disorders

Diseases of the neuromuscular junction typically involve the generation of an end-plate potential that is too low to propagate an action potential in the muscle fibre. These diseases are associated with weakness and fatigability with exercise. Diseases of neuromuscular transmission may be acquired or inherited and may be the result of autoimmune disorders, such as myasthenia gravis; congenital disorders; toxins such as those present in botulism; and some drug-induced disorders.

Primary Diseases and Disorders

It seems that the maintenance of muscle mass and function depends on its use. For instance, weight lifters and sprinters have muscle fibres with a large capacity for glycolysis (and thus ATP production) and sudden force generation. Striated muscles can regenerate after damage and can adapt to the loads they carry. Thus, in a muscle biopsy from an individual with any of the muscular dystrophies, there is likely to be a mixture of the cellular changes associated with damage and those associated with regeneration and growth (hypertrophy). Muscular activities in which the muscle resists an extending force (eccentric contractions) cause more damage to the muscle cells than contraction of the muscle at constant length (isometric contraction) or where shortening occurs (concentric contractions). The greater damage with eccentric contraction occurs despite the fact that the metabolic

rate may be one-sixth of that of an equivalent concentric or isometric contraction.

Muscles that are immobilized, as by a plaster cast following fracture of a long bone, tend to waste rapidly through shrinkage of the muscle fibres. A consistent finding is that the oxidative capacity of the muscle is reduced. These changes are reversible with muscle-strengthening exercises.

The Muscular Dystrophies

The muscular dystrophies are a group of hereditary disorders characterized by progressive muscular atrophy and weakness. In most varieties the muscles of the limb girdles—the pelvic and shoulder muscles—are involved. Measurement of the activity of creatine kinase in the blood, analysis of a muscle biopsy, and recordings from an electromyograph frequently establish that the muscle weakness is due to primary degeneration of the muscles. Creatine kinase is an enzyme of muscle fibres that is released into the bloodstream when the fibres degenerate, as in the muscular dystrophies.

Muscle biopsies reveal the characteristic degeneration and attempted regeneration of muscle fibres. Electromyography shows differences in the electrical patterns of normal muscle, myopathy, and chronic denervation, such as in the spinal muscular atrophies. In contrast to the several varieties of muscular dystrophy that are relatively benign, theDuchenne type, which predominately affects boys, is severe. It causes difficulty in walking at about the age of four years, loss of the ability to walk at about the age of 11, and death before the age of 20, due to because of respiratory failure or pulmonary infections. There is a paradoxical increase in the size of the calf muscles, giving rise to the term*pseudohypertrophic muscular dystrophy* (because the increase in size is the result of replacement with fat and fibrous tissue rather than growth of fibres, as in true hypertrophy).Duchenne muscular dystrophy is an X-linked condition; a defect of a gene on the X chromosome is responsible for the disease. Females do not manifest the disease

but have a 50 percent probability of transmitting the gene to their sons and their daughters (who themselves become carriers).

Muscle degeneration is due to the lack of a protein calleddystrophin, which causes a disruption of the membrane covering the muscle fibre; the results are the entry of excess amounts of calcium ions into the cell and cell degeneration. Treatment with glucocorticoid medications, specifically prednisone, may delay progression of the disease.

Becker muscular dystrophy is similar to the Duchenne type except that it appears later in life and progresses more slowly. It is because of different damage to the same gene on the X chromosome that causes Duchenne muscular dystrophy; some functional dystrophin is produced.

Facioscapulohumeral muscular dystrophy starts in the face, the muscles around the shoulder blades, and the upper arms. It progresses more slowly than Duchenne muscular dystrophy, and most individuals with this form of muscular dystrophy have a normal life span.

The leg weakness frequently causes "foot drop" and a waddling gait. Facioscapulohumeral muscular dystrophy is inherited in an autosomal dominant fashion; thus, the affected individual will receive the gene from one parent and will have a 50 percent chance of passing the disease to his children.

Limb-girdle muscular dystrophy is similar to facioscapulohumeral muscular dystrophy, but the face is not involved. Where inheritance is observed, it is generally autosomal recessive; i.e., both parents must donate the affected gene for expression of the disease.

There are several other muscular dystrophies, each characterized by an individual pattern of muscle weakness and inheritance. Ocular muscular dystrophy, or myopathy, predominantly affects muscles moving the eyes. Oculopharyngeal muscular dystrophyaffects not only the eye muscles but also those of the throat; it is usually autosomal dominant in inheritance, with

onset in the later years of life. Distal myopathy particularly affects the muscles of the feet and hands.

Treatment includes physical therapy, spinal supports, and splints for the limbs. Prevention of obesity is considered important, particularly in Duchenne muscular dystrophy, and infections are promptly treated. The identification of carriers of the trait and genetic screening and counseling represent the best hope of reducing the incidence of this group of diseases.

Myasthenia gravis

Myasthenia gravis is an acquired autoimmune disorder that involves a failure in the transmission of nerve impulses to the muscles and is characterized by persistent muscular weakness and a tendency of muscles to be easily fatigued. Affected individuals have weakness, particularly of the face, limbs, and neck. Symptoms include double vision, difficulty swallowing and breathing, and excessive muscle fatigue during exercise with partial recovery after rest. Autoimmune antibodies (those produced against the body's own cells) cause the destruction of acetylcholine receptors of the neuromuscular junction. Removal of thethymus, treatment with high doses of corticosteroids (which depress the immune response) and anticholinesterase medications (which stimulate the transmission of nerve impulses), and plasmapheresis (a procedure in which the autoimmune antibodies are removed from the blood) are effective in controlling this disease.

Toxic myopathies

Striated muscle may be damaged by various kinds of drugs and toxins. Some, such as intramuscular injection of the anesthetic drug bupivacaine, cause damage to the muscle fibres by disrupting the membrane and allowing calcium to enter and destroy the cell. Other drugs, such as chloroquine (an antimalarial drug) and vincristine (a medication used in the treatment of cancer), seem to disrupt the internal biochemistry of the muscle fibre. Still others, such as corticosteroids (used to reduce inflammation), affect the muscle metabolism; this is particularly true of the fluoro-substituted

corticosteroids, which cause increased catabolism and thereby produce proximal muscle weakness especially of the upper limbs.

Finally, other drugs, such as the antihypertensive hydralazine, produce an autoimmune lupuslike disorder and are associated with dermatomyositis or polymyositis.

There are rare individuals who suffer malignant hyperthermia, a potentially lethal attack of muscle rigidity and hyperthermia, when exposed to anesthetic agents such as halothane and muscle relaxants such as succinylcholine. During or after induction of the anesthesia, the patient develops rigidity and an increase in central body temperature. Death may occur suddenly when the central temperature reaches above 43 °C (110 °F). There is a high death rate in such attacks; should the patient recover, there will be recurrences with future exposure to these drugs.

The condition tends to run in families, and it may be inherited as an autosomal dominant trait. The cause is not completely known but apparently relates to an abnormality in the chemistry of calcium in the muscle fibre. Excess calcium is released into the sarcoplasm during exposure to the anesthetic agents, stimulating the mitochondria to burn glycogen and thereby produce heat. The excess calcium also causes the muscle fibres to contract and become rigid. Medications that prevent calcium release in the muscle appear to prevent the attack and are given at the first sign of attack. After the onset of the attack, the anesthetic agent should be removed and the patient cooled.

Inflammatory myopathies

Bacterial myositis, an inflammation of muscle tissues as the result of a bacterial infection, is commonly localized and occurs after an injury. *Staphylococcus* and *Streptococcus*organisms are usually responsible. General indications of infection, like fever and increased numbers of white blood cells, are accompanied by local signs of inflammation, like reddening, swelling, and warmth. Abscess formation is rare, except in persons who reside in tropical regions. In general, bacterial myositis responds to treatment with

antibiotics and minor surgery. An instance of viral myositis is pleurodynia (also called Bornholm disease, epidemic myalgia, and devil's grip), which is caused by the Coxsackie virus.

Affected persons recover completely after a brief period of intense muscular pain and fever. The muscles also may be invaded by protozoa and helminths, or worms. Trichinosis is an infection with the roundworm *Trichinella spiralis* that results from eating infested pork that has not been thoroughly cooked. Reproduction of the worm takes place in the intestines.

Larvae migrate from the intestinal walls and bury themselves in muscle tissue. Symptoms include fever, muscular pains, and sometimes weakness. Most persons afflicted with trichinosis recover after about two months, but death may result from invasion of the heart muscle. The autoimmune diseases of muscle, grouped together under the term *polymyositis*, frequently are associated with inflammation of the skin in a characteristic distribution. The eyelids, cheeks, knuckles, elbows, knees, and backs of the hands are frequently involved. The combination of polymyositis and the typical dermatitis is classified as dermatomyositis. Muscle weakness can be proximal or diffuse. Frequently, swallowing is difficult and the neck is weak. The disease can develop acutely within a few days or chronically over years. A muscle biopsy shows infiltration of the striated muscle by white blood cells, mainly lymphocytes. These collect between the muscle fibres and around small blood vessels and appear to damage the muscle fibres.

Vascular damage also is a major feature, specially in the childhood form of dermatomyositis. The cause of the autoimmune reaction to the striated muscle is not known. The disease frequently occurs in association with other autoimmune diseases, such as rheumatoid arthritis and progressive systemic sclerosis, and it can be associated with cancer in a great proportion of older patients, particularly those with dermatomyositis. High-dose corticosteroid treatment, often combined with a cytotoxic immunosuppressant drug (i.e., one that destroys the cells and suppresses the immune

system), such as cyclophosphamide, is frequently successful in suppressing the disease and allowing destroyed muscles to regenerate.

Endocrine and metabolic myopathies

Hormones

Striated muscle is directly or indirectly affected in most disorders caused by the underproduction or overproduction of hormones. This is true because the rates of synthesis or breakdown of the proteins of muscle are affected. If the thyroid gland is overactive (thyrotoxicosis, hyperthyroidism), there is muscle wasting of both type 1 fibres (oxidative-rich fibres responsible for endurance) and type 2 fibres (glycogen-rich fibres responsible for rapid sprint-type muscle contraction). If the thyroid exhibits underactivity (myxedema,hypothyroidism), there is a predominance of type 1 fibres and sometimes a decrease in type 2 fibre size. If the adrenal gland is overactive (Cushing syndrome), there is selective atrophy of the type 2 fibres. This pattern is also seen in prolonged treatment with corticosteroid drugs (such as prednisone for asthma), which can result in profound wasting and weakness of proximal muscles.

Vitamin D Deficiency

A similar mechanism underlies the wasting and weakness related to lack of vitamin Din which marked atrophy of type 2 fibres may occur. The actions of vitamin D in muscle are not fully understood, but it seems that at least one of its metabolites, 25-hydroxycholecalciferol, may influence the resting energy state of the muscle and also the protein turnover. Unlike the inherited diseases of muscle, endocrine causes of disease may be eminently treatable.

Mitochondrial Myopathies

Mitochondria are the cellular structures in which energy (in the form of heat and work) is produced from the oxidation of fuels such as glucose and fat. So many biochemical defects in

mitochondria have been discovered. There is no single entity that can be diagnosed as a "mitochondrial myopathy." In those mitochondrial defects in which a defective oxidative metabolism exists, a common result is a tendency for the muscles to generate large amounts of lactic acid. This is a consequence of needing to provide energy from the nonoxidative breakdown of the glycogen stored in the muscle.

Glycogenoses

In 1951 British physician Brian McArdle discovered a disorder of muscle that caused cramplike pains yet was not associated with the normal production of lactic acid from exercise. The defect was later identified as an absence of phosphorylase, the enzyme involved in the first step in the splitting off of the glucose-1-phosphate units from glycogen. Since blood-borne glucose can still be used to make glycogen, this disorder is classified with the glycogen-storage diseases (glycogenoses).

Lipid Storage Myopathies

Lipid storage myopathy is a potentially confusing term because the more severe forms of muscle disease (e.g., muscular dystrophy) are often associated with the replacement of the lost muscle fibres with fat cells. In the lipid storage myopathies the fat, or triglyceride, is deposited as tiny droplets within the cytoplasm of the muscle fibre. Normal type 1 muscle fibres have a greater amount of lipid droplets than type 2 muscle fibres. In the early 1970s two disorders of muscle fat metabolism were discovered to affect a component of the shuttle system transporting free fatty acids into mitochondria for subsequent oxidation. This shuttle requires the fatty acid (acyl) molecule to attach to the carrier molecule carnitine in the presence of the enzyme acylcarnitine transferase.

Theacylcarnitine that is formed crosses the outer and inner mitochondrial membranes and then is split in the presence of another form of the enzyme acyltransferase to give carnitine and the acyl molecule, which is then oxidized. A deficiency of carnitine results in the storage of fats in the cytoplasm. Deficiency of

acylcarnitine transferase results in muscle damage on severe exertion. Early recognition is important because the conditions are potentially treatable.

Myotonic Diseases

Myotonia is a difficulty in relaxing a muscle after contraction; it may manifest as difficulty in relaxing the hand after a handshake. Though slow relaxation may be due to delayed disengagement of the thick and thin filaments of myosin and actin, most cases of myotoniaare due to continuing electrical activity of the sarcolemma (the membrane of striated muscle fibres). In this most common type of myotonia, a single nerve action potential causes multiple firing of the sarcolemma, thereby continuing muscular contraction.

The cause of this problem lies in abnormal ion channels or ion pumps in the sarcolemma, although the exact cause is not known. In many forms of myotonia, cold exacerbates the condition. Weakness is another symptom of the myotonic syndromes; myotonia tends to be more pronounced after inactivity, with a rapid "warm up" on commencing exercise. Myotonic dystrophy is the most common of the myotonic disorders.

It is an autosomal dominant disorder affecting various systems of the body in addition to muscle. Symptoms include premature balding, cataract formation, mental impairment, gonadal atrophy, endocrine deficiencies, gastrointestinal tract dysfunction, and muscle fibre degeneration. While the disease has manifested itself by the age of 25 years in most cases, some affected individuals may escape developing significant symptoms throughout their lives.

Myotonia congenita, also known as Thomsen disease, is an autosomal dominant disorder, but it is not associated with any dystrophic features. The onset is at birth, generally with severe difficulty in relaxing the muscle after a forced contraction, such as a sneeze. Myotonic goats (fainting goats), which are affected by hereditary myotonia congenita, experience severe muscle stiffening when startled. Insight into the molecular mechanisms

underlying this reaction may help shed light on the equivalent disorder in humans. Myotonia can occur in a number of other conditions, including the periodic paralyses. Drugs that suppress the extent of the myotonia, such as quinine, procainamide, and phenytoin, have had variable success on the symptom of weakness. No cure of these diseases is yet available.

The periodic paralyses

Individuals with periodic paralysis suffer from recurrent attacks of muscle paralysis that may last from half an hour to 24 hours. Attacks particularly affect the legs and to a lesser extent the arms and the trunk muscles. During an attack the muscles may be slightly swollen and tender. Attacks frequently occur with rest after vigorous exercise. There are two types of periodic paralysis. In hypokalemic periodic paralysis, the level ofpotassium in the blood falls during the attack, which also can be precipitated by anything that tends to lower the potassium level. Hyperkalemic periodic paralysis, on the other hand, is associated with an increase in the potassium level.

An attack may be caused by oral therapy with potassium. Both periodic paralyses are autosomal dominant disorders. Though neither is likely to lead to fatal muscle weakness, the temporary incapacity may be severe. In the attack the muscle fibres lose their electrical potential (they become depolarized) and thereby become incapable of excitation. The disease appears to be due to changes in the movements of ions through membranes of the skeletal muscle. Potassium appears to be one of the ions responsible for the condition. Abnormal ion channels or ion pumps in the membrane may be the cause. Treatment with medications appropriately altering the potassium level, such as acetazolamide, may be effective.

Fatigue

Fatigue is a failure of the muscle to sustain force in a prolonged contraction or to reattain force in repeated contractions. The mechanisms underlying fatigue share various features with those

underlying weakness: electrical excitation of the muscle cell; electromechanical coupling; and the major processes supplying energy for contraction, work, and heat production.

The action potential that is conducted along the length of the muscle cell originates in a depolarization of the postsynaptic membrane of the neuromuscular junction caused by the release of acetylcholine from the presynaptic nerve terminal. The synapse is thus potentially a key control point in the chain of command for muscular contraction.

Complete failure of neuromuscular transmission occurs from poisoning with curare or botulinum toxin and results in complete paralysis. Incomplete or variable neuromuscular transmission is a feature of myasthenia gravis, the diagnosis of which can be confirmed by finding evidence of fatigue in response to electrical stimulation of the nerve supplying the muscle. This behaviour is a consequence of the immunologic damage to the postsynaptic membrane of the synapse by antibodies to the acetylcholine receptor. Electrical stimulation of a muscle via its nerve is a means by which some of the mechanisms underlying muscle fatigue can be analyzed by stimulating the nerve at a range of frequencies and measuring the force of the contractions produced.

Failure of force at high stimulation frequencies is seen with myasthenia gravis. In conditions in which normal muscle is cooled or lacks blood supply, there is also a high frequency of fatigue.

There is a relationship between the development of fatigue and the depletion of energy stores in exercising muscle. In prolonged exercise, such as marathon running, fatigue is associated with glycogen depletion due to oxidative glycolysis. Intense exercise that lasts only a few minutes is associated with the accumulation of lactate and an intracellular acidosis due to anaerobic (nonoxidative) glycolysis. In both types of exercise there is a reduction of phosphocreatine, although no appreciable depletion of adenosine triphosphate (ATP). Contrary in individuals with myopathies, more striking changes are seen with only low total

work or power output. Fatigue in individuals with McArdle disease, in whom glycogenolysis is absent, is not associated with the usual acidosis. Pronouncedacidosis is found in individuals with defective mitochondrial metabolism, in whom there may be a slow resynthesis of phosphocreatine after exercise.

NEUROPATHOLOGY OF PRION DISEASES

Neuropathology has a major role in surveillance of, and research on, prion diseases. For surveillance, it contributes diagnostic confirmation as well as potential identification of new disease (sub)types. This is important in view of the wide and gradually growing spectrum of clinical and pathological phenotypes and prion protein (PrP) gene (*PRNP*) genotypes. For research, it contributes to our pathogenetic understanding of prion diseases. The present brief review focuses on recently emerging points to consider in the neuropathology of human prion diseases.

Macroscopy of human prion Diseases

Gross inspection of the brain in sporadic Creutzfeldt-Jakob disease (CJD), the paramount human prion disease, may not reveal obvious abnormalities. More commonly, however, there is some degree of cerebral atrophy, which can be diffuse [Plate X(A)] or have focal accentuations. Based on preferential involvement of specific regions, occipital, striatal, thalamic and cerebellar varieties have been described. However, these subtypes are part of a spectrum of lesioning of the brain. The hippocampal formation is usually well preserved even in cases of severe brain atrophy, at variance with other degenerative dementias including Alzheimer's disease. Gerstmann-Sträussler-Scheinker disease (GSS) with the classical ataxic clinical phenotype features prominent cerebellar atrophy and degeneration of spinal tracts.

Histopathology of human prion Diseases

Histopathological features of human Prion diseases have been extensively described (*e.g.* Budka) and will not be fully elaborated here. The classical triad of spongiform change, neuronal loss, and

gliosis (astro- and microglia) is the neuropathological hallmark of prion diseases. Since neuronal loss and gliosis accompany many other conditions of the CNS, it is the spongiform change that is mostly specific to prion diseases.

This spongiform change may be mild, moderate or severe [Plate X(B)] and is characterised by diffuse or focally clustered, small, round or oval vacuoles in the neuropil of the deep cortical layers, cerebellar cortex or subcortical grey matter, which might become confluent. Ultrastructurally, the spongiform changes correspond to enlarged cell processes (mainly neurites) containing curled membrane fragments and amorphous material. Spongiform change should not be confused with non-specific spongiosis. This includes status spongiosus ('spongiform state'), comprising irregular cavities in gliotic neuropil following extensive neuronal loss (including also lesions of 'burnt-out' CJD), 'spongy' changes in brain oedema and metabolic encephalopathies, and artefacts such as superficial cortical, perineuronal, or perivascular vacuolation. Focal changes indistinguishable from spongiform change may occur in some cases of Alzheimer's and diffuse Lewy body diseases. In contrast to prion diseases of animals, the presence of vacuoles in nerve cell bodies is uncommon in CJD.

Ballooning of neurons observed in some instances is related to accumulation of neurofilament proteins. Spongiform changes and astocytosis may also involve the white matter,. Extensive white matter degeneration distinguishes the 'panencephalopathic' form of CJD, which is particularly frequent in Japan. Presence and distribution of spongiform change vary greatly between cases and disease subtypes. An almost constant location is the head of the caudate nucleus. By contrast, spongiform changes are rarely present in the brainstem and spinal cord, although PrP accumulation can be demonstrated at these sites.

Generally, extensive sampling from various brain areas (including frontal, temporal, and occipital lobes, basal ganglia, and cerebellum) is mandatory in every suspected case. However, one block of tissue with typical histological changes and/or

unambiguous PrPimmunoreactivity is sufficient for a definite diagnosis. Brain biopsy has been found to be diagnostic in 95% of CJD cases in which the disease has been confirmed at autopsy or by experimental transmission. However, this procedure should be restricted to rare instances where a treatable alternative diagnosis is suggested by clinical or laboratory findings. In sporadic CJD, the regional distribution of spongiform change in distinct patterns was shown to depend upon PrP fragment sizes and glycotypes, and codon 129 genotype in the PrP gene, *PRNP*,. However, some prion diseases have equivocal, little, or no spongiform change, such as fatal familial insomnia (FFI) that is specifically characterised by prominent thalamic atrophy with profound astrogliosis. Then immunohistochemistry for PrP and *PRNP* genotyping have a decisive diagnostic role. Current neuropathological criteria for human prion diseases, including the specific diagnostic features of variant CJD (vCJD).

CJD brains may also show age-related Alzheimer-type amyloid deposits immunoreactive for the ^{2}/A4-peptide, with or without PrP^{Sc} co-localisation. Neuro-axonal dystrophy may be widespread in some CJD brains.

IMMUNOHISTOCHEMISTRY FOR THE PRION PROTEIN (PRP)

Use and Importance

The function of the normal cellular protein (PrP^C), the molecular prerequisite for the manifestation of any prion disease, has not been clarified. However, immunohistochemistry and other methods found it predominantly expressed in neural tissue, including neurons and glial cells; other organs (*e.g.* uterus, placenta, thymus, heart, lung, muscle, gastrointestinal tract) also contain considerable amounts. Up-regulation of PrP^C seems to be important in inflammatory conditions of muscle, skin and liver, as well as in neurodegenerative disorders including Alzheimer and prion diseases. The conformationally abnormal, disease-associated isoform (PrP^{res}, derived from proteinase-resistant, or PrP^{Sc}, the

latter term derived from scrapie) accumulates in the CNS in the whole group of prion diseases and has become the most important diagnostic marker.

Routine detection of PrP^{Sc} for diagnostic purposes uses methods such as immunohistochemistry, immunoblotting or ELISA assays performed on diseased tissue samples from patients obtained at autopsy, or from slaughtered animals as is done with current EU-wide testing of cattle for BSE and sheep for scrapie. Immunohistochemistry for PrP^{Sc} has emerged as an indispensable adjunct to the neuropathological confirmation of prion diseases, especially in cases with equivocal histopathological changes,. It is suitable on routinely formol-fixed and paraffin-embedded tissues, although the technique may prove capricious, and pitfalls require to be considered. It is noteworthy that, as for the spongiform change, PrP deposition may be focal and, in rare instances, the detection of PrP immunoreactivity may require staining of several blocks. Unfortunately, routine immunohistochemistry for PrP^{Sc} might yield a negative result in exceptional cases, particularly in FFI.

More recently developed techniques such as the paraffin-embedded tissue blot or the use of Carnoy's fixative are promising alternatives to increase sensitivity for the detection of PrP^{Sc} in tissues. However, in our European neuropathological study of human prion diseases that now encompasses tissues from almost 1000 patients, we have seen only 2 FFI brains negative with immunohistochemistry for PrP among tissue specimens fulfilling criteria for a human prion disease.

Given the long incubation periods that make experimental transmission impractical, immunohistochemistry for PrP has also been used as a surrogate marker for infectivity in peripheral tissues that are significant for considerations of infectivity risks, such as the lymphoid system or the peripheral nervous system..

Moreover, PrP is also an important marker for development, spread and distribution of pathology. However, the amount and distribution of PrP deposits do not always correlate with type and

severity of local tissue damage. In a sequential experimental study on the time course and intensity of tissue lesioning and immunohistochemistry for PrP in mice inoculated with a human CJD agent, PrP accumulation does not precede, but follows spongiform change in some brain regions.

Local PrP^{Sc} deposition requires the local presence of neuronal, but not glial, elements: in pre-existing brain lesions such as infarctions in which neuronal elements had been focally destroyed and replaced by a gliotic scar, PrP deposition is absent [Plate X(D)].

PrP^{Sc} and infectivity are not uniformly distributed in an individual or animal affected with a prion disease. Two distinct groups can be distinguished: in the first, PrP^{Sc} and infectivity have been detected in a distribution mainly limited to the central nervous system (brain, spinal cord, parts of the eye, trigeminal and spinal ganglia). This pattern is typical of sporadic and iatrogenic CJD, genetic human prion diseases and BSE of cattle. In the second, PrP^{Sc} and infectivity involve also peripheral tissues, in particular the lymphoid system, and this distribution is characteristic of vCJD, natural and experimental scrapie, experimental BSE in sheep, and CWD. In all prion diseases, however, most PrP^{Sc} and infectivity reside in the CNS during clinical disease or late in the incubation period. This differential distribution of infectivity according to species and disease phenotype is one important factor when considering risks for transmission.

Technique and pitfalls

Since all anti-PrP antibodies that are currently used in immunohistochemistry do not distinguish between PrP^{C} and PrP^{Sc}, specific pre-treatment of tissue sections is required for a prion disease diagnosis to abolish simultaneous reactivity with PrP^{C}, just as tissue extracts have to undergo proteinase K digestion before detection of PrP^{res}by immunoblotting. In our hands as well as those of others, a protocol using formic acid, guanidine thiocyanate, and hydrated autoclavinggave the strongest and most

consistent signals for formol-fixed and paraffin-embedded brain tissue. Minor modifications have been recommended, but are not necessary for optimal immunostaining. It should be noted that the possibility of pitfalls requires extensive experience in technique and interpretation. Sometimes unspecific labelling of diffuse neuronal somata, dystrophic neurites, ^{2}/A4 amyloid, and neurofibrillary tangles may be seen, probably representing incomplete abolishment of PrP^C immunoreactivity.

Thus, diagnostic interpretation of positive labelling has to be made by experienced observers and must consider the morphology of obtained signals. Antibodies such as 6H4 and 12F10 failed to give this type of labelling and are, therefore, less likely to recognise non-pathological PrP material in immunohistochemistry.

Patterns and distribution of PrP deposition

Characteristic patterns of PrP deposition are synaptic, that is the most difficult to reveal, patchy/perivacuolar, and plaque types [Plate X(C)] and which may overlap in the individual brain; sometimes prominent perineuronal deposits surround neuronal somata and processes. Frequencies of these patterns differ between cerebral and cerebellar cortex.

Synaptic-type deposits and unicentric PrP plaques occur both in CJD and GSS, while abundant multicentric plaques are peculiar to GSS. Plaque-like deposits are the only type of PrP deposits extending to the subcortical white matter and are more frequent than true compact Kuru-type plaques with fringed outline that are clearly visible without immunohistochemistry [Plate X(E)]. They also stain with periodic acid-Schiff, alcian blue, Congo Red (staining disappears after formic acid treatment) and thioflavine S. Kuru plaques decorate a minority of sporadic CJD brains and are most frequent in the cerebellar cortex where they are usually confined to the granular layer. While very rarely 'florid' or 'daisy-like' plaques may be observed in other prion diseases, their prominence is restricted to vCJD [Plate X(F)]. As with spongiform change, also type and distribution of PrP deposition in sporadic CJD were

shown to depend upon PrP^{res} fragment size and *PRNP* codon 129 genotype.

New patterns of PrP deposition in the PNS and vessel walls

In currently past, granular ganglionic and tiny adaxonal PrP deposits were described in spinal and vegetative ganglia, spinal roots and peripheral nerves in rare cases of human prion disease and experimental scrapie. It remains to be established by sequential studies whether this involvement of the peripheral nervous system reflects centripetal or centrifugal spread of PrP deposition and follows the pathways of travel by the infectious agent.

In sporadic and variant CJD, we also found PrPdeposits in intracranial vessel walls by immunohistochemistry and paraffin-embedded tissue blotting. Using double immunofluorescence, these deposits co-localise with HLA-DR and S-100 immunoreactive cells in the intima, which are components of the vascular-associated dendritic cell network, as well as with HLA-DR and CD-68 immunopositive macrophages of the intima and media. Thus, mobile haematogenous cells in vessel walls may be involved in the spread of disease-associated prion protein and possibly also of infectivity.

PATHOGENETIC CONTRIBUTION

One enigma of prion diseases remains the pathogenesis of brain tissue damage, in particular of neuronal drop-out and subsequent tissue loss that is generally much more striking in human than in animal and experimental prion diseases. In principle, models involving a neurotoxic gain of function (most likely for aggregated PrP^{Sc}) or loss of function (of PrP^{C}) are conceivable and might even co-operate to manifest disease. A variety of studies were interpreted to support either model, or even both.

Both in human and experimental prion diseases, oxidative stress was identified as an important pathogenetic event. Neuronal loss appears to follow an apoptotic pathway that is apparently

independent of local deposition of PrP^{Sc} but correlates with astrogliosis, microglial activation and axonal damage. Specific vulnerability of a peculiar, parvalbumin-expressing subset of inhibitory GABAergic neurons was found both in human and experimental prion diseases. In fact, this vulnerability was detectable early in the incubation period and thus represents the earliest changes ever described after experimental inoculation.

However, FFI differs in such vulnerability from all other human prion diseases. Other vulnerabilities include that of the granular layer of the cerebellum that is frequently depleted in sporadic CJD, and variable involvement of the basal nucleus of Meynert, either mainly or secondarily to cortical neuronal loss. The molecular basis for such selective neuronal vulnerabilities is still obscure.

DEMYELINATIVE DISEASES

Demyelinative diseases of the central nervous system are characterized by loss of myelin with variable loss of axons. Contrarily, infarcts, contusions, encephalitis, and other conditions destroy myelin and axons equally. The main demyelinative disease of the CNS is multiple sclerosis (MS) and its variants. Its counterpart in the peripheral nervous system is inflammatory demyelinative polyradiculoneuropathy (Guillain-Barré syndrome-GBS) and its chronic variants. MS and GBS are autoimmune inflammatory diseases. There are also virus-induced demyelinative diseases, like progressive multifocal leukoencephalopathy. Demyelinative diseases should be distinguished from leukodystrophies, which are inherited metabolic disorders of myelin lipids and proteins.

Multiple Sclerosis And Variants

MS affects one in every 500 persons, women twice as frequently as men. It is more common in young adults and causes a variety of neurological deficits (visual loss, paralysis, sensory loss, ataxia, brainstem signs, psychiatric disorders, dementia). Various MS cases evolve over a long period (20-30 years) with remissions and exacerbations. Some cases have an acute, fulminant, even fatal

course, and others go into a relentlessly progressive phase after a period of remissions and exacerbations.

Pathology Of MS

The pathology is characterized by multifocal lesions, the MS plaques. The usual evolution of the MS plaque is as follows: in the acute phase (active plaque), activated mononuclear cells, including lymphocytes, microglia, and macrophages destroy myelin and, to a variable degree, oligodendrocytes. Myelin debris are picked up by macrophages and degraded.
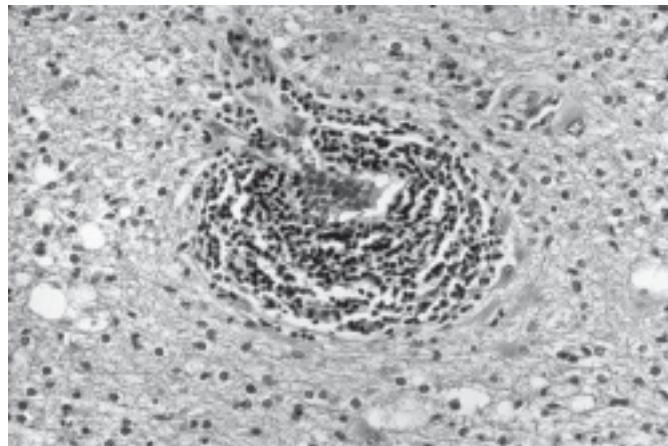
Fig. MS plaque-myelin stain

At an early stage, macrophages contain myelin fragments; later, they contain proteins and lipids from chemical degradation of myelin. This evolution takes a few weeks. With time, gliosis develops, and plaques reach a burned-out stage consisting of demyelinated axons traversing glial scar tissue (inactive plaque). Remaining oligodendrocytes attempt to make new myelin. If the inflammatory process is arrested at an early phase, plaques are partially remyelinated (shadow plaque). In more advanced lesions, remyelination is ineffective because gliosis creates a barrier between the myelin producing cells and their axonal targets. The pathological process may be arrested at any time, sometimes after partial demyelination. The pattern described above is variable. In

most cases, the inflammatory reaction subsides only to appear at another location or at another time. Some lesions expand at their periphery while activity in their center dies down (smoldering plaque). In fulminant MS cases, large lesions with diffuse activity develop and expand inexorably. Although myelin is preferentially affected, axonal loss is significant, and necrosis and cavitation may develop, especially in severe, acute lesions.

In H&E stains, plaques appear pale compared to normal white matter. Active lesions are cellular because they contain inflammatory cells and reactive astrocytes. Diagnosis of acute MS, especially with stereotactic needle biopsies, may be tricky because cellularity and reactive astrocytes in the lesions may be misinterpreted as a neoplasm. Activity is generally confined to the borders of plaques. Myelin stains show complete loss of myelin or pallor of myelin staining. The "normal appearing white matter" around MS plaques is not entirely normal but shows milder pathology.

Immunopathology. The inflamatory cells in MS include primarily CD8 T-lymphocytes, microglia, and macrohages. In addition, components of humoral immunity, including B-lymphocytes, plasma cells, immunoglobulins, and complement have been identified in plaques. Grossly, MS plaques appear as irregular, sharply demarcated, gray areas in the white matter.
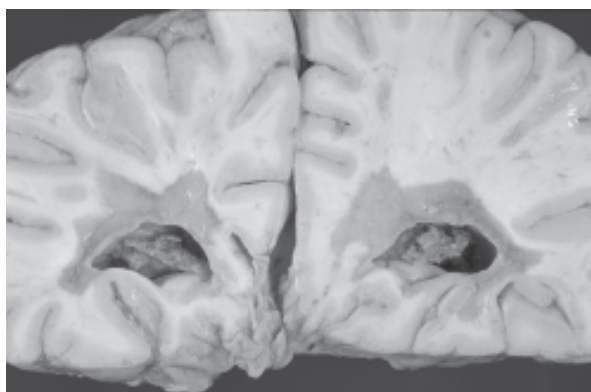
Fig. MS-periventricular plaques
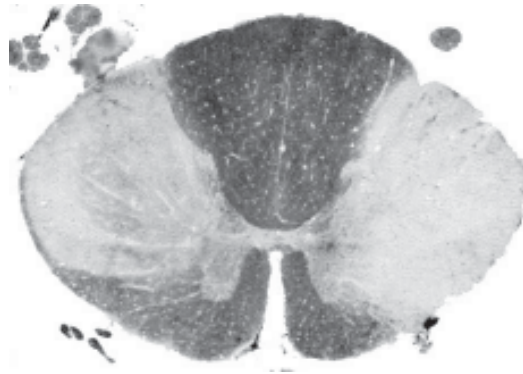
Fig. Spinal cord plaques.

They are usually multiple. Long-standing plaques are firm (sclerosis) because of gliosis. Plaques are randomly distributed. They have a predilection for the periventricular white matter, optic nerves, and spinal cord but spare no part of the CNS. They may involve gray matter such as cerebral cortex, deep nuclei, and brainstem. In these locations, they involve myelinated axons while sparing the neuronal bodies. Because of the predilection of plaques for the optic nerves, most MS patients present with visual loss (optic neuritis). Spinal lesions cause paralysis and sensory loss (transverse myelitis). Usually, these patients have plaques elsewhere in the brain or develop them later. These other plaques may be clinically silent, whereas the optic and spinal lesions always cause symptoms.
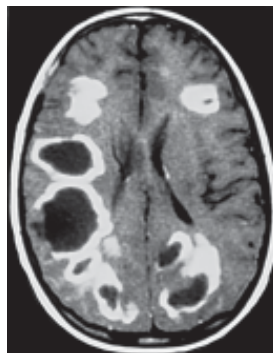
Fig. Schilder's disease
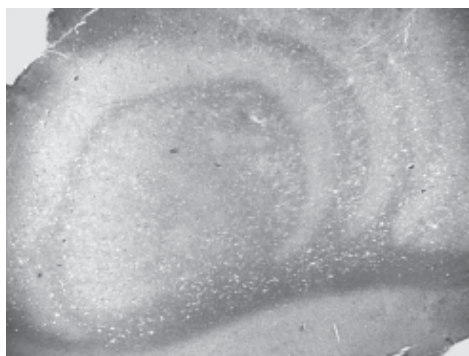
Fig. Concentric sclerosis of Balo

Clinical and radiological variants of MS include tumefactive MS (characterized by a large, acute, tumor like lesion with cerebral edema and mass effect), Marburg type MS (a form of tumefactive MS), and concentric sclerosis of Balo (another severe form of MS, with an unusual pattern of concentric rings of demyelination and partial preservation of myelin, which can be detected by MRI).

The pathogenesis of this pattern is unclear. Schilder's disease is an acute relentlessly progressive form of MS seen most commonly in children and young adults. It causes extensive confluent demyelination instead of multiple focal lesions. This MS variant has been confused in the past with X-linked adrenoleukodystrophy. Neuromyelitis optica-NMO (Devic's disease) is a special monophasic or relapsing inflammatory demyelinative disease that causes transverse myelitis and optic neuritis.

Formerly classified as a variant of MS, NMO is now recognized as an autoimmune encephalitis caused by antibodies directed against neuronal-glial surface antigens, specifically antibodies to the water channel protein Aquaporin-4 (AQP4), which is present in astrocytic processes along the BBB. A commercially available test, which detects NMO IgG in serum, distinguishes NMO from other inflammatory demyelinative diseases. NMO has diverse clinical manifestations besides optic neuritis and transverse myelitis, including intractable vomiting and pain.

Imaging Studies

The best test for diagnosis of MS is MRI. Old plaques are hyperintense on T2-weighted and FLAIR studies. Active plaques showgadolinium enhancement. The latter correlates with inflammation and increased vascular permeability, and disappears after treatment (or with time), when the integrity of the blood brain barrier is restored. Mass effect, mimicking a malignant brain tumor, may also be present in acute MS (tumefactive MS).

Schilder's disease tends to cause bilateral lesions that join across the corpus callosum, a feature seen also in some glioblastomas. MRI reveals inactive plaques, usually around the lateral ventricles, n most cases. Advanced MS causes brain atrophy. Extensive periventricular plaques cause dilatation of the lateral ventricles.

CSF Findings In MS

CSF protein is moderately elevated, and there is mild mononuclear pleocytosis. The latter is a measure of the activity of the disease. Total protein exceeding 110 mg/dl and cell counts higher than 50/cubic mm make the diagnosis of MS unlikely. The IgG fraction is elevated above 11% of total CSF protein, especially in chronic MS. The IgG/albumin index in CSF is elevated in 90 percent of MS patients, comprising some who have normal total protein. Elevation of IgG/albumin index in CSF but not in serum means that IgG is produced inside the blood-brain barrier.

Oligoclonal IgG bands are detected on agarose electrophoresis in 90% of patients. This pattern may be present even when the total amount of IgG is normal. Oligoclonal bands indicate that IgG represents antibodies to specific antigens. About 70% of MS patients and only 5% of controls have antibodies to measles. A smaller number have antibodies to rubella, mumps, and herpes simplex. Similar CSF changes are seen in some chronic CNS infections such as chronic measles encephalitis and syphilis. Myelin proteins such as myelin basic protein leak from plaques into the CSF and can be detected by radioimmunoassay.

Etiology-pathogenesis of MS

MS is thought to be an autoimmune disorder which is perhaps triggered by a viral infection. Genetic susceptibility and environmental factors play important roles in its pathogenesis.

Genetic factors: The risk of MS in relatives of patients is 7 times higher than in the general population. Monozygotic twins are 25.9% concordant for MS; dizygotic twins are only 2.3% concordant. Genetic susceptibility is probably conferred by MHC molecules that modulate the immune response (particularly autoimmunity) and cell-cell interactions. MS patients express with high frequency certain class I and II HLA antigens, particularly DW2 and DR.

Environmental factors:The incidence of MS is higher in high latitude zones. Prevalence in the northern US is 4-6 times higher than in the South. Individuals who grow up in high prevalence areas retain the high risk even if they subsequently migrate to low-risk regions. These findings suggest that an unknown predisposing factor is acquired by prolonged exposure to some environments. Viruses, particularly measles and HTLV-1, have been suspected (but not proven) to be involved in the pathogenesis of MS.

There are several immunological abnormalities apparent in MS, including perivascular T- and B-lymphocytes, activation of T-lymphocytes, intrathecal immunoglobulin production, and the presence of immunoglobulins, complement, and cytokines in the plaques. Pregnancy, which causes a diffuse immunosuppression, suppresses MS activity. The disease flares up postpartum. Interferon (INF) gamma, which enhances the immune response, provokes MS attacks. Infections such as URIs stimulate secretion of INF gamma by immune cells and exacerbate MS. On the other hand, INF beta, which suppresses the immune response, decreases the frequency of attacks.

The first event in the pathogenesis of MS may be a viral infection in childhood. Activated T- lymphocytes generated during such an infection cross the blood- brain barrier and become

sensitized to myelin antigens. Alternatively, lymphocytes are sensitized to viral proteins that may have some similarity to myelin proteins. How, after remaining latent for years, these lymphocytes re-enter the CNS and initiate an immune reaction against myelin is a subject of speculation. B-lymphocytes entering acute plaques become sensitized and produce antibodies to myelin antigens.

Myelin, oligodendroglial cells, and axons are damaged by inflammatory cytokines, glutamate, NO, and other toxic substances produced by microglia/macrophages. While the agents of CNS damage are the same, the immune reactions that initiate and propagate the process may vary among different forms of MS.

Pathophysiology of MS

The neurologic deficits, in MS, are following loss of myelin and axons. Demyelination causes loss of saltatory conduction. Linear conduction along demyelinated axons is slow because the internodal axon membrane has few ion channels. In addition, lack of insulation of axons allows impulses to disperse laterally to adjacent demyelinated axons.

The abnormal physiology of demyelinated axons results in inefficient conduction or conduction block. This is reflected by abnormal evoked response potentials, an electrodiagnostic test that measures conduction velocity in the CNS. Loss of axons, which occurs during the acute inflammatory phase of the disease, explains the permanent disability. While loss of function is easy to explain, clinical recovery is not. Remyelination is limited and does not fully explain the remissions. The neurological deficit from an acute MS plaque is caused not only by the loss of myelin and axons, but also by inflammation and edema that involve a wide area around the lesion. Even without remyelination, neurological function returns to some extent when the inflammatory reaction subsides and homeostasis is restored. In tracts that are partially involved by MS lesions, remaining axons may carry out the function. New ion channels may develop on axonal membrane, helping demyelinated axons conduct more efficiently.

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Neurology

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Preface

Neurology implies the branch of medicine pertaining to the study and treatment of disorders of the nervous system. The nervous system is a complex, sophisticated system that regulates and coordinates body activities.

Neurologists can recommend surgical treatment, but do not perform surgery. When treatment includes surgery, neurologists will monitor surgically treated patients and supervise their continuing treatment. Neurosurgeons are medical doctors who specialize in performing surgical treatments of the brain or nervous system.

Behavioural neurology is that speciality of one, which deals with the study of neurological basis of behavior, memory, and cognition, and their impact of damage and disease and treatment.

Behavioural neurology is a subspecialty of neurology that studies the neurological basis of behaviour, memory, and cognition, the impact of neurological damage and disease upon these functions, and the treatment thereof. Two fields related to behavioural neurology are neuropsychiatry and neuropsychology.

Neurophysiology is a medical specialty that focuses on the relationship between the brain and the peripheral nervous system. As its name implies, neurophysiology is in various ways a melding of neurology, which is the study of the human brain and its functions, and physiology, which is the study of the sum of the body's parts and how they interrelate. Neurophysiologists examine the many ways in which brain activities impact nervous system activities.

Generally nervous tissues are made of nerve cells and their various processes, together with a supporting tissue called neuroglia, which, however, is found only in the brain and medulla

spinalis. Some long processes of the nerve cells are of special significance, and it is convenient to consider them apart from the cells; they are known as nerve fibers. To the naked eye a difference is obvious between certain portions of the brain and medulla spinalis, viz., the gray substance and the white substance. The gray substance is largely composed of nerve cells, while the white substance contains only their long processes, the nerve fibers.

The nervous system is a control system of the body and is a bit like a computer. The brain is similar to the software and is responsible for making decisions and the nerves are like the hardware or wiring that communicates those decisions with the rest of the body.

The nervous system is integral to our ability to function in everyway. As we know muscle creates movement by contracting and pulling on our bones. However it is the nervous system that is responsible for stimulating the muscles and causing them to contract. Without the neural impulses of the nervous system, muscle would simply not work. When someone experiences a severe trauma to their spinal cord, it will often result in paralysis of their body below the point of trauma. For example if the spinal cord is damaged above the nerves that stimulate their lower body (legs etc), then they will not be able to walk again. This is because the messages which are intended for the legs can no longer reach them.

It is hoped that the book will serve the purpose of students and scholars on the subject and can be useful to them in allied fields.

—*Author*

ABOUT THE BOOK

Neurology implies the branch of medicine pertaining to the study and treatment of disorders of the nervous system. The nervous system is a complex, sophisticated system that regulates and coordinates body activities. Neurologists are principal care providers or consultants to other physicians. When a patient has a neurological disorder that requires frequent care, a neurologist is often the principal care provider. Patients with disorders such as Parkinson's disease, Alzheimer's disease or multiple sclerosis may use a neurologist as their principal care physician. Behavioural neurology is that speciality of one, which deals with the study of neurological basis of behavior, memory, and cognition, and their impact of damage and disease and treatment. It is hoped that the book will serve the purpose of students and scholars on the subject and can be useful to them in allied fields.

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