Neurological Bases of Behavior (PSY610)

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LESSON 01

INTRODUCTION

Objectives:

- To familiarize the students with study of brain behavior study.
- To orient them towards its historical and scientific roots.
- To relate it to other areas of specialization in Psychology.

Introduction

The mastermind of all our living being is the brain which controls every aspect of behavior from molar to molecular—a universe within the small cranium. Millions of neurons and glial cells interaction, firing constantly resulting in the gross behaviors we see or experience.

Pinel (2002) defines Biopsychology (also known as psychobiology, behavioral biology, behavioural neurosciences) as the scientific study of biology of behavior.

Carlson (2005) calls it the physiology of behavior where the brain and physiological correlates and modulators of behavior are the domain of study.

We put together a definition encompassing these and simply state that **"Behavioural Neurosciences aims to study brain-behavior relationships utilizing all its specializations and methodologies"**

Basic questions in the study of brain and behavior

There are several basic questions in the study of brain and behavior which are part of a continuing and recurrent discussion,

- Is brain's relationship with behavior controlled by nature or nurture, is it genes or environment?
- Where did the study of the brain start (and who are the major contributors, how far do we go)?
- How does the brain know what to process, where and what about (people, places, objects)?
- How does the brain grow (evolutionary and developmental perspective)?
- What and where are the controls of our motivated behaviors?
- Why do we remember (smells, visuals, kinesthetic) and how do we retrieve these memories? Why do we forget, what can go wrong (Alzheimer's)?
- Where does pleasure, pain, happiness addiction happen in the brain?
- What are neurochemicals, what are the various electrical, electro-physiological, neurochemical, biochemical, and other changes that take place in the brain, which molecules go where and do what?
- What happens if the systems malfunction, does one affect the rest, or things go on as before?
- What happens after brain damage- do we reconstruct?
- Why is it important for psychologists to know about the brain?

These are the questions which make the study of brain so exciting, and many questions are answered, which raise more questions! Research is ongoing throughout the 24 hours somewhere around the world. Neuroscientists are working around the clock and discoveries are being made, explanations offered theories formed or rejected.

There are many ways of looking at the brain behavior interactions:

- **Descriptive:** To study behavior and brain functioning as it occurs without interfering in the ongoing processes. This gives one a perspective of how behavior would occur under natural circumstances.

- **Comparative, evolutionary perspective**: This is used to see when researchers are looking for continuity among species as well as why and how changes in brain and behaviors have evolved and what do they lead to. Further this also answers many questions raised about behaviors which can be partially answered by studying animals. Are evolutionary changes ongoing processes? Also if there are any species specific behaviors which are found in other species and the homosapien (human).

- **Developmental (over life span**). How does the brain grow from the time of fertilization to maturity, aging and death? What are various developmental stages? The question keeps arising over and over again whether nature or nurture triggers or controls it, whether it is biological and genetic programming or external stimulation which moves development in a particular direction. Where can things go wrong or where does the environment and nature interact. How many degrees of freedom for either to act and when?

Experimental and/ or Natural Studies
The continuum of research and investigation extends from the naturalistic ethological studies i.e. from Joan Goodalls chimpanzee studies and Konrad Lorenz's earlier investigation to experimental/ laboratory studies to brain manipulation studies.

Molar and molecular
The level of studies on analysis within the brain varies from studying behavior of a large number of neurons or just one under the microscope. The Molar view focuses on groups of networks, neurons or neuroantomical areas whereas the Molecular investigation focuses on single units, single cell, single molecule, single impulse and the brain behavior relationships.

In addition to the above there are many areas which form part of neuroscientific study i.e. neurohormonal influences on growth, development and subsequent expression and modulation of behavior, the role of sleep, dreams and how the brain controls these are also important in understanding brain behavior relationships. Behavioral neuroscience studies the brain-behavior relationship from a wide range of perspectives and specializations.

Range of Behaviors:
Areas in brain/behavior relationships which have been studied and researched range from simpler to complex behaviors, as they form part of human and animal behavioral repertoire.
Some of the simpler behaviors (as they can be measured as activity is ongoing and the neurochemical interactions, neuroantomical substrates are fairly well identified) are feeding, thirst, sexual behavior, temperature regulation aggression etc. Similarly, neuroantomical and neurochemical substrates of vision, perception, audition, movement of body parts are also fairly well defined by research carried out so far.

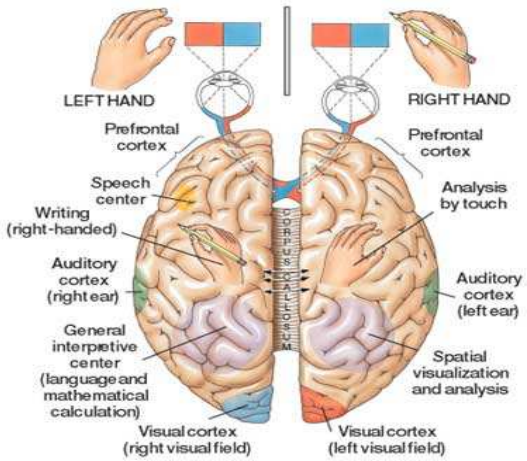

Fig.1.1 Cerebral Hemispheres

However, complex behaviors are of special interest. We are intrigued by the brain mechanisms of memory, learning and forgetting (why do we have different types of learning and /or memories), attachment, addiction, emotional states (anger, fear) etc.

There are even more complex behaviors such as brain hemispheric functioning of the cerebral cortex and these become more interesting as new technologies such as MRI emerge which pose challenges to scientists. Further more, Depression, Schizophrenia are far more complex and are not easily investigated**.**

Neurosciences:

The most interesting area has grown rapidly in the last century. The 21st century is the century of the brain. In the middle of the 1970's a brain scientist, Valenstein wrote a book **"Brain Control"** predicting possibilities emanating from the study of the brain. Researchers investigate how behavior is related to neuroanatomical localizations, neurochemicals and how behavior can be controlled with the manipulations of these as well as drugs and external "controls".

The most interesting aspect of this area is the intricacy and interdependence of brain-behavior relationship and connections. It is most fascinating to discover how the brain masterminds behaviors of organisms. This is the Pandora's Box, the more we know the more questions emerge and the more we realize we don't know enough, i.e. the less we know. Researchers and fields have multiplied incredibly from the 60's in the last century and research is ongoing 24 hours of the day around the clock in labs around the globe. So much so that Behavioural Neurosciences has emerged as a discipline where boundaries between chemistry, biochemistry, ethology, physiology, neuroanatomy, pharmacology, psychology, neurobiology and even neurophysics have melted and merged into one discipline while spawning others.

Issues in Neurosciences:

This discipline has many issues, some of which we have discussed earlier, however, we must remember it is not easy to study the brain, and there are many views of how the brain functions. We can generally categorize viewpoints regarding the brain functioning as follows:

1. **Localization vs. Equipotentiality:**

Among the major issues investigated in Behavioural Neurosciences is the localization of functions. Is it one area or a group of areas working together (you need to see or feel or estimate distances when walking), how do they "talk to each other and who listens to whom". Are functions and neuroanatomical areas localized (specialized) or equipotential (all areas have similar capabilities) or is it a combination of both.

2. **Nature vs. Nurture**:

The eternal nature-nurture debate continues in this discipline, i.e. whether the behaviors such as Schizophrenia have a genetic, biochemical basis or are the behaviors environmentally influenced. Related to this is the major issue of development of the brain. Does the brain during development, accept environmental influences or is it preprogrammed to develop in a predetermined manner. **Findings have shown that both nature and nurture play a very important role in the development**.

At present the Behavioural Neuroscientists are wiser and do not take up such controversial either/or positions It appears that genes or environment do not act alone, so nature provides the template on which the environment can act. Behaviors are not categorized simplistically as one or the other; they are resultants of complex interactions of both. Research in future may be able to pinpoint exactly how much each contributes to the development of behaviors. **Till such time it would be appropriate to remember that both have important roles to play in the appearance, development, growth and expression of behaviors.**

3. Molar level vs. Molecular level:

The scope of behaviors studied in the neurosciences vary from microscopic to holistic levels, Micro-(reductionism as it reduces behavior to its cellular component) **to macro** (holistic and more as a total than sub components). The behaviours studied under the micro level could be that of a cell, or components within a cell, its electrophysiological functioning, its ionic movements etc. Whereas **macro** could be a group of cells, or neurochemical pathways or behaviors emanating out of neuroanatomical location or even behaviours of a species.

Behavioural neuroscientists now use both methods in combination (Can do observations in lab using open field technique and experimental methods in open ranging animals –implant electrodes to study natural behavior).

Behavioural Neurosciences thus is as wide as the fields within the scope of its domain and every single aspect of brain/behaviour relationship of any organisms comes under its preview. This has extended more recently to a point where disciplines such as neurophysics have emerged, and mathematical modeling of neural connectivity and communication as well as computer simulation of complex experiences (and neural networks) is very much part of robotics.

Historical Roots of Brain Sciences:

- **Hippocrates** stated that the brain was the seat and center of sensation, thought, emotions and judgment.

- **Muslim contribution** is the first recorded brain dissection with anatomical details were given by Muslim scientists. This is experimental as well as descriptive (not speculative work). While dissecting, they discovered the hard protective covering protecting the brain and named it as Umm ul Dafah (hard protective covering) and the inner covering also the fragile mother. These were translated verbatim into Latin during the renaissance as Dura Mater and Pia Mater (Mater from Umm mother, protective covering).

- **Franz Gall** presented the concept of phrenology where faculties were located in centers of the brain. The bumps on the cranium were also part of his formal theory. However, he also presented the concept that the two hemispheres were joined by corpus callosum.

- Around 1800's, **Flourens** was the first one to experiment with ablation of avian brains. He demonstrated loss of function with damage. He proposed the concept of equipotentiality of the brain on the basis of his investigations.

- In 1861, **Paul Broca** presented evidence for speech expression in specific brain areas, i.e. frontal motor areas for speech. This area is formally known as the Broca's area now.

- In1868, Hughlins **Jackson** presented the idea of differentiation of two types of language functions- expressive and receptive, he also elaborated on a particular form of epilepsy known as the Jacksonian seizure.

- In late 1800's **Wernicke's** presented evidence for control of receptive speech in temporal lobe. This area is now known as the Wernicke's area.

- Many eminent names followed up on brain research some of those who got Nobel prizes are **Gazzaniga, Sperry** for their work in the 1960's. **Lashley and Hebb** are known as the fathers of Behavioural Neurosciences as we know it today.

Roots of Behavioural Neurosciences

Basically the roots of experimentation in psychology emerge from adaptation of methods of Physics. The well known psychophysical methods were developed by Weber who experimented on relationships of stimulus and responses. Relating experiences to the brain has its origins in the work of William James, Karl Lashley, Sherrington and Pavlov. To put forward the view that biological functions and experiences are related to the brain two names stand out, that of **Lashley and Pavlov**. If we look at the following continuum we see the range of work, areas and eminent names under each category.

Areas: **Brain-**---------- -**experimentation----------natural study**
Specialization: Neurophysiology----------Psychophysics----------Ethology
Names :Sherrington……Weber,Fechner……..Darwinian
Lashley……...Helmholtz……Niko Tinbergen
James……Young……Konrad Lorenz

Experimentalists believe that uncontrolled observation is nonscientific; there are too many uncontrolled variables in behaviors for us to draw any conclusions.

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7. Source of the image of cerebral hemisphere was taken from the site www.cwx.prenhall.com/.../medialib/images/F02_11.jpg

LESSON 02

BRIEF HISTORICAL REVIEW

Objectives:

- To orient students towards its historical and scientific roots.
- To relate it to other areas of specialization in Psychology.

Behavioural Neurosciences is as wide as the fields within the scope of its domain and every single aspect of brain/behavior relationship of any organisms comes under its purview. This has extended more recently to a point where disciplines such as neurophysics have emerged, and mathematical modeling of neural connectivity and communication as well as computer simulation of complex experiences (and neural networks) is very much part of robotics.

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Experimentalists believe that uncontrolled observation is nonscientific; there are too many uncontrolled variables in behaviors for us to draw any conclusions.

Experimentalists such as Pavlov believed in controlling all possible conditions to study behavior. According to this view, unless all conditions are controlled, studies of behavior would be unscientific. As we all know, Pavlov the Russian physiologist accidentally discovered a different route to studying brain behavior relationship. He was also one of the first to connect physiology with abnormal behaviors and gave the concept of experimental neurosis. This was a condition of extreme emotional reaction which he saw in his laboratory dogs which were required to make finer discriminations beyond their capacity.

Ethologists and naturalists on the other hand believe that when behavior is controlled and studied under laboratory conditions what we see is not "real" behavior but a construction in the laboratory. Ethology studies behavior of organism as it occurs in nature, under natural conditions. Ethologists such as Konrad Lorenz (imprinting), Niko Tinbergen (aggression, biological basis), contributed important findings regarding expression of behavior. Imprinting has had a strong impact on child and developmental studies. The belief that controlling and restructuring behavior led to unnatural situation, unnatural response offered another methodology of studying behavior as well as theoretical inputs. The Yerkes Primate Institute (Georgia: Chimp language studies) and Wisconsin Primate Center (Wisconsin: Harlows' Chimpanzee studies), Bar Harbor Maine (Sociobiology) emerged out of this tradition.

Neurophysiology was another input and came through the work of Sir Charles Sherrington, and Charles Bell's research on the reflex systems. An excellent book on the nervous system functioning and integration and the reflexes systems was published as a consequence. Thus, providing the beginnings of the study of nerve cells, their development, and mechanism and functioning.

Apart form the input from the major names, if we look historically there are three major inputs into this discipline—from Europe, Russia, and the US.

The **European inputs** are from Germany (Weber, Fechner, Helmholtz,), France (Broca), Britain (Bell, Sherrington), Russia (Pavlov) and America (William James, Lashley, and Watson). There are the

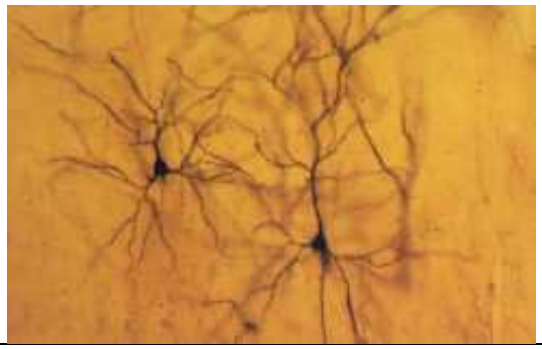
strands which reflect the scientific culture of the region as well as the thinking and working of the scientists at the time.
Germany: The emergence of Psychophysics (S-R relationships) from Weber's labs, Fechner's work relating of experiences/ physiological responses to physical stimuli are well documented as the beginning of psychological experimentation.

Helmholtz, another important contributor from Germany, measured for the first time the speed of nerve impulses. His main contribution was in the area of vision and analysis of the visual apparatus and processes. His contribution of the study of emotional/physiological states is also well known and studied even today. The two important names of Fritz and Hitzig emerge for relating the brain to motor control of functions.

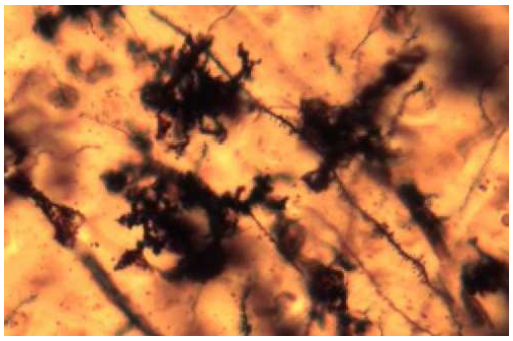
Johannes Muller's famous "Law of Specific Energies of Nerves" (1838) was given after an experiment demonstrated that the stimulation resulted in a response by the nerve.

France: Flourens work on phrenology (areas of brain and behavior) is also well known. Marc Dax is the first one to note that right side paralysis affect speech as well. Broca located the motor control of speech known as Broca's area. Later Jouvet's contribution to sleep research is also well known.

Italy: Camillio Golgi is the first one to selectively stain the cell bodies. This stain is now known as Golgi Stain.



Source:www.neurostructural.org/images/eleven.jpg



Source:www.coloradocollege.edu/.../14.golgi2.JPG

Above you can see the images of Golgi stain .Towards the right is an image of a Golgi Stain of astrocytes at higher magnification.

Spanish: Ramon Cajal in 1889 anatomically studied synapses and individual neurons. He also studied cells and their interconnections.

Russian: Pavlov's major contribution in connecting physiology and behavior. His work was very much focused on experimental studies. Luria is known as the father of Neuropsychology and his studies were on gunshot wounds of WWI head injured soldiers.

Britain: Same time as Americans studying brain substrates of behavior, the Germans studying the S-R relationships, the British studying the basic properties of the brain, physiology, anatomy and Chemistry. Sherrington, Father of Neurophysiology, prepared a report on the nervous system as acting in an integrated coherent manner. The Reflex system was clearly analyzed (reflex arcs) and laid down the basis of studying the neuron.

South America: The first systematic attempts at human psychosurgery occurred from 1935, when the neurosurgeon Egas Moniz teamed up with the surgeon Almeida Lima at the University of Lisbon to perform a series of prefrontal lobotomies —a procedure severing the connection between the prefrontal cortex and the rest of the brain. Psychosurgery is a term for surgeries of the brain involving procedures that modulate the performance of the brain, and thus effect changes in cognition, with the intent to treat or alleviate severe mental illness. It was originally thought that by severing the nerves that give power to ideas you would achieve the desirable result of a loss of affect and an emotional flattening which would diminish creativity and imagination; the idea being that those are the human characteristics that are disturbed. Historically, the procedure typically considered psychosurgery, prefrontal leukotomy is now almost universally shunned as inappropriate, due in part to the emergence of less-invasive or less-objectionable methods of treatment such as psychiatric medication and modified electroconvulsive therapy. In modern neurosurgery however, more minimally invasive techniques like gamma knife irradiation and foremost deep brain stimulation have arisen as novel tools for psychosurgery.

American: William James made the first ever laboratory in US. He studied the role of brain as basic to all behavior and experience. Karl Lashley worked on learning and its brain substrates. He also worked on the distribution of information circuitry. There are integrated circuits which connect the various parts of the brain. His student was Hebb, one of the foremost names in neurosciences, whose book, "organization of behavior" in 1949 actually triggered the involvement of psychology in brain science. Some of his studies on sleep and motivation are also a landmark. James Watson, a behaviorist, stated that behavior can be measured through cause-effect sequence relationship. Bigelow (1850) first reported case of Phineas Gage in relation to the change in personality with brain injury. Later many names in the US such as Valenstein, Gazzaniga, Sperry, Rakic, Merzenich etc. worked on the brain behavior relationship

Table 1: Important Contributors To Neurosciences

Nobel Prizewinner	Year	Contribution
Ivan Pavlov	1904	Digestive systems and their physiology
Camillo Golgi and Ramon Cajal	1906	Histological identification of the structure of Neurons and their connections
Charles Sherrington and Edgar Adrian	1932	Discoveries of neuronal functioning and reflex systems
Walter Hess	1949	Control of brain in behavioural expression
Egas Moniz	1949	Development of the prefrontal lobotomy technique
John Eccles Alan Hodgkin and Andrew Huxley	1963	Ionic basis of neuronal conduction
Bernard Katz, Von Euler and Julius Axelrod	1970	synaptic transmission
Karl Von Frisch, Konrad Lorenz, and Nikolass Tinbergen	1973	Contribution to studies of animal behavior
Roger Sperry	1981	Brain Hemispheric differences
David Hubel and Torsten Weisel	1981	Information processing within the brain structures of visual system
Rita Levi Montalcini and Stanley Cohen	1986	Discovery of the Nerve growth factor
Erwin Neher and Bert Sakman	1991	Ionic Channels

Alfred Gilman and Martin Rodbell	1994	Discovery of G-protein receptors
Arvid Carlsson, Paul Greengard, and Eric Kandel	2000	Elaboration of Synaptic transmission

Source: From Pinel (2002) p 8.

Sub Specializations

Areas of sub- specializations within the neurosciences;

1. **Biological psychiatry**: studies biological basis of psychiatric disorders and treatment utilizing brain manipulations.

2. **Biopsychology:** Focuses on biological basis of behavior i.e. how brain and other biological processes affect psychological behaviors. This has very strong laboratory based studies.

3. **Neurobiology and Developmental neurobiology:** Biological systems (especially animals) are the focus for this area. The development and maturity of the nervous systems and the processes involved are studied in detail.

4. **Neuroanatomy**: This entails study of the structures and systems of the brain and how they control and modulate behavior.

5. **Neurochemistry:** The area investigates neurochemical modulations of behavior, especially synaptic transmission (intra and inter neuronal).

6. **Neuroethology**: Study of the brain and biological basis of behavior as it occurs in the natural environment basically how behavior evolves changes (using an evolutionary perspective).

7. **Neuroendocrinology**: studies hormonal influences within the brain and modulation of behavior by hormones.

8. **Neuropathology:** The focus of this area is disorders of the brain, how and why these occur.

9. **Neuropharmacology**: studies the drug interactions within the brain and their effects on neuronal transmission and subsequently behavior.

10. **Neurophysiology:** is the study of the electrical signals/impulses; both interneuronal and intraneuronal and related changes in behavior.

11. **Neuropsychology:** studies brain and behavior correlates especially for higher order brain functioning and assessment rehabilitation of patients.

Behavioral Neurosciences aims to study and understand the neurobiological, neuroanatomical, neurochemical substrates of behavior. It aims to understand the brain substrates, modulators and precipitators of behaviors. This is wide ranging and includes an understanding of a large number of related disciplines, keeping in view the complexity of the organ and behaviors involved.

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LESSON 03

SUB-SPECIALIZATIONS WITHIN THE BEHAVIORAL NEUROSCIENCES

Objectives

- This would elaborate the characteristics of research in behavioral neuroscience.
- This would elaborate on the understanding of various sub-specializations within the behavioral neurosciences which contribute to the understanding of brain and behavior relationship and how each relates to the other areas.

According to Pinel (2002) the major areas of behavioral neuroscience research are multiple but they have some of the following characteristics:

Range: The range subjects whose behavior has been studied through natural or experimental work includes all organism: animals to humans. In some cases the studies have been carried out on simple cellular mechanism.

Controls: They vary from extreme to naturalistic (as we have discussed earlier).

Research: It can be pure or applied. Research should be done purely to understand behaviors and to develop theories and it should have no practical implications. This is known as pure research. On the other hand research is considered to be meaningful only if there are practical implications coming out of research data. Suck kind of research is known as applied research. Sometimes the lines are not dividing these areas but applied research can lead to pure research and Vice-versa.

Approach: It can either be experimental or Clinical. Sub specializations differ in what they are studying and if it involves applied clinical practice or not. Some areas such as psychobiology focus exclusively on laboratory, experimental work whereas neuropsychology has a strong clinical focus.

The major subdivisions of Behavioral Neurosciences are as follows:

Physiological Psychology: Studies the neural modulates of behavior through direct manipulation of the brain, using controlled experimental settings. The manipulation of the Nervous system can be through surgical, electrical or chemical means and these are carried out primarily on animals. The formal experimentation is carried out with strictest control of variables. Use of human subjects is eliminated (not allowed, for ethical reasons even animal experimentation has a strict code). This is an area which focuses on identifying variables, creating theoretical frameworks rather than producing applied oriented results. Pure research is a priority. It may or may not have an applied implication later.

Psychopharmacology: Earlier psychopharmacologists were also researchers in physiological psychology; the lines were diffuse and not bifurcated. The two disciplines are still quite similar. However, the experimentation under strict control conditions may have a different focus—one is more interested in neural activity and interaction of drugs and the other with neural activity and its influence on behavior. Psychopharmacology, as specialization, focuses primarily on identifying the effects of the exogenously created substances on behavior. Pure research carried out is on laboratory animal subjects, however, at a more advanced level of testing human volunteers are also included in the studies,(clinical or patients suffering from the psychopathology for which a drug has been developed), however, there are stringent procedures for doing this kind of experimentation. The Psycho-pharmacological research can be both **pure and applied**. Pure when we are testing out these substances to develop a theoretical model or framework. As an example "SPEED" or amphetamines are abused as stimulants, chronic use of these leads to a psychotic like state. Since

amphetamines increase release of dopamine thereby increasing its levels in the brain, this has formed basis for developing dopaminergic hypothesis of schizophrenia. The research in Psychopharmacology becomes APPLIED when a drug is developed for therapeutic use in clinical setting. Many drugs being used as psychotropic drugs were developed in the laboratories (and are still being developed through psychopharmacological studies). This has contributed immensely to the understanding of how brain works with exogenous chemicals through the neurotransmitter changes.

Comparative psychology

This is an area which is more related to biopsychology, or psychobiology, ethological, ecological, evolutionary basis of behavior. The studies in this area can range from naturalistic studies such as those of Konrad Lorenz, (Imprinting in birds) and Niko Tinbergen (aggression in the red stickle back fish) and Jan Goodall (Chimpanzee studies carried out in the jungle) to laboratory investigations, (creating a model of attachment of animals as in the case of Harlows studies on rhesus monkeys and chimpanzees at the Wisconsin Primate Center). The focus can be micro (where we can compare cells, parts of the brain and their functioning)- to macro and holistic (which is extended to animal families, social and group behavior: specially studies on pheromonal signals have carried out extensive free roaming animals social behavior studies). Some researcher focus on the phyletic difference in behavior while others focus on higher order behaviors. Comparative psychology studies similarities and differences in animal behaviors. Thus simply put, it studies and compares behaviors across species and across animal kingdom.

Neuropsychology

This is the study of behavioural deficits which result from human brain damage. The focus of area is mainly the highly developed cerebral cortex, (neocortex) in humans. It is not possible to create lesions or damage brain to see the aftereffects, therefore this discipline uses:

a**) Case studies** of patients who have suffered some damage or trauma (stroke, deficits- as an example we have two famous cases: Phineas Gage, and H.M), to identify the relationship between the brain areas and the functioning. These two cases will be discussed in detail in later chapters but the case of Phineas Gage is famous as it showed that damage to the orbito-frontal area led to personality change, and the case of HM is famous as he lost the ability to store memories after brain surgery, he lives in short term memory.

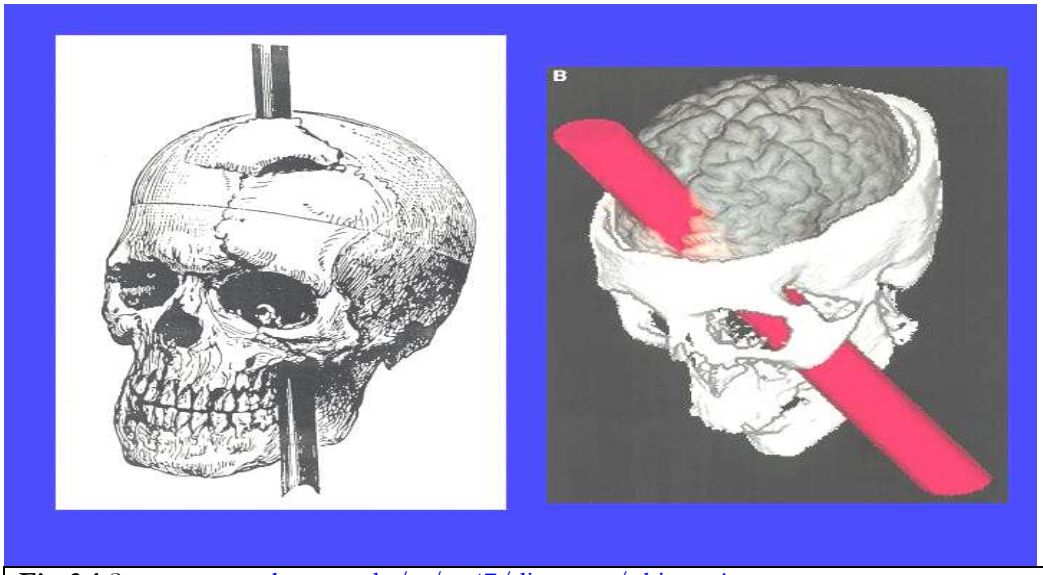

Fig 3.1 Source : www.brown.edu/.../py47/diagrams/phineas.jpg

Fig 3.1 shows phineas gage: reconstruction from his damaged skull showed extensive damage to the orbitofrontal cortex.

b) **Co-relational** studies of damage/deficits resulting from surgery lesions. Extensive Tests are given to identify the deficits and then these are correlated with the damage reported by the neurologist, or surgeon or the other advanced technologies (such as MRI, PET scan etc).
In addition, the following are the areas which define neuropsychology as a speciality.

Neocortex: The focus of Neuropsychology is mainly on the neocortex, the association and other higher order functions, but this is not necessarily true. Neuropsychologists do assess sensory motor functioning involving the lower order brain areas as well.

Applied: Neuropsychology has a very strong applied focus, where neuropsychological assessments are essentially done to understand the deficits- with the aim of localizing deficits to help the patient. The aim of this discipline is to identify, provide diagnosis of the area of deficit with the specific goal of care counseling and developing rehabilitation strategies to help the patients.

Non –Invasive: This is non-invasive specialization we do not damage brains or insert tubes within the brain to test the patient. We use tests and extrapolate functioning on the basis of performance on the test (paper pencil, construction, memory etc).

Controls Vs Flexibility: The neuropsychological approach can vary form extremely controlled to flexible testing. There is a strong school of thought within the discipline which believes in flexibility of testing and assessment (especially considering that we are testing brain damaged patients). The father of this discipline Luria (Russian Neurologist) did not believe in standardization, but qualitative assessment and keen observation. The American school believes in strong standardized and controlled conditions of testing and responses.

- **Psychophysiology**

-mStudies the relationship of physiology and behavior by recording the brain and body electrophysiological responses both in animal and human subjects. In humans, Scalp electrodes are placed on surface of scalp to measure electroencephalographic changes (EEG) on muscles, eye movement, skin to measure electromyographic activity, electro-oculographic activity, and electrodermal changes(EMG,EOG EDR). Psychophysiological measures also include autonomic measures such as GSR, heart rate, B.P. Pupil dilation etc.

This is Non- invasive, can be applied or even pure research such as sleep research which uses EMG, EOG and EEG recordings. We also have single cell recordings, event related potentials. Further, electrophysiological recordings can be made of one cell or a large group of cells for an orchestrated response.

- Cognitive neurosciences

It is the newest and most exciting, and the most active of the sciences. Cognitive neuroscience brings together scientist from cognitive sciences (mathematicians, physicists, computer scientists who build theoretical models) life sciences (biochemists, biologists, chemists, who actively work to identify living tissue and functional correlates) and cognitive psychologists. It has emerged as a distinct enterprise only recently and has been driven by methodological advances that enable the study of the human brain safely in the laboratory. Cognition is defined as the neural basis of higher intellectual functioning such as memory, thought, perceptions, attention, judgment, imagination, creativity, speech and language, action, foresight and planning.

Very interesting issues are part of research in cognitive neurosciences such as how information is stored, processed and retrieved. Is there multistage or parallel processing of information, mathematical and computer modeling of how neural networks are formed etc.

This is mainly non-invasive. Using techniques such as functional imaging (which measures ongoing behavior). This is more exciting as technology develops; therefore this specialization is essentially interdisciplinary.

In summary, all approaches work in conjunction with each other, to formulate theory and to test it. Experiments from Physiological Psychology can be complemented by applied work in Neuropsychology and vice-versa

Reference

Pinel, John P.J. (2003) Biopsychology (5th edition) Allyn and Bacon; Singapore

LESSON 04

RESEARCH IN BEHAVIOURAL NEUROSCIENCES

Objectives:

This would familiarize the student with:

- Research in behavioural neurosciences, research areas, animal vs. human subjects, applied vs. pure research in these areas.
- Scientific method, research issues and focus on scientific research critical concerns. Answer such questions "Does scientific research justify everything?"

Research is intensively ongoing and rigorously reviewed in this discipline. Not just are the methodologies scrutinized and critically evaluated but also ethical concerns while working with humans or animals are a priority. The research findings are continuously replicated tested for authenticity, as is it is easy to understand keeping in view the importance of brain.

Animal Subjects

Biopsychological research is carried out on laboratory animals such as mice, rats, cats dogs, chimpanzees, birds. These are all part of the subject population used in the varied specializations. Major findings have emerged out of research with animals such as self stimulation, learning, feeding). The question frequently asked is why do we need animals to study and talk about the human brain? First of all, we must remember that it is impossible to carry out experimental manipulations on human brains. We cannot create or bring about the changes in humans as we can in animals. Secondly, findings of research on animals have provided impetus for therapy in neuromuscular disorder, neurochemicals modulation, pain, brain opioids, drug addiction, aggression and fear. The series of experiments carried out by Harlow and Harlow and their research group on young rhesus monkey and chimpanzees from the University of Wisconsin primate Center provided a great insight into the biological need for attachment and the drastic consequences of not having early bonding and attachment opportunities. Furthermore,

- In using simpler organism and animals, we can isolate brain structures and study even the microcellular processes to identify brain-behavior relationships.

- We can also use naturalistic experiments or observation while controlling variables such as stimuli, responses, environment and behavior to study animals in the open field or laboratory conditions.

Experiments on animals also have the following benefits:

- These provide us with controls of genetic progenies (can identify genetic propagation of abnormalities), and continue our studies longitudinally, rats live much shorter lives than human.
- We can study and compare brains of different species mice, rats, cats, dogs, rhesus monkeys to see continuity of behavior-brain connections.
- Brain structures and areas similar across animals, therefore we can extrapolate or generalize to a great extent the biological processes, the difference being that the human brain has the most evolved cerebral cortex.

Brain manipulation in animals opens up avenues of investigation for humans. The Developmental neurobiology findings are based on studies carried on rhesus monkeys early brain development (Pasko Rakic and colleagues).

Whether we work with animals or humans, all research in the Neurosciences is scientific and strongly based in the method of science.

Scientific Method
Scientific method is a process of thinking and working. The scientific method is inherently simple yet has given complex discoveries. It involves both experimental as well as non experimental work (naturalistic studies). This method uses rules of logical thinking, critical review and testing of the theories developed. It is said that the Scientific method is circular in nature. It begins with observation and ends with observation, with several stages of hypothesis formulation and testing.

The Process:
a) The Hypothetico-deductive method begins with a speculation or a theory; we operationally define its concepts, give logically deduced measurable behavioural outcomes, and test them. This testing takes us back into the loop of evaluating the theory with evidence (this is similar to Sherlock Holmes method).

b) Empirico-inductive is the method which places greater reliance on experience and observation. Darwin used this method for gathering data on development of his theory of Evolution. Each individual case is studied carefully and then on the basis similarities and differences are seen, generalizations for theories and general populations are derived.

Experiment is a well regulated procedure where all variables are controlled and only the variable of interest is allowed to vary and measurements carried out (assumption is you know your variables and their relationships and the possible outcomes). Even before the outcomes you are required to predict what you expect. The more you know your variables, the better you would be able to predict the outcomes, (need to study before forming hypothesis).

Experimental Method
Is the method which aims to reduce random variability and help us control all variables, letting only one variable of interest stand out for measurement? This uses various experimental designs which can give us control in different ways:

a) Between groups design (Group A vs. Group B, Drug A vs. Drug B)
b) Within group design (We may have the same subject run through several conditions for comparison i.e. Drug A, Drug B, control condition, the best possible match for him is the subject himself).

Controls– This is the condition in which we don't introduce any variables, but keep them as close to normal as possible. Why do we need them? They provide a template for comparison, a base where no change was introduced otherwise how we would be sure of our results and the how we know what was the normal with which we could compare.

Experimental design: As an example we have the following experiment which was actually run and successfully published.

Experimental group
4 rat pup born to mother on the same day

- Two males two females
- Handled everyday
- Injected memory drug twice a day
- Run into mazes

Control group

- 4 rat pups born same day to Mother A same litter
- 2 males, 2 females
- Handled everyday (avoid confounding)
- Injected saline twice (a the same time experimental subjects injected with memory drug)
- Run into mazes

Difference in the errors and time taken would be noted and run for statistical analysis.

Research Issues:

1. **Confounding:** We may have too many variables that may be operating which we are not aware of and which affect our results, these may be the age, gender, inheritance, learning, experience etc.
2. **Experimenter bias**: We look for data to support our hypothesis even with animals, thus the results we see may actually be our own expectation of what we wanted to see, this is true of all behavior especially drug experiments.
3. **Use Double Blind:** In it neither the experimenter nor the subject knows which the experimental condition is or the control especially in drug studies/learning studies.
4. **Placebo effect:** This is a well known effect where we may get a drug like response when injected with saline or distilled water. These work from expectations, and has actually demonstrated changes in neurochemicals.

Single case versus Group studies

We may take many detailed measures of one subject over a longer period of variables of interest where as in group studies many subjects are measured simultaneously. Scientist A (400 mice) scientist B (4 rats) and both could get the same results (only methodology is different).

Replication

It is important to show that your findings are not just a one time chance experience. It is very important that data and studies are replicated to authenticate findings. The repeat of all conditions should give the same results.

Quasi Experimental Studies

Studies of groups of subjects (usually humans) when we cannot change or control all the conditions such as drugs taken before/ age of onset of a disease etc.

Pure Research versus Applied research

Pure research is motivated by the curiosity of researcher to understand why brain has its own opiates may be pure research. Further, for knowledge acquisition and theory building we need to understand the basic principles of the functioning and relationship of variables. These can eventually form the base for applied research. **Applied research** is focused on results which would bring benefit in terms of treatment or drugs (either monetarily or otherwise). This does not concern or consider it necessary to understand and build theories, only the end result is important. This is also more funding oriented as more available for applied research to benefit humankind**.**

Should research focus on the future or the past while working on the present as behavior occurs or has occurred. Why do we need to go to the past? Should we be able to predict and understand the future outcomes or do we explain what is past? There is a continuity of the past, present and the future, we understand the past to predict and control the future behaviors.

Why should we study the abnormal behaviors or should we just study normal behaviors, Both ends of the continuum are tied, the normal is one end and the abnormal is the other. Understanding why deficits occur can give us a good idea of what functions were performed by brain areas (like a car when it has broken down—then we understand how each part contributes to its working.

There is a strict formal code of ethics for research and laboratory work with animals and human subjects. Each laboratory has to justify the use of animals and ensure ethical issues are taken care of to the teams which can visit at random (this happens in the advanced countries)

Moniz's psychosurgery technique of frontal lobotomy to treat patients with behavior and other disorders was developed out of surgery on one chimpanzee. No side effects? He did not pursue it further, also did not do any between and within species comparison. At that time it seemed a revolutionary procedure (and till about the mid 1970's) this was a procedure of choice.

There was a serious lack of scientific and social responsibility, in experiments such as drug experiments using psychoactive drug in human subjects without the subjects being aware of the effects or without having the choice to say no.

Best advice for a budding psychologists and scientist is to question and be skeptic. This is the best way to do research to learn and to be a scientist.

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LESSON 05

EVOLUTIONARY AND GENETIC BASIS OF BEHAVIOUR

Objective:

To understand

- The Brain behavior relationships from the perspectives of biological systems.
- The concepts of theory of evolution and its developmental process.
- Evolution of the homosapien and to understand brain development and behavior changes.
- Where is the genetic programming of behavior (if any) and what are the similarities and differences between species, progenies of higher order animals, including homosapien?

Evolutionary and genetic basis of Behavior

These lectures would take the students through Evolution of the brain, evolution of mammalian species, the evolution of man, links with brain development. Classification on the phylogenetic scale, similarities across the phylo-genetic scale, development of the concept of evolution, the Lamarkian, and Darwinian theories, concepts of natural selection, survival of the fittest, speciation and adaptation, how gene transmission take place, the double helix Watson and Crick model of the components of genetic material and process of transmission.

Also the nature nurture debate with Ethologist and Sociobiolgists (based on Darwinian evolution) and Experimentalists.

Man: defined in biological terms ***as Homosapien*** is a comparatively newly evolved species, with a biological presence of not more than 50,000 years.

There are several distinctive characteristics of the ***homosapien:***

a) The only animal with an upright walk and true bipedalism. This is an extremely complex development, as it needs changes in the pelvic bones, the vertebral column, the cranium placement on the top of vertebral column, the visual system etc. man can cover long distances without losing stamina or strength to hunt.

b) Language as an "integrated system",. It is more learned, more refined communications where combination of sounds and intonations are used in a sophisticated system. All cultures and tribes have their own language. Humans have a specialized cortical area for language.

c) Specialized hunter-gatherer roles differentiating according to biological functions for male-females. The females have greater responsibility of looking after the offspring and stay with the young while males foraged.

d) Domestication of other animal's specialized abilities to benefit his survival (camels, horses, cows, dogs, chickens).

e) Highly evolved and complex societies.

f) Kills own species without biological benefit, warfare and murder in other animal's species specific survival purpose.

g) Highly evolved abstract thinking, aesthetics, tools painting in primitive caves. However, homo sapien is similar to other biological species as can be seen through the taxonomic classification.

Taxonomic Classification:

All animals in the animal kingdom categorized into this classification, which categorize animals from general to specific. For example for homosapien we can see how this classification works

- Kingdom---Animalia: most general, all animals on the face of the earth
- Phylum: Chordata (notochord, pharyngeal gill slits)
- Subphylum: Vertebrata (vertebrate column)
- Class: Mammalia
- Carnivorous, herbivorous, omnivorous
- Order: Primate
- Family: Hominids, (for humans)
- Genus: Homo
- Species : Sapien

Species: Basic to classifying animals, usually clear and apparent difference between species.

Phyletic scale: a scale ordered in terms of differential characteristics

Species specific: Differences in appearance, shape and form- horse donkey, zebra come from the same family EQUUS but different species. All three are herbivorous with similarities in behavior and appearance yet there are differences. A horse may kick like a donkey, but is more territorial.

Class: vertebrates that bear their young and suckle them (humans belong to this category).

Order: What they forage/ hunt flesh/vegetable eating.

Species don't Inter breed (not in the naturally occurring circumstance), not because they are incapable of doing so but for reasons unknown (answer lie sin genetic fitness). Cross mating is not biologically beneficial as the genes are not propagated any further. Biologically, this is not a fit response. The case of cross breeding of Horse and ass equals mule (sterile), fit for human as beast of burden but not for wither species as this would be the end of the genes of the horse, the ass and the mule

Evolution of Evolutionary theories

Linneas: believed that animals were created as one act of creation, and that species fixed and unchanging, variation within species possible however each species independent in its creation.

Comte Georges Du Buffon 1707-1788. Degeneration one species become another- concept of change? Degeneration of monkey into man- effect of environment, forces of migration, environmental variation, and struggle for existence introduced concepts used by Darwin later

Lamark 1744-1829 wrote the book ***Philosophie zoologique*** presenting his views. The concept of Transmutation given by him was that animals are in a constant state of flux, constantly being perfected and the direction of change is towards higher forms; Lamarkian change gives a ladder of life where animals move upwards to higher forms and dead material returns to regenerate.

Change not fixity of species was elaborated for the first time and that the environmental pressures bring about small heritable changes. Organs grow and shrink from use. Concept of use and disuse was also given by him

Lysenko: gave his theory of inheritance of acquired characteristics, where he proposed that if there

were some changes made in one generation they would be passed on to next generation.

Darwin: 1809-1882: traveled to the Galapagos Island on the HMS Beagle. His nine famous voyages over 22 years were actually very well documented evidence of the animal species he saw on those islands. His meticulous observations and notes, led him to see some patterns in similarities and differences in the appearances, behavior and other patterns wrote the book "Origin of species" on the basis of the documentation. The conclusions drawn are:

a. There is diversity and variation in the genetic composition of a population and this provides the rough shape that natural selection works on.

b. Organisms vary (could be due to mutations or other mechanism of genetic variability) and this variation is then inherited.

c. Natural over productive tendencies, but natural tendency to maintain a constant population

Reference

Pinel, John P.J. (2003) Biopsychology (5th edition) Allyn and Bacon Singapore

LESSON 06

EVOLUTIONARY AND GENETIC BASIS OF BEHAVIOUR

Objective:

To understand

- The Brain behavior relationships from the perspectives of biological systems.
- The concepts of theory of evolution and its developmental process.
- Evolution of the homosapien and to understand brain development and behavior changes.

Evolution:

As we have seen in the last lesson, the concepts of evolution were also evolving, Darwin has built on what was already being thought about, but what makes his theory unique is what we are going to talk about today

Theory of Evolution:

Darwin was the first one who actually gave **the mechanism** of how or why the process of evolution takes place. The first premise being that there are limited resources and all living organisms compete for the limited resources available. Therefore a struggle for existence is essentially a struggle for resources and a struggle for survival.

Who wins the battle? Clearly the species which has even slightest advantage, (long neck for giraffes if food higher up in the trees), will have the best chances for survival, and can continue to propagate under hostile and competitive conditions. The best adapters are therefore the best reproducers and the best reproducers are the ones best fit for survival.

Decent With Modification

Variation in genetic population provides a rough template for natural selection to work on (the variation can also occur via mutation: change in chromosomal order or genetic code). Modification of genetic variation takes place through natural selection.

What is Natural selection?

Natural selection affects all living organisms, in keeping a species strong and fit for existence under the conditions in which it is living. NATURE SELECTS! Natural selection pressure s can work only in the presence of genetic variability

Adaptations made in one generation, if beneficial would be carried on to the next generation there is constant process of adaptation. If species do not adapt they do not survive (dogs which do not learn to watch for cars on the road, die–which means the end of their genes). Primates developed extensions to help in survival/hunting (young chimps use hollow sticks for ants), as they could not compete with the stronger hunters and predators.

Genetic Variation: What is Genetic variation or phylogenetic inertia, these can be defined as basic inherited properties in which there is a variation and can be changed and the extent they can. All organisms have combinations of characteristics; however each has a unique combination. These combinations can change.

Changes in the genetic combination can occur through a) combinations of different gene pools i.e. interracial marriage or marriage of completely unrelated individuals b) mutations; these are changes in the gene material through radiation or a genetic accident (or now genetic manipulation). These changes would lead to a new and unusual combination of genes.

Survival of the fittest: qualities which enable survival and further propagation in a hostile environment. We are not talking of being healthy or physically strong but having qualities with which animals can propagate successfully and offspring survive to continue to contribute to gene pool. The gene pool for the next generation is better as weaker genes do not survive to contribute to gene pool. The fittest genes live on, propagate and make up the upcoming successive generations.

What if we have a species doing very well, this would increase the number of surviving animals. This would again lead to competition for food thereby struggle for existence would continue

Evolutionary adaptation and speciation: these are also evolutionary processes/ changes which a species goes through to enhance its survival.

Evolutionary adaptation: there are two kinds of adaptations which can take place during the process of evolution, 1) Centripetal: which means the organism would remain in the same state, for millions of years as there are no environmental pressures to change. There is stability, and no change is beneficial for survival. The animal does not change e.g. silver fish is the same for millions of years. 2) Centrifugal: when there is a non stable environment with very rapid changes taking places, therefore rapid change in the species occurs to survive. It is during centrifugal change that mutations occur in large numbers and very rapidly as the selection pressures are intense.

Speciation: when the same species spread to different geographical locations, they evolve differently into different species. The same birds in the sea would develop qualities of sea- birds, those which go up into the hills would develop characteristics needed for survival in the hills.

Isolation: whenever a species was geographically isolated and there was no competition, theses would evolve into different species depending on the locations (divide territory for mutual benefit).The animals in Australia, and Galapagos are good examples

Adaptive radiation: adaptive process where the same species develops different characteristics. In Australia the marsupials radiated into different species such as tasmanian cat, koala (trees), duckbill (water), kangaroo (land) spreading and foraging across grass, tree, water, hill, land),

Evolution: Mammalian, Primate To Homosapien

The first major phase in evolution is speculated to be when fishes move on to land, they evolved into amphibians dinosaurs. The dinosaurs ruled earth in various forms they were huge, physically but had very small brains. At about the end of reptilian era a very small mammalian species evolved: a) it had a fur coating for thermoregulation b) had strong olfaction (brain grew-due to olfaction?) c) better hearing (had to compete with large animals so had to forage in the dark)-bones in jaws moved to side to form ear bones, d) Vision gradually highly evolved for higher primates

Mammalian evolution began with the monotremata these were egg layers like reptiles but were fur bearing and nursed their young (this led to attachment– benefit for survival teaching young to survive. young to stay with mother till they are out of vulnerable stage).

Advantages: instead of having 10 eggs and have none survive (open to predators), have one (major investment which develops slowly and lives to propagate). POPULATION GROWTH SLOW BUT STEADY

This also brought about change in the maternal role. : The young suckles and stays with mother, Purpose of such a development, a) nurturance provided directly so that there is fitness, b) learning directly form an adult: Learns to run when mother does, to eat what she does, c) is protected from all

bigger and more dangerous animals by the adult (mother: maternal aggression is well documented). Thus, early development became and important period where attachment and bonding began. This is a sensitive period where the young is tied to the mother through pheromonal signals. The highest form of attachment bonding with mother developed in primates

Human Evolution

- Hominids evolved into at least 7 different species their names specify the location their remains were discovered in: Australopithecus (about 2 -3 million 500 cc brain), Java (Indonesia), Peking (China), Olduvai man (in the Olduvia Gorge in Africa), Pithecanthropus, Homo Erectus,(brain size about 900 cc) Neanderthal (brain 1400cc) (Germany), Cro-magnon

- Pithecanthropus: the earliest man-ape who was cage living, used stone tools. There is evidence in the cages of use of FIRE (therefore fire had been discovered). There is also evidence of cannibalism, especial favourite appears to be the brains (cracked cranium is evidence for such activity). There appears to be family and some social groups.

- Neanderthal: remains found in the Neander Valley in Germany. The evidence indicates that the Neanderthal was present around 1, 00,000 to 50,000 years. In appearance they were small and heavy set, brutal looking, slightly larger brain size but very efficient brain compared to earlier species. This was the beginning of a man shaped like an ape. There is increased tool use with specialized tools for cutting, piercing, shaping. This ape-man migrated by traveling across as indicated by the finds of remains which are spread over Europe, Africa, and Near East.

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Pinel, John P.J. (2003) Biopsychology (5th edition) Allyn and Bacon Singapore

LESSON 07

EVOLUTIONARY AND GENETIC BASIS OF BEHAVIOUR

Objective:

- The concepts of evolution and its developmental process.
- Evolution of the homosapien to understand brain development and behavior changes as they evolved.

Important developments of Homosapien development

Stereoscopic vision

Vision for seeing depth is more specialized. This reduced dependence on smell (early mammalians developed smell as a strong evolutionary change to compete with dinosaurs). In the evolved primate vision not olfaction became the primary sense especially depth perception and distance vision (in upright posture) worked very well for hunting and locating prey across longer distances.

Bipedalism

Pelvic bones of early ape man underwent a change. The pelvic is shorter in length and wider in man. This is to give support for upright posture and balance. However, this is longer in Ape and thinner as this supported the bent posture. Bipedal running emerged earlier in the man ape (and even in the higher primates) before walking. Walking is an efficient method of covering long distances without exhaustion. Apes can outrun man in short distances, but on longer distances man wins as he can continue. This is why man became a more efficient hunter,

Why bipedalism is an important change. It is important as

a) Walking and maintaining stamina over long distances enabled man –ape to cover l more hunting grounds

b) Hunting efficient as it allows the walker's hands free for tools! (Tool use and bipedalism emerged around the same time).

This has been seen as a most important development by Darwin: Tool use the cause and effect of bipedal locomotion.

There were other major developments relevant to the brain and behavior.

- **Skull and brain size**: increase in brain size, indicating that there were developments in specialized functions as well as growth in the size of the brain, neurons, and cells. This system became more evolved.
- **Increased cortex:** In lower animals the cerebral cortex primarily has sensory-motor functions, whereas in man the functions of the cortex have become more specialized. Sensory motor functions are reduced and higher order functions such as association have evolved in the cortex. The cortex has taken over as the master control in humans.
- **Thumb**: The separation of thumb from finger is a major development. In apes we see in less evolved primates. However, this is larger and separated in man, making the hand more efficient and useful for grasping and efficient tool use. These are prehensile hands.
- **Language** evolved in humans as a strong means of social and other communication, visual cues no longer remain that important. This language can easily learnt by infant by being with the caretaker (usually mother). Language also sharpened the capabilities of homo sapien for planning, foresight, language, art and culture.

- **Teeth and jaw (and forehead) development**: In baboons and other apes the size of the canine is different for males and for females. The males have much larger canines as they are the fighters. Their canines are used to threaten (through display), attack, hold, shake, pierce the enemy. Females have smaller canines as there is no need for a fight against predator. So we see a reduced canine size with development of differentiation of the female role. Further, the jaws moved to a point where the jaw bone's position with reference to position of the vertebral column moved for balance the body for support of bipedalism. The forehead slope is also reduced. The facial appearance is less brutish.
- **Family evolved**: Since the females carry the young in utero for the period of gestation, the female role/investment and involvement is greater with infant. The female has to remain with the infant cannot move around freely while carrying the young- both can be endangered. Therefore the male role as hunter evolved. Sexual dimorphism has evolved, to keep family together and for protection of the offspring.
- **Social groups:** Since male hunting alone would be vulnerable to predators, therefore hunting in groups evolved females nursing stay behind. Males hunting together would also be able to hunt large animals food would last longer. Thus, social living was evolved first in the caves. There was food sharing, increased social contact which led to increased use of language and signals.
- **Reduced fat deposits on body** as there was not much need to store food and also discovery of fire and fur coverings also reduced the need for fat to keep the body ready for times of starvation and cold**.** There was also reduced hair on the body perhaps as this created impediment in running. Since body hair was reduced, specialized sweat glands for rapid diffusion of heat were evolved.
- **Improved power of stereoscopic vision and other functions**: This was most beneficial (as described earlier) but along with this came other benefits and evolvement. Since longer distances could be seen standing, there was development of perception and memory. These became important for remembering food sources and water holes (and predators to watch out for).

Evolution of the human brain

There is a rapid growth in both size and intellectual functioning. However, the growth in intellectual capacity was more important. In comparison elephants (8000cc) and whales (5000cc) have bigger/heavier brains than man (1300cc). Genius brains are not different from common men. The total brain size may not be the critical issue. It is the growth of the cerebral cortex– its size has grown enormously and it has taken over the functions form lower (and earlier evolved areas). The cerebral cortex ahs grown so much that it has to be folded to fit into the cranium. Thus, convulations (folds), deep grooves are formed to fit in more cortexes in a small cranium case! The Cerebral cortex has taken over association functions, not only sensory or motor functions. The higher the animal on the evolutionary scale the greater the control of the cerebral cortex, homo sapien being the highest evolved primate therefore has at the highest degree of encephalization.

What has evolution to do with psychology?

Evolutionary psychology have been studying the evolvement of a wide range of human and other behaviors such as monogamy, polyandry, gender roles. These studies provide insights into the most complex social and other human behaviors. These behaviors have resulted from adaptations of millions of years

- Behaviours of all animal kingdom evolved and similar

- Evolution-influences genes---gene programmed for neural development need interaction from the environment/ experience. Brain continuously interacting with environment, whatever is successful is passed on to next.

Man's rate of biological evolution may have been slowed, but social/cultural evolution increasingly complex and fast…where are we going? Speculate. Points to ponder and think!

The Nature or nurture debate keeps coming up in research and discussions among scientists working in behavioural neurosciences. In order to answer this we must remember that a) behaviour occurs in relation to some event i.e. it has to have an interaction with the environment, affect it and be affected by it, b) organism comes already equipped to face the world in a particular manner, i.e. is programmed "genetically determined animal possessing biological structures and capabilities and limits"

Thus, behavior is genetically determined as well as exploited when an appropriate environment is provided. Some behaviour is completely determined while others are somewhat determined whereas there are some which are not at all controlled by genes. The range of behaviours extends from completely innate to completely learnt. In the lower animals such as fruitflies the behaviour is carried out as per genetic programming in response to the environmental cues. On the other hand in humans language apparatus is biologically developed, but languages are learnt (language which is taught to the growing child depends on the environment he is raised in). Similarly culture and traditions are not biologically determined.

The continuum below shows that in lower animals and simpler organisms behavior is innately determined, whereas in humans there are some completely learnt

Innate (completely determined)----------Only learned
Fruitflies----------human languages

The question is do genes produce innate behaviour? The answer is No; they only provide templates for synthesis of appropriate proteins, protein chains and timing of release. There is programming of genetic proteins and chains which determine the brain program and developments which can flourish in a certain environment. The triggering cues for genetically programmed behaviors come from the environment. These can be cues from the external environment e.g. External cue could be lion hunting for food; deer sees the lion it runs to save itself. The internal cues come from within the organism's systems the hormones, the needs and the signals form these lead the organism to action. For example, internal cues may be signals for food/nutrition; the animals feel hungry and seek food. If there is rise in the prostaglandins levels birds start nest building. There can also be a combination of both the external and internal cues, that you see food or smell food and immediately feel like eating.

Can experience affect innate behaviour? Yes, in some cases it can. Mothering behaviour is due to hormonal changes after birth. However, we cannot induce mothering with drugs only, unless this has been experienced earlier (naturally). This experiment was carried out with ring doves.

Reference

Pinel, John P.J. (2003) Biopsychology (5th edition) Allyn and Bacon Singapore

LESSON 08

GENES AND EXPERIENCE

Objective:

- To understand the Brain behaviour relationships from the perspectives of biological systems.

The Nature or nurture debate keeps coming up in research and discussions among scientists working in behavioural neurosciences. In order to answer this we must remember that

a) Behavior occurs in relation to some event i.e. it has to have an interaction with the environment, affect it and be affected by it.

b) Organism comes already equipped to face the world in a particular manner, i.e. is programmed "genetically determined animal possessing biological structures and capabilities and limits".

Thus, behavior is genetically determined as well as exploited when an appropriate environment is provided. Some behaviors are completely determined while others are somewhat determined whereas there are some which are not at all controlled by genes. The range of behaviours extends from completely innate to completely learn. In the lower animals such as fruitflies the behavior is carried out as per genetic programming in response to the environmental cues. On the other hand in humans language apparatus is biologically developed, but languages are learnt (language which is taught to the growing child depends on the environment he is raised in). Similarly culture and traditions are not biologically determined.

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Can experience affect innate behavior? Yes in some cases it can mothering behavior is due to hormonal changes after birth. However, we cannot induce mothering with drugs only, unless this has been previously experienced naturally. This experiment was carried out with ring doves.

Nature-Nurture: Interaction

The interaction of nature-nurture has limits. Rats can only learn food related tasks (press lever for food) as this is the kind of behavior which exists and occurs in their natural survival repertoire, but they would not groom face for food as this is not part of their innate feeding program.

The fact is that there is greater influence of environment with higher order animals or animals with

larger brains size. Thus, this means there is greater adaptability in animals on the higher evolutionary scale. These have very few typical behavior patterns. Thus, we can safely state, the higher the animal on evolutionary scale greater, the greater the encephalization, (larger cerebral cortices and control). And the greater the encepahlization (animals with larger cerebral cortices) the more they are affected by environment.

Ethology: A branch of life sciences which studies behavior in its natural environment. The underpinning theoretical view is Darwinian evolution. The view is that behavior is predetermined and preprogrammed, is set in motion by a cue and is carried through in a fixed action pattern. These processes of behaviours are determined through natural selection (only adaptive are behaviours maintained).

Fixed Pattern: once a behavior is initiated it will go through the whole innate process to completion. This behaviour has the following characteristics. It is a)stereotypic: the same behaviour pattern is repeated again and again : the dance of the peacock, b) innate: the behaviours of the mother toward young and infant towards mother would be different, so each species and within that young or old, male or female would have their innate behaviours c) repetitive: same form repeated every time stimuli presented (peacocks dance) d) completed once initiated: even if we try we cannot stop it, the animals would stop when the behavior ends e) cannot be modified through learning.

Ethologists have studied why behaviour occurs in such a manner. They have found that Signs (stimuli) which act as releasers are important. They have the following characteristics:

A specific sign stimulus will affect one species only. It can affect only males/females or both in different ways- a sign stimuli can be the sight of another (visual: male sees female) or hear the sound of a call (acoustic: Males battle call out to another male) smell odor of the other (Olfactory/chemical) and also behaviour (the male wolf snarls to display his canines to the other males).

Sign stimuli would then lead to fixed action patterns in one animal. This then leads to a response of further sign stimuli. This exchange of signals can lead to full range of behaviors. For example a distress signal of mother hen for chicks when she sees an eagle, and they respond with distress calls and run to hide under her feathers. Lehrman developed the goose-hawk model; the same wood board cut looks like a goose from one end and a hawk from another. Goslings (baby geese) freeze with fear if the model flown in one direction (hawk) not the other. There have been experiments in which it was shown that Herring Gull leaves its egg to sit on larger one!

Is there a fixed action pattern in humans? Yes, infant turns away from noxious, smiles at pleasant look or a smile. When an unpleasant face is made indicating threat, the baby cries. Who teaches the infant? Further, there are innate fixed emotional expressions. Studies were carried out photographing faces with expressions across primitive and advanced world). These were rated by judges: anger, surprise, sadness, and happiness came across the same whether it is from the primitive Island of New Guinea or the US.

Why does the baby stops crying when the mother holds him/her close, the baby s responding to mother's smells/odor which are signals from pheromones which communicate her presence and closeness.

However, not everything ethologists say exactly is as they say. Man learns from experience to suppress anger to smile when angry. Man is a generalized animal whereas other animals are specialized (cheetah runs faster than man, snake better smeller, but man can change his environment to suit needs)

Genetic basis of behaviour; if we look at the following chromosomal composition it would appear the genetic makeup does influence behavioural characteristics:

With one X and one Y chromosome we have normal males (XY), however with increase in one additional Y chromosome (XYY) evidence of aggressiveness in males has been shown in studies of inmates and it was found that a lagrge percentage of inmates who had committed physically aggressive and brutal criems in Scottish jails studies).

With two XX chromosomes we have normal females; with a Y chromosome attached to these we have a female with male characteristics. The trisomy (three chromosomes) XXO, XYO lead to the Downs syndrome (abnormalities).

Thus genes determine the female/male but also the expression of characteristics of being a male/female. Keeping the above in view we do know that genes have an important role in the development of physical and other characteristic

Genetic basis: fundamental concepts
The basic structures of gene transmission i.e. chromosomes, genes, proteins, genotypes, phenotype, mutation, DNA, RNA would be discussed in detail.

Chromosomes are strands of chemical proteins found in the nucleus of all cells of the organism. These are composed of a large # of genes (the basic unit of heredity) located throughout on the threads of chromosomes. Chromosomes occur in matched pairs one of a pair received from the mother and the other from father at fertilization. Chromosomes are specific for each species: humans have 23 chromosomes (one pair for sex 22 for other traits) and drosophilia (fruitfly) has 8. Chromosomes are composed of double strands of DNA molecules (knit like a rope, details in the following lesson).

Genes are located on the chromosomes and these determine the combinations of chains of proteins involved in growth and development, and maintenance of organism's systems.

Proteins: there are two kinds of proteins a) structural proteins those which determine structure of the organism i.e. bones teeth, hair, organs b) enzymes; these modulate the metabolism of the organism (and other physico-chemical events).

Genes express themselves in two ways:

1. Genotype: set of genes which form the underlying genetic makeup of the individual e.g. hair genes could be for straight or curly, brown or black hair.

2. Phenotypic: These are observable or measurable traits which form the outward expression of genetic basis after interaction with the environment. Behaviour in all higher animals is more phenotypical as compared to lower animals.

As an example we can say that the Drosophilia would develop wings at a particular temperature and flowers would bloom with the right weather conditions. Children who have undergone severe starvation during early childhood—(such as children is Ethiopia or Somalia) would not be able to regenerate brain or other growth cycles

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LESSON 09

GENES AND EXPERIENCE

Objective:
To understand the Brain behavior relationships from the perspectives of biological systems.

In this section of the module the students would go through and understand Biological systems- their genetic basis and similarities with other animals. Mendelian Genetics. Where is the genetic programming of behavior (if any) Watson Crick Model. What are the similarities and differences between species, progenies of higher order animals, including homosapien?

Mendelian Genetics:
Based on a series of studies which began accidentally when an Austrian Monk Gregor Johannes Mendel planted sweet peas outside the monastery walls. He noticed a certain pattern in the colors and then he manipulated the plantation, wherein the Mendelian genetic began through Pea studies. However it appears that I may not have been that accidental as Mendel was following the readings of Lamarkian and Darwinian theories.

In 1866, he drew the following conclusions:

Heredity is transmitted by hereditable units.
When both parents transmit the same trait it is expressed in the young offspring, but when the two parents have a different gene, a hybrid form is established, which carries a unique combination of traits.
Dominant traits are traits that are expressed, whereas the recessive traits are inherited but not expressed (they remain in the background and get expressed when the offspring gets a recessive gene from both parents.
Experience cannot affect the hereditary unit (genes).

For fifty years, Mendel's work went unnoticed, but came into eminence in the 1900's.

Hugo de Vries added the concept of mutations which are characteristics accidental created in the genetic material and then transmitted in the mutated form to the offspring.

Mutation is defined as an inheritable change in the genetic material, not reshuffling of the old gene material/combination. It could be genetic mutation: change in only one gene or chromosomal mutation: which is change in the chromosomal combinations.

Immediately after fertilization the cells start dividing. When the cells divide, the chromosomes also reproduce in the zygote (fertilized cell). Cell division is meiosis (within each cell of parents which produces the gamates), mitosis is the process of cell division which takes place in the zygote).

The two genes at one location are known as alleles. If the alleles are same at the same location (from two parents), then the newly formed zygote is homozygous for that gene. However, when two different paris of genes or alleles in the same location i.e. a different allele from the father or mother, then the gene is heterozygous (where one become dominant and the other recessive)

DNA
Heredity is transferred through DNA: deoxyribonucleic acid. DNA is found only in the cell nucleus (and it stays there), it is most stable, and is self-replicating. It is composed of basic components i.e. simple sugars (deoxyribose) phosphates and four nucleotide bases: Adenine, Guanine, Thymine and Cytosine),

Watson and Crick broke the DNA molecule code, which is double helix model. Each consists of two strands wound around each other like a rope of two strands and these are attached to chains of phosphates and deoxyribose (like a ladder). The four nucleotide bases, adenine, thymine, guanine and cytosine are in permanent combinations where adenine always bonds with thymine and guanine with cytosine (AT, GC).

DNA replicates itself during cell division, the sequence is remembered, and copies made. When the cell is replicating the DNA strand unwinds itself. One strand remains stable while the other breaks up. One pair of the bases in these strands also separate, while one base of each pair remains attached to each strand (look at the figure to see how it opens up). A continuous sugar –phosphate –sugar phosphate chain supports this double helix strand. Two identical strands are then created. This self replicating process continues (sometimes things can go wrong- mutations can occur to change the DNA sequence).

How is heredity transferred when DNA does not leave the nucleus, how is heredity transferred?

The required proteins are manufactured and metabolized in the ribosomes, the message of genetic code and materials needed is sent through the Ribonucleic acid which is similar to DNA. Therefore the code can be transferred and transcripted by the RNA. The RNA which does this is called the messenger RNA or mRNA which carries the genetic code from the nucleus of the cell to the ribosomes in the cell soma. The Transfer RNA t RNA transfers the needed amino acids for manufacturing to the ribosomes. The kinds of proteins made and when they are made determine whether the organism is male or female, human or ape or drosophilia, tree or flower. If flower what color? What height etc?

Behaviors and Genes
Behaviour genetics is the specialization which aims to identify the genetic basis of behavior.

Genes: are arranged in a linear sequence along the chromosome.

Alleles: are genes occurring a given location Homozygous if both pairs of genes at same location carry same (brown eyes, heterozygous if different genes on same site. If different then one is dominant, and the other remains recessive.

Dominance is the tendency for one type of characteristic to express itself; however, this is affected by a number of factors such as sex e.g. the same gene may be dominant for males and recessive for females (baldness).

The continuous shuffling and reshuffling of chromosomes during reproduction leads to genetic variation in the population on which the natural selection can work.

Example:
If we have a dominant homozygous gene of sickle cell anemia in African American the receiver cannot survive beyond infancy (in this case both parent had to have recessive genes for this condition where the red blood cell Is shaped like a sickle and does not have a normal shape

Sickle cell was a beneficial selection in Africa, especially for malaria infested areas, where this lead to adaptation and ensure greater survival rates. This did not work when they moved to colder climates such as the USA where greater levels oxygen was needed and the sickle shaped red blood cell was deficient. The survival in high altitudes is challenging even if the trait is recessive.

Genetic variability vs. In breeding

Genetic variability is important as it increases gene pool, thereby making a wider range of different genes available. This increases the chances of transmission of healthier genes and lowers the chances of bad recessive genes from showing up as in cousin marriages where because of in breeding behavioral and other defects are expressed and have devastating effects on families. Why? The gene pool is restricted and the same gene pool is used again and again. Thus genetic variability is beneficial as it can a) lead to the development of a new species through sexual recombinations, natural selection and even mutations, b) ensure survival of existing species when the environment changes, there is need to change/ to adapt to the changes in the environment e.g. African slaves with sickle cell anemia in cold America, those survived who were heterozygous for this gene.

The inheritance of traits is also linked to the sex chromosome or the distribution of sex chromosomes (gene follow the distribution of the sex chromosomes). There are several different ways in which the transmission follows the sex chromosomal distribution.

1. **Sex Linked traits**

This means that the sex inherited is also linked to traits that are inherited. When traits are located on a gene which is carried on the X chromosome it is said to be sex linked. The chromosome Y is small and carries very few genes. In sex linked trait, the X chromosome carries genes for the trait along with the sex. Thus it is determined by following the X distribution. This does not mean that these characteristics are linked to male or female sex, it is only X linked, thus it would go wherever the X on which this gene is located, goes). Sex linked is X linked.

As we already know that the Male has one of each XY chromosme, and females have two XX chromosomes, if there are two XX's then trait carried by the X can be overcome in competition (cannot express itself). However, in males since there is only one X, so the defective gene expresses itself. In males the X chromosome contains genes which are lacking in Y; therefore the traits on it are expressed. Thus in Males these characteristics are expressed, whereas in females there are not. This can happen only if both XX's have it, then the trait is, expressed. The following traits are sex linked:

- Hemophilia,
- Colorblindness,
- Huntington's chorea
- Turner's syndrome (this has XO, i.e. one missing sex chromosome, no YO found yet).

These are transmitted from the mother's X to sons it is expressed and if transmitted to daughter's recessive it remains recessive.

Two important characteristics of Sex linked traits:
a) The incidence is higher in males
b) it is never transmitted from male parent to male offspring

2. Sex Influenced Traits

The trait is inherited and transmitted equally by both sexes; however sex determines the dominance, (gene dominant in one sex and remains recessive in the other). The two famous examples are the white forelock, and baldness.

Characteristics of sex influenced traits:
a) It is more common in men than women (not sex linked as the father's gene is transmitted equally to sons and daughters, whereas in sex linked father did not pass on any genes to sons).

b) The trait shows up in men when neither mother nor father shows it (double recessive).

c) Shows up in all the sons of a woman who has the trait.

3. Sex Limited

When traits are expressed in one but not in the other sex. These characteristics are carried by the sex genes as well as other genes. However these require the right amount of hormones for expression. It is not necessarily complete dominance always; it can be incomplete sex limited trait. Reproduction only is only found in females, and in men there is growth of hair on ears with age and beards. The sex not genes which condition the expression of these traits, Montague (1954) reported that albinism was more in males 95 as compared to 5 females (incomplete sex limited). Similarly alkeptonuria (black urine) a disorder of the breakdown of phenylalanine also occurs more in males than females

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LESSON 10

GENES AND EXPERIENCE

Objective:

- To understand the Brain behaviour relationships from the perspectives of biological systems.

In this section of the module the students would go through and understand Biological systems- their genetic basis and similarities with other animals. Mendelian Genetics. Where is the genetic programming of behaviour (if any) Watson Crick Model. What are the similarities and differences between species, progenies of higher order animals, including homosapien? How much do genes contribute to behavior: The discipline of Behavior genetics?

Genetic Basis of behavior

- Genes not act directly on behaviour, but on the proteins/aminoacids which are responsible for the structure and metabolism of the organism.

- Behavior geneticist and studies in this area agree that a) environment and experience are important as they interact with genetic material. The researcher try to pinpoint how much of each contribute to behavior. b) a single gene at a single location cannot lead to one behaviour. Behavior is the sum total of different genes at different loci. It is not an all or none characteristics. It is always a combination of different genes, polygenic systems.

Experimental Studies: Genetic Manipulation

There have been experimental studies which manipulate genes using artificial selection and other conditions in animals reared in labs. This is done because the environmental conditions in the laboratory are held constant (temperature, day/night cycle , food and the social environment),selection of specific traits of interest which can be followed up, and animals with those characteristics mated and progenies (offspring) followed up and tested for behavioral as well as other characteristics.

How do the behavioural geneticists measure and test behaviour of interest in the laboratory animals. The characteristics of interest are taken and animals tested and their scores/ performance looked at carefully. Then animals scoring on both extremes separated form the group that is the High and Low scorers taken and separated. Then low scorer females and low scorer males mated. The same procedure was carried out for the high scorers. The progenies were then developed into two separate populations by repeated selective testing and mating. This has been done as early as in the 1930's.

Tryon (1934) carried out an experiment at the University of Berkley where he bred maze bright (who did extremely well on maze tests) and maze dull(those who made a lot of errors in maze) rats for 21 generations. By the 8th generation no overlap in two he found that there was no overlap in the two populations. The question that it could be possibly due to rearing as bright mothers were rearing bright offspring. This was ruled out as he designed an experimental cross fostering design in which the maze bright offspring were reared by maze dull parents; they still made significantly less errors. Similarly, using the same cross fostering procedure he had dull rats reared by bright rats. Since then many behaviors such as open field activity, alcohol and morphine preference has been identified using such designs. However we must remember that behaviour is complex, and has multiple variables. There is not just one single gene for maze running, (there are a lot of cues involved). Further, Searle (1949) reported that in comparing two groups, he conducted 30 different tests on the maze bright and maze dull. He reports that maze bright rats were superior in performance and less emotional, therefore the better learner may learn because there is more emotional stability not because they are more intelligent!

Are there any Environment effects? Cooper and Zubeck (1958) raised the maze bright/dull rats in three different environments a) impoverished(cage made from wire netting with groups living), b) stimulating and enriched housing with wire netting, group housing but it had toys, ramps for animals to play with. His findings showed that the maze dull rats perform similar to the maze bright if reared in stimulating environment. Bennett, Diamond, Krech and Rozenweig (1964) found that rats in richer environment have thicker cortices! This means that their brain development is affected by early stimulation (more on this later in the chapter on brain development)

The foremost names in the field of genetics and behaviour are Theodosius Dobzhansky and Seymour Benzer. Their work on Drosophilia (fruitfly) is pioneering work. They took a genetically heterogenous population and through selective breeding created new breeds to show that behaviour genetically linked. A lot of work was needed to identify which behaviours were linked to which genes and were located on which chromosome! Further, constant selection was to be maintained or genetic pool could be broken into, genes may get re-assorted and effort gone waste (and behaviour under observation may get lost). It could be a simple careless mistake of a stray fly getting into the experimental breeding cage.

In Dobzhansky and Benzer's experiments, the gene material was also changed through radiation and bio engineering manipulations. They developed mutants who were sluggish (slow movers) hyperkinetic (very fast movers, who died soon as they consumed more oxygen and body metabolism faster) non climbers (those who could not climb against gravity), easily shocked (goes into seizure) negatively phototactic (those who move away from light source- normal flies move towards light).

Similarly dogs were identified for characteristics by John Paul scott in his laboratory in bar harbor Maine. The breed beagle (snoopy dog of the cartoons) became the model for hyperactivity.

Mouse strains were identified and bred for different characteristics; aggressive behaviors, alcoholics vs. nonalcoholic, hoarders vs. non-hoarders, emotionality (defecate in a novel situation), waltzing mice (inner ear defect). All of this is a consequence of in breeding

In breeding

Simply defined this is repeatedly using the same gene pool which leads to expression of recessive genes which may carry both behavioural and physical defects.

In a study Theisen (1972) reports that the death rate in children below 10 years of age is 24 per 1000 in normal population. In interrelated marriages it rises to 81 per 1000. In closer marriages the rate rises even more. There are other more serious effects such as physically less capable, weaker and age when they walked and talked was much later than normals. This showed developmental lags. Other deficits that Theisen (1972) reports are lower Intelligence scores, with lower verbal scores, and language scores were even lower than normals.

In summary, it is well documented that if the gene pool is reduced more recessive disorders show up. Larger gene pools lead to a healthier and longer surviving offspring which can compete in a wide range of environments.

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LESSON 11

GENES AND EXPERIENCE

Objective:

- To understand the Brain behaviour relationships from the perspectives of biological systems.

In this section of the module the students would go through and understand Biological systems- their genetic basis and similarities with other animals. Mendelian Genetics. Where is the genetic programming of behaviour (if any) Watson Crick Model. What are the similarities and differences between species, progenies of higher order animals, including homosapien? How much do genes contribute to behaviour: The discipline of Behavior genetics

In breeding

Children of very close genetic relationships (incestuous), were studied by Adams and Neal (1967). There were 18 unrelated, 18 such cases in their study. They reported that in these cases 5 died and 2 mentally retarded and there were other problems and only 7/18 were normal (physically and otherwise). As compared to this group there was problem in only one case in normal and there were 17/18 normal (any physical or other defect). Thus, restricting the gene pool further leads to serious aftereffects.

Sociobiology of incest: why forbidden in all religions?

Barash (1977), states "close breeding reduces the fitness of the participants because of the reduced viability of the offspring produced. Incest taboo has genetic predispositions."

Natural selection pressures work on the gene pools, if reduce gene pools; reduce genes available bad genes show up.

Hybrid vigor: if two different gene pools are mated their offspring is stronger and there are greater chances of survival in animals (horses, dogs, cows,) birds or vegetables, flowers or people of Asia!

Behavioural Defects Due To Genes

The following behaviours and genes have shown to be linked

Deficiencies Due To Single Gene Defects

In some cases defect in one gene at one locus affects total behaviour. Some of these are discussed in details as follows:

Phenylketonuria (PKU): This is characterized by mental retardation and queer smelling urine, which is identified as the presence of phenyl pyruvic acid in urine. This is an amino acid disorder. Asbjorn Folling (1934) Austrian dentist first noticed it in two of his children with symptoms of vomiting, irritability, seizures and hyperactivity. This is due to inheritance of a double recessive gene for this disorder as parents are homozygous. This disorder completely upsets the biochemical pathway creating toxins which damages the brain irreversibly. There is Irreversible brain damage due to buildup of phenylpyruvic acid and byproducts—toxin what can be done? Hospital checks immediately after birth if results are positive then these babies are place on a controlled diet to reduce the damage. However, the timing of treatment is important especially when the brain is developing rapidly. Diamond and colleagues (1997) have shown that early control reduces but not completely eliminate cognitive deficits which are similar to prefrontal damage.

Tay-Sach's disease: Infantile and juvenile cerebral lipdosis or amauratic idiocy. This is a defect in the lipid metabolism due to a double recessive gene at single locus which means that both parents are

carriers. This is found mainly in Eastern European Ashkenazi Jewish families. Homozygous for this gene do not survive.

Infantile form of this disease is found mainly at a few months of age (during 1st year); the symptoms are motor weakness, blindness (cherry red spot in the retina) and mental deterioration. Death occurs in 1-3 years.

Juvenile form is found at around 2-10 years of age with similar symptoms i.e. optic atrophy, blindness, paralysis, mental deterioration eventually death.

1. Huntington's chorea: is characterized by a progressive degeneration both physical and mental. This is due to a dominant gene which is transmitted to males only. In this disorder the cortex and Basal ganglia are affected. Damage to the Cortex results in dementia (forgetting) and damage to the, Basal Ganglia leads to involuntary jerky movements. Drugs are given to control movements. The onset of this symptom is between 30-50 years, death occurs between 5-20 years with rapid progression of deterioration.

2. Alzheimer's genetic transmission is shown to occur especially in cases where it shows up in young. Chances increase if a close relative has it. The case of Hannah's heirs- Jewish mother from Russia had it and 5/8 children developed Alzheimer's during their late 40's

Chromosomal Abnormalities

The abnormalities which occur to the defect in the chromosome and follow the transmission of the chromosome are several. These are discussed as follows:

- **Downs Syndrome (mongolism).** In a normal human there are 23 pairs of chromosome (23from other and 23 from father) which is then 46 chromosomes. However, in some cases there is an additional chromosome which adds up the total to 47 chromosomes. There is a trisomy (instead of two there are three chromosomes) at pair number 21. This can occur sometimes at pair number 15, (or pair number 21 intermingled with #15- during sex cell formation and the #15 carries an extra #21). The older the age of the mother, the more chances of downs syndrome in the child. Therefore now amniocentesis is routinely required to test for this to prepare parents and to advise them.
- **Klienfelters Syndrome (XXY),** this is a genetic anomaly related to the sex chromosome. One extra X is transmitted to an otherwise normal male pattern-male with female characteristics or a masculinized female. There is atrophy of reproductive ducts, sometimes mental retardation and some personality problems (not in all cases)
- **Turner's syndrome:** this involves a missing sex chromosome. There is only one X chromosome. These are females, short stature, with ovaries not developed. They have normal intelligence however are deficient in spatial discrimination (spatial discrimination space-form blindness- cant copy figures right.- hypothesis that this trait may be sex linked?)
- **XYY Syndrome:** this is also a chromosomal anomaly where an additional Y chromosome is attached to the normal male pair. These males are taller, muscular, and sturdy slightly retarded. The extra Y increases in maleness and aggression. Research on jail inmates with aggressive, brutal crimes (Jarvick, 1973) Incidence 2-13% in Jail pop whereas in normal it is about 1%.
- **Lesch-Nyhan syndrome:** this is due to a recessive gene carried on the X chromosome found only in males. The symptoms are Cerebral palsy, involuntary movements of the limbs, hands, feet and facial muscles, self-mutilation lips mouth and fingers. This is due to an

enzyme deficiency with an extreme over production of uric acid. Self-mutilation is due to increased Dopamine B-hydroxylase in plasma.

Behavioural Characteristics
Studies have used the monozygotic (same egg, same sperm, same time fertilization)) or dizygotic twins (different eggs, different sperms, same time of fertilization) to identify behavioral defects due to gene defects. Genetic influences on Human behaviour utilizes twin studies paradigm:

The MZ twins have 100% genes common, and the DZ are like other siblings with 50% genes in common

Monozygotic and dizygotic twin studies follow many different methodologies from comparing those who have been reared together in the same environment to those reared apart in different environment (adoption /foster parents)

In adoption studies if behaviour is similar to that of the biological parents then behaviour is due to genes, however, if their behaviour was similar to their adopted parents then the behaviour can be attributed to the effects of environment. Comparisons of performances of related and unrelated individuals are made on a wide range of tests. It is the behavior geneticist who would be able to estimate how much is due to gene (variation: genetic), and due to environment (variation: environment)

In studying genetic basis of behavioral (especially complex behaviours), it must be remembered that a) more than one characteristic make up a trait and b) these traits are continuous i.e. in gradations of more/less such as I.Q., Schizophrenia, alcoholism. Therefore, the task of the behavioral geneticist is not an easy one; however, there have been studies which have identified genetically transmitted mental illness as well other disorders.

Schizophrenia
Twin Studies: This is a genetically inherited disorder as evidence by multiple research studies has supported this. The incidence of schizophrenia in general population is 1% .This rises if there is a close relative with schizophrenia ie. With siblings and dizygotic twins this rises to 10-15%, and the expectancy of schizophrenia if one parent has it is about the same i.e.-10-15%. However, if both parents have it then the expectancy rises to 40-65%. Schizophrenia is due to chemical, neural and biological imbalances created by genetic codes. These imbalances in could be due to inheritance of a) recessive gene from both parents or b) a dominant gene from one parent who has this disorder. Evidence from genetic predisposition twin studies a review of 17 studies from 1928 to 1972 from all over the world showed that the highest incidence is among MZ twins and lower among DZ.

Rosenthal's (1959) study on MZ twins with schizophrenia reports 60% presence in concordant twins, males had a later age of onset and a more favorable outcome. Inouye (1961) reported studies carried out in Japan and identified 3 groups of monozygotic twins. There was chronic schizophrenia (17/23: 74% concordant). Mild transient 9/23 (39% concordant).

Foster child studies: excellent, now classic study by Heston (1966) followed 50 children born to schizophrenic mothers and separated within a few days after birth. For controls he took 50 children born to normal mothers. There was a higher Incidence of schizophrenia/personality disorder and other abnormalities in 47/50 children of schizophrenic mothers. There were 5 schizophrenics, 4 were mentally retarded, 9 were antisocial, and 13 had neurotic personalities. In controls there were only 2 with personality and 7 with neurotic personalities.

Thus there is strong evidence to link schizophrenia with genes transmitted to the offspring. Research in the more recent years has also shown the same (see Pinel page 463-464).

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LESSON 12

GENES AND EXPERIENCE

Objective:
To understand the brain behavior relationship from the perspectives of biological systems

In this section of the module, the students would go through and understand biological systems, their genetic basis and similarities with other animals. Mendelian Genetics. Where is the genetic programming of behavior (if any) Watson Crick Model. What are the similarities and differences between species, progenies of higher order animals, including homosapien? How much do genes contribute towards behavior: the discipline of behavior genetics?

Behavioral Characteristics
In this lesson, we would continue with the discussion on the genetic basis of higher order behaviors. In the last lesson we had discussed Schizophrenia which has strong genetic basis as shown by research.

Intelligence: Sir Francis Galton and Darwin were first cousins. Both started new ways of thinking. Sir Francis Galton laid the basis of Statistics and Darwin gave us the theory of Evolution. Galton started the lineage of famous English men found genius is hereditary but we cannot rule out the possibility of environmental influences (upper class, royalty provided better breeding grounds for training children to take on important assignments-like training a crown prince). Sir Julian Huxley (biologist) Aldous Huxley (writer), both grandsons of Thomas Henry Huxley and great grandsons of Leonard Huxley. Thus it appears genius runs in the family! John Noyes started a new thinking called Eugenics, where propagated that scientific breeding can produce brilliant offspring leading to perfectionism. He initiated a complex system of community living of highly educated and well to do professionals. There were 57 children born in the community. They were healthy, only 6/58 died compared to the mortality rate of 45. The surviving children started corporation, hospitals which were bases of present day entrepreneurship and business of the US.

The view that intelligence is inherited is controversial as there are several issues which come up how is intelligence defined or measured?

Intelligence is a sum total of many abilities. It is possible that these are inherited, but there is evidence that environmental stimulation does make a difference (early stimulation?) It is well documented that black children who performed poorly on IQ tests when coached on test taking showed an improvement of scores of as much as 20 points. This coaching is more effective if children younger. Early stimulation is important.

Environmental Influences
Environmental influences can affect intelligence, if the same individual is tested again after a period of several years it is possible to gain about 20 points (Does this mean IQ increased?)

In Israel children have to live in the Kibbutz, separate from their parents. Children in Kibbutz coming from European descent had IQ scores above 100 points, whereas children from Oriental/African descent 80-90 points. However after 4-5 years their scores are similar.

Similarly, monozygotic (MZ) twins reared together had a higher correlation on IQ scores (r=.92). This is the same for height, weight and school achievement. When MZ are reared separately the correlation of IQ falls to .88 and school achievement falls to .66. In dizygotic (DZ) and siblings the correlation falls and in unrelated individuals the correlation of IQ falls to .25.

Critical thinking about intelligence testing

Is Intelligence influenced by culture?

2. Intelligence Tests?? Do they measure innate intellectual capacities or cultural learning?

Alcoholism: is another trait which evidence has shown to be genetically linked, especially that it is transmitted from father to sons. Longitudinal studies have been carried out in Scandinavian countries by Goodwin and colleagues (1979) as it is possible to follow children in foster homes through records. It was reported that predisposition to alcoholism is 4 times higher in males. Research by Schukit, Goodman and Winokur (1972) showed that alcoholism in half sisters or half brothers with an alcoholic parent (living with them as well) was 46% (same if they did not live with alcoholic parents). On the other hand, if foster parents were alcoholic the frequency is much lower about 15%.

There have been a large number of researches to identify the genetic basis of other behaviors. In one study it was reported genetic predisposition to opiate addiction in rats. Rats were fond of morphine, preferred it over water after tasting it for the first time!

We still have a lot of research to do before we can separate clearly the effects of environment or environment and it is ongoing keeping in view the large number of variables.

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LESSON 13

RESEARCH METHODS AND TECHNIQUES OF ASSESSMENT OF BRAIN FUNCTION

Objectives:

To familiarize the students with:

- The various techniques used to study the brain and its function and structures. Invasive vs. Non- Invasive methods, Stereotaxic surgery.
- Stereotaxic Atlas used for brain surgery and manipulation.
- Histological and cytological methods for Cell staining, Radio labeling, Fluorescence, autradiography, Lesioning and electrical stimulation, single cell recordings, push-pull cannulae.
- The advanced techniques such as MRI, fMRI, CAT, PET, CT, EEG, EOG, EMG, X ray etc.

Research techniques in the Neurosciences:

Measuring, researching, and studying brain which is an extremely complex systems with 10^{11} (100 billion) neurons, with multiple synapses and 10^{15} (1000 trillion) connections. This is as complex a system as the Milky Way. On the average 1 cubic millimeter of the brain has about 10^{9} (billion) synapses. We need to understand the physical structures (from visible to naked eye to barely visible with e-microscope), functional organization (from a single neuron to an anatomical area working together as an orchestra), and the ongoing activity of a few milliseconds to watching a brain grow across time. The techniques and methods have grown enormously since study of the brain began, with more sophistication and finer measurements possible now than ever before.

There is good news for those who wish to study the brain:

- The brain similar in structures, neuroanatomical organization, function, and development to animals on the phylogenetic scale, therefore it is possible to study the primate brain or the rat brain and see commonalities and extrapolate to the human brain.
- The brain structures are grouped together simplifying the study of the brain therefore it is easy to locate, to verify, and to study the areas which are connected. For example the thalamic nuclei are connected with the central cortical areas and if we damage cortical areas this leads to degeneration of the corresponding thalamic nuclei.
- The human brain cells require similar nutrients and materials as other living cells, therefore the neurons, and other structures as well as the biochemical processes can be studied in other animals, **in vivo** (within**) or in vitro** (outside the living system).
- Development of Techniques clarify the role of different areas, several techniques can be utilized simultaneously.
- There is a consistency of patterns of responses within cells and neuroanatomical areas, (electrophysiological, neurochemicals, other chemicals, ionic changes etc)

Then there is the bad news:

- The brain is extremely complex with intricate networks; it is not easy to study one area independently.
- Identifying one area or process is not enough as areas/ processes are interconnected and there are several levels of functioning and controls (chemical, physical, electrical, ionic etc).
- The brain functions at molecular and molar levels (the invisible behavior of molecules and neurons to the more visible motor and behavioural actions), where the movement/action of molecules are translated into gross behaviors.

- Measurements of these behaviours can be made at each of these levels, and tiny miniscule molecular communication and movement of ions and amino acids across gaps which are in Angstroms result in major behavioural changes. What role does each play?
- Many interconnections and many neurochemicals work in one setting in one synapse. Isolating and studying one leads to an incomplete picture.

Inspite of all these difficulties scientists have been able to locate and identify functions using the techniques which we would discuss in the lesson today.

Techniques
There are as many as researchers working in the brain areas, they vary in the kind of area the scientists are working in or the area of their interest.

Techniques vary depending on:

1. Area, on which the researchers are working with, and whether they are working with simpler or complex behaviors, whether the brain areas are at the lower levels (motor basal ganglia) or higher levels (thalamus) even higher (motor cortex).

2. Techniques available. Although there is a wide range of techniques available but as more advanced techniques become available with advancement of technology these open up more areas that the scientists can work on.

3. The research goal whether it is exploration, understanding, or manipulation, to develop theoretical frameworks or to describe functions of brain areas.

Basically all methods aim to understand, control, simplify and objectify behaviour at microscopic a macroscopic/gross levels. The simplest methods and techniques would

- measure neurons, their size and their interconnections (structural /histological procedures) or,
- measure the electrical activity of cells or measure and manipulate their metabolic processes (glucose, oxygen, blood flow)

The more complex methods would be using

- Radiolabelling, neurophysiological or neuro psychological tests, behavioural paradigms.

Far more complex methods for measuring ongoing functioning would be advanced technologies such as MRI's, PET scans etc).

There is a variation in the subjects of brain sciences investigation. A wide range of animal species are used as subjects from the lowest organism with the simplest nervous system such as the Aplysia (much work has been done on learning and memory using this organism), to highest order primates such as the Chimpanzees.

Animal's studies: these can be studied using in vivo techniques, microelectrodes, invasive techniques which allow manipulation of the brain measuring electrical potentials of various areas creating electrical stimulation or lesioning studies creating animal models.

Human studies post mortem As we cannot manipulate the human brain to bring about changes (except the mad scientists in films !) therefore post mortem studies are used which have provided a great insight into brain damage and through that the brain functioning. For example we know more

about Alzheimer's after studying brain of patients and the areas of damage identified. Also studies following brain trauma can help identify areas linked with behaviours as in the cases of Phineas Gage, and HM (ref: Bridgeman 58-63, Pinel 104-131).

Neuroanatomical studies: These are to identify brain areas and their structures and function: Therefore this involves techniques which are mainly histological and invasive.

- **Histology:** This is the study of brain cells and their projections after the removal of the brain which requires special training.
- **Staining techniques:** where a certain dye or chemical is used to identify the structure form or connections of cells and their locations.
- **Invasive:** where we actually invade the intact brain to create a lesion, or introduce radioactive substances, or stimulate or use in combination. Changes in behaviors are noted if we are working in a living animal and later brain studied histologically.

Histology:
We need to carry out histology for verification of location of lesion or the stimulation sites (cell, fibers, connections) after our experiments are over. Histology is primarily used for location, structure, functional organization of the CNS. Various techniques and histological procedures are available which are carried out on the intact brain. This can be done only after the experiments are over and the animals sacrificed, brain taken out of the cranial bone and sectioned. These are steps which are followed as follows:

First step, Perfusion of the circulatory system of the live but anesthetized animal through heart using saline to wash out the blood from the entire system so that it does not coagulate.

Second step After the saline comes through clear the **fixative is perfused into the heart using the same needle. The fixative, formalin (formaldehyde**) is injected to prevent degeneration of tissue, fixes protein bonds at the point of death.

Third step: Hardening the tissue by a) freezing using the freezing microtome (a machine which cuts thin slices of tissues). We have to be very careful, because if it freezes hard the brain tissue would become brittle and break or it remains too soft, it cannot be cut.

Fourth Step: Embedding: one of the procedures is to embed the brain before cutting. It can be Nitrocellulose which would allow thin sections of the brain to be cut.

Fifth Step: Staining the cells. Many different stains are available and each with its special characteristics. The stains bring out different structures of the cell or their projections.

Types of Stains more frequently used:
- **Nissyl blue**: this is a special stain in which only the cell bodies are stained in a typical blue. This was developed by Nissyl, one of the pioneers of histology.
- **Weil Stain:** Myelin stained brown: stains only cell projections/ fibers with myelin .
- **Golgi-Cox Silver**: heavy metals such as silver absorbed by tissue- only 2-3% neurons stained, but completely-can see soma, dendrites, and axons to the branches.
- **Histoflourescence:** This method utilizes a special technique in which the cells are exposed to dry Formaldehyde gas. Cells fluoresce in different colors. This can be sued to identify neurotransmitters the areas of heavy concentration. This technique was used for

noradrenaline and Dopamine neurons, the NA fluoresce bright yellow. This can be used to identify single cell or a group of cells.

Tracers: These are methods which are a special procedures involving injecting the animal while the animal is alive. This can be used to where the tracer chemical end up- can be used in learning and memory and the animal injected while it is performing. Or the animals can be injected with tracers during early brain development and then the tracers located in later period to see how far neurons have traveled during the early phase.

Neuroanatomical tracing methods are therefore used to follow up projections of neurons their connections. There is wide range and types of tracers which can be used depending upon the area of investigation and the interest of the researcher.

Procedure is to Inject a tracer into the nucleus of a neuron or other areas such as the synapse (where two neurons connect), and to follow it through.

- **Anterograde tracer:** The direction of transport is toward the periphery i.e. when the tracer is carried away from cell soma to projections, (dendrites, and their branches).
- **Retrograde tracer:** Where the direction of transport is towards the cell i.e. when the tracers move towards the cell soma. This kind of tracer enters from the synapse. This shows connections and interactions of a neuron.

The three major techniques are as follows:

Radio labeling, autoradiography (writing with own radiation (cell's)),Horse Radish Peroxidase: In all these techniques a chemical or other Substance normally used in the brain (and is of interest) is tagged with a radioactive tracer for follow up, and injected in the brain.

- **Radiolabelled (radioactive) Glucose**: radiolabelling glucose to check out brain glucose cues. A substance, 2-DG (2-Deoxy glucose) is injected and it enters the cell like a virus. It uses the cells own metabolic mechanism (all cells use glucose during activity). This travels wherever the glucose would have gone and it stays there. It emits radioactivity when exposed on to a photographic plat.
- Similarly **radio-labeling** other substances such as **Amino acids** for locating and identifying amine activity, **endorphin**s for brain opioid sites etc. This is done using the receptor binding autoradiography for the neurotransmitter or drug which binds to a receptor, it is thus radio labelled. Neural tissue is then exposed to a labelled ligand (molecule that binds to a target) and these areas show up as radioactive on the photographic plate or under the microscope.
- **HRP: Horse Radish Peroxidase**- this is an enzyme which travels through the retrograde axoplasmic transport system moving through axons to the cytoplasm and traveling further to the cells, their projections i.e. the dendrites. This is capable of breaking down certain peroxide molecules turn into soluble salts, which are then are taken up by the terminal boutons. This technique works well with a single cell as well. The stains glow or flouresce under specific wavelengths light. This is also one of the histoflourescence techniques.
- **Histoflourescence:** a technique developed by Falck and Hillarp in Sweden in the 1960's where the monoamines exposed to formalin fixative, glow when exposed to flourescent light. This was used to identify the locations and projections of Neurotransmitters.
- **Immunocytochemistry**: introducing an antigen, to create antibodies (monoclonal antibodies). Can use specific proteins for specific Neurotransmitters. The regions of radioactive accumulation or dyes show up under microscope as location of the neuroprotein (the antigen). Thus we can use labelled antibodies for target sites called labeled ligands.

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LESSON14

RESEARCH METHODS AND TECHNIQUES OF ASSESSMENT OF BRAIN FUNCTION

Objectives:

To familiarize the students with

- The various techniques used to study the brain and its function and structures.
- Invasive vs. Non- Invasive methods, Stereotaxic surgery.
- Stereotaxic Atlas used for brain surgery and manipulation,
- Hislotogical and cytological methods for Cell staining, Radio labelling, Flourescence, autoradiography, Lesioning and electrical stimulation, single cell recordings, push-pull cannulae.
- The advanced techniques such as MRI, fMRI, CAT, PET, CT, EEG, EOG, EMG, X Ray etc Histological, electrical chemical and pharmacological processes and techniques why so many?
- Advanced technologies and methodologies

In order to identify brain areas specific sites and relate behaviors and functions with these sites, traditional neuro anatomy uses techniques which are invasive. These techniques actually involve entering the brain to record, to lesion or to bring about a change in the normal brain areas/systems. There are many techniques which are used to do such as stimulation of brain areas using electrical current to those areas, damaging (lesioning) areas of interest, drawing chemicals from a site through push-pull cannulae technique and many others. Again, these can be used in combination with each other or with other techniques (usually histology follows such manipulations). Keeping in view the complexity of the brain, each of these techniques requires skills and training in order to the surgery-brain surgery of animals. This requires being well trained in using the Stereotaxic instrument and the Stereotaxic atlas

Stereotaxic instrument and surgery

Stereotaxic instrument allows the restriction of the animal's body and head so that it is immovable, and sensitive insertion of fine electrodes can be made. Using the Stereotaxic instrument the scientist can place electrodes or conduct other surgical procedures using precise positioning. These are in 3 dimensions, anterior-posterior (A-P: front- back), dorsal-ventral (D-V top-down), Medial-Lateral (M-L: center –sides). The Stereotaxic instrument is made of steel with several main parts.

a) It has a head holder (for making sure that there are no head movements),

b) The ear bars which support the head in a position by locking onto the ear bones,

c) The electrode holder which can move in three dimensions described above (sideways, front and back, up and down using a system which allows movement of electrode holder to follow exact measurements.

How does one use the Stereotaxic instrument? We follow the specifications given in the Stereotaxic atlas (check out figure: one page out of the rat brain atlas). These are prepared after studying dissections of several hundred brains, here are specific atlases for each species (monkeys, mice, cats, dogs, etc)

Stereotaxic atlas: This is like a geographical atlas where dimensions are given to arrive at particular location. These locations are identified using two major sutures (lines where bones of the skull join) and the point they meet. In the anterior we use Bregma, Lambda is the posterior line. Using these as

the reference points we can move in any direction in accordance with the atlas, and drill a hole in the skull to lower the electrode in place.

Activating brain: This can be done using electrodes (to pass the electrical current) or through chemical stimulation

- Electrical stimulation. Electrodes (extremely thin for microelectrode, and insect pins for macrolectrode) are prepared using insulated needles, leaving .5mm uninsulated tip to allow current to pass through in the e brain are stereotaxically implanted in the brain. Insertions are carried out using directions from the stereotaxic atlas placing the animal in the Stereotaxic apparatus. The electrodes are implanted using dental cement to fix electrode for permanent use. Once the electrode is set then weak electrical current can be passed through the electrodes to the neurons to see the effect on behavior. Bipolar Electrodes are used to stimulate and measure electrical charge and behavior at the same time. Behavioral and electrical response is dependent upon the site in the brain, the amount of current/ charge the intensity and duration of stimulation.
- Animal's studies using electrical stimulation have provided researchers a lot of information about the brain. For example, one of the major behavior is self stimulation, and the discovery of self stimulation areas those areas in which animals send themselves electrical current to the point that they forego food and water to get this current in their brains ii) unilateral electrical stimulation of the substantia nigra(rich in Dopamine) and circling behavior iii) aggression.
- In Humans, extremely interesting studies were carried out by Roger Penfield and colleagues who have identified areas by carrying out electrical stimulation prior to surgery to see which areas and behaviors are going to affected, this led to the development and preparation of the Motor homunculus (dictionary of motor movements)
- Microiontophoresis: This is an interesting method in which the chemical response of the postsynaptic neuron is measured using a extremely thin double barreled glass pipette. The tip of inner pipette (which contains saline) is inserted into the membrane of the connecting cells. The cell soma is then stimulated with a weak current; this is then passed to stimulate the neuronal ending leading to an electrical chemical discharge. This discharge is then is pulled out for analysis, this requires extreme precision and skill.
- Chemical stimulation: push –pull cannulae. This is a method similar to the one above but instead of the electrodes we can use thin glass cannulae to insert chemicals and immediately draw out metabolites for analysis of activity and NT. This we can use to measure effects of stimulation or inhibition by using appropriate chemical solutions.
- Recording on going activity: we can check for Excitatory or inhibitory electrical aftereffects on an instrument known as the oscilloscope.

Inactivating the brain; these are the procedures in which we can inactivate the parts of the brain by using specialized procedure.

- Ablation: This is a procedure in which we remove a major part of the brain to study what behaviors and functions would be affected. There are various techniques, these are discussed below this is irreversible, as once we make the changes, lesions, we cannot reverse the process.
- **Suction or aspiration**: In this technique brain tissue is sucked out through a glass pipette. This requires extreme precision. Also it is difficult to go through thicker white matter on the surface to get to the inner deeper areas. Ablation or suction is not a very commonly used procedure because we may be damaging larger area without knowing or intending to do so.

- **Radio frequency lesions**: in this procedure we use the alternating high frequency current from tip of electrode which is placed in a precise location in the brain. The heat from the current destroys the tissue and the size region of damage is the same as that of the tip of the electrode. The intensity and duration of current, the area in which we have lesioned would also be important in the effects. It is a fairly safe procedure as the electrode passing through top tissue leaves the overlying areas unharmed. This is also irreversible damage.
- **Knife cuts:** very thin knifes are used to section out /cut or to damage connections between brain areas. This helps us isolate are using precision knife cuts. What about remaining/adjoining areas? How has the damage affected their functioning? This is also irreversible damage
- **Cryogenic freeze:** (reversible). In this technique we freeze the brain area with cryoprobe (a thin pipe with some mechanism to cool/ or artificial ice). The coolant is inserted and as soon as the brain area freezes, it stops functioning. We can assess behaviors which do not occur. This brain areas returns functioning when the it becomes warm For other reversible techniques, local anesthetics are also used effectively (the sodium amytal test for language functioning and assessing brain hemispheric differences)

Lesioning irreversible This is an irreversible technique, meaning that the damage is permanent. Lesioning can be electrical, (or radio lesioning as discussed earlier).

- **Electrolytic:** This involves passing a high frequency direct electrical current through the stereotaxically placed electrodes and precise location/area is damaged through electrolysis. There is minimal damaged and very focused in the area.
- **Chemical:** This involves injecting selective neurotoxins (poisons) and other degenerative substances which can kill off living neurons. There are substances such as 6-OHDA which are selective toxins for dopamine. This is retrograde and travels from the synapse to the cell body.
- **Bilateral lesions:** These are lesions carried out on the areas on both sides (left and the right hemisphere), therefore the effect is more intense.
- **Unilateral lesions** involve only one side of the brain: This is good experimental design as one side acts as the control for the other, but the changes may be small and may not be easy to detect.
- **Shortcomings of this technique:** Lesions require histological verifications after behavioral tests are over. Further, the areas adjacent to the lesions are also affected and the behaviors observed and tested may be confounded by these. There are difficulties in interpretation as there is the irritation of neighboring neurons. Furthermore there are issues of adaptability of the brain areas (to the damage), plasticity of the brain (recovery and learning).
- **Points to ponder:** Do these changes measure actual changes?

Electrophysiological methods: these are methods which measure changes of the electrical potential and charge in the brain

- Single microelectrode recording: a single thin neuron about 5-10 UM (micromolar), or a microelectrode (1-3 UM) glass tubing or steel pens are used to record electrical potential. This is how the all-or –none axonal activity was measured and identified. This is also how responses to a single stimulus single resulting in neuronal firing were first measured by Hubel and Weisel using the visual systems of the kittens (intracellular/ extracellular recordings are possible with this technique.
- Macro electrodes: these involve inserting large electrodes in large neurons. The large tips help measure evoked potentials (EP's) of these areas, (response to a stimulus or stimulation.

There are many neurons firing in an area, and these are then magnified to a point one can hear the loud firing of the neurons in a typical EP average evoked potential.

- Surface/Scalp electrode in a region: Electroencephalography recordings are done for the human brain and recording can show variation (during sleep) and other behaviours.

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LESSON 15

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Objectives:

To familiarize the students with

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- Stereotaxic Atlas used for brain surgery and manipulation,
- Histological and cytological methods for Cell staining, Radio labelling, Flourescence, autoradiography, Lesioning and electrical stimulation, single cell recordings, push-pull cannulae.
- The advanced techniques such as MRI, fMRI, CAT, PET, CT, EEG, EOG, EMG, X Ray etc Histological, electrical chemical and pharmacological processes and techniques why so many?
- Advanced technologies and methodologies
- Electrophysiological methods: these are methods which measure changes of the electrical potential and charge in the brain

Single microelectrode recording: A single thin neuron about 5-10 UM (micromolar), or a microelectrode (1-3 UM) glass tubings or steel pens are used to record electrical potential. This is how the all-or –none axonal activity was measured and identified. This is also how responses to a single stimulus single resulting in neuronal firing were first measured by Hubel and Weisel using the visual systems of the kittens (intracellular/ extracellular recordings are possible with this technique.

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Surface/Scalp electrode in a region: Electroencephalography recordings are done for the human brain and recording can show variation (during sleep) and other behaviors.

Advanced Technology:

Earlier investigations in the neurosciences were limited by the techniques available to the researcher. Since the 1970's with the advancement of technology and the development of sophisticated equipment, it became possible to carry out intricate experiments and measurements. These technologies which could scan the body and brain opened up new areas of research. These are now used for research in brain sciences and in combination with other techniques; the canvas for researchers becomes larger.

- **Contrast –rays:** The contrast X rays involves injecting part of the brain with a dye or some substance which would block X rays. This is then contrasted with its surrounds or the lateral part which is not injected so, basically the contrast is compared with the non injected X-Rays. This does provide some basic information such as the location and size of a tumor in the brain or cerebral circulatory system.
- **X-Ray Computed Axial Tomography:** CAT scan was initiated in early 70's. This is a procedure involves taking multiple X ray's from different points while the patient is lying in a chamber and information fed to computers attached . The rotating X ray tube and detectors thus provide the basis for the 3 dimensional images developed by computers. This method is better than a black and white X ray which only gives very simple information; however, this cannot measure on going changes as this is a static method.

- **Magnetic Resonance Imaging (MRI).** (Resonance means echoing).The patient is placed in a chamber of which is a highly charged magnetic field. The MRI's are high resolution images reconstructed on the basis of waves, emitted by the hydrogen atoms after these atoms are activated by radio frequency waves in the magnetic field chamber. It is possible to get 2 or 3 dimensional images with MRI. Due to the high spatial resolution, MRI gives clear differences between different loci, and tissues as is done in structural MRI. The functional MRI is used when the brain is functioning to get images which are a clear indication of the areas where most activity is taking place or most oxygen being used, such as testing a patient and asking him to remember a list of words. This way we can see how different brain parts are used during learning.
- **Positron Emission Tomography PET** Brain images of ongoing brain activity rather than just the brain structure (earlier techniques did just that). The technique of injecting radio labelled substances such as 2-DG glucose works in combination with this technique. 2-DG glucose is injected into the carotid artery which is taken up by the brain and, shows up in brain areas of high activity (where glucose is normally needed). High usage would show up red (highest levels of radioactive glucose), yellow orange, blue (least levels of glucose, therefore least activity). The PET scan can also use blood flow, using nitricoxide (vasodilator). This shows activity and blood usage, as wherever there is activity, there is greater blood flow. PET scans are also effective in assessing ongoing activity
- **fMRI vs. PET**
  a) no injection needed in fMRI whereas in PET we inject radiolabeeld substances
  b) fMRI's are both structural and functional, whereas the PET is only functional (of varied kind blood, glucose usage)
  c)fMRI has clearer resolution of various parts Both techniques cannot collate information over time (to see how changes taking place before and after comparison)

Assays: These are procedure undertaken using various chemicals using blood urine, extraction, and tissue of the brain (taken postmortem). There are many procedures.

- Assays a) whole brain various metabolites are assayed post mortem. This can be done taking the whole brain or specific brain areas to measure amount of chemicals in the areas the brain is homogenized in the homogenizer and the chemicals and their levels measured.
- Assays b) other assays can be carried out on the blood or urine or the Cerebrospinal fluid (CSF). The findings that Schizophrenics urine has high levels of MHPG, a metabolite of neurotransmitter catecholamines, indicating that they are involved in the disorder.

Neurophysiological measures There are many procedures which measure electrical activity of the brain and other tissues to give us an assessment of the working of these areas.

- **EEG: Electroencephalography:** This gives us an idea of the ongoing electrical activity in the brain. Scalp electrodes are placed at various locations (temporal, frontal, occipital, and parietal) to get a recording of the electrical charge and electrical activity of the different parts at the same time. These electrodes pick the electrical signals and then these are sent to a magnifier where they can be seen on the oscilloscope. Though this does not give us a clear idea of how each neuron is working, but the general patterns are consistent and have been shown across species. For example, the sleep state recording would show us when a person or animal enters deep sleep the recording show Low frequency, high amplitude waves (1-3 cycles per second).
- **EOG Electro-oculograph:** These measure the electrical activity of eye muscles to monitor the eye movement using electrodes placed on the eyes. This is most effective in sleep studies where Rapid Eye Movement (REM) sleep stage can be seen through changes in EOG activity. This works well with the EEG recordings to study sleep.

- **EMG: Electromyograph:** Measuring electrical activity of the muscle. In this procedure electrodes are placed on the muscle that we are measuring. The muscular tension/ tone of the neck muscles is also measured in sleep and is a very good indicator of the changes form Non REM to REM sleep.
- **Polygraphic recording** For measuring electrical skin conductance along with other measures such as Blood pressure, Pulse rate, and breathing is measured as an orchestrated response,

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LESSON16

RESEARCH METHODS AND TECHNIQUES OF ASSESSMENT OF BRAIN FUNCTION

Objectives

To familiarize the students with

- The various techniques used to study the brain and its function and structures.
- Invasive vs. Non- Invasive methods, Stereotaxic surgery.
- Stereotaxic Atlas used for brain surgery and manipulation,
- Hislotogical and cytological methods for Cell staining, Radio labelling, Flourescence, autoradiography, Lesioning and electrical stimulation, single cell recordings, push-pull cannulae.
- The advanced techniques such as MRI, fMRI, CAT, PET, CT, EEG, EOG, EMG, X Ray etc Histological, electrical chemical and pharmacological processes and techniques why so many?
- Advanced technologies and methodologies

Pharmacological paradigms: Drugs administered into the system in a wide range of procedures varying from drugs entering the body (various procedures again) or directly into the brain. This is done to identify the changes in behavior or electrical/chemical changes of the neurons, their transmission and also to assay metabolites for chemical analysis. There are several methods for drug administration and different routes:

a) Through oral ingestion: drugs fed to the subject (human, animal)
b) Administration/ Injection through various routes: When the drug is tubed directly into the stomach bypassing the oral region this is known as the intra gastric (IG) procedure. When a drug is injected into peritoneum (the stomach region) it is known as the intraperitoneal or IP procedure. When drug is injected into the in large muscles such as the forearm or the thigh this is known as the IM or intramuscular route. When drug is injected under into the space under skin this is known as the Sub Cutaneous (SC) procedure. The IV (intravenous) is injecting directly into circulatory system for a rapid action), and even more rapid is the IV (intraventricular) where substance is injected directly into the brain, into the ventricles, using the stereotaxic apparatus. This procedure is quickest way of reaching the brain, but needs skills of a neurosurgeon.

Behavioral paradigms: are used to control, simplify and objectify behaviour at molar level. Behavioral paradigms are used to produce investigate measure behaviour under control conditions. They measure higher order functioning through experiments in which behaviors are manipulated.

Psychological/ Experimental paradigms

Conditioning: One of the most commonly used paradigms in early research on brain-behavior relationships. These experiments have provided information on sensory, motor, motivational and cognitive state of the animal through its ability to learn task or unlearn it. The findings of some of the experiments are a) self stimulation behaviors: animals were trained using the conditioning paradigm of pressing the level for food, and it was discovered that animals preferred to electrically stimulate themselves, b) animals learn to avoid certain foods which made them sick: Conditioned Taste aversions c) T maze and homing behaviour: Using the T maze experiments were carried out, where animals had to make a choice between food or drugs (variation could be food or mother), or young animals could learn to locate their nest

Seminatural learning paradigm. These are paradigms which use a combination of laboratory conditions+ naturalistic behavior which are measured and observed under control conditions. The

following examples are given:

a) **Addiction:** rats in the laboratory housing were given free access to choose between water or morphine bottles. These were available and refilled whenever these bottles are empty. The amount consumed gives a comparison.
b) **Early experiences of Harlow's monkeys.** These experiments were carried out by Harry Harlow and his colleagues at the University of Wisconsin Primate Center. He studied the effects of separation and lack of contact on the development of the young primates.
c) **Water Mazes.** These experiments are carried out to assess motor development of young animals, their ability to learn using a different modality.
d) **Other paradigms:** the Sleep platforms where rats are set up to sleep, and when they go into REM they fall off the platform. Hoarding behaviors: increasing temperature in the cage, or lowering food available to see the effects on animals trying to hoard material in their cages.- crowded vs. solitary those animals reared in crowded conditions, vs., normal conditions with mother and siblings, and those without any of these. The difference in the three groups would show the importance of social influence. External stimulation during early development, many experiments have shown that early stimulation during early development affects brain development.

No one method is the right or the wrong one. These can be sued separately or in combinations. It depends on the research area the question, and the expertise of the researcher.

Neuropsychological Testing: Neurologists assess damage to the Nervous System using simple, sensory- motor functional tests. Psychologists ask the question, what about emotional, behavioral and cognitive functioning? The specialized functions are assessed by the neurophysiologists who aim to understand the extent of the damage and to identify areas which can be used for rehabilitation. Neuropsychological testing requires several hours spread over 2-3 day. Why does it take so long? Because we use the test results

A) To identify diagnose and support finding of other (PET, CAT, MRI),
B) Provide rehabilitation and counseling
C) To assess and evaluate if treatment or therapy ahs been effective

There are specialized tests for memory, language, intelligence, cognitive functions, attention, perceptual and motor functions. There are also tests for hemispheric functioning

WAIS as a Neuropsychological test

The General Intelligence test Weschler Adult Intelligence Scale (WAIS) and Weschler Child Intelligence Scale (WISC) are used as part of Halstead Reitan Battery.

- If a patient scores low on verbal as compared to the performance tests we can suspect left hemisphere deficit,
- If the Picture completion performance is poor then we suspect memory and visual spatial deficits, which are right hemisphere functions
- Poor performance on the Block Design indicates Left/right Posterior parietal damage
- For Language: the Sodium Amytal tests (where an anesthetic substance is injected in the carotid artery whereby one side of the brain is anaesthetized and cannot function or respond. The dichotic listening test simultaneously words or sounds are given to both ears- and the preferred ear responds, Speech and Rhythm tests (Hallstead Reitan and Luria Nebraska batteries)
- **Harris Tests of lateral Dominance:** these are 11 quick tests to assess dominance of eye, ear, foot, and hand; Assessments also give scores on congruence of hand eye ear and foot

dominance. Difficulties such as reading and writing deficits arise if there is non congruence between eye, hand and feet.

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LESSON 17

DEVELOPMENT OF THE NERVOUS SYSTEM

Objectives:

To familiarize the students with:

- Development of the brain: from the fertilization to the various developmental stages in-utero, and postnatal. Cell migration, (inside-out), cell competition, Cell death, growth Cones, Nerve growth Factor and its role
- Various stages of neuronal development.
- Teratogenesis Genetic anomalies which affect development of the brain. Plasticity of the Nervous system.
- Development and growth (from intrauterine to neonate stages) to give an understanding of the stages of development and the processes involved.

Development of the brain

Before we study the development of the brain it is important to understand life before birth

The process begins with the fertilization of the egg, and once fertilized this is known as a zygote. The zygote undergoes rapid cell division and Mitosis is the process of cell division by which zygote grows

- **Zygote:** After fertilization, fertilized and rapidly growing, enlarged egg travels towards the uterus in 1st two weeks, after reaching the destination; it attaches itself to the uterus walls with its tendrils. This is a very important linkage as it provides nurturance and nutrition which is required for rapid growth of the zygote. This process of attachment is known as Implantation.
- **Embryo:** After the successful implantation in the uterus, immense and rapid growth takes place. This is when the embryo starts resembling human form. The amniotic sac ("bag"} created, it is filled with amniotic fluid which protects the embryo and provides constant temperature within the sac. The embryo is connected to the mothers systems and is dependent on the mother through umbilical cord. Placenta is the container in which the embryo is contained and attached to the mother. The double walled cavities of the placenta provides support, nurturance (nutrients) needed by the embryo. This forms the placental barrier which protects the embryo form harm and toxics.
- **Fetus:** After four months of life after fertilization, the embryo develops into the fetus which is the next stage. Now an individual with Reflexes which can be seen. The suckling and swallowing develop halfway through the prenatal period. We also know that internal and external stimulation affects are responded to by movements. So now we have a fetus responsive to the environment (within the placenta).

Differentiation takes place in the germinal layers and then rapid division and multiplication of the germinal cell layers into different types of cells takes place during these stages. The form shape and development of the body and brain takes place following the principle of growth:

Operation Head Start. The brain and body grows in the cephalo-caudal (head to tail principle). This means the development of the head and the brain if the first stage.

If we look at the reflexes of the neonate we see a very well documented development and progression (of the brain and the body):

Reflexes of the neonate

Plantar: if we stroke foot of the neonate the toes fan up and out

Rooting: If a cheek is softly touched, the newborn turns mouth towards the cheek which has been touched.
Suckling: if an object is placed in the mouth, the newborn starts sucking placed in mouth. This is readiness for feeding.
Moro responses: if there is a sudden noise the newborn stretches out at first then hugs itself together.
Grasping: If a round object or finger is placed against the fingers, the fingers curls around finger or rod placed. The curling forms a very strong grip.
Other reflexes: Swimming, (remember they have been swimming through out the first 9 months in-utero), vomiting, hiccough, sneezing, yawning, blinking normally occurs within an hour after birth.

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LESSON 18

DEVELOPMENT OF THE NERVOUS SYSTEM

Objectives:

To familiarize the students with:

- Various stages of neuronal development.
- Development of the brain: from the fertilization to the various developmental stages in-utero, and postnatally.
- Cell migration, (inside-out), cell competition, Cell death, growth Cones, Nerve growth Factor and its role, Influences in growth and development of the brain

Intrauterine Development of the Brain:

Genes determine the growth and development from fertilization to death. Therefore the programmed direction of development would continue within the intrauterine development. The Intrauterine environment is stable and protection is provided to the embryo/fetus, by the placental barrier. However, if even a minor alteration occurs it can lead to serious defects in the process of the development of the body and the brain. Serious malformations can take place. The study of the effects of substances which affect normal development is known as Teratology.

Teratology studies: The effects of Poisons, drugs, X-Rays, radiation, abnormal blood conditions of the mother, excess/lack of vitamins, proteins deficiency, psychological stress which can affect the intrauterine environment by crossing the placental barrier, and thereby altering the normal course of development. The timing of exposure is important. There are critical periods (highly responsive) in which the embryo/fetus can be affected by growth stimulating influences and at the same time is vulnerable to disruptive influences.

Some of the deformities are listed below:

- Anencephaly: (lack of brain)
- Harelip, Cleft palate
- Phocomelia (seal like flippers: extremities)
- Reversal or ambiguity of sex

Development of the Nervous System

As has been said before we must remember, that genes determine growth and development throughout the life span. However, there is an interaction between the genetic programming and the environment. It appears to happen from the time of birth; however, developmental neurobiological researches have shown that the intrauterine environment is extremely important. The influence of the immediate environment is important even during this cushioned state in the womb, and the effects are in some cases irreversible. Intrauterine environment is important at every phase of intrauterine development

Stages of development and influences:

Immediately after embedding (implantation) of the fertilized egg onto the uterine wall Takes place, three germinal cell layers are formed from the increasing number of cells that have been dividing. All three germinal layers are exactly the same. The nervous system develops from one of these layers. These are known as the Ectodermal, the mesodermal and the endodermal cell layers. The Endodermal layer eventually forms the internal organs, Ectodermal layer forms the Brain cells and the Nervous system, and the Mesodermal forms the skeletal muscles etc. How do these layers become different and develop in different direction would be discussed in the later section

Development of the body and the brain
The development of the organs from the endodermal, brain from the ectodermal and muscles etc from the mesodermal tissue begins immediately after differentiation takes place. The cells in each layer multiply and the organs, muscels etc start being visible

At the Embryonic stage which is the 1st two months in gestation, the heart beat starts in 1st month, and other organs such as kidneys start functioning around 3 months.

At the Fetal stage which is between the 2nd months to gestation to 9 months (immediately before birth) the skeletal motor functions growth and development is initiated and after 5 months there is actual movement of the muscles (and connection s being formed with the appropriate brain areas). Immediately at birth the Neonate has functional lungs but these are filled with embryonic fluid. The first time the little organism breathes is at birth.

Stages of development (from V. Casagrande 1988)
There have been philosophers, early scientists and thinkers who have tried to unravel the mystery of birth and the formation of the newborn. This process has now moved form mere speculation to scientific research and evidence. We would talk about three important milestone names only: Aristotle, Van Baer, and Haeckel.

Aristotle: studied the development of the chick brain and gave the concept of preformation- animals were preformed into the shape they were born. The zygote according to Aristotle is a mini individual that grows from egg into shape and form of the animal.

Van Baer (1792-1876) Pre Darwinian evolutionary theorist provided evidence against preformation. Since he saw similarities in the various animal embryos he studied, he stated that young stages of higher animals resemble young stages of lower animals. That is to say that all embryos have the same shape and form. He further said that all animals higher up on the evolutionary scale go through the various developmental stages of the animals lower on the evolutionary scale.

Ernst Haeckel gave the famous concept of **ontogeny recapitulates phylogeny,** appears a logical progression of Van Baer's premises. During early growth and development (ontogeny) go through the same series of forms which resemble with the biological and evolutionary ancestry (evolutionary history– phylogeny). If we look at the figures without identifying the embryo we would have difficulty naming the human embryo in its stages from other embryos.

We also find that Baer's was correct in his assumption that there are no pre-formations.

Further, those general features of all animal embryos appear earlier than special features, which would explain the common shape and form of all embryos. During the later embryonic periods, these depart more and more towards specialized development. The similarity a) the embryonic gill pouches in mammalian as well as fishes, though these are not functional in mammalians, b) brain development is also similar till specialized development takes place (i.e. specialized development of the cerebral cortex).

Before we begin to understand the development of the brain, we must know the basic concepts of the neuronal development.

Concepts in development of neurons/brain

Embryogenesis: is defined as the process of development during embryonic stages: the processes which take place during embryogenesis are: induction, neurulation, vesicle formation, and neural proliferation,

Histogenesis: This is the process where neurons (cells) specialize and move to relevant neuroanatomical sites: cellular differentiation, determination, cellular maturation, cell migration, cell aggregation, cell competition, cell death

Growth: Axonal growth and synapse formation

Differentiation and Induction. These are key changes and important stages in all vertebrate embryos. At all stages of the development-(structural, functional or behavioral) there is a complex interaction of genes and environment. The genes predetermine layers, and shape and form they eventually take. However, environment is also very important, as it provides the trigger for the genetic program take place.

As has been said before all three germ cell layers all exactly the same, this is called being, Totipotential i.e. each layer has the potential to develop/ become any one of the layers, these are the STEM CELLS. If cell layers rearranged, the top layer would always become brain tissue. Within the three layers rapid cell division/ multiplication is taking place within the layers, and would continue to do so, if the trigger for change does not occur (imagine having just three flat layers of membrane growing in size, not becoming the brain or other organs!). Thus, differentiation takes place and this places restriction on direction of growth—specialization begins.

In the three germ cell layer sandwich, the Ectodermal tissue always lies on top of Mesodermal tissue which lies on top of Endodermal layer. The top one would always be the brain. We can shuffle the layers- and the layer on the top would become the brain cell layer. So far there is one stimulation for the growth- the position of the cell layer relative to the others. However the next major steps would change the fate of the cells forever--- Differentiation and induction.

Differentiation takes place when a rod shaped tissue of Mesodermal layer forms under Ectodermal layer. Attaches itself stretching from head to tail of the embryo, this is the Notochord

Induction: is the process which signals change (induces change), leads to cell determination (cells fates are determined) leads to differentiation (cells develop in different directions). Thus, this induces development of 3 cell layers by differentiation.

NOTOCHORD INDUCES ECTODERMAL TO BECOME NEURODERMAL

Notochord is the signal for Ectodermal tissues to start differentiating and to become nervous system, and initiate development of nervous tissue

Notochord very important, without it the Ectodermal tissue cannot differentiate

If placed elsewhere these tissues will start dividing and become nervous tissue, if nervous tissue is placed instead of the internal organs, the layer would become internal organs. The location of the cell layers with reference to notochord is the important key to differentiation. Thus, the Ectodermal tissue cell layer needs environmental signal and stimulation.

"In all cases it acts to limit or specify the developmental opportunities of one group of cells through their interaction with another". When the initial division of cells is differentiated, the change is induced by the notochord, the fate of the cells and their future is determined.

Cells would grow in only the direction determined (by biological and genetic mechanisms) but the stimulation was needed, and as we shall see in the later sections would continue to be affected by external environment.

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LESSON 19

DEVELOPMENT OF THE NERVOUS SYSTEM

Objectives:

To familiarize the students with:

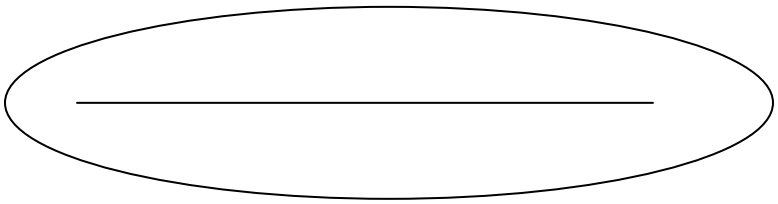
- Various stages of neuronal development.
- Development of the brain: from the fertilization to the various developmental stages in-utero, and postnatally.
- Cell differtiation, determination migration, (inside-out), cell competition, Cell death, growth Cones, Nerve growth Factor and its role, Influences in growth and development of the brain

Once induction of the ectodermal layer by the mesodermal tissue has taken place, the cells start differentiating as their direction of growth is determined by the induction. The three cell layers would develop in different direction after the signal has taken place. The initial division of cells is differentiated into different organs (heart, kidney, brain, stomach) this change has been induced by the notochord which ahs thus determined the fates of cells/layers

Stages of development

There are several distinct and measurable stages of development of the brain which takes place.

- Attachment of mesodermal tissue to ectodermal tissue leads to the formation of the notochord. The notochord is the strip at the center of the upper surface of the ectodermal layer.
- The neural plate is formed from this tissue and this line in the center grows as the plate grows. A bulb like head end forms at one end to eventually form the forebrain and eye field/eye cups area around the 17th day of intrauterine life. If the bulbous end is cut, it would quickly replace itself. The cells are still rapidly dividing
- The neural plate starts becoming longer and broader-growth in both directions (as the cells are still dividing and multiplying at an extremely rapid rate)
- On the18th day there is thickening of the outside ends. This leads to rising of ends and deepening of the center. The sides rise joining in the middle. Thus, the rising of the plates form a groove, this is called the neural groove. The neural groove deepens as the sides rise higher and higher (remember, there is rapid cell growth and multiplication taking place).



Neurulation

- Neural tube (rapid cell multiplication and division), the tube folds and becomes tubular this is when the primary neurulation takes place. The brain and spinal cord are formed at this stage. On the 21st day, the fusion of the tube takes place and little groups of cells break away to form bunch on both sides. These are called somites and extend in both directions (somites: bodies of cells in the middle/top) to form the neural crest. These develop into the peripheral Nervous system and the ganglionic system. The inside of this tube, the neural canal, is empty at this stage.

- The neural canal remains empty as the ventricular zone, where the next phase of development will take place. Secondary neurulation: During the process of secondary neurulation (forming of the neural systems) the tail end part of spinal cord is formed

The closure of the tube is simultaneous and inside cells starts dividing and multiplying, growing within the tube. The cells inside increase in number rapidly, as cell division takes place in the ventricular zone.
Internal part of the tube consists of single layers of cells which keep multiplying and increasing in number and as they increase in number the cells start moving out (The interesting question is who tells them where to go, and where do they go? Does the region get crowded??). This is the phase when Cell Migration takes place

Cell migration: it is an inside-out process, cells move form the inside of the tube towards outside. The growing cells then form three layers: internal, middle, cell free:

1. **The Internal layer:** The inner most layer has cells which are still dividing
2. **The Middle layer:** Consists of cell bodies which eventually form grey matter. These cells do not divide after this, these are the same cells found in the adult brain.
3. **Cell free zone:** This contains the fibre processes of the first two layers and as yet empty of cells. The migration is still taking place. Once cells reach their destination they grow dendrites and axons to reach out to meet other cells. Cells sprout growth cones for the axons and dendrites, which lead the cells to grow to and to develop synapse.

Neural crests are forming ganglia, inputs into spatial column and outwards, Optic stalk grows out of diencephalon to form eye cup- eye cups induce formation of lens from overlapping ectodermal tissue. The frontal the eyecups: retina forms as an invagination of the bulging optic vesicle: ganglionic cells first, and then bipolars, and photorecpetors last: eye born directly from brain tissue! Common substance in both

Formation of the brain:
Forebrain, mid brain, hind brain: On the 24th day intrauterine, the head end part of neural tube forms three bulbs. These three bulbs would form the forebrain, midbrain, hind brain (The question is how do the cells know and the areas know that they are going to be the in front or middle or back?) The front most becomes the forebrain, and the end toward the tail becomes the hind brain. The hind brain connects with the spinal cord. At this point all three bulbs are not differentiated. These are exactly the same. (How do they become different?). In the same manner as in the first stages, each area depends on the other to be stimulated and through this interaction they differentiate. At the stage also the surrounding area induces differentiation. The environmental influences are important at every stage.

What if the three bulbs cut and rotated, always the bulb in the front forms the forebrain and the middle, the mid brain and the last part forms the hind brain. The position determines direction of development! The same cells develop into different regions if their locations are changed (environmental change!). At this stage cell division is rapid, and the neurons and glial cells are forming. The migrating cells unite to form groups of neurons. Nuclei are forming as a result of rapid proliferation of nerve fibre tracts and connections.

- Cell division is rapid:
- Migrating cells unite to form groups of nuclei\nuclei form connections
- Rapid proliferation of fibre tracts and connections
- Formation of the ganglionic systems from the neural crests, inputs into the spinal column and outwards

- Optic stalk grows out of the diencephalons to form the eye cup (the eye is formed from the same tissue as the brain, eye has similarities with the brain)
- Eye cups induce formation of the lens from overlapping ectodermal tissue

Concepts
Regulation: If cells keep growing, connections expanding then how does it stop- who controls the development, differentiation, and migration etc.
Self regulating: This is a process regulated by itself. A) Muscles move without the sensory input or stimulation b) nuclei develop even if isolated from the organs, if we denervate (cut the nerves).
Cells proliferate at more than 40 times the normal adult brain**.** What happen that cells size reduces?
Cell proliferation (increases in number), cell migration (cells travel to their destinations form inside toward the outside), maturation (developing extensions) interconnections formed (forming connections with other cells); cell death (cells die off) is taking place.
Cell proliferation: Cells are dividing, spreading and increasing in number. Specific parts of the brain begin to differentiate. Small piece of ectodermal tissue removed defect replaced by proliferation of neighboring cells, however if surgery is done later, then it would remain as a permanent deficit. The cell growth is in extreme density in ventricular zone. Cell growth much more than required about 1 ½ times more than adult brain then cell death takes place and has to follow some principles.

Maximal cell division is taking place at this stage and neurons are being formed at 20.000 neurons per minute.

Growth spurt: This is time when maximal cells are being formed, connections being formed and systems of brain areas organized. This is between the 10-18th week of gestation. This is the time when the brain cells of the growing embryo are sensitive to radiation, chromosomal anomalies, viral infections (measles etc.). The fetus is born with defects such as mental retardation and blindness. The sensitivity of the fetus and the newborn to other effects are from the 30th week- 2nd year post partum. The effects of malnutrition on cell size, brain cell connections and myelination are irreversible.

Cell Migration: Cells migrate towards periphery from the inner core of the ventricular zone. The principle of inside –out migration is followed here. There is formation of radial glial fibres on which cells travel from the periventricular zone. These form the transport system on which neurons travel! These cells move up to the different cortical regions which would eventually form the 6 layers of the cortex, some remain.

Radial Glial: cells attach on both sides, neurons move up, some slow, some fast… those which are fast arrive earlier and form connections with other neurons. Once they form connections they survive. The sooner the connections are formed, the greater chances of surviving.

Cellular maturation.
This has four stages
a) The development of outgrowth and elongation of axons
b) Dendritic process emerging out of the cell body
c) Biochemical properties appropriate to the location and function of the location to which the cell would stay
d) Development of synaptic connection.

The axons grow out of neurons first and these have a growth cone (a specialized structure with filopedia cytoplasmic extensions—feelers needed for movement which lie on the growing processes). This is affected by the Growth Factors, the active factors being the Nerve Growth Factor (NGF) in

the growing nervous system and factors that maintain metabolism of neurons (tropic factors). This is planned for a specific site and target.

Dendrites develop after neurons/axons. Immediately upon reaching their destination neurons attach to the site after detaching from the transport radial glial, and send out projections. If the neurons cannot travel, they cannot compete, they would not survive. If they cannot from connections, they cannot compete, they would die. In order to survive, cells sprout more extensions and form more connections. This increases the cell's ability to compete for connections. If the connections not formed, cells will not be able to survive. Only those cells survive which have successfully formed connections and would now be able to continue receiving the NGF

Cell Aggregation: Cells make their way to the area in which they will function as adults using cell adhesion molecules (CAMs). These cell adhesion molecules are formed on the surface of neurons and other cells. These also give the cell ability to recognize the molecules and surfaces. Cells form alignment in precision with other cells in the region. The question is how it is done. There is an intricate programming which is still under study.

Fate Mapping: researches such as Pasko Rakic sued the fate mapping procedures. This involves injecting labelled substance in the growing brain at various embryonic ages and following the migration of the neurons later to see where they end up. These studies have shown that a) Regional specialization of areas and neurons appears early on in development, b) The deeper cortical layers generate first and most superficial layers are formed last c) Inside-Out migration: The migration is at a fast pace, the cells migrate to the inner layers first. Neurons of the outer layers formed later must migrate through the earlier formed layers to eventually arrive at their destination, d) In the development and growth principles i) large cells develop before small ii) motor cells develop before sensory neurons and iii) neurons develop before the glial cells.

Thus, we have seen an intricate relationship of genetic and biological programming with environmental stimulation in the development of the brain. Even though the paths of development are well laid out, stimulation is important for neurons to continue moving, developing and surviving.

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LESSON 20

DEVELOPMENT OF THE NERVOUS SYSTEM

Objectives:

To familiarize the students with:

- Various stages of neuronal development.
- Development of the brain: from the fertilization to the various developmental stages in-utero, and postnatally.
- Cell differtiation, determination migration, (inside-out), cell competition, Cell death, growth Cones, Nerve growth Factor and its role, Influences in growth and development of the brain

If all cells keep growing, connection expanding, how does it stop- who controls development, differentiation, migration As research ahs shown this is a Self regulatory process and the cell number in early development is 40 times more than the normal adult brain, what happens how do cells reduce in size?

Cell competition: Cells compete for limited resources; some have to die so others can live there is fight for,

a) Life preserving factors NGF and Tropic factors from the targets site are limited
b) There are few sites available for the millions of neurons

Cell death: some cells will die off and only the fittest would survive. Cells would die off

a) If connections were not formed
b) If the neurons reach the sites but fail to send out projections to appropriate targets
c) And if cells do reach but are unable to compete for post synaptic space
d) If the NGF is more than or less than required.

Synaptic Rearrangement:

Cells sprout and make a large number of connections eventually these are refined and made more precise. Is cell rearrangement possible? Yes, weaker or incorrectly placed connections or cells die and leave space for others. Synaptic rearrangement makes for more efficient systems. This ensures that a specific and selective system for transmission remains functional

Important for the migration and growth of the developing neurons are the

a) Radial Glials which form the transport system to take the neurons from the inner ventricular zone where they are born to the sites where they would eventually form the brain and
b) The Nerve Growth factor which is important for Axonal Growth cones and for cells to locate themselves and connect.

Since there are a huge number of cells and limited resources and locations, cells compete for these (Cell Competition) and those who cannot do so die (Cell Death). Therefore forming of connections is important for survival and each cell forms more synapses then needed (to compete with others). These connections are reformed later to make the system more efficient, also depending on the stimulation received

Destinations for Migration:
The question that how do the newborn cells know where to go, how are their destinations for migration "decided" is an interesting and complex one. Several hypothesis have been developed to explain this phenomenon

The Chemoaffinity hypothesis:
This theory is based on the work of Sperry and his colleagues on the regeneration of ganglionic neurons of retina. They cut the optic nerves and rotated the eyeballs of frogs by 180 degrees. They report that after regeneration when tested it was found that visual world rotates at same angles. Sperry then hypothesized that chemicals to attract axons are released by the growing postsynaptic surface, and axons attracted to the "label: during neurulation and migration and well as during regeneration (if these are damaged during early period).There is strong evidence that a) in vitro, when growing axons are laid with tissue in the Petri dish, axons move to connect to their targets (there is no signaling from the other parts of the brain in the Petri dish!) b) There are chemical signals which attract or repel growth cones from the extracellular tissue. However, this hypothesis cannot explain extra growth with transplanted organs areas such as the experiments by Whitelaw and Hollyday (1983) where they added an extra thigh to the two normal chick legs, (where the chick's legs had two thighs instead of one!). Where did the 2nd thigh get its nerves from (from the calf, or from the 1st thigh?). Secondly, this does not explain why and how do some axons find their way to same targets in every species using a roundabout route, not go by the shortest routes directly (!). Lastly if this is genetically programmed then there should be genes in each body cell to produce and release its own chemicals, this is not possible!

Therefore we go for the next possible hypothesis and see if that one is tenable

The Blueprint Hypothesis:
This hypothesis states that the undeveloped Nervous system has a blueprint in the form of specific chemical, biological/mechanical pathways which the growing axons would follow to get to their destination. These pathways are laid out by the Pioneer Growth Cones, which are the first growth cones to travel on the specific radial glial and the route. These pioneer growth cones do so through their interaction with the CAMS (it's like the blind feeling the walls along the way). Interestingly the axons are also growing while traveling. This is called fasciculation. If these pioneer axons are destroyed the following axons get lost and go to different destinations! However, this hypothesis cannot explain in vitro travels (no radials) as there are no pioneer axons there. It also cannot explain how neurons in vivo still reach correct destination even when starting points changed In experiments on transected and then inverted spinal cord of chicks, the axons were able to reach their correct target muscles, inspite of starting from an inverted location.

Since this hypothesis also has not been able to explain the migratory programming of the neurons, we move to the next hypothesis

Topographic gradient hypothesis:
This hypothesis proposes that cells follow their topographic gradients or locations. Though Neurons develop in topographic layers, they maintain their relationships with topographically different groups of neurons. For example, the relationship of the optic tectum in the brain with retina: cells growing out of an original sheet of cell bodies retain their relationships as they grow in different locations even if they have migrated. There are in the same point to point relationship (held previously on the sheet: whether up down or left-right gradient)

Evidence from retina and tectum cells connections, when mapped show that cells are maintaining their earlier relationships. There is evidence that this hypothesis has more strong evidence in favor of it.

This is an interesting piece of the puzzle that we in the developmental neurosciences are still trying to unravel. There are other mysteries such as what is the role of the environment if the cells are programmed. We would discuss it in the next lecture

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LESSON 21

DEVELOPMENT OF THE NERVOUS SYSTEM

Objectives:

To familiarize the students with:

- Various stages of neuronal development.
- Development of the brain: from the fertilization to the various developmental stages in-utero, and postnatally.
- Cell differtiation, determination migration, (inside-out), cell competition, Cell death, growth Cones, Nerve growth Factor and its role, Influences in growth and development of the brain.
- Teratogenesis Genetic anomalies which affect development of the brain.
- Plasticity of the Nervous system.

Environment or Genetic Programming

It is well researched and documented that during early brain development the outside stimulation from the periphery becomes important as cells make connections with other cells and with the muscles. It is well established that when connections are made, the neurons with connections survive, those who don't, don't survive. Further, if the peripheral structure is removed, cells for that structure degenerate in the brain and die off. There were a series of experiments carried out on the visual systems by the famous Nobel Laureates, Hubel and Weisel. In one of the experiments, one eye of the kitten was removed during early development and it was found that the striate cortex (cortical area for vision degenerates for the eye that has been removed and enlarges for the other eye: i.e. for one it enlarges whereas the areas for other it diminishes. The neurons from the non-deprived take over the areas vacated by the deprived

Similarly experiments were carried out in which the whiskers (whiskers on the face of the rats) of the growing rat pup were removed. These are in the form of barrels. If the whiskers were removed there was also degeneration of neurons which were responding to the whiskers. However, the neighbouring neurons get bigger. If peripheral structure gets enlarged then fewer neurons die off as they get a site to connect with normal die or degenerate. If structure added such as another eye or another limb then that part also gets innervations (Hollyday and Hamburger 1976).

Functionality of peripheral organs correlates with their influence on the neural development

An interesting series of experiments by Merzenick were carried out to test out the influences of external stimulation on the development of brain areas. The third and fourth fingers of the monkey's hand were joined together, and it was found that the area in brain also merged. However, if a finger is removed then the neighboring fingers extend areas to use the "vacated area" in the brain. Using advanced technology such as the MRI this has been confirmed further. Those who use a particular body area (or exercise it), have enlarged corresponding brain area. The brain MRIs of violin players were compared with the non musicians for the finger areas representations it was found that the violin players had larger areas, these were the stimulated areas, and were much larger than the ones which were not stimulated.

The question which is important environmental stimulation or genetic programming keeps coming up again and again is a major issue in developmental neurobiology.

a. Is the Brain preprogrammed to grow in a particular manner and develop specific functions?
b. Is the Brain affected by outside influences and interference affects growth?

Yes: In an intriguing experiment Mriganka Sur (1988, personal communication) modified the embryonic neuronal connections in such a way that fibers coming form the visual system such as the optic nerves and the eyes were connected to auditory -cortex, and vice-versa . The question was would the auditory cortex start seeing or visual cortex start hearing. Nothing of this sort happened, the: visual cortex developed in auditory areas, where the inputs were coming in. Thus, these experiments showed the environmental stimulation was important for brain areas to grow.
On the other hand experiments carried out by Hubel and Wiesel, and Rizzolatti and colleagues show that brain cells respond to only one kind of stimuli (they are preprogrammed). According to them, the brain is preprogrammed to develop and respond in a particular manner. The brain is not influenced by environmental influences and no feedback can affect brain development. Experiments by Hamburger on chick embryos show that there is an autonomous development of the brain. In Hamburger's experiments differentiation (messages do not get back towards the brain) at different stages of embryonic development was carried out. This means cutting spinal cord at different points without causing complete paralysis. Decreasing the input from skin and other areas does not affect development of the brain from day 3 embryonic ages to 3 days before hatching (what if there was stimulation even before 3 embryonic days?). However, there was also no change in development of behavior patterns

The issues still remain!
Lesson to take away Brain development and outside influences interact with each other. This is important for the development of the Nervous System

Points to ponder and take away

What about adults: Is neurogenesis possible? When neurons die in the adult brain do we grow new ones?
Earlier this was not thought to be possible, and once neurons die off they do not regenerate was the standard. Now, more evidence has come in showing that regeneration of neurons in adult brains is possible. In adult birds, areas responsible for songs grow new cells prior to the mating season (evolutionary benefit?). Similarly, the in the rat hippocampus (area important for memory) cells grow (adult neurogenesis: new cells @ 2000 per hour!) while rats are learning a task. Similarly in the primates and in humans, there is growth of cells in the association cortex (higher order functioning). We have seen reorganization of cortical areas due to experience in adult brain, (violin players, remember!)
With the ongoing stem cell research, possibilities for regenerating and repairing damaged brains using these cells may provide hope for the brain damaged.

Early Embryonic development: quick summary

Cardiovascular and Nervous system

Heart------- ----------3 weeks
1st NS reflex---------8 weeks
Swallowing----------11 weeks
Stretching movements 22 weeks
Sucking development ---29 weeks
20,000 neurons per minute

Post natal development and growth: quick summary
New Born
Brain weight: 350 g– 10% of body weight.

Brain layers: 6 layers, (as in adult brain) but very few connections or processes
Cells density: dense packing, greater number of cells
Little or no myelination (insulation sheath for the fibres)

Adult
Brain weight: 1400 g, 2% of body weight
Brain layers: Six Layers with many connections
Cells density: less dense packing, decrease number of cells, increase number of connections

Myelination of axons and dendrites
From the above comparison we can see that the neonate brain has a long way to go before it can resemble the adult brain. The differences are contradictory, the cells number greater than the adult brain, but this is enclosed in a smaller sized "container" therefore it is very densely packed. There are fewer connections and smaller brain weight, in the adult the brain weight increase due to increases (in millions) in cell connections.

In the next lesson we would discuss the growth and development of the brain as it progresses towards the adult size and functioning.

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LESSON 22

DEVELOPMENT OF THE NERVOUS SYSTEM

Objectives:

These lessons would familiarize the students with

- The stages of development of the brain and the changes which takes place
- Various stages of neuronal development.
- Development of the brain: from the fertilization to the various developmental stages in-utero, and postnatally.
- Cell differtiation, determination, migration, (inside-out), cell competition, Cell death, growth Cones, Nerve growth Factor and its role, Influences in growth and development of the brain
- Teratogenesis Genetic anomalies which affect development of the brain.
- Plasticity of the Nervous system.

Brain development:

Post natal

Brain development is modulated by external influences, and the interaction with external stimulation is important for the growth of the brain. The development of behaviour matches the development of the Central nervous System.

The brain development can be seen from the following tables

Table 1: Age and brain development and functioning

Age	Brain weight	Structural development and changes	Behaviours
neonate	350 g	Dense cells, very few fibres	Sub cortical reflexes, moro grasp,rooting
2-3 mos	500 g	Grey and white matter is poorly differentiated, not densely packed neurons (Nissyl staining)	Visuo sensory motor integrative functioning
6 -8 mos	660 g	Cytoplasm more , and distinction between grey and white matter	Higher Cognitive and cognitive functioning
8-12 mos year	925 g	Reduced cell number, increase in neuronal/glial fibres (for connections)	Interaction with their surroundings and show strange anxiety
3 years	1080 g	Further reduction in cell number and increases in cell connection	
6-14 years	1350 g	Maturation and myelination of cells continues	

Motor development (movement and coordination) and sensory development are interactive. Therefore motor stimulation inputs into the sensory and stimulates the formation of connections and action. Similarly, the sensory input stimulates the motor connections. This leads to the development of the brain from the neonates brain being subcortical (functioning form the reflexive systems, not the cortex) at 1 month from this the infant moves to grasp objects, raising head, smiling at familiar faces, focus on objects, then learn to roll, sit, crawl, pick small objects with fingers, and eventually stand and walk all within the space of a year (or a little more). It must be remembered that the development of Central nervous Systems matches these behavioral and motor/sensory development.

Influences which affect brain development

The brain is vulnerable to external influences during the period of rapid growth and development. We would be talking about some of these influences. One fact must be clearly understood that the fetus does not have any protective own mechanism of protection (except for the placental barrier). It is at the mercy of the mother, as whatever it gets (nutrition, blood, cleaning up of toxics) is through the mother (the umbilical cord is the connection. However, there is a critical period when the influences can affect the brain, and the areas of the growing brain that are most vulnerable. The influences would not be effective wither before or after the period.

Critical sensitive period

The periods within which the growth of the organism can be affected by influences i.e. the period of development, differentiation, and proliferation. The period prior or subsequent to the critical period is not important. The influence/substances will not affect development before/after the critical periods. Brain most susceptible only during that period. Normal development can be affected by presence/absence, increase /decrease in the required/normal levels. Each of the following influences has its own critical /sensitive period, depending on where or what was required.

Influences:

- **Nutrition**
- **Hormones**
- **External stimulation,**
- **Oxygen levels e) motor stimulation**
- **Viral and other diseases such as measles**
- **Drugs, radiation, etc.**

Nutrition (ref Brown and Wallace, 1988).If the mother and the embryo suffer from malnutrition during the period when brain cells are dividing rapidly, and then there is decreased division of cells leading to decreased number of cells in the growing brain. Cells need nutrition and material to divide and grow. If this is not available, the cells would not divide further. The sensitive period is from 2nd trimester (gestation) to 1st year post partum (after birth). This is extended as the neurons in different areas are developing at different times. The effect of malnutrition depends upon the time during which specific cells are dividing (Winnick and Russo, 1975). The damage is permanent, causing irreversible damage to the Nervous System. The multiplying neurons require proteins, NGF, other tropic factors, if this process is blocked; this leads to the irreversible damage that researchers have reported. The damage can be categorized as follows:

1. **Reduced Cell size:** Cells do not develop to their normal size. Histologically, we see small cells (starved cells) as compared to normal. This effect is reversible i.e. if proper nutrition is given the cells would grow to normal size.
2. **Reduced Cell Number:** Cell division is affected by malnutrition of cells. Proliferation would not take place, as without sufficient nutrition, cells will not multiply. If nutrition is provided during the critical period when cells are proliferating, the effects are reversible. However, once the period is over and cellular proliferation ends, no change is possible.
3. **Reduced Cell Connections:** Connections between cells and of cells with other tissue are being formed. Therefore there is sprouting of cell extensions. If enough nutrition is not available then there is decreased sprouting of dendrites. We must remember that in order to have an efficient communication system, neurons need multiple connections. These input connections are provided by the dendrites and their extensions (dendritic spines). If there is an increased number of dendritic branching (spines), there would be large number of connections available. Thus, this results in a more efficient and quicker system of communication. This becomes a more

intelligent and alert young brain as it can get information from a large number of sources (it's like a computer with a larger connectivity). Intellectual functioning is affected by reduced cell connections. However, this is a reversible effect only if nutrition is provided within the critical period.

4. **Myelination:** Myeliantion is a fatty sheath for insulation of neuronal processes (just as electrical wires have rubber covering to insulate them). If the formation of myelin covering does not take place it can affect the efficiency of neuronal processing and functioning. Myelin loss is not extensively reversed by nutritional rehabilitation.
    - **Severe protein deficiency:** This is a selective deficiency of proteins leading to decreased number of neurons, glial cells, dendrites, and deficient myelination of the processes. Every part of the growing neurons is affected by protein deficiency.
    - **Kwashiorkor:** Is the disorder where selective protein deficiency or depletion has taken place. The symptoms are thin muscles, but fat is present on the body, with edema on the feet etc.
    - **Marasmus:** Is the symptom of malnutrition (due to reduced caloric intake) in the fetus. Even if the newborn appears physically healthy, there is irreversible brain damage. There are decreases in brain capacity by 10-20% as a consequence of this decreased caloric intake. The Brain weights are lesser than normal, and the brain size is smaller than normal (fewer cells)

There are also deficits due to decrease amount of Vitamins and minerals (such as iron and potassium) on the brain development.

Monkeberg (1975) studied 500 pre school children, relating nutrition and intellectual functioning. He reported that in the malnourished group there were 40% children below the IQ 80. As compared to this in the normal group were only 3% below the IQ of 80.

Interesting experiment by Weiner (1977) shows that rat mothers spend more time with their alnourished young as compared to the healthy one.

POINTS TO PONDER:
How does the mother know the young is weak?

Hormones: Hormones affect the developing brain and body by the presence/absence or increases /decreases in normal amounts. We are going to discuss the Sex Hormones: Androgens testosterone, (male) Estrogens, (female), the thyroid hormones and the stress hormones and their influences on growth, (Cotman and Mcgaugh (700-705), Brown and Wallace 428-435)

1. **Androgens:** The hormones are important for developing neural substrates of male organs and male sexual behavior. The release at the appropriate time determines what reproductive organs would grow and elaborate, but the release also primes the way the brain is organized. If prenatal androgens are there then the organism would develop a hypothalamus which directs pituitary to release gonadotrophin in a tonic fashion. In its absence, the pituitary has a cyclic pattern of release which is the female pattern. If females are injected with male hormones during early preganancy, they would have more masculinized children, i.e. females with male characteristics– psuedohermaphrodites (Male+female organs in females). On the other hand if male hormones are injected at prenatal periods and later in puberty"male behaviors". Perhaps tomboys are females with androgen exposure during early prenatal period. This could also explain Sexual preferences, sexual identity disorders such as transvestites and transsexuals.
2. **Estrogens** Do not appear to be as important for bringing about changes in the NS or body. (This is controversial as there is evidence of feminization of male fetus and development of female organs upon repeated injections of estrogens). The young animal would develop into

a male or female depending upon the stimulation of androgen. Those which are not exposed to androgen will emerge with brain responses only to estrogen and not androgen and develop typical female behavior.

3. **Cretinism:** This is a disorder of the growing brain caused by severe Thyroid hormone deficiency and the child has below normal intellectual functioning. The sensitive period for responding to thyroid is around the last trimester (6-9 months of gestation). The deficiency or normal amounts of thyroid results in poorly developed cerebral cortex shows thyroid is important in growth, metabolic rate, glucose absorption etc. Thus thyroxine is important in growth. The deficiency results in decreased brain size, decreased number of neurons, axons, dendrites, decreased connections between axons and dendrites, decreased electrical activity. If thyroid is given within the first year of life some damages can be repaired. There is a reversible effect if hormone therapy given early enough when presence of thyroxine important. Questions: if Hypothyroidism is bad, is hyperthyroidism good? No, early sprouting of growth! Out of synchronization with the body and brain development
4. **Stress:** Levine (1960) showed that early stress beneficial. Stress was induced through handling or mild shock in rat young. Wit was found they matured earlier, explore more in novel environment. These animals could cope with stress later (How is stress in rats measured? Through their emotional responses).These rats remained undisturbed and did not defecate or urinate with fear. The normal rats showed a typical emotional response and cannot cope with stress and also matured later. The handling stress lead to increased secretions of adrenocorticotropic hormones(ACTH) which leads to increased Adrenal secretion in stress and with quicker absorption in the body (stress immunization). This leads to an earlier development of stress response, as the release of ACTH normally occurs at 16 days in rats, in the stressed rats this appears at 12 days (4 days earlier).Stress can be bad too, as well as increasing the duration of stress. Ackerman,Hofer & Weiner,1978, compared adult rats which had been separated from mothers at 15 days) with adult rats separated from mothers at 22 days. They report that early removal from mother leads to a high risk of ulcers, these animals also had defective thermoregulatory systems. They could not survive in extreme cold or heat (cold and hot challenges).

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LESSON 23

DEVELOPMENT OF THE NERVOUS SYSTEM

Objectives:

These lessons would familiarize the students with

- The stages of development of the brain and the changes which takes place
- Various stages of neuronal development.
- Development of the brain: from the fertilization to the various developmental stages in-utero, and postnatally.
- Cell differtiation, determination, migration, (inside-out), cell competition, Cell death, growth Cones, Nerve growth Factor and its role, Influences in growth and development of the brain
- Teratogenesis Genetic anomalies which affect development of the brain.
- Plasticity of the Nervous system.

Main Purpose:

This module would take the students through the development and growth (from intrauterine to neonate stages) to give an understanding of the stages of development and the processes involve.

In the last lesson we discussed some of the influences which can affect normal brain development, we would continue on the same topic

- **Oxygen level**: oxygen is very important for the brain cells during growth as well as throughout life. As the embryo depends on the mother for its oxygen supply, any reduction in the normal level would affect the growing brain. If the mother is not getting enough oxygen during last trimester, this leads to hypoxia (low oxygen levels) of the fetus. If the mother's blood circulation is faulty, then it would lead to damage of the brain areas which may have developed normally, (anemia, and heart disorders in mothers' leads to this problem). This damage is similar to that of mental retardation. Why? Because neurons die off and lesser number of cells remains leading to deficient functioning of these areas.
- **Prenatal motor activity**: This is important as there is evidence if there increased activity in uterus this leads to stronger muscles. This is exercising muscular connection, and their pathways. Thus motor connections are strengthened even within utero. Not just motor exercises, but sensory responses are also there. Evidence has shown that the embryo/fetus responds to mother's lullabies and voice. Those fetuses which are stimulated during the prenatal period are more alert when they are born.
- **Drugs**: Though the placental barrier protects the embryo, there are some substances which manage to pass through the protective membranes. It was discovered in the 1960's that drugs affect the normal growth of the fetus, leading to serious deformities. Thalidomide was the first drug to have been identified to have teratogenic effects. This sedative was given to expecting mothers in the 1st three months; it caused major deformities in the growing embryo. Similarly, morphine, heroin, alcohol, nicotine, cocaine and tobacco also affect the embryo. Mothers are warned against taking these or other pharmaceutical substances during pregnancy teratogenic effects
- **External Stimulation**: This is very important for the growing embryo. Unless external stimulation is received the organs and muscles do not develop normally. Therefore sensory deprivation leads to irreversible defects in normal growth of the brain. In the now classic experiments Hubel and Weisel (1963) closed one eye in newborn kitten creating monocular deprivation. They found monocular response to visual stimuli (only one eye could respond even though the visual system was not damaged). In another experiment, kittens were kept in dark room from birth onwards; it was found that visual pathways atrophy. Similarly, visual cortical brain areas also degenerate- in this case there is irreversible damage causing

blindness. Thus, early sensorimotor stimulation is important for the brain to grow normally. To stimulate the brain now some mobile and brightly colored toys are placed in the cots for the newborn to see.

- **Complex environment**: Rozenwieg et al (1969, 1972) raised rats in an enriched environment (more toys, swings, ladders, etc). They took out the brains and measured various parts of the brain. They report a) increased brain weight (especially cerebral cortex), b) increased thickness of cortical tissue c) larger size of neurons d) more glial cells e) more dendritic spines f) chemistry of brain also different (enzyme activity). Greenough (1975) and colleagues also report that rats raised in a complex environment a) had increased dendritic sprouting b) responded to novel environment in same way as mildly stimulated rats.
- **External stimulation** environment extremely important– but only during the periods in which it is needed to be present in the system. beyond that neither effect nor repair is possible

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LESSON 24

BASIC NEUROANATOMY

Objectives:

These lessons would familiarize the students with

- Systems, structure, Cells of the NS Neurons, Types of neurons, axonic and dendritic communications,
- Neuronal conduction and functioning, ionic and electrophysiological properties,
- Localizing brain areas planes of reference (anterior-posterior etc).
- The Brain and the Peripheral systems: Brain: Forebrain, Mid brain, Hind Brain functioning of each anatomical location in the CNS. Starting from the posterior located areas upto the anterior-most. Cerebral Cortex: its layers, Corpus Callosum and the two hemispheres.

Brain and spinal cord:

When we study the brain and the spinal cord we will first study the basics of neuroanatomical structure and systems. The basic component, like all systems in the body is the cells. The building blocks which the Nervous System is composed of are the neurons, the brains cells and the glial cells. There is also the cerebrospinal fluid (CSF) which cleans and insulates the brain.

Neurons:

Neurons are the specialized cells of the Nervous System. They are critical in the reception, conduction and transmission of information (many things in between, like chemical processes). There are about 10-12 billion neurons in the adult brain (as many stars in the Milky Way). For each neuron there are about 10-12 Glial cells. Make a very crowded brain, especially if their processes are also included.

We would be discussing these first followed by the cerebrospinal fluid, the blood brain barrier and lastly the neuron.

Glial cells

These are the supportive cells found in the brain. They have many important functions. A) They hold neuronal systems together. The synapse, the neuron, the synapse, and the dendrites are supported and held in position by the glial cells. B) They do the housekeeping chores such as moving out the dead cells and, keep the intra and extracellular space clean of debris c) they also provide nutrients to the cell and its processes.

There are three major types of glial cells, the astrocytes, the oligodendrocytes, phagocytes, and microglia.

Astrocytes:

The Astroglial extensions cover blood vessels and capilliaries (as insulation); these glial cells form the blood brain barrier (V.IMP). Astrocytes cover the neuronal cell bodies and their branches to keep them in place as well as separated from the fine branches. These also provide nutrients and chemicals which pass through blood into the cell.

Oligodendrocytes:

This is a glial cell which sends out several layered extensions which wrap around the axons. These are rich in myelin which is a fatty sheath. This sheath provides insulation and support to the axons and the dendrites. This increases the efficiency and speed of transmission. In axonal processes, the gaps between the folds are known as the Nodes of Ranvier, for messages to renew and jump across. One Oligodendrocyte can send extensions to many axons at the same time.

Microglia:
Smaller glial cells which keep the cells clean by moving debris out of the cell and move them out of the cell.

Phagocytes:
These are like the little Pac-man eating away all debris unattended and dead cells. They go around eating up and removing them.

Glial cells not passive providers or caretakers; they are actively involved in chemical transmission. They control, establish, and maintain synapses.

Protection of the brain
Brain is a highly protected area; there are many levels of protection. Firstly, the brain is encased by a bony skull case covering, Additionally three coverings known as the 3 meninges, which are connective tissues holding the brain in a protective net covering? The outer most menix is known as the **Dura mater** (translated from Arabic "tough mother"). This is the tough outer most covering of the brain, white colored. The second layer lying inside the Dura mater is the **arachnoid membrane** a web like structure (made of spongy filaments like a wire mesh). Beneath arachnoid membrane lies subarachnoid space where many large blood vessels (part of the vascular system) and the cerebrospinal fluid (CSF) floating around. This provides protection and the blood supply. A network of blood vessels can be seen if we open this space. The inner most covering– the most delicate membrane is known as the **Pia Mater** (Arabic translated into Latin= the soft or pious mother). This sticks to every convulation, every groove, thereby ensuring covering is comprehensive. As can be seen the brain is extremely well protected against injury (protection against jolts).

Cerebrospinal fluid: CSF:
This fluid fills the arachnoid space, the spinal cord (central canal) and the ventricles of the brain. These connected through a series of opening, and the CSF travels through the brain and the spinal cord. Essentially it is one big fluid reservoir. This fluid supports the form and shape of the brain (brain is very soft tissue), from inside and outside.

The cerebrospinal fluid traverses through the brain using the **ventricular system.** There are four ventricles. The first two (laterally placed) are very large cavities continuing in both hemispheres. The third ventricle lies in the mid brain at the level of diencephalic area. The fourth ventricle is found lower at the brain stem/cerebellar level. This is connected to the central canal of the spinal cord. The Choroid plexuses in the PIA mater produce the CSF. Small capillaries that get through the PIA mater lining produce the fluid. This is constantly being produced and circulated. It is about 125 milli litres and replacement of half of it takes place every 3 hours, indicating a continuous circulation. Blocking of the fluid or any infections may alter the level of functioning:

Cerebral aquaduct is the link between the 3rd and 4rth ventricles. The CSF is made up of water, proteins, gases glucose, and other chemical ingredients (Carlson, Pinel)

Blood brain barrier:
This is not a fence or a barrier which is visible, it is essentially cerebral blood vessels and the glial cells in the brain very tightly and densely packed together. These provide protection through the insulating glial cells, creating difficulty for large molecules to pass through such as some Proteins, but large glucose molecules to actively transport through blood vessel walls. The Blood brain barrier is also selective depending on the locations. It makes some substances easier to pass than others at some specific locations.

Thus we see the complexity of the brain emerging through the various specialized parts, the glials, the CSF, the Protection of the brain, and the glial cells. They all work to keep the complex system of the brain functioning smoothly.

Neurons:
There are many types of neurons which have been identified using the a) silver staining b) electron microscopic techniques c) the golgi and other histological/cytological techniques.

The neuron mainly has three distinct features a) the cell soma, the cell body b) the axon one and only output end which carries the commands out of the cell c) the dendrites which bring in messages and information to the cell.

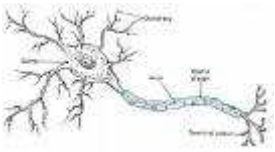
Types:
The neurons fall in three major categories, the Unipolar, Bipolar and Multipolar.

i) **Unipolar:** The Unipolar is the neuron which has only one process emerging out of the cell body and extending to both ends for quicker communication.
ii) **Bipolar:** the Bipolar neurons are neurons with two poles, one axon (output end) and dendrite (input end) and these are mainly for horizontal communication as the sensory neuron, found in the eye and the ear
iii) **Multipolar:** This is the most commonly found neuron. This type of neuron has more than more than two processes i.e. there is always one axon but multiple dendritic connections. These again fall into different categories, there are neurons with short branches (such as the Astro type cells), these are the **Interneurons** with shorter or no axons, for quick integration and processing of information, The Pyramidal cell which have very long Apical dendrites but short axon.

Neurons: Special Characteristics
Neurons are different from the cells in the body because of two main properties.

a) They can conduct bioelectric signals over long distances without loss in signal strength, unlike the sound waves which become dimmer and dimmer with distance. These carry signals at exactly the same strength from the point of beginning to the end

b) The Intercellular connections with other cells and tissues such as muscles and glands are multiple. The information which can be sent out and which can be received by the neurons is determined by the connections it has. There are many connections and for each there are specialized neurons and groups of neurons. When neurons group together they are known as nuclei. Neurons clustered into bunches of nuclei, tracts are fiber systems connecting these nuclei



Neurons Types:
Neurons are heterogeneous with respect to cell size, shape etc. because the kind of work the cell has to do depends on the location, the systems, the connections and the neurotransmitters that it is specialized in. (motor neurons are different from the sensory neurons, visual cells are different form the auditory cells)

Cells in all cases are composed of the soma -perikaryon (surrounding the nucleus), the axon (efferent: output) the dendrites (receiving and input), and majority of the neurons are multipolar.

Neuronal Codes of communication:
How does information get processed and transmitted by the neurons. Information is coded in two different codes the Digital code and the Analog code.

Digital code:
This is the code used by the neuron to pass information from one end to of the neuron to the other. This is like the Morse code, where the changing number of dots and dashes change the message sent out. In this the Rate of change is constant and in the same unit when the axonal end talks to the soma and the dendritic ends. This determines how and what message sent. This is the **electrical in nature;** the electrical impulse is generated and sent.

Analog code:
This is the code used when two neurons are communicating with each other. This is a biochemical signal, varies with the intensity of the message. ***The more intense the message the more Neurotransmitter released (Chemical)***

Can the two codes be linked/ transformed one into other? Yes, this is happening constantly. Neurons are communicating to each other as well as passing information within the neuron. The frequency or rate of information in the digital would lead to amount of neuro-chemical released in the synapse and when the neurotransmitter molecules crosses over to the other neuron, their contact transforms into an electrical signal. Therefore it is a continuous **Electrical---chemical---electrical change taking place**. The neuron can communicate effectively in both information systems.

The transmission of a neuron takes place when the axon sends in the impulse to the cell soma, and then the cell responds by triggering a message to the dendritic synapse (with axons /somas of other cells). ***This is known as the axonal transmission and the junctional transmission.***

Axonal transmission:
a) In this transmission the impulse travels both ways i.e. from the cell body to terminal is known as orthodromic or anterograde, and if the impulse travels from the Terminal to cell body it is known as antidromic or retrograde.
b) In the axonal transmission there is no time delay
c) This is not affected by drugs or other substances
d) This is an all or none firing. Firing begins and ends with stimulation, there is no after discharge

Junctional Transmission:
a) Junctional Impulse travels only in one direction from the presynapse to the post synapse.
b) There is time delay between transmissions. Neuro Transmitter molecules travel across synapse .1 to.2 milli seconds.
c) Spatial and temporal summation. In this transmission, the messages get summated at the axonal hillock before a decision is made to fire or not i.e. they reach threshold where the cell fire an action potential.
d) Affected by drugs, as drugs can be used to change the rate of transmission.
e) It is not all or none transmission it is graded response

In the next lesson we would discuss more about the neuron and the processes which take place within the neuron.

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LESSON 25

BASIC NEUROANATOMY

Objectives:

The students will be familiarized with the functioning of the neurons and their components

- Systems, structure, Cells of the NS Neurons, Types of neurons, axonic and dendritic communications,
- Neuronal conduction and functioning, ionic and electrophysiological properties,
- Localizing brain areas planes of reference (anterior-posterior etc).
- The Brain and the Peripheral systems: Brain: Forebrain, Mid brain, Hind Brain functioning of each anatomical location in the CNS. Starting from the posterior located areas upto the anterior-most. Cerebral Cortex: its layers, Corpus Callosum and the two hemispheres

Brain and spinal cord:

When we study the brain and the spinal cord we will first study the basics of neuroanatomical structure and systems. The basic component, like all systems in the body is the cells. The building blocks which the Nervous System is composed of are the neurons, the brains cells and the glial cells. There is also the cerebrospinal fluid (CSF) which cleans and insulates the brain.

Neuron Structure

The neuron is like the other cells of the body but is specialized cell it is similar in structure and composition of cell structures but then it differs in other characteristics.

The neuron comprises of three distinct parts as has already been described earlier. The Cell body or cell soma, the axon (output end) and the dendrites,

Cell Soma

The Cell soma is made up of cytoplasm and contains the nucleus, the nucleolus, the free ribosomes which are sites for ribonucleic proteins, the Rough endoplasmic reticulum and smooth endoplasmic reticulum, Mitochondria and other bodies.

Cytoplasm: The jelly like semi fluid in which all the components of the cell float around in Nucleus. The center the master mind of the cell which contains the genetic code, the DNA. It uses the DNA as a template to manufacture the mRNA (messenger Ribonucleic acid), which carries the required information to the Ribosome, where this is needed to manufacture structural proteins, and enzymes needed for catalytic action within the cell.

Nucleolus: the structure within the nucleus which manufactures the ribosomes to carry the genetic code outside the center, are manufactured.

Ribosomes: manufacture amino acids basics for proteins for use within the cell and for use outside where they are transported via the Endoplasmic reticulum

Endoplasmic reticulum: There are two kinds found in the cell, the Smooth Endoplasmic Reticulum (SER) and the Rough Endoplasmic Reticulum (RER). These are folds of membranes (like folds of cloth). Both are for transporting material within and outside the cell. The RER's look rough because of the beaded appearance, which is caused by the ribosomes being transported by RERs. The SER's transport lipids

Golgi Apparatus: named after the discoverer Camillo Golgi, are where the membranes for vesicles are prepared.

Mitochondria: The power house of the cell. It provides energy needed to run the cell. Interestingly they are the respiratory organs of the cell, and they are microorganisms which have survived within the cell because of the evolutionary advantage to both the cell and the mitochondria. All metabolism of the cell takes place in the Mitochondria.

Microfilaments and microtubules: supportive network of tubes and fine membrane filaments which are continuously being formed and broken down as the cell changes learning requires cells shape and form to change).

The Axon: The Axon is the output end of the cell. It emerges from the cell at the axonal hillock where summation of messages takes place. It has neurotubules for supporting the shape and from form inside and also providing a transport system. There are vesicles for carrying neurotransmitters, since axon is involved in using a large amount of energy for transmitting messages, there is mitochondria floating around in the axonal processes. Myelin Sheath covers the axon with gaps which are called Nodes of Ranvier across which message jumps across. At the pre synaptic end the axon has synaptic boutons which have vesicles and process the transmission using neurtransmitters.

Dendrites are the receiving ends of the neurons, they have multiple branches and there can be extensive branching and synapses depending on the sites.

Cell membrane: is highly active cytoplasm where constantly ionic and electrical changes are taking place. Further, complex biochemical processes are also taking place within the cell membrane. These processes are important as they play an active role in
a) Transmission of signals through the axon to other neurons,
b) Biochemical processes of the soma and
c) Receiving of the transmission by the dendrites,
d) These processes also sustain and keep the cell alive and free of toxins,
e) Controls the number and amount of molecules leaving or entering the cell body

Cell membrane important because main role in
1) Conductance of signals along the axon,
2) Reception in the dendrite
3) control the molecules moving in and out of the cell The Intracellular membrane is composed of double layer composed of fats and phosphates that is known as the phospholipid—These molecules have 2 parts: hydrophobic (water repelling) tail, and hydrophilic (water seeking) head. Fatty acid tail inside and phosphate head outside. All the hydrophilic heads are on the outside facing the intracellular and the extracellular medium which is made up of mainly water and other chemicals. These look like little beads. The hydrophilic ends are towards the inside (like the bread in a three layer sandwich), and they are retained where each layers lipid tails face each other. There are also some proteins (glycoproteins), channel proteins, and cytoskeletal elements, which float around the layers, as these are needed for any living organism. Within this there is a system of regulation of the movement of molecules across the pores of the membrane

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LESSON 26

BASIC NEUROANATOMY

Objectives:

The student would learn about the ionic and molecular movement of the neurons and how the electrophysiological properties of neurons change

- Systems, structure, Cells of the NS Neurons, Types of neurons, axonic and dendritic communications,
- Neuronal conduction and functioning, ionic and electrophysiological properties,
- Localizing brain areas planes of reference (anterior-posterior etc).
- The Brain and the Peripheral systems: Brain: Forebrain, Mid brain, Hind Brain functioning of each anatomical location in the CNS.

We have studied in our earlier lesson how the neuronal membrane is structured, and how the phospholipids form a tight mesh from which substances and molecules have difficulty leaving or entering. We would discuss this more in detail

Control of molecules:

In the Phospholipid layers, the movement of lipid molecule through the membrane is easier and also that of smaller molecules. The cell membrane also allows materials to move in and out depending on the changes in the membrane permeability. Increased Permeability mean that membrane can allow those materials to pass which had earlier not been able to pass through, and decreased permeability means that the gates of passing in/out are closed

Membrane permeability is determined by ionic state of membrane:

The most important task of the neurons is to communicate, and we have seen that neurons are active as living systems. There is a constant movement of ions in the intracellular and the extracellular membrane. This constant state of flux in which these ions (Ions are molecules which are negatively charged, or positively charged depending on the number of electrons they carry) are moving generates electrical charges which then enable neurons to communicate and to send out electrical signals.

Electrical charges are measured in terms of volts (milli volts in the case of neurons) and the difference of electrical charge between the intracellular membrane and the extracellular membrane is known as the Potential

Using a voltmeter by which we can place one electrode on the intracellular and one on the extracellular membrane we would find that the inside has a large concentration of negatively charged ions whereas the extracellular membrane has more positively charged ions. Thus, the inside of the cell is negative as compared to outside and the difference in potential is recorded at -70 mV (this is about 1/15th of the difference of charges in the household battery). This is known as the Resting Potential of the neuron. At this stage the cell is at a Resting state. When positively charged ions enter the cell, the inside becomes positively charged as compared to the outside, and the charge is recorded at +50 mV, the cell will fire an action potential. The voltage difference is about 120 mV to get to an Action Potential (How?).

ION	Concentration Inside	Concentration outside	Cell State
Sodium NA^+ (large molecule)	50	460	Resting, (impermeable to NA^+ inside the cytoplasm
Potassium K^+ (Small molecule)	400	10	Resting, small molecule, moves in and out
Cloride CL^- (Small molecule)	40	560	Resting, small molecule moves in and out of the cell
Anions A^- (large molecule)	345	0	Resting (impermeable to A^- outside the cytoplasm)

As we can see there is a high concentration of negatively charged molecules inside the cell, and these ions are trying to equalize the two sides of the cellular membrane.

Ionic movement follows two processes to maintain equilibrium and thereby causing the movement of electrical charge. Ions move along their osmotic/concentration gradient and electrostatic gradient. When molecules move from areas of high concentration to areas of low concentration to create equilibrium especially in a permeable or a semi permeable membrane this process is known as osmosis (nature strives for equilibrium). Therefore if the concentration of ions is low on one side the ions would move to equalize the balance on both sides. From the above table we can see that all the four would move to equalize concentrations. This is known as the **osmotic gradient.**

Similarly, the law in electricity is that like charges repel and unlike charges attract, therefore molecules would move towards balancing the electrostatic gradient.

Both the forces of osmosis and electrostatic gradient are working together continuously to create a constant state of movement of ions.

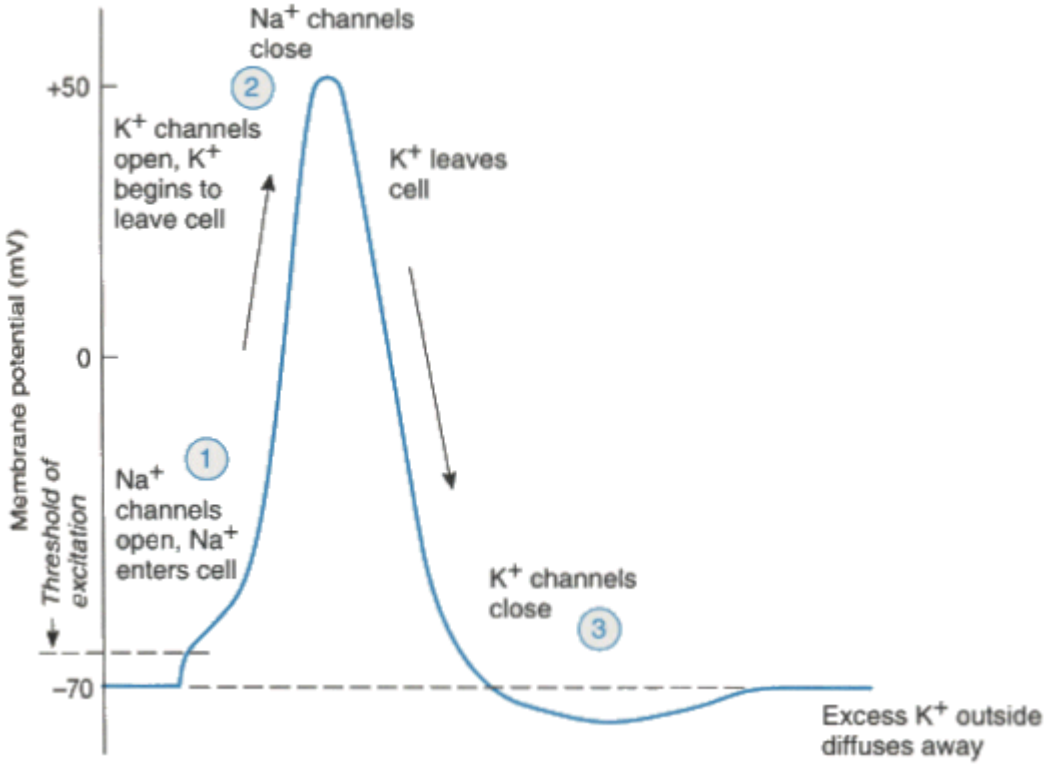
As an example let's take a glass of water, divide it with a fine muslin cloth (or sieve) drop a teaspoon of salt (sodium chloride = NA^+ CL^-) on one side only. There would be diffusion as the molecules move to equalize both sides as one side has both NA and CL and other does not. Therefore both NA and CL ions would move to equalize both sides of the glass moving according to their Osmotic gradient i.e. to equalize and balance concentration. However, the sieve does not allow large ions to pass, therefore large ions get stuck on side and the small ions move to other side, leaving CL- on one side and NA+ on the other. Now we see the **electrostatic gradient** come into action, as there are negatively charged molecules on one side and the positively charged on the other. This leads to attraction and movement of ions again. However, only the smaller positively charged molecules can cross over. Thus, in turn osmotic gradient moves ions to equalize, then negatively charged attract to move ions again. This movement across the sieve causes flux in the glass.

This is the same kind of action taking place in the neuronal/axonal membrane leading to the resting and the action potential.

In the resting state of the axon the membrane is impermeable to both large ions a) positively charged sodium ions (which are outside) and the Anions (which are inside) and the smaller chloride (negative) and Potassium (positive) are continuously moving back and forth according to the osmotic and electrostatic gradients. However, this changes when the axons receives inputs from the cell soma to

fire, there is a change in the concentration of ions as the cell membrane becomes permeable and large sodium ions rush in, making in the inside of the cell positively charged.

Sodium potassium pump:
When the cell permeability changes, large ions rush in NA+, inside becomes positively charged. The cell becomes impermeable again, but it is stuck with the large sodium ions inside. Then, the cell membrane uses a biological pump known as the sodium- potassium pump to push out the NA+ and carry molecules of potassium back inside the cell. This uses up to 40% of the cell's energy as the cell is pushing them against their osmotic gradients.

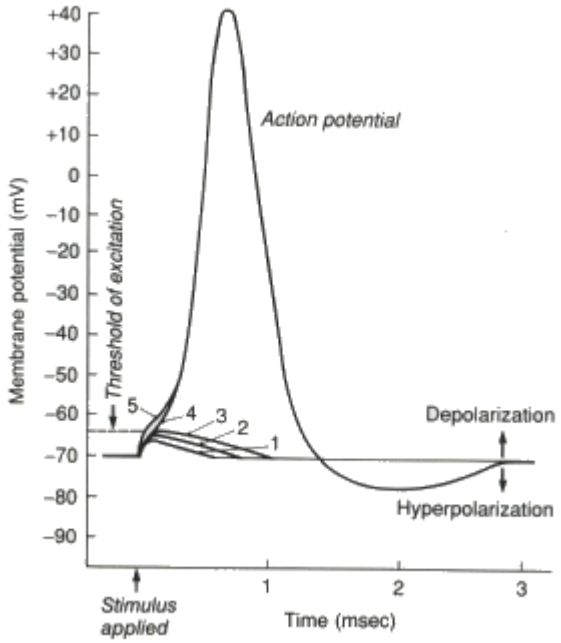


How does the resting potential change to an action potential. The cell at the resting state is receiving inputs form all over which are being summated at the axonal hillock. There are changes in the cell's electrical threshold that are taking place.

The inside is negative as compared to the outside membrane, and the difference is of -70 mV. This negativity can increase resulting in Hyperpolarization is where there is an increase negativity from -70 to -80. On the other hand the Depolarization are decreases in negativity from -70 to -65, or -60 (these are small depolarization) but a larger depolarization of leads to crossing the threshold and going upto +50mV. This is an action potential which leads the cell to fire. Once the peak AP is reached, the inside electrical charge starts becoming negative, to the point that it drops below the -70 mV.

After action potential has been fired, the cell goes into a refractory state- hyperpolarized- to about -75 mV. It will not fire, till it returns to the resting state

The action potential lasts for about 1/1000th of a second, and the refractory period can continue for about some milliseconds



Firing of the action potential leads to the conductance of the signal. The rate and speed of conductance is equivalent to 224 miles/hour which is equal to 100meters per sec in cat brain, in humans it is about 60 meters per second.

The axonal conduction is an all- or- none phenomenon, the cell would fire an action potential once the threshold is reached. The action would be completed once it begins.

Once the axonal transmission has crossed to the postsynaptic site, it can lead to two types of action: The Excitatory Post Synaptic Potentials (EPSPs), this would cause the post synaptic site to fire an action potential. This stimulates action in the post synaptic site.

Inhibitory Post Synaptic Potential (IPSPs) inhibits ongoing firing of the cell that it synapses on to. So activity of the cell would be brought to a resting state.

Since there are multiple synapses on each cell (at the dendrites, the cell soma), there may be some which are IPSP and some which are EPSP's, these stimulations are summated and if the stimulation crosses the excitatory threshold to arouse the cell , it would fire otherwise it would stay in the resting state.

Spatial and temporal summation: multiple synapses are continuously adding together the EPSP's and IPSPs received by them. There are two kinds of summations of stimulation that are carried out at the cell soma and the axonal hillock,

A) Spatial summation: When a neuron receives inputs from several locations these can EPSP's which create depolarization and IPSP's which lead to hyper polarization. These spread across the cell membrane and reach the axonal hillock at the same time they are integrated and summated

algebraically if the sum is slightly negative then a small hyperpolarization would take place and the cell would go from -70mV to -75 mV.

B) Temporal Summation: When a neuron receives input from the same location but repeatedly over time (could be EPSP's or IPSP's) the are summed together received one after another (how can this happen – one stimulation is received and has still not faded away, the 2nd one received adds up as does the third and the fourth one). After summation at the axonal hillock, the neuron may either depolarize further or hyperpolarize

Basic Neuroanatomy: Anatomical Axis, Directions and Planes of Reference

Before we study the brain we have to understand the basic concepts of the locations, sites and their relationship to each other is defined. Just as we use the directional reference of North-South, and East-West in Geography, we also have specialized terms for identifying the directions in the brain

Basic neuroanatomical axis: Anterior- posterior, dorsal- ventral, lateral -medial;

In humans we follow the same system that is followed for all other animals, especially the vertebrates.

Anterior-posterior: Anterior towards the front: the nose end, and posterior is towards back,: the tail end, so all structures in the front would be anteriorlly located and the structures in the back would be posteriorly located. This is also known as the rostral-caudal axis (rostral: towards the face and caudal: towards the tail, easier in animals which have tails!)

Dorsal- Ventral: This axis is easier to understand with a four legged animal or the fish than in humans. Dorsal means towards the back for example the dorsal fin of shark of head and body, ventral is towards the chest /stomach region or the bottom of the head. In humans the dorsal surface becomes the back side as we stand. The top of the head, the back side facing the vertebral column are then the dorsal areas

Medial- Lateral: The third axis in which medial is used as reference for areas towards the center or the mid line. The nose is medially located with reference to the face and ear are laterally located that is they are located toward the sides. Therefore the brain areas towards the outside are laterally located. It is important to remember the other terms of reference which are continuously being used with reference to the brain and various neuroanatomical sites

Ascending- descending fibers: Descending refers to the groups of nerves/ processes which travel down from the higher areas to lower areas: from cortex, the nerves descend to the Thalamus and from the thalamus to the lower areas. Ascending refers to the nerves and the projections which carry messages up to the higher brain areas.

Superior-inferior: Superior is those structures, nerve fibers or projections which lie on the top, whereas the lower structures, projections, fibers, areas are referred to as inferior (because they lie lower than, not because their functioning is lower).

Proximal-distal: proximal areas are those which lie closer to the brain or to each other. Those areas which are farther are known as distally located areas. Ipsilateral-contralateral: Ipsi means the same side and contra means the opposite side. Therefore ipsilateral would means those areas, or fibers, or nerves or structures which are on the same side, whereas the contra lateral would be structures, fibers or areas on the opposite side. The ipsilateral fibres would travel from the left side occipital cortex to the left eye; contralateral would cross over at the optic chiasm to the right eye. Afferent- Efferent: afferent are those which are bringing messages into the brain: these refer to the nerves which carry information to the brain form the sensory areas Efferent taking info out of the brain or carry commands messages from the brain to motor areas.

Planes of reference: When brain is dissected for studying the sections are cut and referred to in planes of reference. Horizontal sections are cut slicing the brain through from the dorsal to the ventral areas. (or vice-versa) the sagittal cuts are made when we move in the lateral to the medial-lateral direction. The mid sagittal section is made through the middle of the two hemispheres at the level of the point of joining. The frontal section is cut from the front of the brain towards the back.

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LESSON 27

BASIC NEUROANATOMY

Objectives:

The main objective of this lesson is to study

- The Brain and the Peripheral systems:
- Brain: Forebrain, Mid brain, Hind Brain functioning of each anatomical location in the CNS. Starting from the posterior located areas upto the anterior-most.
- Cerebral Cortex: its layers, Corpus Callosum and the two hemispheres

Main purpose:

Students will become familiarized with the location of various brain areas, their functions and their relationship to other areas. The students would also understand how control and modulation of behaviour related to each neuroanatomical site takes place

Basic Neuroanatomy is based on the following assumptions:

- The cortex is newly evolved as compared to the other structures, and it controls all major functions (especially in the higher animals)
- The higher areas cover the lower areas as they have grown over these areas. The lower brain areas have to send information to the higher areas and then the commands for actions come back from these areas (the thalamus send all messages it receives to the relevant cortices and receives commands)
- The lower underlying areas are more primitive in terms of functions, their functions are more survival functions (the brain stem areas)
- These lower areas are similar in locations, site and functions in lower and higher order animals (e.g. the hypothalamus, the thalamus).

Phylogenetically, encephalization (control of the higher brain areas) has occurred leading to increased ability to interact and respond to the environment (greater adaptability).

The greater the encephalization, the more the functions are controlled by the higher brain areas, therefore if these areas are damaged the animals cannot function at a normal level (Bridgeman, 1988, Thompson 1980).

The following would elaborate how the brain is located with reference to the spinal cord and how other areas within the brain and the top of the spinal cord

Brain----------spinal cord

There are three major divisions of the brain: The Forebrain, the midbrain and the hind brain.

The Forebrain comprises of the Telencephalon (coritcal and some subcortical structures) and Diencephalon (the Thalamus and the hypothalamus).

The Mid brain consists of older structures, the Mesencephalon and

The Hind brain The posterior most part of the brain is called the Hind brain, which has two sections the Metencephalon and the Myelencephalon

We will elaborate these areas further moving from the frontal and dorsal areas to the more caudal ventral areas. The anterior most and the dorsal area is the Telencephalon, with Myelencephalon at the caudal most end

Telencephalon: comprises of the Cerebral Cortex, the Corpus Striatum, Cingulate Gyrus, Septum, Amygdala, Hippocampus (these last three are also part of the limbic system). Therefore this is cerebral cortex which is a phylogenetically a newer structure, and some older primitive structures which underlie the cerebral cortex

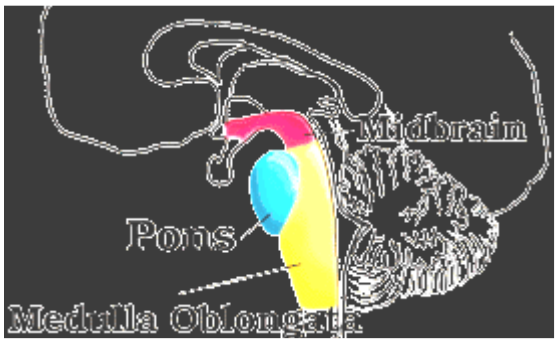
Diencephalon: Comprises of the Thalamus which is the junction and the gateway for all sensory-motor and association pathways and the Hypothalamus which is the primitive survival centre

Mesencephalon: has the Tectum which comprises of the Inferior (for auditory systems) and the Superior colliculi (for visual system) Tegmentum, cerebral peduncles Metencephalon: comprises of the Cerebellum which lies dorsally over the Pons, and the Pons

Myelencephalon comprises of the Medulla Oblangata

Brain stem: includes the Mesencephalon, Metencephalon and the Myelencephalon i.e. technically everything between spinal cord and cerebral cortex

Myelencephalon: Medulla Oblongata (Oblong and narrow structure) is continuation of spinal cord and the caudal part of the brain stem .Another important structure which is located in the Brain stem are is the reticular formation.



Medulla contains all the acending and descending fibre pathways connecting the brain and the spinal cord. It also has nuclei for the cranial nerves especially related to the control of respiration; heart and digestive activity enter the brain at the level of medulla. Cranial nerves for tongue, larynx, pharynx, ear, vestibular, involved in control of breathing while sleeping (sleep apnea), sneezing, swallowing, vomiting are also found here.

Cranial nerves:

Hypoglossal nerve (tongue) - Cranial Nerve XII
Accessory (larynx, voice, mouth mastoid) Cranial nerve XI
Vagus (taste, larynx, pharynx, ear) Cranial Nerve X
Glossopharyngeal (Taste, posterior part of the Tongue) Cranial IX
Vestibulocochlear related to ear and vestibular Cranial VIII

Sneezing: when nasal mucosa is irritated. The sneezing center is located in the medial part of medulla (it also involves the trigeminal nerve).
Vomiting is found in the Medullar Reticular Formation

Reticular Formation: this is a criss cross of nerve fibres , nuclei and cell bodies (like a net (reticulum means: the net). It extends from the spinal cord to the Thalamus. It is a phylogenetically older structure. It is a well organized are with both efferent and afferent ascending and descending fibres:

Ascending fibers go to thalamus, cortex, and are involved in sleep and awakening. Raphe Nuclei produces serotonin and extends from the lower pons, andmedulla. Analgesia is produced by the electrical stimulation of the Periaquaductal greay (PAG), is through the Raphe nuclei. It gets input from cerebral cortex, the cerebellum and output to cerebellum and the spinal cord. "The reticular activating system" (RAS) which is important in arousal. Sleep, arousal, muscle tone, alertness was found to be located here by experiments of Moruzzi and Magoun (1949) on cats. They stimulated the raphe Nuclei of a sleeping cat which led to an arousal EEG response (low voltage, high frequency theta response), it woke up, and when the awake cat was stimulated and it became more alert. However, when this area was lessioned animals went into a comatose stuporous state.

Destruction of the Raphe Nuclei led to Insomniac cats thus it was found that the RAS is important in sleep and attention.

Metencephalon. Has many tracts going up and down,and contains two important brain areas the Cerebellum and the POns.

Cerebellum: lies over Pons, it is a phylogenetically older structure, for sensory motor coordination, movement and balance. It has two lobes like the CC with a large number of lobules separated by fissures (vermis, smaller grooves) with a large number of convulations, but these are similar all over (unlike the cerebral cortex in which there is a difference). The nerve cell layer is 2mm thick below which lies the white matter under which lies the cerebellar nuclei

Cerebellum receives inputs from the vestibular system, auditory and visual system, reticular formation, and various regions of the cerebral cortex. It sends out fibers to the reticular formation, thalamus and the vestibular system

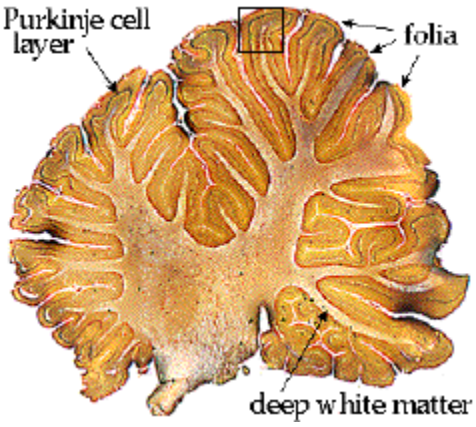
Damage to the cerebellum leads to disturbances of gait in all regions. If one lobe is damaged then there is postural imbalance. If both cerebellar poles are damaged there is tendency to fall backwards because of the inability to maintain upright postures and gait disturbance with damage to the posterior region.

In Humans, Ataxia, characterized by unsteadiness of gait is seen, this is with anterior lobe syndrome: with the following symptoms:

- Abnormalities in force, rate, and direction of rapid movements a) overshooting while reaching targets b) jerky not smooth movements. Damage to the cerebellum impairs standing, walking and performance of coordinated movements
- Birds and reptiles have large cerebellums? Why?? To maintain balance during flight and since sensory –motor fibers are coming and going out to various areas, coordination of smooth movements takes place in this area.

The oculomotor signs of cerebellar damage are: Nystagamus (rythmic and involuntary oscillatory movements of the eyes)

Cerebellectomy (removal of the cerebellum) lead to inability to maintain gaze, defective smooth pursuit movements, difficulty of fixation



Cerebellar neurons: Purkinje cells (long dendritic trees), Basket cells (short axons, dendrites cover Purkinje cells), Stellate Cells (axons terminate on Purkinje cells), granule cells (smallest, go vertical for communication)

Pons: Bridge between the medulla, midbrain, and the cerebellum. The medulla is caudally located with refernce to POns and the midbrain is rostrally located. The Dorsal surface of PONS is covered by the cerebellum. Large rounded pontine nuclei contain ascending and descending fibre bundles. One such bundle connects the rbain stem and the cerebellum and contains the Pyramidal fibres from Cerebral cortex to the spinal cord (part of the cortico-spinal tract). The Trigeminal cranial nerve enters and leaves the brain at the level of POns. Further the Cranial nerves for feeding, facial expression, respiratory nuclei, relay nerves for auditory systems are also located here.

The cortico-ponto-cerebellar tract is the largest group of fibres which originate form a wide area of the cerebral cortex 9 has over 19 million fibres on each side). These rises from the primary cortical areas are involved in rapid correction of movements.

PONTINE NUCLEI, THE GIANT PONTINE CELLS play an important role in rapid eye movement sleep by inhibiting the movement of body muscles to prevent damage which could occur due to activation of the body (as the brain is active)

Mesencephalon is a small portion between the hind brain and the diencephalons- the anterior section of the brain stem, it is tubular in form. It has three main areas: tectum, tegmentum, and basis pedunculi

Tectum comprises of two pairs of relay nuclei, which look like 4 little lumps on the surface of the brain stem. These are the Superior Colliculi and the Inferior Colliculi

Superior Colliculi: laminated grey and white matter important in visual reflexes and eye movement, well defined and organized in terms of receptive fields and maps of visual space. It is part of the pathway coming from the optic tract to the visual cortex for eye movement and gross spatial localization. This is important for vertical gaze and pupillary reflexes. It receives inputs

from retina of eyes, thalamus, and inferior colliculus and sends outputs to thalamus and frontal and visual cortices.

Inferior colliculi: it is an oval mass of small and medium sized neurons and is major relay nuclei for the auditory pathway. Fibers come in from the Thalamus (Medial Geniculate Nuclei), auditory cortex and cerebellar cortex, and fibers from Inferior colliculi project to the MGN, superior Colliculi and the cerebellum… turn to look at sound reflex and localizing the source of sound. Therefore both the inferior and superior colliculi work together as part of the reflex system which take care of attending and turning to wards the direction of a sound (This is why we see extensive connection with the thalamus, the cerebellum and the relevant cortices)

We would be continuing discussion on location of various brain areas and their connections and functions in the next class.

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LESSON 28

BASIC NEUROANATOMY

Objectives:

The main objective of this lesson is to study

- The Brain and the Peripheral systems:
- Brain: Forebrain, Mid brain, Hind Brain functioning of each anatomical location in the CNS. Starting from the posterior located areas upto the anterior-most.
- Cerebral Cortex: its layers, Corpus Callosum and the two hemispheres

Main purpose:

Students will become familiarized with the location of various brain areas, their functions and their relationship to other areas. The students would also understand how control and modulation of behaviour related to each neuroanatomical site takes place

In lesson 27 we discussed some parts of the Mesencephalon, and now we continue with the remaining areas which fall under Mesencephalon.

- **Tegmentum:** This lies between the Tectum and Substantia Nigra. It contains nuclei and relay fibres of ascending and descending tracts. It also contains the motor cranial nerves for eye movements (oculomotor) and the trochlear cranial nerves. The three major fibre bundles are the **Medial Leminiscus** (ML)and the **Trigeminal Leminiscus** (TL) and the **Spino-thalamic tract** (STT)

- The **ML** lies above the **Substantia Nigra** (SN) and conveys kinesthetic and discriminative touch sensory information to the Thalamus.

- The **TL** also are tracts which travel upto the **Thalamus**

- The **STT** conveys the pain and temperature sensations from the contralateral hemisphere (e.g from the left arm to the right side of the brain).

- **PAG: Peri-Aquaductal Gray.** This is the grey matter which surrounds the cerebral aquaduct: This has the neural circuitry for sequence of movements for species specific behaviors (fight, flight, and mating). Research ahs also shown this to be an important area for pain sensations. If opiates are injected in this area they reduce the sensitivity to pain (raise the tolerance threshold)

- In the basal portion of tegmentum we have the cerebral peduncles which are large fiber bundles which are placed in the ventral region of the mesencephalon. These carry fibers of **the cortico-spinal tract**, and the **cortico-pontine tract**. There are also large projections such as the **pareito-occipito-tempero-pontine** projections which carry projection from cerebral cortex down through pontine area into the spinal cord.

- **Substantia Nigra:** dark pigmented mass of neurons, between cerebral peduncles and tegmentum, zona compacta rich in Dopamine and brain opiate receptors. This is part of the brains motor control and modulation sys tem, and is involved in movement and balance. If we create an imbalance in the bilaterally located SN areas by a unilateral lesion, we see asymmetric body posture. The body turns from the high to the low region (lopsided posture). If the Dopamienrgic neurons degenerate in this area it leads to Parkinson's disease. This is characterized by tremor rigidity, slowness of motor activity, stiffness in muscles, pin rolling

movement, loss of adaptation (facial expression and gait). Inputs come from the Neostriatum, cerebral cortex, Globus Pallidus, and other parts of the Tegmentum

- **Red Nucleus:** neurons with a pinkish hue are an important is importna area in Tegmentum. Inputs come in from deep cerebellar nuclei and the cerebral motor cortex. If the deep cerebellar input is damaged, tremor is manifested when the hand or foot is in motion (reaching out). The gross movements of body are controlled by this system. If there is unilateral electrical stimulation, it leads to circulatory motion, and lesions result in disturbances of gait (walking).

The Medulla, Pons, and the lower areas had evolved earlier on the revolutionary scale and are similar from fish to man. The fish don't have a cerebral cortex, but have large inferior and superior colliculi, as this is what fishes would need for determining direction while swimming in water. Bats are nocturnal creatures which fly and hunt at night. For bats audition becomes more important for survival more than vision, therefore the bats have bigger inferior than superior coliculli. The brain stem areas serves as a connection between upper and lower areas, that is they connect the Telencephalon and Diencephalon to the Spinal Cord

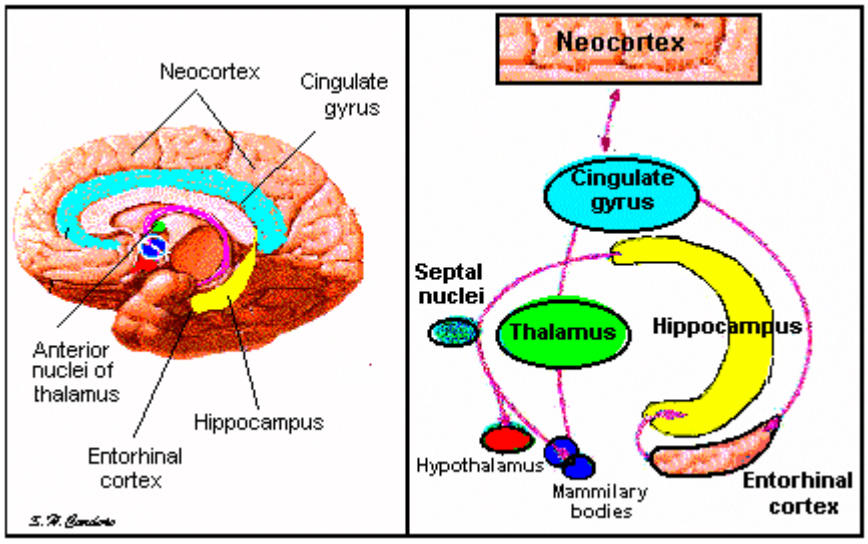
MID BRAIN areas: These comprise of the Corpus Striatum: Striated bodies(corpus) This group of structures includes the Basal Ganglia the Caudate (Tail Like) Nucleus, Globus Pallidus (Pale Globe), Putamen . These areas lie underneath the cerebral cortex

The Corpus Striatum receives input from and sends output to the cerebral cortices, especially the frontal areas where the motor lobe is located. They also send fibres to the Thalamus (output). There are numerous interconnections between different areas of the corpus striatum. These areas appear to be involved in the modulation of motor movement, especially the movement/modulation of contralateral aspect of the body. This also has the controls of initiation of movement, contralateral head turning, circling, licking, chewing, gnawing etc. This is also important part of the Dopaminergic pathway involved in Parkinson's disease. Bilateral lesions of pallidus lead to hypoactive and sleepy animal. Thus, this appears to be the basis of decreased movement and hypokinesia of Parkinsons' disease. On the hand, the Caudate promotes arousal of motor system. So they balance the controls of motor movement.

- If we look at the hierarchy of movement starting from the highest control, the cerebral cortex, we see that the Motor cortex-sends commands to the striatum, from there the commands go through the nigral system and then the action takes place. As motor skills are learned the basal ganglia takes over role of executing learned strategy. So the commands go from the striatum to the nigral for preparation of action to take place. This becomes more automated and programmed. Think about how a child learns to walk, slow deliberate balancing takes place initially and then gradually locomotion becomes a routine. However, when basal ganglia are damaged the individual reverts to slower less automatic cortical response. Basically the preparation of execution of movement is the main function: We could call it a Gating function: This means gating of sensori-motor processing (controlling the gates of channels which provide information). Thus, it limits the access of information to motor systems.
- Huntington's chorea is due to degeneration of Basal ganglia. This degeneration results in reduction of inhibitory output of BG- which leads to increased access of sensory information, which leads to increased activity (hyperkinesis, sudden jerks, tics, and jerky movements of head, trunk and extremities, facial grimaces, repetitive dancing movement.
- On the other hand in Parkinson's disease, there is decreased Dopaminergic input which inhibits action in Basal Ganglia. As you have seen earlier, if the basal ganglia is not working the cortex would take over. Therefore the reduced Dopamine in Basal Ganglia then allows cortical areas to stimulate the motor system. There is an increased inhibition of inhibitory BG output, (stimulates

the inhibitory hypokinesia). The damage to Basal Ganglia also results in deficits in Cognitive functions such as deficits in spatial memory, and inability to switch to appropriate behaviour.

Limbic system



Limbic system: ref www.healing arts. Org/n-r-limbic.htm

- **Limbic system:** It borders the Telencephalon, and Diencephalon, in appearance looks like a ring around the Thalamus.It was first described by Broca in 1878. This is also known as the Circuit of Papez, as Papez (1937) first identified it as a reverbrating circuitry which was important in emotions. Limbic areas are spread into parts of the Frontal, Parietal and Temporal lobes. Therefore it appears to have diverse connections and functions. These are mainly emotions but also memory, homeostatic and survival functions (fight, flight, feed, and mating). The areas which are part of the limbic system are: Cingulate Gyrus, Septal Nuclei, Hippocampus, Amygdala, Hypothalamus, Anterior Thalamus, Mammilliary Bodies

- **Hippocampus** like a sea horse lesion- is important in the formation of memories especially long term. If lesioned bilaterally there is damage to learned emotional response and memory is severely affected (both recent and long term). Hippocampus is thus involved in Emotions, memory, homeostatic responses fight/flight, motivational states

- **Fornix:** This is a large fibre bundle shaped in the form of an arch which connects the hippocampal formation to subcortical areas such as thalamus, hypothalamus, and septum. It runs directly under the runs under the corpus callosum (bands of fibers which connect the two lobes)

- **Amgdala:** (almonds: greek) major part limbic system: located at the tip of temporal lobe beneath the cortex and rostrally to hippocampus. Have connections with hippocampus, septum, emdaildorsal thalamus and the prefrontal areas. It is because of these connections that the amygdale is important in emotional responses love, friendship fear, and rage aggression. This is involved in physiological response of emotions: heart rate pulse etc. orienting to novel stimuli, déjà vu. If stimulated of olfactory and gustatory hallucination (temporal lobe epilepsy). Bilateral lesions of amygdala lead to the Kluver-Bucy syndrome: hyperorailty, hypersexuality (animate or inanimate objects) docility, learned fears (and aggression) such as fear of snakes gone as the animals put snakes in their mouth. This accompanied by lack of affect, apathy and blunted

expression. This syndrome was first described by Kluver Bucy in 1939 after bilateral lesions in monkeys

- On the other hand electrical stimulation of Amygdala lead to a rage reaction the amygdale involved in identification of danger therefore is important for self-preservation. When triggered, it gives rise to fear and anxiety which lead the animal into a stage of alertness, getting ready to flight or fight.

- **Septum:** lesion in the septum leads to intense rage reaction (called the Septal Rage) as does stimulation of the amygdale. Septum leads to increased activity in a novel situation, increase reward feeling with stimulation. This also plays am important role in motivational states such as feeding and drinking etc.

Cingulate Gyrus: (Cingulate: encircling) located between the cingulate sulcus and the corpus callosum The anterior area gives rise to déjà vu that is smells and sights with pleasant memories of previous emotions., also important role in emotional reaction to pain and agression cingulectomy tames unruly and wild animals. If a single bundle of this gyrus is cut (cingulotomy) it interrupts the limbic areas communications with each other (reverbratiung circuitry affected) thus leading to reduced depression and anxiety levels (which preexisted in the patients). (Points to ponder- looks like a good option for treatment—but who is to decide?)

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LESSON 29

BASIC NEUROANATOMY

Objectives:
The main objective of this lesson is to study

- The Brain and the Peripheral systems:
- Brain: Forebrain, Mid brain, Hind Brain functioning of each anatomical location in the CNS. Starting from the posterior located areas upto the anterior-most.
- Cerebral Cortex: its layers, Corpus Callosum and the two hemispheres

Main purpose:
Students will come to relate the importance of location of various areas in the Diecephalon and the Telencephalon, their functions and their relationship to other areas. The students would also understand how control and modulation of behavior related to these neuroanatomical site takes place

Diencephalon:
This comprises of two major areas of the brain both equally important in their functions and their involvement in a wide range of behaviors and connection, the hypothalamus and the Thalamus

Hypothalamus: it lies at the base of the brain, on both sides of the 3rd ventricle. It is very small in size a compared to other brain areas but is very important in it s role and function. Hypothalamus is located immediately beneath the thalamus and lies above the pituitary.

Hypothalamus is part of the Limbic system, and in all situations requiring a fight-flight or other survival responses. There are several important fibre bundles passing through the hypothalamus, including the-MFB Medial forebrain bundle which carries major neurotransmitters along with other fibers to the higher areas.

Underneath the hypothalamus lies the superchiasmatic nucleus (SCN). The SCN plays an important role in the day night cycles i.e. diurnal cycles. Within this region we also see the mammiliary bodies which are important in memory.

The hypothalamus also secretes its own hormones which act as releasing factors for hormonal secretions in the pituitary. The neurosecretory cells of the hypothalmic hormones are located near base of hypothalamus, very close to the pituitary. Therefore hypothalamic-pituitary connection is important for the neural and endocrinal connections. The brain talks to the pituitary through the hypothalamus, and vice –versa. All the endocrinal glands communicate for fear aggression, temperature regulation, food and water, and mating. The Anterior hypothalamus is important in thrist regulation and there are important sensors which continuously monitor fluid (and isotonic saline levels) of neurons. The Ventromedial (VMH) and Lateral Hypohtalamus (LH) are involved in regulation of feeding. Research has shown that the VMH is the satiety center (have- enough- food - stop -signal), and the lateral hypothalamus is the center for initiation of feeding. Hypothalamus important in all major survival and maintenance functions; it is related to the management functions of the body and survival rather than intellectual functioning.

- **Thalamus:** this is the largest component of Deincephalon with an ovalish shape; it has two lobes which are connected by the mass intermedia which go through the midline of the third ventricle. The thalamus comprises of large clusters of nuclei. The thalamus is a staging area, information received from sensory receptors systems and other lower areas and then it is projected to the relevant cortical areas. 1. Sensory relay nuclei: All afferent sensory input are received classified, sorted and the passed through the thalamus, these go from the receptor

to the Thalamus which then sends the selected projections to the related cortices. The Visual, auditory input goes through the lateral geniculate nuclei and the medial geniculate nuclei, and somatosensory sensory fibers go to the somatosensory cortices. There is a reciprocal one to one relationship of these connections in the cortex. If one fiber degenerates in the cortex, it would lead to atrophy of the relevant thalamic areas.

- **The Dorsal group of fibers is multimodal** (that is it receives and sends input to different sensory areas). This receives input from within the thalamic regions, and project to the association cortex. There is another group of fibers in the thalamus the Intrinsic or the non-specific. If this area is stimulated it leads to wide spread electrical discharge in the cortex and other areas, evidence that this bundle is important in electrical activity of the cortex. It is involved in sleep awakening as well as attention. It is also important in affective behavior, memory (there is severe amnesia after lesions to midline thalamic area). Thus the thalamus is important in every aspect of behavior.

Telencephalon: The End brain comprises mainly of the areas of the cerebral cortex and some parts of the Corpus striatum, the limbic system. The two hemispheres of the cerebral cortex and the other parts are connected to each other by commissures (bands of fibers connecting the left and the right hemispheres).

- **Corpus Callosum** is the major band of fibers joining the two hemispheres it is wide, white and visible to the naked eye. The commisures are mainly for interaction between the two hemispheres and for crossing over of information (so that the two hemispheres acna coordinate decisions).

- **Cerebral Cortex:** (cortex means outer covering: bark of the brain). This is made up of layers of grey matter which covers the white matter. The thickness of the cerebral cortex varies from 1.5 to 4.5 mm; the average is about 2.00 mm. It is thickest in the primary motor cortex about 4.5 mm thick and thinnest about 1.5 mm at the primary visual cortex. It is laid out in a straight line; the total surface of the cerebral cortex would be about 20 sq.foot. How does this fit into the cranium, it is sqeezed into folds. These folds are irregular convulations and grooves called sulci (for smaller size) and fissures (for large sized). The area lying between two fissures is called gyrus and there is 2/3rds of the cerebral collosum is these gyri. The two major fissures which are used as the dividing/identifying borders are the Central fissure or the Fissure of Rolando separates the Frontal from the Parietal Lobe and Temporal Fissure (or the Sylvian fissure) which separates the Frontal from the Temporal Lobe. The Central Fissure divides Cerebral Cortex into the anterior-posterior (frontal parietal).

There are several types of cortices the neo cortex- the newly evolved areas of cortex, and the allocortex - the older cortex

The allocortex or the paleocortex (/archicortex) is a three layered older cortical structure subdividied into the apleo cortex and the archicortex. These two have very close ties with the kinbic system and the olfactory system.

Paleocortex: (Have the primary olfactory cortex and other areas)

Archicortex (consists of the hippocampal formation) this is similar to the human cerebral cortex in terms of a) connections b) characteristics, c) kinds of neurons found in these areas.

Mesocortex: the middle cortex is found in the cingulate gyrus, parahippocampal areas and also between the iso cortex and the allocortex

Neocortex: the new cortex, the iso cortex, consists of 6 layers which are more recent evolution: organized in one-one: incoming in specific areas. Outgoing in others, association cortex takes care of higher order functions

The higher the evolutionary scale, the greater the neocortical development to the extent that in humans where cortical development is maximal, 90% of the cortex is neocortex. In the primitive or less developed animals the cortical surface is smooth, whereas in the more evolved and sophisticated animals the surface is rough and convulated. In rats the cortical surface is relatively smooth, in the squirrel monkeys it is somewhat rougher and the cortex of the chimpanzees and humans increase in convulations. In humans, rhesus monkeys or chimpanzees have a very large disproportionate, rough surface of the cerebral cortex.

The cortex is organized in a one-to-one manner a) incoming information goes to specific areas (most of the cortex is receiving information) b) Outgoing information is sent out from motor cortex and other relevant areas (visual information sent out by visual cortex) c) Association cortex takes place of other important and higher order functions.

Lobes of the cerebral Cortex:
Frontal Lobe: lies rostrally to the Central fissure, and caudally to the precentral fissure are the primary motor area. The primary motor area is most important in movement of the body. The motor homunculus is the dictionary of motor movements, where each motor movement and muscle is mapped. The body parts are represented in well defined but a disproportionate manner. For, example the tongue and the thumb gets greater representation as compared to the body torso and the extremeties (depending on the evolutionary importance of the areas) Electrical stimulation of specific areas in the primary motor cortex leads to movement in the contralateral area of the body, and lesions lead to contralateral paralysis (as in stroke). Rostral to the precentral sulcus is the premotor area; this is involved in initiating of a movement and changes in the already ongoing movement. Rostral to premotor is the Bordmanns area 8 which is has the frontal eye fields, (for conjugate eye movements). There are other important areas such as the Brocas area which is important in speech articulation and production. If this area is lesioned it leads to aphasia.

Parietal: lies caudally (behind) the central sulcus, and primary somatosensory cortex is located here. The sensory homunculus is mapped in the same manner as the motor humonculus (not in proportion to the size of the body part, but in direct proportion to the needs). Stimulation of the areas leads to sensations of tingling and numbness in the contralateral part. The parietal lobe is also involved in the behavioral interaction of individual with the space around him. If lesioned these lead to sensory neglect of contralteral space (e.g. the patient would shave contralteral half of face, eat half the plate, and not respond to chairs and tables in contralateral half of damage). The parietal is also involved in object recognition, and language comprehension.

Temporal: lies caudal to the lateral gyrus in the superior area and is primary auditory cortex, Wernicke's area important for speech comprehension. The spoken language is comprehended here.

In the inferior temporal lobe, the perception of visual form and color is located (this is in the close vicinity of the occipital and the parietal lobes.

Occipital Lobe: The primary and secondary visual cortex visual processing is carried out here. This is laid out in very well organized layers, in Brodmanns areas 17, 18, 19. This is the striated cortex, i.e.

the layered cortex, where both the left and the right eye images get represented in these layers. Hubel and weasel have identified coular dominance columns.

Cytoarchitectonics: The cellular architecture of the cerbal cortical layers. There are six layers in which cortex can be divided (not on an all or none basis), but it is mainly in terms of the organization of cell layers.

Layers of cerebral cortex

Layer	Cytoarchitecture, name	network	Area	Order of migration
I	Molecular layer	Fibers going in a network fewer interneurons and glial cells	Primary area for synapses	Oldest (cellular)
II	External granular layer	Dense packing of small and medium pyramidal cells and interneurons from other layers.	Dendrites of the pyramidal project to layer 5 and other extensions go deeper	5th wave of neuronal development
III	External Pyramidal (medium and large)	Pyramidal cells which increase in size as the cell layers deepens	Dendrites send extensions to layers 1, axons extend to other deeper layers in the same and contralateral hemisphere	4th wave of the neuronal migration
IV	Internal granular layer (pyramidal and granular)	Pyramidal cells are densely packed. There is stellate and granular cells terminating in this layer	Most densely packed, project to deeper layers, thalamocortical fibers end here	3rd wave of neuronal migration
V	Internal Pyramidal	Large and medium sized pyramidal stellate cells. Betz cells (apical dendrite)	Lowest density as cells sends out projections to other areas.	2nd wave of neuronal migration
VI	Multiform layer	Varying shapes and sizes short axons and dendrites		1st wave of neuronal migration

- The first layer contains cells with horizontal fibers and horizontal cells of Cajal
- Granule cells- Short branching axons and amny dendritic branches
- Pyramidal cells shaped like a pyramid, send axons to layers below cortex. They also have long Apical dendrite which extend to other layers (and even down to the spinal cord) therefore a bigger cell body is need to energize the cell to send messages out for longer extensions and carry messages effectively.

Cerebral Cortex: Two Lobes

There are two independent lobes connected with the commissures. Many researchers have worked on the question do we have two brains or one. Are there two independently functioning brains or do they coordinate as one. Research by Gazzaniga, Milner, Sperry and others has shown that the two hemispheres are specialized for different functions, Speech in left hemisphere (first identified by Broca) and spatial functioning in right hemisphere. Milner carried out the WADA TEST on patients, in this test one side of the brain is anesthetized with slow infusion of sodium amytal through the carotid artey (major artery of the brain). It was reported by Milner that all right handed persons have left hemisphere speech dominance (92%), as their speech stopped with the anesthetization of the left hemisphere.

There are specific disorder known as Aphasias, which are language and speech disorders with left hemisphere damage

The Apraxias are movement disorders which occur when patient is required to perform on a verbal command and fails to do so, even though spontaneously it can be performed.
(Additional references, Graham 735, Gazzaniga, Pinel, Kolb and Wishaw)

- In order to explain the cerebral differences, there are several theories of cerebral asymmetry: Levy and Sperry state that there are two basic modes of thinking: the analytical (LH)/synthetic and the (RH) more gestalts more organized therefore the neural circuitry is differently wired.
- Both hemispheres are equipotential upto two years states Lenenberg, that each hemisphere can take on any role of specialization. However, Kinsberg states that each child is born with specialized functions of the two hemispheres (the planum temporale, in the temporal lobe is large in the left side in the fetus)

The research is ongoing and continues to this day to identify the specializations and roles of the two Hemispheres.

The complexity of the cerebral cortex and that of the mysteries of how each neuron adds up to the behaviours we exhibit are an interesting ongoing journey.

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LESSON 30

BASIC NEUROCHEMISTRY

Objectives:

- Familiarize the students with the Neurochemicals,
- Definition, techniques to study Neurochemical classification Neuromodulators, neurotransmitters, neurohormones.
- Criterion for NT, The process of NT transmission.
- Processes and Interaction within and outside the cellular membrane:

Main purpose:

The main purpose of this lesson is to study the

- **Types of Neurochemicals:** including Neurotransmitter, neuromodulators, neurohormones . Criteria of an NT, Processes of NT transmission from synthesis to degradation
- Importance of neurotransmitters in modulating behaviors and Aberration
- Drugs and Behavior.
- Interaction of Neurotransmitters and Drugs., effect of drug at various sites in the neurons, the NT transmission

Neurochemicals

NeuroChemicals are defined as the chemicals found within the brain, most of them are either manufactured within the brain or are transported to the brain through the blood circulation. These substances needed for biochemical metabolism of cells, ionic movements, enzymatic action, changes in metabolism, neural communication and other mechanisms for support of activities within the nervous system. All neurochemicals have three main characteristics, a) these must be substances with demonstrated electrophysiological activity i.e. changes in electrical/ physiological potential of the neurons and therefore can e measured as changes in the brain areas) These are found only in the CNS or found in very high concentrations in the CNS as compared to the other areas of the system, and, c) Any changes in their concentration levels would lead to changes in the brain and behavioural states.

We can classify the neurochemicals into four major categories based on their chemical composition, their roles and their functions. These are the neuromodulators, neuroregulators, neurohormones and neurotransmitters.

Neuromodulators. These act to modulate ongoing action within the neuronal systems.

Neuroregulators: These substances regulate on going action act as as 2nd messengers in neuronal transmission. They support the ongoing transmission by acing as a gating channel (calcium gated channels)

Neurohormones: These are secreted by the pituitary and hypothalamus, and these hormones act during the regulation of motivational and other states (circadian rhythms, stress) to influences hormonal levels and thereby influence behavior.

Neurotransmitter: These are substances involved in the transmission of neural messages. There are many neurotransmitters which have been discovered so far and their influences on behaviors well known. The neurotransmiter first to be identified was Acetylcholine, (Ach) which acts on the neuromuscular joints.

There were three major breakthroughs in the early 1950's/60's

- The discovery of the monoamines serotonin, dopamine, epinephrine (monoamines) in the brain. These were made by a group of European researchers (Sweden, UK, and Italy) and in the US. In 1950's, 60's brains of patients suffering from Parkinson's disease were seen in post mortem to have degeneration of a specific area, the dopaminergic rich areas. Then those patients of Parksinon's who were given L-Dopa (dopamine stimulant) had a remarkable reduction in Parkinson's like symptoms. This led to the discovery that this Dopamine is important in the Parkinson's disease. See the film The Awakening
- Biochemical procedures for examination of putative NT's were developed. These were sophisticated techniques such as spectrophotoflourescence which made the investigations into the neuronal processes possible.
- Increased interest after the manufacture and use of reserpine form rauwolfia alkaloids, and chloropromazine for treatment (by Roche) and of Lysergic acid diethylmide (LSD), mescaline, marijuana for recreational purposes. The last three were the drugs which beamce the drugs of choice for the hippies and the flower children of the 60's and 70's.
- These breakthroughs opened the doors for investigating neurotransmitters further and it has been shown in the last two decades of the 20th century that a large number of brain chemicals are candidates for neurotransmission. Further, complex chemical interactions are discovered with every new technique which can expand the researcher's ability to search microscopically.

Putative Neurotransmitters are those which are suspected as/ possible Neurotransmitters (NT). There is strong evidence to suggest that status, but these NeuroChemicals have yet to complete the criterion of a NT. These are some 50 neuropeptides (such as brain opioids: endorphins) which are still waiting to be verified. Simialrly, some aminoacids and other chemicals which are found in the brain may be NT, depending upon how well they clear the conditions laid down for the NT status. There are several stringent conditions which are laid down for NT status, these we will discuss in details a little later.

Psychopharmacology as a discipline emerged around the time psychotropic drugs were discovered and manufactured late 1940's early 50's. Psychoactive substances (major tranquilizers, Chloropromazine (CPZ) and Reserpine were found to alleviate symptoms of schizophrenia. This appears to be the first links between drugs and behavior, eventually the discovery that this action takes place in a very minute and specific site. Where does the action take place? In the synapse!

Synapse: The synapse is the junction between two neurons where one is communicating with the other. The usual communication is between the axon of the messaging neuron and the dendrite of the receiving neuron (axo-dendritic), but then there are axo-axonic, axo-somatic synapses as well. Each synapse ahs three amin components the resynaptic ending, the synaptic cleft and the post synaptic ending. This is a very small space (a few Angstroms) within which a large amount of chemical activity is taking place.

Pre-synaptic membrane is a very busy place. It has many synaptic vesicles (storage containers made up of membrane) containing NT, mitochondria to provide energy to the cell as metabolism generators. The vesicles i.e. Storehouses where the transmitter is stored moves from the cell soma to the presynaptic ending. Once the excitatory action potential stimulates the presynaptic ending to action these would fuse with the membrane to release NT through a process known as **Exocytosis**. In Exocytosis the synaptic vesicles blends with the pre synaptic membrane, opens up and ruptures to release the molecules of the Neurotransmitter in the cleft. The rupture eventually mends. The NT molecules spill out in the cleft and travel across the cleft to reach the sites of the post synaptic area

Synaptic cleft: This is a minute space between pre and postsynaptic membranes and is surrounded by the extra cellular fluid. A synaptic web (a fine web like mesh made of glial cells) holds the pre and post synaptic sites together in the same configuration that they exist. This is not an inactive place, there are large numbers of chemicals floating around in the cleft to inactivate NT molecules which have not been able to successfully cross over to the postsynaptic site and which would otherwise be harmful if they remain in this area. After release NT, molecules travel to the post synaptic site. They cannot stay in the cleft and cannot continue to activate the post receptor site even if the passages are open, otherwise once released NT molecules can last a lifetime. Nature has a balance and has mechanisms of cleaning up the debris. The NT molecules have to be inactivated and disposed of so as to leave the passage clean for other NT molecules. The processes of inactivation or reuptake take care of these stray molecules. There are two kinds of inactivating enzymes and we would talk about them in detail later.

Post synaptic membrane: The postsynaptic membrane can either be the cell soma (axo-somatic), dendrites (axo-dendritic) or even axons (axo-axonic) of other cells. These are the receiving ends with appropriate "sites" for: molecules get into these sites to lead to an excitatory post synaptic potential (EPSP) or an inhibitory post synaptic potential (IPSP). When NT molecules get successful entry into the postsynaptic site they change the electrical charge or permeability of the membrane leading to ionic and electrophysiological changes in the post synaptic membrane. These changes depend on a) type of neurotransmitter (some are inhibitory, some are excitatory) b) the neuroanatomical sites on which they are located some NT are excitatory at one location and inhibitory at another b) the amounts of NT released.

The synapse is an area which will be discussed in detail for each NT and the events taking place in the synapse would be related to the action of the NT and drugs which affect the NTsynthesis and metabolism.

Criterion for NT

As discussed there are over 200 candidates for the candidacy of a full neurotransmitter. However, very few have satisfied the scientific and strict criterion laid out which ahs to be fulfilled before a Neurochemcial can be termed as an NT. The putative NT's have to fulfill the following criterion:

1. **Localization:** The presence of the NT molecules has to be identified in the presynaptic ending of the neuron. This is done using the cytochemcial methods such as histoflourescence techniques, autoradiography and later visualizing them using the light and electron microscope.
2. **Storage** of the NT or its precursor in the presynaptic terminal: There has to be a clear evidence of the vesicles which contain the N in the presynaptic ending as well as the presynaptic neuron.
3. **The presence of precursor** (the chemical from which the NT is to be synthesized) and appropriate enzymes for synthesis of NT should be found within the presynaptic neuron. Each neuron independently manufactures its own NT (like a small factory).
4. With the appropriate stimulation the release of the NT should be demonstrated from the presynaptic ending into the synaptic cleft. There should be movement of the vesicles towards the presynaptic area, through the exocytosis, release of NT molecules should take place. This release should be measurable, in amounts of NT released (through the push pull cannulae)
5. **Synaptic mimicry:** Since the NT has a particular chemical configuration, drugs with the same chemical composition, if injected into the synapse should lead to a mimicking(copying) of the Neurotransmitter effect (as if the neuron is stimulated). We can measure using the push pull cannulae, the chemicals and metabolites which can be drawn from the synapse to see if the action was simiar.

6. Recognition of and binding to sites in the postsynaptic areas. Once the NT molecules are released they must travel across the synapse and recognize the sites to which they can bind in that area.
7. **Existence of receptors on the post receptor sites:** there has to be a clear demonstration that there are receptor proteins to bind to the NT, the shape and the form of the receptors should be in the same chemical configurations as the NT (so they match), then the NT can be accepted into the postsynaptic site.
8. **Effect on the post synaptic membrane:** Once it is accepted in the post synaptic site, it should lead to an action whether an EPSP or an IPSP. This would demonstrate the effect of the NT
9. **Inactivating/ Deactivation mechanism:** The released NT molecules have to be inactivated; there must be demonstrated presence of the inactivating mechanisms or processes. These chemicals or enzymes should inactivate the free NT molecules in the presynaptic membrane and the cleft. There should also be a demonstrated reuptake mechanism.
10. **Predictable pharmacological effects:** Endogenous substances with known pharmacological (synthetic) compounds, properties should have the same demonstrable and similar effects.
11. **Post synaptic effects:** enhanced by similar chemicals and blocked by antagonists or blocking agents that is those drugs which are similar should stimulate the NT activity, and those which are anti agents should block its activity.
12. Selective Electrical or chemical stimulation should lead to release of the NT from the prejunctional endings and amount of NT released should be correlated to the amount of stimulation

Thus we see that the criterion for a NT is tough, but ongoing research shows that more and more NT's are joining the list of active NT's. We will discuss the NT more in detail in the next lessons

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LESSON 31

BASIC NEUROCHEMISTRY

Objectives:

To familiarize the students with the

- Various NT and their role in the modulation of behaviors
- Classification of Neurotransmitters. Monoamines: Catechoalimnes and Indolemaine, acetylcholine, amino acid, and Peptide
- Neurotransmitters role in modulation of behaviors and Aberration
- Drugs and Behavior:
- Classification of Psychopharmacological substances
- Behavioral correlates, Treatment:
- Mechanism of synaptic transmission

Neurotransmitters: synaptic transmission

Synaptic transmission can be divided into several clear cut and major steps– these are relatively independent, however each one step has to occur before the next one can take place

1. **Synthesis of the NT and storage in the synaptic vesicles**. As we have learnt earlier that the synaptic vesicles are storage containers where NT is protected from the deactivating enzymes, thus the synaptic vesicles protect NT from degradation by enzymes in cytoplasm. These vesicles are also the safe transporters of the NT. Where do they come from? The synaptic vesicles are manufactured from proteins in the cytoplasm of the cell body by the Golgi apparatus. These then travel down towards the axonal endings to the synaptic buttons. The packaging for Peptides group of NTs (which are short chains of amino acids) takes place in the Cisternas in the synaptic buttons (button or bead like bulbous ends). For the Non-Peptide class of NTs, the packaging into vesicles is carried out within the cytoplasm, before they are transported down to the axonal synaptic buttons. The material can be transported in two different directions by the axonal transport system, the anterograde transport and the retrograde transport.

    - The **Anterograde** (forward) axonal transport is a fast track transport mechanism which moves materials out from the cell body, through the microtubules towards synaptic ending. The synaptic vesicles go through this rapid system traveling very fast speed of 400 millimiteres per day. (It is like driving in the fast lane). This is known as the **fast anterograde transport.**

    - When materials and synaptic vesicles ooze along the axon in the cytoplasm at a very slow speed of less than 10 millimeters per day, they use the **slow anterograde transport**

2. **Release of the Neurotransmitter:** When the action potential reaches the presynaptic ending it is translated into a chemical message (remember the neuronsa can communicate in both systems). The arrival of the action potentials translated using the calcium gated channels. The process is as follows: The action potential arrives at the terminal button; it leads to the opening of the Calcium channels. This allows the calcium to get into the button and to trigger the release of the neurotransmitter. If calcium is reduced in the extracellular space then the amount of NT is also reduced, and it the extracellular Calcium is increased the amount of NT released is also increased. Release is identified to occur through a process called exocytosis.

    a) The NT vesicles move out towards the terminal to empty contents into the synaptic cleft,

    b) The NT vesicles fuse with presynaptic membrane, at contact the membrane opens up and NT molecules are released into the cleft.

c) The vesicle merges as part of the pre synaptic membrane, and the ruptureor the break in the membrane eventually mends

3. **Generation of the post synaptic potential:** this means action at the receiving end at the post synaptic potential after the NT molecule is received. When the NT molecule crosses over the synaptic cleft (it is like crossing over a river full of alligators!) and gets transferred to post synaptic membrane for action. There are several processes which would now take plce at the post receptor sites

a) Binding of NT molecules to post receptor site. All molecules released would rush to reach and enter the postreceptor sites, the entry requires that they must connect or "bind" chemically with the membrane site (a receptor protein). The membrane is very specialized with a particular configuration therefore only those which resemble that shape and chemical composition would bind these sites. This means the gates would open to allow only specific molecules to enter

b) Changes in ionic gates: The NT molecule leads to changes in the chemically gated ionic channels in the receptor membrane for further action either through the direct or the indirect method,

i) **The direct method:** The binding of the NT to a receptor can directly open or close the chemically gated channels in the areas surrounding the membrane (to make it more permeable) or ii) a series of chemical changes can take place in the molecules in the cytoplasm which can bring about a change in the status of the of the chemically gated ions channels of the postreceptor site. These changes take place in chemicals/molecules (2nd messenger, Cyclic Adenosine MonoPhosphate which is involved in conversion of Adenosine triphosphate to CAMP through enzymes. Note: the Cycic AMP is needed for the energy in the cell for action). The second method uses classof molecules which are called the 2nd messenger (because they are the ones which intervenes the messages and translate further action). The effect of CAMP is brief...

4 **Action in the Post Receptor membrane:** In the post synaptic membrane, there are two kinds of actions that can take place, either an excitatory post synaptic potential (EPSP) or an Inhibitory post synaptic potential (IPSP'). The EPSP's generate an action potential in the post synaptic membrane,and the IPSP's inhibit ongoing activity in the cell membrane. Both of these actions depend on a) the type of NT involved, i.e. some NT's are classified as excitatory NT's and some are classified as inhibitory (such as GABA), and , b) the site at which the action is taking place. The NT action may be excitatory at some sites and inhibitory at other sites, as some NT is excitatory at one site and inhibitory at another.

5. **Inactivation of the NT:** What happens to an NT if it is released from the vesicles

a) It cannot stay in the neuron, or in the cleft,

b) It cannot keep activating the post synaptic membrane (otherwise one single dose of amphetamine stimulant can last a life time!!!),

c) It cannot continue to stay in the cleft and keep the site full of molecules. This would clutter the cleft and the sites. The NT has to be removed or degraded so that the systems remain efficient and clean.

There are two well documented processes by which neurotransmitters are deactivated:

- **Reuptake:** By this mechanism the NT can return to the presynaptic areas and be taken in

for recycling and use. The reuptake processes allows the presynaptic area to reuptake and absorb the molecules back. These are then repackaged into the vesicles and used

- **Deactivating:** The active chemical state or composition of the NT is deactivated by chemicals/ enzymes which are specialized to do this job. These enzymes locate free floating unprotected NT molecules in the synaptic cleft (and also in the presynaptic areas) to degrade them and then so that they are excreted out of the cleft. Imagine that these are like the little Pac men running after the little molecules.

6. **Recycling of the vesicular membrane:** The vesicles which had ruptured are recycled. When many synaptic vesicles release molecules after fusing with the presynaptic membrane and the process of exocytosis, the terminal button gets swollen with so many left over vesicles. Then the pieces of excess are broken off and returned to cytoplasm. There these may be used again as packaging material in one of the following forms;

a) They may be filled with non-peptide NT by the cisternas.
b) They may be sent back to the cell body by the retrograde transport (traveling at the rate of 200 millimeters per day.
c) They may be refilled with NT by the golgi bodies in the cell soma
d) They may be broken down and molecules recycled.

Methods of Locating NT:
Apart from the many given techniques of neuroanatomical tracing the following techniques are especially used for the NT localization identifying their sites and their projections.

1. **Histoflouresence Technique:** This was developed by Falck and Hillarp around the early 1960's. In this technique the monoamine group of NT's when exposed to formalin fixative glow when exposed under a flourecent light. This technique was useful in locating the various monoamines, their sites, their systems. However, this is none specialized as it does not differentiate between various NT within the class of monoamines.

2. **Receptor Binding Autoradiography:** The NT are radiolabelled with a radio active isotope (Hydrogen3 or carbon3) Then the neural tissue is exposed to the labeled ligand (molecule that binds to a target). We can also inject this directly into the brain and expose the slices for a longer period after decapitating the animal head and slicing the brain tissues. The slices are exposed to a photographic plate which reacts to radioactivity and high radio active areas show up in the plates.

3. **Monoclonal Antibodies:** These involve immunocytochemistry procedures. Just as the lymphocytes secrete antibodies, and hybrid lymphocytes and bone marrow cells secrete antibodies and subdivide. We can use this same process to identify antibodies for particular proteins (remember all NTs are chains of amino acids). Specific monoclonal antibodies are developed and injected and they identify specific regions and target proteins.

4. **Microiontophoresis (push pull cannulae).** This procedure analyzes the chemicals being released within the synapse. The response of the postsynaptic sites is monitored using a double barreled pipette. The tip of the inner pipette (contains saline) is inserted into the postsynaptic membrane to record intracellular voltage. Weak current when passed to stimulate the neuronal ending leads to a discharge which is then pulled out for analysis, and also checked at the oscilloscope for EPSP's or IPSP's

Major Neurotransmitters:
There are a large number of neurochemicals which have been classified as neurotransmitters; there are six (6) major groups, and within each group there are several independent neurotransmitters which have specific actions. These major groups are as follows:

1. **Amino acids:** These are neurotransmitters which are formed from chains of amino acids, the basis of proteins. In this group the major NT's are Glutamate, Gamma aminobutyric acid (GABA), Glycine (gly), and aspirate. This is the largest group with relatively quick acting synaptic connections. Glutamate is excitatory, while GABA is known as the inhibitory neurotransmitter.

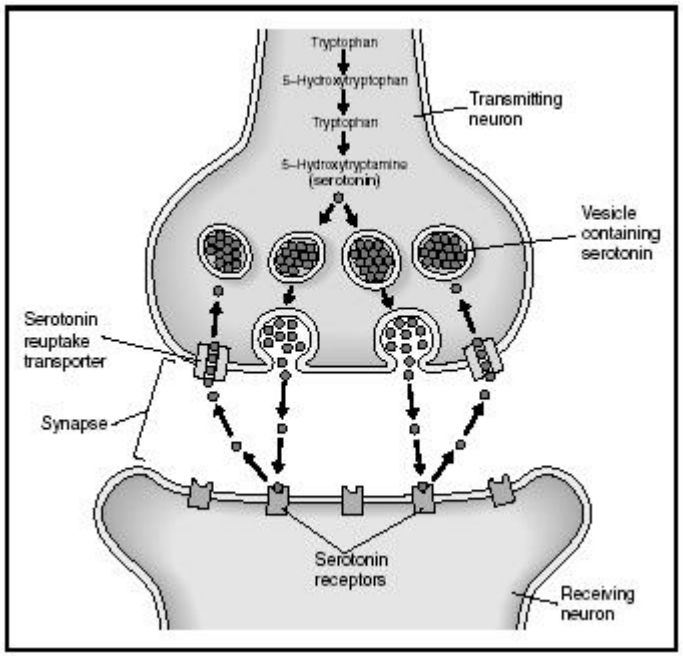
2. **Monoamines I: Catecholamines:** This group of neurotransmitters is synthesized from a single amino acid; therefore this is called mono (single) amine. The monoamines modulate a wide range of behaviors. The neurons of monoamines have little bulbous bead-like knobs throughout the length of the axons, through which the NT appear to seep out. This particular group of Monoaminesis called catecholamines because they have one catechol group. The catecholamines are Dopamine, Norepinephrine (also known as Noradrenaline) and Epinephrine also known as Adrenaline.

3. **Monoamines: Indoleamine:** This also belongs to the monoamine group, but has a different structure attached to the amine group, the indoleacetic acid. The Indoleamine NT is known as **Serotonin**

4. **Soluble gases:** These are small molecule NT. These follow a different mechanism of transmission. Since they are lipid soluble they diffuse through the cell membrane into the extracellular space to pass into the other cells. They work through 2nd messengers and break down immediately after action. Nitric acid and Carbon dioxide are two which have been discovered so far.

5. **Acetylcholine:** a small molecule transmitter,one of its kind—there are no other NT's in this group. This is the only NT which works on the neuromuscular joints

6. **Neuropeptides:** a large number of peptides (chain of 5 molecules) floating around in the brain- and are possible candidates for NT status. Among the well known are the brain opioids, the Endorphins (large molecules) and enkaphalins (small molecules), the pituitary peptides, Substance P and many others



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LESSON 32

BASIC NEUROCHEMISTRY

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To familiarize the students with the

- Various NT and their role in the modulation of behaviors
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Major Neurotransmitters:

Catecholamines: Dopamine

Dopamine (DA) a major catecholaminergic neurtotranmitter was discovered by Udenfriend in 1964. This is the first step in the synthesis chain of the Adrenergic (also known as Epinephrine) and Noradrenergic (also known as Norepinephrine) NT systems, however, this was the last to be given the status of an NT, because DA was thought to be only an intermediatary step in the synthesis of Norepinephrine. Dopamine has been found to have a major influence on behavior, especially motor behavior and schizophrenia. These chemical are also found in the body, in the adrenal glands and used in the sympathetic action in emotional states; however, whatever is produced in the body cannot cross the blood-brain barrier to get into the brain. The brain is very well protected (as you have seen in the last module). In order to keep the environment sterilized, the brain manufactures all the chemicals it needs from the precursors (the first compound in the chain, which can then be acted upon by enzymes). The precursors are taken in from the blood circulation.

The Synthesis chain of DA, NE and E begins with tyrosine (we will discuss this in detail later.
DA has two types of receptors in the brain the D1 and D2

D1.are linked to the stimulation of the adenylate cyclase. These are present in thew Corpus Straitum and the Butrypheneones (a class of drugs known as neuroleptics, anitpsychotics) are weak antagonist for these receptors.

D2. These are linked to the inhibition of adenylate cyclase. These are present in the pituitary and the Corpus striatum. The Butryphenones are potent antagonists for these receptors

DA Pathways: There are three major pathways of this system

1. **The Nigrostriatal DA system.** This is largest and longest bundle of fibers of neurons containing DA. This is a major tract which has 80% of brain's Dopamine It originates in the Zona Compacta of Substantia Nigra and sends projections to the Corpus Striatum. The degeneration of this systems leads to Parkinson's disease (a major motor disorder in which voluntary movements become increasingly difficult and there are only some stereotypic movements seen). This is also involved in schizophrenia. Reduced levels of DA in this system lead to Parkinson's disease and increased levels lead to schizophrenic symtoms.

2. **Mesolimbic:** This is a medially located diffuse (wide spread out projections) systems. This system sends out nerve fibers which go out to the forebrain areas such as frontal cortical area, the cingulated cortex, the amygdale and the septum. As the names implies this is

involved with the limbic system (emotional system). The anti psychotics drugs act here to reduce the apathy and lack of affect (emotional content) which is characteristic of schizophrenia.

3. **Tuberoinfundibular**: This is also known as the hypothlamic –hypophyseal connection. It originates from arcuate and periventricular regions of hypothalamus, and there are very short fibres which end up in the intermediate lobe of the pituitary. This appears to play a role in the hormonal controls and modulations.

Dopamine is also found in other areas in the brain

Synthesis Pathway. As a rule it must be remembered that the brain manufactures its own neurochemicals including Dopamine from the precursor taken in from the blood supply (circulatory system**).**

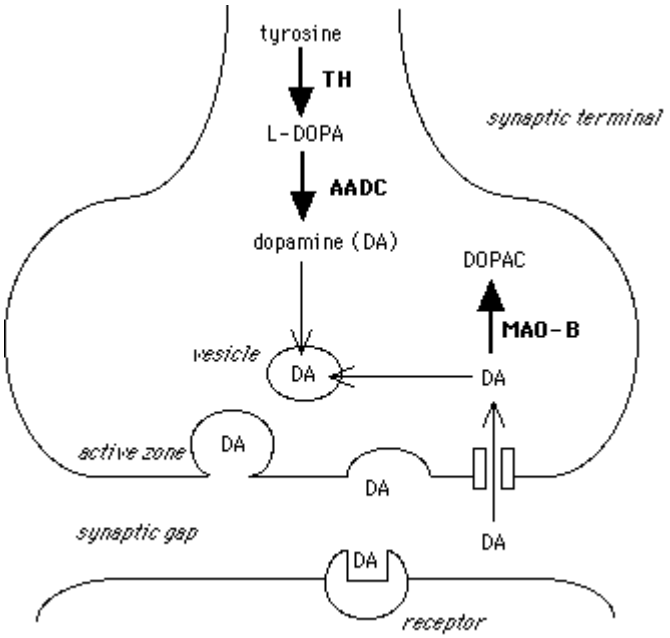
1. **Phylalanine** which is taken in from food and is immediately hydroxylated (add a hydroxyl molecule) by the enzyme phylalanine hydroxylase to convert to Tyrosine

2. **Tyrosine:** tyrosine is then immediately hydroxylated *by* tyrosine hydroxylase. This is known as the rate limiting step (and is sensitive to pharamoclogical manipulations), we can control the amount of DA (as well as NE, and E) manufactured in the systems. This hydroxylation leads to the formation of ***DOPA***

3. **Dopa:** This is similar to a drug known as L-Dopa, effective in the treatment of Parkinson's. Dopa is then decarboxylated (removal of the carboxyl molecule) by the enzyme dopa decarboxylase, to form Dopamine

4. **Metabolic degradation**:

a) Dopamine is then metabolized by Monoamine Oxidase **(MAO)** which converts monoamines to aldehydes to make them inactive. Monoamine oxidase is not specific for dopamine, but acts on all mono amines NE, E, and serotonin. This is found in the presynaptic region.
b) COMT- catechol O methyl transferase, acts to transfer the methyl from the catechol molecule to deactivate it. This is found in the synaptic cleft as well as the presynaptic areas



http://tcw2.ppsw.rug.nl/~vdbosch/pd.html#Heading18

Pharmacological interventions: Step where DA synthesis pathway can be blocked or altered

It is clear that pharmaceutical substances/ drugs act in the central nervous systems through the neurchemical systems.
confer
Agonists: are drugs that copy / mimic the action of the neurotransmitter or have similar effect as the NT or have an excitatory effect on the NT systems.

Antagonists: are drugs that block, inhibits or in any way opposes the action of the NT.

Drugs: or exogenously administered substances can affect the NT pathway at various levels

a) They can act directly on neurons containing the NT
b) They can act on various points of the synthesis pathway the pre-post receptor site
c) They can act on the inactivating enzymes in the cleft or within the presynaptic area.

Steps where drugs can interact in the synthesis pathway

Step 1: This is first step in the precursor transportation pathway within the neuron. Phenlalanine has to be hydroxylated to form tyrosine which would then be available for the synthesis into DA. However, this conversion can be blocked as in the case of the genetic disorder PKU (phenylketunuria) where Phenylalanine is build up and transforms into toxics which damage the brain cell. The PKU buildup blocks the transport of both tyrosine and tryptophan in the brain. Therefore no tyrosine, no DA!

Step 2: This is where the enzymatic synthesis of Dopamine begins. Tyrosine is the first amino acid in the chain of metabolism of catecholamines and is the most susceptible to blockade. The hydroxylation action can be blocked by A-Methyl Para Tyrosine (AMPT) which methylates the tyrosine (instead of hydroxylation). This reduces the level of Tyrosine available, which then leads to

reduced Dopamine, Norepinephrine and, Epinephrine. AMPT is effective in reducing catecholamine levels in the brain.

Step 3: Conversion of DOPA into dopamine by dopa decarboxylase can be blocked by a false enzyme A-methyl dopa. This enzyme competes for DOPA and uses it so that it cannot be converted in the correct form in order to become dopamine
Step 4: Storage vesicles: The storage vesicles are packed with Dopamine. Reserpine, a drug manufactured from Rauwolfia Alkaloids is classified as a major and long lasting tranquilizer. Reserpine ruptures all vesicles irreversibly and the contents get spilled out into the presynaptic area where they get deactivated if they do not get out into the synaptic cleft. These vesicles cannot be repaired till new vesicles are manufactured; therefore no DA molecules can store. Another drug, Tetrabenazine also opens up the vesicles and blocks reuptake of DA into the vesicles. However, this is not irreversible as the vesicles are not ruptured only opened up.

Step 5: This is where the release of the Nt for the presynaptic ending, and the reuptake back form the synaptic cleft can be blocked. The drug Amphetamine (a stimulant) releases and blocks the reuptake of DA for a prolonged agonistic action. Similarly, Cocaine (another stimulant, and street drug) and Tricyclic group of antidepressant also block reuptake of DA, NE

Step 6: Action within the neuron, axonal ending and the synaptic cleft. The deactivation process can be blocked by drugs which block action of MAO. The drug Pargyline, and MAOI, can increase amount of DA available by blocking the deaminating process (blocking the blocker!).

Step 7: The post receptor site-can also be blocked or stimulated. Apomorphine is a DA receptor stimulant at pre and post receptor sites and thereby increases the levels of DA available for action. Haloperidol which is a potent antipsychotic drug is a DA blocking agent.

Therefore drugs can be used to modify the action of the neurochemcicals at the various sites of synthesis pathways.

DA and Behaviors

The behaviors that are affected or modulated by the DA systems would be discussed in details

Dopamine and Motor Activities:

SN and Corpus Striatum. The Dopaminergic Nigrostrial system is atypical in the CNS format that SN fibers do not cross over to the contralteal hemispheres i.e. they remain on the same side of the brain. This system innervates the extrapyramidal structures (the basal ganglia) which controls motor behavior at the sub cortical level.

A) Damage to SN leads to Parkinson's disease. This was first discovered by pathologists who reported that the SN of Parkinson's patients was pale as compared to normal brains. The dopaminergic neurons in Substantia Nigra have dark pigmentation; therefore the pale SN indicates damage to the DA neurons. Thus, reduced levels of DA in SN leads to Parkinson's symptoms.

Logically it can be assumed that if we inject dopamine in these patients we should see a reduction in Parkinson's symptoms. This is exactly what happens if we increase levels of Dopamine by injecting Dopa (or L-Dopa) in SN.

B) Evidence that rats injected with **6-OHDA** a toxic agent which selectively damages only the DA pathways and neurons by retrograde transmission, exhibit the same symptoms as in Parkinson's (rigidity, tremor, etc). This also indicates that DA is involved in Parkinson' as well as motor behavior

C) If DA levels are increased in animals or humans by injections of L-Dopa, it leads to stereotypic (repetitive) motor behavior. The stereotypic behavior is a symptom of higher than normal levels of DA in the brain. In rats we see repeated running back and forth, or grooming their faces with their paws or any other motor activity. Stereotypic behavior is also seen in human Parkinson's patients who are treated with high doses of L-Dopa. Furthermore, apomorphine and amphetamine (both strong agonists of DA) at high enough doses lead to stereotypic behaviors.
D) Injections of Haloperidol& Chloropromazine (anti psychotic drugs which block DA activity) block the stereotypy induced by the amphetamine injections. This means the following:
Increase DA by amphetamine-> Stereotypy,

Block DA.by Haloperidol-> Reduce Amphetamine induced stereotypy

E) Unilateral lesions of 6-OHDA lesions lead to a symmetry in body postures that is the body becomes lopsided. The body turns from the side with high DA to the side with low DA. This lopsided body posture is exaggerated by amphetamine and apomorphine (Ungerstedt et al, Najam 1980). So if we lesion the right side, the body turns from left to right (right side has lost its DA) On the other hand, unilateral electrical stimulation in the intact brain also lead to same kind of body asymmetry. If we stimulate the right side, then the posture would be lopsided from right to left. The body Postural asymmetry is from side with more DA to the side with lesser DA

F) Bilateral Lesions with 6-OHDA lead to a compelte reduction of DA in the brain. Animals with bilateral lesions do not eat, (aphagia) drink (adipsia), and cannot survive. They recover feeding only is forcefed.

Dopamine and Depression

- It is very well researched that Antidepressants such as Monoamine oxidase inhibitors (MAOI) and the Tricyclics both increase the levels of DA
- Alpha methyl para tyrosine (AMPT) if injected reduces both the NA, DA levels in the brain. If we then inject MOAI, there is reduced effectiveness of the anti depressives effect of MAOI. This indicates that some levels of DA is needed in the brain (However, evidence indicates that these have greater interaction with NA than DA (Desipramine an antidepressant has no effect on DA neurons, and Tricyclics also greater interaction with NA).

Dopamine and hyperactivity
Hyperactivity is due to increased levels of dopamine in the brain. This is also seen with injections of Amphetamine and apomorphine.

The market drug **"speed"** is actually amphetamine, which users take to feel tireless and increased energy and euphoria (I can conquer the world feeling!)

Dopamine and Schizophrenia
There is strong evidence that DA is involved in Schizophrenia.

1. Drugs which are effective in treatment of schizophrenic symptoms are strong DA blockers. The more effective the drug is as a DA blocker, the greater would be its anti –psychotic potency/efficacy in treating the symptoms.
2. The greater the efficacy of treatment (reducing DA) the greater the side effect of

extrapyramidal symptoms (Parkinson's like tremor, rigidity). The extrapyramidal symptoms such as body tremors appear because DA is decreased postsynaptically. The DA synapses are blocked by these antipsychotic drugs such as Phenothiazines (largectil and haloperidol: haldol)

3. The patients of Parkinsons when treated with L-Dopa start exhibiting symptoms of schizophrenia- as a side effect of the treatment
4. Chronic users of amphetamine end up with symptoms of paranoid schizophrenia

Therefore DA is important in a wide range of behaviors, from motor activity to schizophrenia

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LESSON 33

BASIC NEUROCHEMISTRY

Objectives:

To familiarize the students with the

- Various NT and their role in the modulation of behaviors
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Major neurotransmitter: Catecholamines

We have already discussed one of the catecholamines, Dopamine which is first in this chain of synthesis. Dopamine is the preceding step in the synthesis of Norepinephrine NE, (also known as Noradrenaline NA, which is the abbreviation used in this section)

Norepinephrine/ Noradrenaline

One of the major neurotransmitters of the brain this NT fall under the general category of monoamines, further categorized as catecholamine because of its chemical composition. In this system synapses are known as noradrenergic synapses, NA is found in various parts of the brain as well as the autonomic NS (in the hypothalamus and the mid brain) in the Peripheral nervous system (very important role in the sympathetic functions and hormonal releases : readiness for fight or flight) and at the adrenal glands.

This is involved in a large number of behaviors with a wider influence as compared to DA. The involvement in mood, emotional states, motivation (hunger, thirst, fight/ flight etc) dream, rewards (learning), sleep alertness and wakefulness is well documented.

NA originates from a small group of neurons located in the back part of the brain and project by sending fibers and axons to widespread region of the brain. This is why it is involved in so many behaviors.

The Noradrenergic synapses lead to Inhibitory Post Synaptic Potentials in the Central Nervous System and Excitatory Post Synaptic Potentials in the Autonomic Nervous System (which includes the sympathetic nervous system), and the target organs (such as the heart).

The Noradrenergic neurons do not release NT from terminal buttons (as other NT's do) instead of it they release NA through the axonal varicosities, which are beadlike swelling of axonal branches. The varicosities give the axonal branches of NA neurons the appearance of beaded chains or like a necklace of beads). NA is synthesized or manufactured in the adrenal medulla and the brain from DA. Remember that the brain manufactures all NT's, and therefore NA also independently. Even though large amounts of NA is manufactured and used in the body, it can not cross the blood-brain barrier to enter the brain.

NA synthesis

1. Synthesis: This is a simple one step process for transforming Dopamine into NA. Dopamine is hydroxylated by **Dopamine B-hydroxylase**. This enzyme was discovered in 1960 in the adrenal medulla, and this is the same enzyme which acts on DA in the brain. The synthesis from DA to NE takes place within the vesicles (unlike other NT's where this is carried out in the cell body).

2. Dopamine is hydroxylated by Dopamine B-hydroxylase, to form Noradrenaline. This hydroxylation process can be blocked by Disulfiram. The blockade leads to a buildup of DA (since the tyrosine is being converted to Dopamine) at the same time this reduces NE levels in the neurons, and therefore in the brain.

3. Deactivating Norepinephrine by MAO and COMT leads to following:

The metabolite after the breakdown of NE occurs in two ways
a) It forms the Vanylmandellic Acid (VMA), a metabolited which is found mostly in the body, very little in the brain (as it is excreted quickly).

b) The MHPG, a glycol derivativethe (abbreviation of 3 – methoxy-4 hydroxy phenylglycol). This metabolite is found that in stress there are increases in amounts of MHPG in the locus coerelleus.

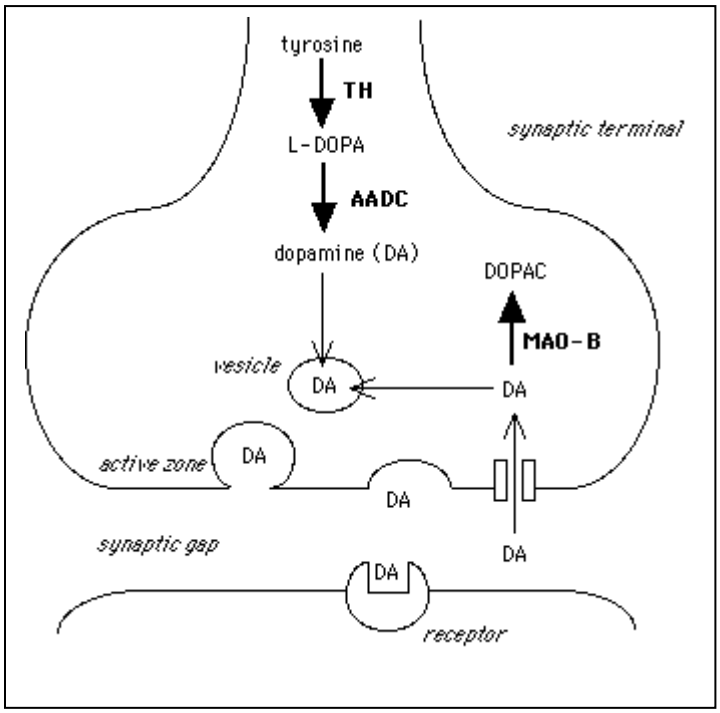
Noadrenergic Pathways

There are two major pathways of NA– the Dorsal bundle and the Ventral bundle with several pathways projecting in each one of these. The pathways are known as a 1, 2,4,5,6, and 7. All these originate in the lower brain areas and ascend to the cortex i.e. they originate in the Pons and the medulla and ascend to the cortical areas, the limbic systems and the hypothalamus.

The A 6 comprises of the dorsal bundle which originates in one area, the locus coerelleus located on the ventral areas of the ventricles, and sends out diffuse innervations to cerebellum-cerebral cortex and hippocampus through the Medial Forebrain Bundle (MFB). This therefore is involved in sleep, awakening, moods, neuro endocrinal functions and temperature regulation.

The A 1, 2, 4, 5, and 7 are the various points or locations from where the ventral bundle originates in the pons, medulla and innervates the brain stem and the hypothalamus

The ascending fibres of A 5 and A 7 project to the cortex, hypothalamus and are part of the limbic system (hippocampus and septum whereas the descending fibers go down into the spinal cord



Receptors. There are types of NA receptors identified by their sensitivities to various drugs: the Alpha receptors and the Beta receptors

a) Alpha1 and Beta 1 are found mainly in the post receptor membranes

b) Alpha 2 is primarily presynaptic autoreceptors (these emerge out of the presynaptic membrane area to monitor and control the levels of the membrane by a self inhibiting action). It is like the one hand of the same person holding the other hand

(for support and for control)

c) Beta 2 receptors are found in the CNS but are associated with glia cells, muscles, and walls of blood vessels.

Receptor

A1- these receptors are located post synaptically on blood vessels and in the spleen and peripheral tissues: Prazosin, Indoramin selective antagonists which work near the heart. So these receptors carry the commands of the brain directly to the organs

A2 – these receptors are located on presynaptic nerve terminals in the periphery (not in the brain): Yohimbine is a selective antagonist (stops/blocks action of NA) and clonidine is selective agonist. These receptors are also located in the pancreas.

B1: these receptors are linked to stimulation of adenylate cyclase. These are found in greater numbers in the heart and cerebral cortex. Epinephrine and NE potent agonists. The presence of these receptors vary a lot in the brain region

B2: These receptors are linked to the stimulation of adenylate cyclase. This is found in high concentration in the lungs and the cerebellum. For these receptors E is more potent than NE. The drug salbutamol is a selective agonist

Steps in NA synthesis where drugs can modulate action:
As discussed earlier we saw that there were drugs which interacted specifically with the DA synthesis, in the same way we will see how drugs interact and modify the working of the NA synthesis process.

Step 1: Enzyme Synthesis:
a) The first step where this neurotransmitter can be modified is at the level of sysnthesis of Tyrosine. The hydroxylation of Tyrosine by Tyrosine hydroxylase can be effectively blocked by Alpha Methyl Para Tyrosine AMPT: This is the same process as in Dopaminergic synthesis. Since Tyrosine is the precursor for both DA and NA therefore this is the rate limiting step for NA as well. Reducing available Tyrosine by AMPT would reduce both DA and NA
b) The second step in the enzymatic synthesis is where Dopamine B- hydorxylase action on dopamine is blocked by a substance known as Disulfiram, and another drug labeled as FLA-63. Both allow a buildup of Dopamine but conversion to NA cannot take place as this is blocked by the drugs

Step 2: Storage vesicles: The two drugs which interfere with the storage vesicles are Reserpine, and Tetrabenazine. Reserpines effects on the storage vesicles are long lasting- thereby the effect on NA is also longlasting. Further, the storage vesicles are irreversibly damaged, and forming new one take time. Tetrabenazien also interferes with the storage vesicles, but this is neither long lasting nor irreversible effect.

Step 3: Release: The release of NA is affected by Amphetamine which increases the release of NA molecules from the presynaptic area, and also blocks reuptake for enhanced and long lasting effects.

Step 4: Post receptor site interaction: This involves interaction at the post receptor sites. This could be agonistic- meaning that they stimulate these sites, or antagonistic when they block these sites. The drug Clonidine is very potent receptor stimulant (agonist), and Phentolamine is an A-blocking agent, and Sotalol a B-blocking agent

Step 5: Reuptake: The action of NA molecules can be stopped by their reuptake into the presynaptic area (and back into the vesicles). The drug Desipramine belonging to the tricyclic antidepressant group, acts through blocking reuptake of the NA molecules (thereby enhancing NA levels in the synaptic cleft)

Step 6: The NA or DA molecules floating in the presynaptic area are degraded or broken down into inactivated forms by MAO. This degradation by MAO blocked by the MAO inhibitors (which inhibit the action of inhibitor) leads to an increase in its levels. The antidepressant drug Pargylin is a potent MAO inhibitor it acts to block MAO action.

Step 7: Norepinephrine can be inactivated by the enzyme COMT in the synaptic cleft. The drug Tropolamine blocks COMT action.
(From Cooper Bloom and Roth pages 180-182).

Thus we have seen the steps in the synthesis of NA which can be modified by drug action. These drugs are mainly psychotropic drugs (act on the psychological states).N

NE and Behaviors:
We will now proceed to discuss the behaviors which are affected, modified changed or controlled by Norepinephrine /Noradrenaline

Arousal:
The behavioral arousal and arousal of electrical activity in the brain is correlated with Increases in NE by MAOI. Thus Momonamine oxidase inhibition leads to an increase in available NA which leads to increases in arousal as seen in behavioral excitation and EEG activity. Furthermore, in states of stress NA levels are also increased. In states of stress where a person cannot go to sleep (stays awake for long periods because of stress), the NA levels are also increased in the brain. It is clearly only NA involvement (No DA involvement- complete depletion of striatal DA still leads to waking and sleeplessness)

If NA is injected intraventrically (directly into the brain) also leads to behavioral excitation. This means that increases in NA leads to a state of arousal, excitation, and increased activity.

NA: Conditioned Avoidance
There is evidence that NA is involved in conditioned avoidance in the learning and conditioning paradigms. If we inject Reserpine (which ruptures the vesicles to spill out the NA molecules) and also Alpha Mehtyl paratyrosine to block any further synthesis of tyrosine (and DA and NA) we find complete abolishment of a learned conditioned avoidance of electric shock. (The animal had earlier learned to avoid shock, but with no NA the response is gone). Thus this shows that NA plays an important role in avoidance behavior. How? Through either the reward and punishment mechanisms or through the learning and memory centers being affected.

How do we make sure that it is only decreases in NA which leads to this response? If we give Disulfiram or FLA-63 which will increase DA but decrease NE by blocking the synthesis of NE. we also abolish the learnt avoidance response.

Thus we have seen that NA is an important NT and is involved in a wide range of behaviors.

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NE and Behaviors (continued)

Stress:

There are various ways in which stress can be induced in the laboratory. One of these methods is to give continous and inescapable shocks. Rats are placed in a cage with a steel wire grid on the floor. Shock is passed through these to the rat's feet (the paw and feet are the only part apart from their nose which does not have fur protection). Stress induced by foot shocks (stress) lead to increased NA levels and turnover in the hindbrain. The turnover rates increase means that more and more NA is being used and being metabolized. This has been measured using the push pull cannulae. Various pharmacological procedures have also shown that only NA increases after footshock.

Similarly, Electroconvulsive therapy also leads to increased NA levels in the forebrain

Trauma of all kinds also increased NA activity in the brain.

NA and Feeding

Feeding is one of the basic motivations of animals. The NA systems also are involved in the control of feeding behaviors. If NA is administered directly in Lateral Hypothalamus leads to increased eating in animals which have already eaten to the point of satiation (they are full and they stop eating in the normal state). How do we know it is NA only? When we inject drugs which specifically for block NA, the NA induced feeding is also blocked (no NA, no feeding!). This is demonstrated by injections of Phentolamine (A-adrenergic blocker), which leads to a blockade of NA induced feeding. Liebowitz (1971), a well known researcher has shown through her experiments that NA may be acting to reduce the inhibition of the normal inhibition of lateral hypothalamic feeding center by the Ventromedial hypothalamus (VMH). So, the LH starts the feeding and the VMH stops it (by telling LH to stop sending signals for eating). When NA is injected it stops the inhibition of VMH, so that messages of feeding can continue.

NE and self stimulation: ICS

Positive Reinforcement or "reward" is linked with NA. Learning and conditioning using positive reinforcers or rewards are linked to intercranial self stimulation or the self stimulation. Positive ICS areas are areas in the brain where implanted electrodes would get maximal response of self stimulation by the animals. The animals would repeatedly press levers for electrical stimulation to these areas in the brain. These areas closely correspond to distributions of NA and DA systems, indicating that these neurotransmitters are modulating the reward behaviors. If we inject alpha methyl paratyrosine, we reduce the amounts of tyrosine, DA and NA. This injection also blocks the self stimulation response in animals which were stimulating before the injection of AMPT.

How do we know which one of these two neurotransmitters is involved, logically following it we would use a drug which would block only DA, or only NA, or 5 HT one by one after AMPT.

When we do so, we see that the AMPT blockade is reversed by the Alpha receptor agonists of NA, not by B-receptor agonists or DA agonists or 5HT agonists. Thus, showing that NA is involved. Researchers have also used the Push pull cannuleas in Ventricle to pull out the metabolites after self stimulation. It was reported that with the self stimulation leads to an increase in the release of NA. Further it has been shown that the NA Dorsal bundle is more than the Ventral bundle

NA and Depression
The effectiveness of Monoamine Oxidase Inhibitors in treatment of depression has provided support to the Catecholamine hypothesis of Depression, and in particular the involvement of NA. This involvement is indicated by the fact that long term anti depression treatment in animals leads to a reduction in NA stimulated cyclic AMP– (Beta receptors involved). This indicates that more NE stays available (as it is not degraded) therefore less needs to be released.

Antidepressant also increases the synaptic availability of NE (more NA becomes available). Reserpine (which has been used for treating mental illness in the Indian subcontinent since ages) when injected inot the brain leads to depression like syndrome (remember, it destroys the storage vesicles and depletes NE, DA and 5HTfrom the presyanptic membrane). Iproniazid (which is an MAOI and an effective antidepressant-) when administered increased brain concentrations of NE and 5HT. Thus showing that NA is involved in depression, as decreases in NA lead to depression, and reward behaviors as depletion of NE reduced self stimulation

Major Neurotransmitters: Monoamines: Indolamines

Serotonin: Indolamine (also known as 5 hydroxytrytamine or 5 HT)
Serotonin is one of the major neurotransmitters of the brain with an important role in several behaviors (ranging from sleep to depression). The neurons are known as serotonergic neurons and the pathways as sertonergic pathways. Scientists had known since the mid 19th century that there is a substance involved in powerful contraction of the smooth muscles. Later, this was also found in the Ohio research labs to be the possible cause of high blood pressure, in American labs, this was called serotonin around the same time Italian scientists were trying to identify the substance in the intestinal mucosa, and also of the gut which led to powerful contractions of smooth muscle of the intestinal tract. This substance was called Enteramine by the Italian scientists. This substance is also found in clotted blood. These two groups of scientists eventually found that this substance was identical to 5 hydroxytryptamine (5HT). This has a strong resemblance to Lysergic acid diethylmide (LSD) molecule

In the brain 5HT is synthesized in the same way as NE and DA from the precursor which is taken from the circulating blood. The precursor for 5HT is Trytophan, which varies according to the daily intake of the tyrtophan rich foods (milk, red meat, fruits such as bananas pineapples etc.). The body and the brain both have a high concentration of 5HT, where it is synthesized independently. About 90% of 5HT is found in the gastrointestinal area (in the enterochromaffin cells of the intestine) and only about 1-2 % in the brain. The highest concentration of 5HT in the brain is found in the pineal gland. The Pineal gland is a very small organ lying on the dorsal surface of the thalamus. The pineal contains all the enzymes for the use of serotoninin addition to two other enzymes for transformation of serotonin. The pineal contains about 50% more serotonin per gram of the brain that the rest of the brain areas. (Wonder why?). The extension of pineal serotonin is Melatonin. In the pineal, Tryptophan is transformed into N-Acetyl Serotonin, which is then transformed into Melatonin. Melatonin is the substance which you see when your skin gets darkened by the sun (more melatonin,

more pigmentatiom). Melotonin secretion is enhanced by light and suppressed by darkness. Thus, Melatonin content is affected by the Light Dark (L/D cycles) and this bring daily and seasonal changes in the 5HT content in the pineal and the brain.

We will talk more about serotonin's involvement in day night cycles (sleep), in the later part of this lesson.

Serotonin Synthesis:
We will discuss the synthesis of serotnonin and where it begins and the enzymatic actions which occur. We must be again very clear that the brain synthesizes its own serotonin from the amino acid

1. Trptophan: This is the first step in the synthesis pathway. Tryptophan enters the cells but in competition with phenlalanine (daily variation depends upon the consumption of tryptophan rich foods)
2. Hydroxylation of Tryptophan: This is the rate limiting step. The hydroxylation of tyrptophan takes place immediately at the 5th position of the molecule to form 5- Hydroxytryptophan or 5HTP. The enzyme involved in this action is Tryptophan hydoxylase. This step can be blocked by a drug called Parachlorophenylalanine (PCPA). PCPA competes with tryptophan for this enzyme and binds irreversibly with this enzyme. In rats one injection of PCPA of 200 mg/kg depletes brain 5HT drastically (to about 20%) and recovery to normal levels can take weeks.
3. Decarboxylation: 5HTP is immediately decarboxylated to form 5HT. The decarboxylating agent is the one similar to Dopa (he same protein is used in the Catecholamines and Serotonin neurons for decarboxylation). The enzyme L- Amino Acid Decarboxylase is involved in this action.
4. Deactivation: Serotnin is deactivated or deaminated by Monoamine Oxidase (MAO) as in the other monoamines. The metabolite of this action is 5-Hydroxy Indole Acetic Acid (5-HIAA)

Serotonergic Anatomical location and Pathways
Though attempts had been made to identify the pathways of 5HT, it became possible only after Falck and Hillarp's formaldehyde induced fluorescence histochemcial procedures became well known, and through the immunocytochemcial methods (through retrograde transport), and procedures using radiolabelled amino acids taken up by the orthograde axoplasmic system when injected into the neurons. Dahlstrom and Fuxe (1964) and other researchers identified about nine clusters of 5HT neurons in the nuclei of the raphe system located in the midline of the pons and upper brain stem. These are spread out like islands (or a bunch of grapes).

Ascending 5HT bundles travel through the Medial Forebrain Bundle with terminals in the reticular formation (You will find out later why this connection is important), hypothalmus, lateral geniculate nuclei, preoptic area, hippocampus and the cortex (crucial role in sleeping and awakening). These also project into the telencephalon and the deincephalon, and descend into the spinal cord (Cooper, Bloom and Roth, 7th edition)

Pathways:
There are several serotonergic pathways each with their own connection and receptors. Nuclei Raphe comprise of several different groups. The Dorsalis, Superior and Magnus nuclei pass through the MFB.

- **Nuclei Raphe Dorsalis:** The serotonergic receptors here are B7. It sends projections to the Neocortex, Olfactory bulb, Thalamus, Amygdala, Hippocampus, Substantia Nigra and the Locus Cerelleus

- **Nuclei Centralis Superior:** The serotonergic receptors are known as B 8. They project to the cerebral cortex, hippocampus, superchiasmatic nuceli (SCN) anterior hypothalamus, medial preoptic area, and the raphe dorsalis.
- **Nuclei Raphe Magnus:** The serotonergic receptors here are B3. They extend to medulla and the anterior hypothalamic area
- **Nuclei Raphe Obscurus:** This is an interesting pathway as the powerful hallucinogen **LSD** acts here. The receptors here are known as B2
- **Raphe Pallidus**– has B1 receptors, it contains substance P (a peptide) involved in Pain, goes down into spinal cord

Steps in 5HT synthesis where drugs can modulate action

Step 1: Synthesis by enzyme: Tryptophan is converted into 5 hydoryxytryptophan by tryptophan hydroxylase in the serotnergic neuron. This process can be blocked by the action of PCPA which uses up the hydroxylating enzyme

Step 2: Storage: Reserpine, a major tranquilizing agent affects DA,NE and 5HT storage vesicles by irreversibly damaging the storage vesicles. It is not clear whether DA, NE and 5HT responsible for behavioural depression.

However, researchers have found that when Reserpine is administered along with 5HTP or DOPA, there are increases in sedation (induced by reserpine). Injections of PCPA (removed 90% of the brain serotonin) before reserpine, no behavioral effects of reserpine were seen.

Step 3: Release. There are no drugs which are specific serotonin blocking agents, but a major hallucinogenic drug Lysergic Acid Diethylmide LSD potentiates serotonin effects in low doses. LSD inhibits the release of serotonin by blocking the firing of serotonergic neurons (indirect blocking)

LSD in high doses- led to an increase in 5HT levels by reducing break down of serotonin (measured through reduced metabolites i.e. 5HIAA)
Increase LSD dosages reduced 5HT turnover rates, how?
1) Serotonin receptor sites occupied
2) Inhibit serotonin production by blocking action of 5HT
3) LSD appears to decrease the release of 5HT

Step 4: Receptor Interaction: LSD acts as a partial agonist at the receptor sites of postrecpetor membrane

Step 5: Reuptake: serotonin action can be terminated by reuptake in the presynaptic area. Tricyclics such as Imipramine also increase 5HT levels by inhibiting reuptake. The Selective serotonin Reuptake inhibitors (SSRI's) are effective for treatment of anxiety.

Step 6: degradation by MAO can be inhibited by MAOI. Iproniazid blocks MAO action in the epresynaptic area

Thus we have seen that in a manner to other neurotransmitters, drugs interact with 5HT at various sites and can modulate levels of 5HT, and these drugs are also effective in treating psychopathology.

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Main purpose:

We continue our discussion on the control and involvement of 5HT in behaviors

5HT and Behaviors:

We will now proceed to discuss the behaviors which are affected, modified changed or controlled by 5HT

There are some very important behaviors regulated by 5HT ranging from temperature regulation to sleep, anxiety and depression

1. Temperature regulation: temperature regulation is an important motivational behavior dependent on the day and night cycles. If 5HT is injected intraventrically it leads to increased body temperature. PCPA is injected to deplete brain serotonin and after this depletion, raphe nuclei are electrically stimulated no rise in body temperature take place. The body temperature would otherwise rise with the stimulation of raphe nuclei (increased serotnonin,leads to increasedbody temperature).

2. Sensory perception: 5HT involved in producing the heightened sensory and visuomotor hallucinogenic effect of LSD. We have talked about LSD effects take place through the serotonergic system. Injections of PCPA(which depletes brain serotonin), reduced motor activity, and reduced emotional reactivity, but increased sensitivity to pain (means that in rats the electrical current given for a response is much lower-they respond at a lower current with avoidance and other behaviors). Further, when 5HT levels are decreased this slows down the process of tolerance to morphine (tolerance means that the effectiveness of drug dosage is lessened, so the dosage has to be increased to have the same effect of response).

3. Serotonin and sleep

Evidence for involvement of 5HT in sleep is provided by experiments in which levels of 5HT are increased by administration of MOAI (reduced deactivation) or 5HTP (increased enzymes) or 5HT. This treatment leads to an increase in levels of 5HT and also increase time spent in Slow Wave Sleep (SWS). If 5HT is decreased then the time spent in SWS is also decreased.

PCPA administration (depletes/reduces 5HT drastically) also leads to reduced Rapid Eye Movement sleep (REM)

Jouvet (1973) was the first one to identify the relationship between 5HT and sleep. Jouvet carried out experiments of manipulating raphe nuclei and seeing its effect in cats. (Why cats are best animals for sleep research as they spend 2/3rd of their life in sleep). The electrolytic lesion of the Raphe nuclei led to decreased 5HT and decreased time spent in sleep. Sleep reduced when 5HT was reduced 85% time in sleep was reduced to 20% (insomniac cats!!)

Further when PCPA was injected, 1-2 days after injection (when complete depletion of brain 5HT has taken place) increases insomnia followed. How was this confirmed? By injections of 5HTP (which increased 5HT and reverses PCPA induced lower levels of 5HT, insomnia induced by PCPA was reversed!

4. Other behaviours
a) 5HT appears to be involved in Depression as there is evidence of decreased 5HT and 5HIAA (5HT metabolite) in brains of suicide victims (Bourne et al 1968). This indicates that in depression 5HT is lower than normal levels (antidepressant such as tricyclics and MOAI also act to increase levels of 5HT)
b) Decreases in 5 HT leads to a disinhibition of behaviors (reduced controls on behaviors), increased impulsivity, increased aggressiveness, and increased suicidal tendencies.
c) Serotonin is also involved in control of sexual and reproductive behaviors. PCPA which depletes 5HT, increased sex drive in males. In females, the ovulation cycle is blocked by narcotics; this blockade is removed by administration of 5HT

Thus, we have seen that 5HT is one of the major neurotransmitters which influences a wide range of motivational and other behaviors.

Acetylcholine: ACH
One of the major neurotransmitters a class by itself, as there is no other like this neurotransmitter. This NT has been well known and around since 1920's. The effects of ACH have been studied in Bioassay and neuromuscular transmission (frog muscles contraction when Ach is applied on the muscle in the experimental solution) demonstrated.Ach is used by neurons which terminate on the neuromuscular junction. Since the 1960's there have been studies suing enzymatic, gas chromatography, flourometric and other studies demonstrating the involvement of Ach in brain-behavior modulation. This is classified as an excitatory NT. Excitatory post synaptic Potentials are released in the muscle cell. ACH has an excitatory effect on the skeletal muscles, but it is inhibitory at heart (remember we earlier told you that the location is as important as the classification of the NT for its actions as excitatory or inhibitory neurotransmitter). ACH is also found to play an active role in brain areas such as hypothalamus and cerebral cortex. It is involved in learning and memory (known as the memory molecule), and Rapid eye Movement sleep.

The study of Ach is easier than other neurotransmitters as it is easy to remove and study outside the brain in petri dish. The nicotinic receptors was the first receptor identified (Agranoff, p205).. Acetylcholine is found in ganglions of the autonomic nervous system and the target organs of parasympathetic nervous system.

This has two distinctive types of receptors the nicotinic- which connects the muscle fibers and works through sodium channels (these are ionotropic receptors). Curare, a poison can block the transmission of Ach at neuromuscular joints. In neuromuscular joints nicotine mimics excitatory effects of ACH

The muscarinic that are found in the CNS and these use G proteins, cyclic AMPs as second messengers. These are classified as metabotropic receptors. Atropine blocks these receptors, this leads to loss of memory (Pinel 2002, p. 95-102)

The ACH receptors are known as the cholinergic receptors
Synthesis
Acetylcholine is synthesized in a catalytic action of cholinesterase on the Co-enzyme A + its acetate ion and Choline. It acts to detach acetate ion from co-enzyme A and attach it with choline to form

acetylcholine and separate the Co Enzyme A. The Co Enzyme A is found in Vitamin B, and choline is broken down from lipids and Acetyl is an acetate ion. Choline is the rate limiting factor of ach (no choline, no Ach)

The Ach is further broken down by these enzymes Choline acetyl transferase whereby. Ach is broken down into choline and acetyl via a process of hydrolysis

Half of choline in this chemical action is retrieved and recycled

Involvement and neuroanatomical sites of ACH
Ach is formed in the cell bodies of the neuron and transported to the neuromuscular junctions. It is released by action potential, crosses over and activates the muscles fiber.
I a) Acetylcholine is found at all neuromuscular junctions, autonomic ganglion and parasympathetic systems
b) Hippocampus receives Ach input from medial septal nucleus
c) Ach projects into the ascending reticular arousal system
d) Involved in Auditory and Visual systems
e) Found in the Caudate nucleus
f) Found in Ventral basal hypothalamus
g) In Suproptic nucleus brain stem
h) Ach acts as a sensory transmitter in thermal receptor. Pain is produced by directly putting Ach on to a blister on the skin.

II Ach is involved in the:
a) Release of catecholamines (works to balance other NT's and has interaction with DA, NE, and 5HT in all functions)
b) Conduction of signals: it acts in the axonal conduction by depolarizing the axon.

Steps in ACH synthesis where drugs can modulate action

Drugs affecting cholinergic synapses

Step 1: Synthesis: Ach Synthesis can be blocked by **styryl pyridine**- a derivative

Step 2: Release of Ach from the presynaptic membrane is enhanced by B-bungarotoxin and black widow spider venom and blocked by butolinus toxin-deadly food poison. The latter acts to block Ach transmission leading to total paralysis

Step 3: Post receptor sites can be activated or blocked in both type of receptors
These are activated by Ach agonists or cholinometic drugs and anticholinesterases (blocking the enzyme which breaks down Ach)

a) Nicotinic receptors are blocked by **A- Bungarotoxin** and **Curare** (Tubocurarine). Local anesthetics and drugs such as phencyclidine bind to these receptors to modulate action.
Curare, a poison used by South American Indians in arrows prevents Ach from reaching post receptor area (occupies the sites), since the muscles do not get activated, this lead to blockade of all muscular responses. Since there is no post synaptic response, no nerve command is processed. This leads to total paralysis of muscles. Poison from cobra, Alpha bungarotoxin acts through this mechanism
b) Muscarinic receptors are blocked by atropine (belladona), and scopolamine

Step 4: Presynaptic receptor blockade: Atropine and scopolamine block these

Step 5: Inhibition of inactivation activity leads to increase in ACH in the brain by **physostigmine** which blocks the **acteylcholinesterase** breaking down of Ach. This leads to increased levels of Ach in the system, resulting in repeated stimulation of muscles. This means that the muscles would be repeatedly stimulated. This results in violent muscular contractions.

It is reported by (Brown and Wallace, p 40) that there is a West Indian tribal custom where Calabar bean extract is used to find if a person is guilty or innocent. If guilty, then the person who had taken the bean extract as a test would die, and if they were innocent the person would swallow and vomit.

Physostigmine is used as a therapy for **Myasthenia Gravis:** (neurological disorder where the muscles are extremely weak, and don't have normal levels of ACH- for muscles to act). The drugs given increase ACH (cholinometics, or anticholinesterases). Increases in Ach using this therapy can lead to nightmares, confusion and hallucination.

Receptor Agonists: a) muscarinic receptors are affected by muscarinic agonists. One of them is the muscarinic extract from poison mushrooms, which if taken increases ACH activity leads to increased sweating, increased salivation, constriction of pupils and decreased heart rate. Also muscarine, which mimics the inhibitory effects of ACH (Agranoff 1989), b) Nicotinic receptor agonists, in neuromuscular joints, nicotine mimics the excitatory effects of ACH

Nicotinic agonists could be useful in the treatment of a variety of neurological disorders including Alzheimer's disease, Parkinson's disease and chronic pain.

Receptor Antagonists:
a) For Muscarinic receptors: Atropine is an antagonist for muscarinic receptors. Atropine Belladonna- night shade poison- blocks muscarinic receptors, acts as a false transmitter. It occupies the post receptor sites and does not transmit message forward it cannot, it is a false molecule). Atropine belladonna liquid leads to dilation of pupils when applied directly on to the eyes. Why Belladonna (beautiful woman) because women used to apply it to their eyelids for wider eye look. From Grecian times, Hippocretes used it for stomach ailments and cosmetics. In 1880's, the breakdown of atropine from the belladonna plant– affects the muscarinic receptor

Atropine and Scopolamine lead to decreased ACH in the brain leading to amnesia (reduced ACH in Alzheimer brain related to their memory loss). This also indicates that ACH is involved in learning and memory.

Muscarinic antagonists are used to control and prevent vomiting, are also useful for the treatment of Parkinson's disease. In large doses however, the muscarinic antagonists cause severe side effects such as hallucinations and memory disturbances.

Step 6: Choline uptake. B-Bungarotoxin and black spider widow venom

Check table 1 taken from the website, it provides a very good summary of the agonists and antagonist we have referred to above

Table 1: Natural Cholinergic Agonist and Antagonists

Agonists	**Source of Compound**	**Mode of Action**
Nicotine	Alkaloid prevalent in the tobacco plant	Activates nicotinic class of ACh receptors, locks the channel open
Muscarine	Alkaloid produced by Amanita muscaria mushrooms	Activates muscarinic class of ACh receptors
a-Latrotoxin	Protein produced by the black widow spider	Induces massive ACh release, possibly by acting as a Ca^{2+} ionophore
Antagonists		
Atropine (and related compound Scopolamine)	Alkaloid produced by the deadly nightshade, Atropa belladonna	Blocks ACh actions only at muscarinic receptors
Botulinus Toxin	Eight proteins produced by Clostridium botulinum	Inhibits the release of ACh
a-Bungarotoxin	Protein produced by Bungarus genus of snakes	Prevents ACh receptor channel opening
d-Tubocurarine	Active ingredient of curare	Prevents ACh receptor channel opening at motor end-plate

Source: http://web.indstate.edu/thcme/mwking/nerves.html#ach

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LESSON 36

BASIC NEUROCHEMISTRY

Objectives:

To familiarize the students with the

- Various NT and their role in the modulation of behaviors
- Classification of Neurotransmitters. Monoamines: Catechoalimnes and Indolemaine, acetylcholine, amino acid, and Peptide
- Neurotransmitters role in modulation of behaviors and Aberration
- Drugs and Behavior:
- Classification of Psychopharmacological substances
- Behavioral correlates, Treatment:
- Mechanism of synaptic transmission

Major Neurotransmitter: Acetylcholine (continued)

ACH and Behaviors.

As we have discussed in the last lesson, Ach has a unique and important neurotransmitter role in the brain. Without the normal levels of Ach and its receptors working effectively the brain would not be able to command the muscles of the body.

1. **Arousal:** Ach has an important role as excitant of neural activity. This means that brain electrical activity is aroused and can be monitored by the Electtroencepahologrаphic (EEG) recordings. When ACH is injected intravenously or applied to cortex it leads to increased EEG activity. Further, when anticholinergics are administered as they block and reduce Ach levels in the brain, the EEG arousal is also blocked. Interestingly, this does not affect the behavioral arousal). Ach is involved in sleeping and awakening via the locus coerreleus, which may explain the involvement of Ach in brain electrical activity arousal.
2. **Drinking:** Ach is important in drinking and fluid regulation. The regulation of the water intake takes place via the Ach mechanism. The cellular dehydration is mediated by the cholinoceptive system of neurons in the preoptic area of the hypothalamus. They monitor the extracellular space for volumetric changes (changes in the volume of fluid) produced after changes in isotonic body fluids. (Whenever the intracellular membrane runs short of fluid it takes in fluids from the extracellular membrane, as the survival of cell is more important!).This leads to the release of Renin from kidneys which lead to increased formation of Angiotensin which then stimulates the neurons in the preoptic area. Thus, this communication goes from the brain to the kidneys and back leading to an increase in fluid and salt intake. The messages begin with the Cholinoceptive receptors sending out the signals.
3. **Sham rage and attack:** Sham rage is the physical appearance of rage without an object of rage in front of the animal (cats and rats). In cats rage appears in hissing and spitting, and raised hair on the dorsal surface of the body and the tail. Sham rage is induced in cats and rats by the cholinergic stimulation of amygdala and septum. Aggression is also produced by midbrain ventral tegmental area. Further, the killing attack pathways in rat (of mice) and cat (of rats) are cholinergically organized. The cholinergic stimulation of amygdala, LH, midbrain tegmental regions leads to a quiet biting attack in rat and cats. How do we know? This attack is blocked by atropine
4. **Punishment:** Reinforcing stimuli increases the probability of a response to it whereas punishing stimuli decreases the probability of a response to it. The intracranial self stimulation is part of the reward systems and reinforcing so an animal would keep self stimulating for its own reward. On the other hand, the periventricular area in hypothalamus part of punishment systems. The ventromedial hypothalamus is part of this punishment system. Rats previously trained for Variable Interval Schedule (VIS) for food are run in an

experiment where every response is followed by a shock. (Remember VIS is when the time between reinforcement varies!). When every response is followed by a shock, a reduction in VIS response follows. If we lesion the Ventromedial nuclei (VMN), it leads to increase in the response which had been depressed (leads to disinhibition). Anti Ach also does the same, which is they lead to an increase in disinhibition of the punished response. Inhibition of punished response means the animal would stop responding, but disinhibition means that the response would return as the inhibitor has been blocked. AntiAch are involved in removing the inhibition.

5. **Alzheimers:** Alzheimer's is a disease of old age where degeneration of brain takes place to a point where the person cannot carry out any function. The important feature of this disease is loss of memory. Recently muscarinic receptor agonists have been used in the treatment of Alzheimer's disease. This replaces depleted Ach in the basal forebrain as the neurons in this area degenerate. Another treatment of Alzheimer's patients is administration of acetylcholinesterase inhibitors this increases levels of ACH in the synapse as the breakdown is blocked), thereby increasing cholinergic activity in damaged brain areas. Physostigminewas used earlier but results indicated strong side effects. Tetrahydroaminoacridine (THA, or tacrine), first cholinesterase inhibitor which has been approved for Alzheimer's patients. Patients given THA shown some reduction of Alzheimer's symptoms were able to resume normal activity. However, not all patients can use it as it has strong side effects on increasing liver enzymes.

Ach is also involved in learning, memory, motor behaviors (it works in balance with DA for Parkinson's and other motor disorders), in pain, in coordination with brain opioids.

Other NT's

In addition to the neurotansmitters, we have discussed so far, the Catecholamines, the Indolamine, and Acetylcholine; there are other neurotransmitters which are active within the CNS. We will discuss them in brief.

1. Glutamic acid: Glutamate and GABA are found in simple organisms. The first neurotransmitter to be evolved in the brain is Glutamate. Glutamate is an excitatory neurotransmitter, its receptors found all over the brain. Chinese food contains a large amount of Monosodium Glutamate. There are three types of receptors: NMDA, quisquilate and the kainite receptors. The receptors are all important in working with other NTs

2. GABA. Gamma Amino butyric acid was first synthesized in 1883 known to be a metabolite of plant and microbial metabolism. It was discovered in the mammalian brain in the 1950's, and in very high concentrations in the brain and the spinal cord. In the brain GABA is found in amounts 10-15 times greater than DA, NE or 5HT also a minuscule amount found in the retina. Even till now it is not very extensively studied. It is generally classified as an inhibitory NT and accounts along with other amino acids for a major part of the neuronal transmission. GABA works to balance the monoamines DA, NA and 5HT wherever they are involved. GABA is implicated directly in Huntington's chorea which is due to degeneration of GAB Aminergic neurons. GABA is indirectly involved in Parkinson's, Epilepsy (abnormality in the biochemistry of GAB Aminergic neurons) and Schizophrenia

GABA Synthesis; This involves only two steps: one to synthesize it and one to break it down:

1. One step synthesis from its amino acid precursor Glutamic Acid which is decarboxylased by the enzyme **Glutamic acid decarboxyalse**.

Glutamic acid----------GABA

Glutamic acid decarboxylase (GAD) and coenzyme pyroxidal phosphate, this process can be blocked by ions such as chloride and zinc.

2. Catabolism: GABA—is trans-aminated by **GABA-A-oxoglutarate transaminase**. GABA is transformed into Succinic Acid Semialdehyde to return back into the Krebs cycle

In the transaminase process- GABA conversion is reversed to Glutamic acid through **alpha ketoglutarate** which acts as amine acceptor.

Distribution and pharmacological agents

From monkey to human brain 1968-1971 studies showed the highest GABAminergic concentrations in the Substantia Nigra (SN) Globus Pallidus (GP), and the Hypothalamus (hyp)

Agonists: The post receptor GABA agonist is muscimol. This leads to increased arousal, self mutilation, increased feeding if placed in the hypothalamus (disinhibition of inhibition)

Antagonists: Post receptor antagonist or receptor blockade by picrotoxin and bicuculine. Benzodiazepines (Valium and Librium) stimulate a particular site of GABA Aminergic neurons. This alleviates the anxiety symptoms/response.

Glycine: is another Inhibitory neurotransmitter like GABA however research is still ongoing to identify its role. It is found in the mammalian spinal cord and the brain. It is found in greater amounts in the spinal grey matter than the brain. Suggesting it may be working with the interneuron. However, no distinct and clear glycine pathways in the brain

Strychnine (poison) blocks the action of glycine and also blocks postsynaptic inhibition.

PEPTIDES: neuroactive peptides are candidates for neurotransmitters. Some of these are like orthodox NT's, some are performing modulatory or regulatory roles, and that these also act as neurohormones.

BRAIN OPIOIDS, ANGIOTENSIN II, (thirst) Oxytocin and Vasopressin, Leutenizing Hormone Releasing Hormones (LH-RH), Substance P and Adreno-Corticotropic Hormone (ACTH)

Brain Opioids: Endorphins (large molecules) and Enkephalins (smaller molecules):

Hughes and Kosterlitz (1975) in Aberdeeen discovered the existence of brain opioids in the brain. This was a landmark finding because for the first time it was found that this chemical compound was similar in composition to the opiates morphine, heroin etc. In later researches, Huda Akil and her research group reported that the highest concentration in Substantia Nigra, lateral hypothalamus, cerebral Cortex, Periaquaductal gray.

Extracts taken out from the brain, when administered to laboratory animals led to analgesia, wet dog shakes upon application (in a manner similar to administration of opiates).Similarly, akinesia, hypothermia, rigidity, catalepsy were also seen.

The question is whether brain opioids are natural neuroleptics or not (neuroleptics are antipsychotic drugs).

In some cases psychotic patients who are not responding to other treatment drugs (neuroleptics) have responded short term endorphin treatment (Mcgreer and Mcgreer 1980).

These are also involved in emotions, growth, pleasure (acting through the mesolimbic DA pathways), stress induced analgesia (Akil et al 1975), growth and development (Najam and Panksepp 1980).

Opioid antagonists have also been found effective in treatment of autism and childhood disorder (Panksepp et al's theory of brain opioids and attachment states that brain opiates are natural conforters in the brain, it is when they are blocked that the addicts turn to morphine/heroin, and autistic children have higher than normal brain opiate level therefore). The discovery that pain and acupuncture pathways are similar to brain opioids pathways in the body and spinal cord provide strong evidence for the involvement of brain opiates in the pain and acupuncture. Narcotic analgesics such as morphine heroin are severely addictive and have a high tolerance value are potent analgesiscs, potent anti congestion, and also for stomach and digestive problems. The interesting aspect of opiates effect on pain is that it is only the affective component which is reduced (one does not feel the pain) the physical component is still there. Pain is still there but the patients do not care about it, the reaction to pain is diminished.

Psychotogenic compounds

Hallucinogens:

1. LSD is a potent drug in fact so potent that a small dose of 1/10,000 gram is effective. This has great tolerance to the point that the same dose is not effective if taken 2nd time which means an increased dosage needed every time for an effect to take place. The LSD "trip" depends on the mood and personality of the user and can be controlled

2. Mescaline also hallucinogenic compound made from plants extracts in Mexico. It is used in religious ceremonies by tribes in Mexico

Psychopharmacology

This area of specialization is the study of the effects of drugs on psychological processes. It is both a basic and an applied science. " A recognition of the interrelationships between pharmacological agents, neuro regulators, and behavior has become essential for those involved in helping individuals who have psychiatric disorders" Therefore in order to develop drugs research in the laboratory is needed before the drugs can be tested and used- especially on humans.

The evidence is provided when the symptoms of a psychiatric disorder are removed linked to neurotransmitter, and then the normalization of behavior should occur with normalization of levels of NT in the brain. Further, known effective exogenous substances should have similar chemical effects as the endogenous (brain) chemicals. Pharmacological substances should be able to interact with NTs at a given sites if they have the same chemical composition.

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LESSON 37

BRAIN AND MOTIVATIONAL STATES

Objectives:

To familiarize the students with the

- Process of homeostasis, the biological systems,
- The brain modulation of these systems
- And how the body's systems can compete with each other for the survival of the organism.
- Brain and motivational states
- Homeostasis, include temperature regulation, Hunger, thirst, bio-rhythms, Sleep and awakening.
- Pathology related to sleep cycles
- Sleep disorders and treatment

Homeostasis:

A balance and an optimal functioning system of the body have to be maintained for survival of the organism. Therefore, there are well defined and in most cases autonomous neurological feedback systems which work to maintain an internally stable environment of living organism. There are feed forward systems, feedback systems that are constantly monitoring and informing each other of the status (think of very efficient information systems of the computer or an organization) the brain areas and organs are kept informed of each other's status. For example, the somatosensory systems- the skin sensors send temperature information to the receptors in the brain and the temperature receptors would send out messages for making appropriate adjustments. However, the receptors do not exist only on the outside but also within the brain. "It is only against a homeostatic background that other more active systems can function, and many of an animals activities are motivated by the homeostatic needs,"(Bridgeman 1988, p 237). Homeostasis has evolved to support survival by maintaining optimal functioning, if any problems the whole system needs readjustments. If these are minor the systems would sustain it and make the changes, however, if major changes are required and cannot be made these may lead to death.

Actions and behaviors are motivated by the homeostatic requirements (which are signals of the body's needs). Behaviors are programmed to respond to the needs of homeostasis and motivated drives.

There are internal receptors, external receptors/stimuli, brain mechanisms, neurochemical regulatory systems and these are all well synchronized. During the process of evolution receptors evolved for specialized functioning such as for temperature regulation, hunger (and nutrient, glucose, fat monitoring), thirst,(fluid and salt levels), sleep (awakening and sleep need). We will discuss these four in detail

Temperature Regulation:

Temperature regulation is a motivated behavior in that it has all the important characteristics of motivated behaviors- According to Mogensen (1980) temperature regulatory behavior is purposive (the goal to warm or cool the body) persistent (behavior would continue till the goal has been reached) has periodicity (winters nest building, fur or hibernating,) and prioritized .

Temperature regulation is a fairly well defined system and the evolution of human temperature system is quite well laid out (and so it is in other animals). This is an important evolution for maintaining optimum body functioning. As the evolution of varied species took place on land and sea, tropics or Iceland, Equator or the Poles emerged the development of a strong and sensitive thermoregulatory system for their needs became necessary for survival

Ectotherms:
Amphibians, Reptilians depend on their external environment for temperature regulation. These animals are not cold blooded but adjust by relocating to an environment. These may be called solar powered animals, who gain heat from the sun and solar heated places. However, they cannot remain in places which are too hot or too cold (if too hot outside, they burrow holes and stay in those holes, if too cold they come out in the sun). These animals have also evolved vasoconstrictors and vasodilators on the skin (vasoconstrictors contract blood vessels so less energy needed to be expended). The animals remain in a state of stupor in the cold—not very efficient workers with this state. In a laboratory in the US where I worked, lizards used in an experiment were anesthetized by keeping them in ice, and surgery could be carried out- and when warm they would come out of this state. This kind of a response in the amphibians and the reptilians is directly controlled by the thermoregulatory receptors in the hypothalamus and the brain and is dependent on the environment.

Endotherms:
Mammalians and birds have evolved an effective temperature control system- a set point around which the body functions like the thermostat of air conditioner or oven. The endotherms have their own internal controls.

Set point:
An internal point: temperature or standard that the body functions to maintain by cooling or heating through homeostasis (increase or decrease metabolism).

There is a neutral zone range around the set point within which the internal temperature can vary a few degrees higher or lower but not more than that. If the temperature rise or drop beyond the range (more or less) than the thermo regulatory mechanisms for cooling or heating are activated and the metabolism works to meet the required (heat up or cool the body).

Because of their regulatory capacities, the mammalian species and birds can manage continued activity for longer periods as compared to reptile (when faced with the temperature challenges. Higher activity and metabolism challenges can be sustained—have a higher threshold.

Like the ectotherms, endotherms can also use changes in the environment.

Environmental adjustments are made
a) To cool the body. Humans and other animals use shades of trees. The body's response is perspiration: dogs perspire through tongue, horses through skin, and humans through specifically active glands. Humans also wear clothes which allow ventilation of heat. In addition humans have invented fans and air conditioners to cool themselves, and

b) To heat the body through external sources such as shelter, fire, covering for heat conservation, huddling together in animals (especially young) and in humans warm clothing, hot beverages high energy providing foods and warm and heated homes (from fire)

Heat production:
What does the body do when heat is needed to be generated? There is Increase in the basal metabolism, increase in muscular activity, shivering, and increase in the sympathetic systems (increased heart pulse rate, adrenaline, and thyroid release)

Heat loss:
Heat needs to be radiated away from the body (form the inside) one mechanism is evaporation through sweating, and conducting the heat out through other sources Conduction through taking a bath—dogs , buffaloes and other animals stay in water during hot days.

Response to cold is constriction of blood vessels in the periphery for maintaining the internal core temperature at a constant, and reducing loss of heat through radiation (to the outside). This is why we have cold hands and feet in winter, and which is why the mountain climbers often loose their fingers and toes because of freezing. Fur bearing animals also respond by pilo erection (raising the fur on their body), and birds do it by fluffing their feathers. The skin sensors important as they also provide information of heat and cold

Though behavioral responses like seeking heat when cold or taking a bath when hot are mechanisms for temperature control, the physiological and brain mechanisms take a priority

Brain /neural substrates of thermoregulatory behavior
Preoptic area in the anterior hypothalamus is the master control in both heating and cooling mechanisms. Heating this area leads to sweating, and cooling it leads to shivering, both these are body's reaction to thermoregulatory challenges.

The lower phylogenetic areas involved in thermoregulation are in the brain stem(which are under the hypothalamic control and the spinal cord, but the range of the spinal neutral zone (about 2-3 degrees) is too wide and therefore primitive (not refined) as the organism can die of **hypothermia** (cold: freeze) or **hyperthermia** (heat: heat stroke), before the body starts responding.

The main control of the thermoregulatory remains with anterior /posterior hypothalamus

The biochemical control of thermoregulation is with the endorphins (brain opioids). Injecting endorphins directly into the hypothalamus leads to an immediate action of lowering the body temperature. Naloxone (antagonist of opiates) block this endorphin induced lowering of temperature. WHY? - Because that pain and temperaturesensory systems are related.

What happens in fever?
What is Fever? Bacteria or virus produce pyrogens which affect the hypothalamic set point of 98.4^0 F. Temperature rises above the set point of 98.4^0 (37^0 C) high temperature damage body cells need to lower temperature inside. Rise in the hypothalamic set point sends out signals to heat up the body:

Under the Normal conditions, the hypothalamic set point is at 98.4^0 and the body is also at 98.4^0 and these both work to maintain the same. In fever the temperature regulating systems (anterior hypothalamus and the preoptic area) bring about changes in the hypothalamic set point. These changes are in response to the attack from pyrogens (form bacteria). Thus, the set point moves up to 101^0 F, whereas the body is still functioning at 98.40 F. Urgently signals are sent to the body that there is need to heat up to meet hypothalamic set point, to preserve heat. Thus, there is a response of heat conservation and generation i.e. shivering, cold hands and feet (circulation to the center) and faster metabolism.

What happens when we take aspirin (antipyretic), it reduces the set point back to normal 98.40 F, whereas now the body has been working at 1010 F. The signals this time are the body needs cooling! So, this is why we see sweating and taking off blankets etc when the fever "breaks". The signals are to slow metabolism, and to radiate heat by evaporation (sweating)

In human, clothes are the thermoregulatory devices and the kinds of houses built for the climate we live in is a thermoregulatory behavioral process as well. In animals studies have shown that they seek active regulation of their environment i.e. rats hoard paper to warm their cages.

Thermoregulatory process is however very limited. Because freezing to death or dying from heat stroke i.e. hypothermia or hyperthermia occur when the behavioral and physiological regulatory mechanisms cannot cope further \

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LESSON 38

BRAIN AND MOTIVATIONAL STATES

Objectives:

To familiarize the students with the

- Brain and motivational states
- Homeostasis, include temperature regulation, Cellular and brain controls of Thirst, Reward systems and addictions, Fear, aggression, attachment
- Hunger, Body weight set point (Theories), Obesity, Anorexia Nervosa, thirst, bio-rhythms, Sleep and awakening.
- Pathology related to sleep cycles
- Sleep disorders and treatment
- Neurophysiology and biorhythms, Sleep and awakening cycles, Dreams, Sleep disorders

Biological Rhythms:

All biological systems are running on some cycle or the other, at any given point in time. When changes occur in the body or behaviorual functioning on a regular basis i.e. rhythmic, these are called biological cycles and these follow a particular rhythm. These cycles could be short within a day (hunger), or diurnal i.e. of day/night or could be monthly (menstrual cycle), or yearly (reproductive cycle in animals). These biological rhythms/cycles have important influence on behaviors of animals

The characteristics of biological rhythms:

1. Period: This is defined as the time required for a rhythm to be complete. This mean when a cycle is called a period (from the beginning to the end)

2. Frequency: The reciprocal of a period e.g. body temperature reaches a peak once a day. The body temperature period would be 24 hours and frequency would be once in 24 hours. There are cycles such a reproductive behaviors in animals of 12 month period with a frequency of one (once a year mating season) per reproductive cycle.

3. Amplitude: is the amount of change from the original starting point i.e. 98.4^0+1 F or 98.4^0+1.5^0 F. How large is the change from the set point or the original point in the cycle. There are individual differences in amplitude. One person may have a rise of .5F the other a rise of 1F degrees

4. Phase: The peak of the rise in temperature may also be different. One person may have a peak at 2.p.m. another at 3 p.m. and still another at 4p.m. Similarly the drop in temperature may also differ from person to person (gender and metabolism). The phase is complete with the peak (highest) and trough (lowest). The phase is always with reference to the time of the day, time of the month, time of the year, or some other external marker. The three people with different peaks would be out of phase with each other. Similarly there are those who stay up all night and sleep during the day and those who sleep at 10 every night and wake up at 5.00 every morning. These two are totally opposite to each other and out of phase with each other.

Biological Rhythms

The biological rhythms /clocks control the functioning of most behaviors that are biological including the thermostat, female estrus cycles, the hunger and thirst, and sleep cycles and these are entrained with the light /dark cycles.

Circadian rhythms

These are biological rhythm cycles which follow a day cycle: circadian: Circa: circle, and dian from diem= of a day. The daily cycles are many such as temperature and most important (and obvious) of sleep/ awakening, feeding.

There are other rhythms and cycles, such as the estrous cycle, (in some animals it appears once a year or so)
Studies have shown that there are rhythms for every biological response in the body measured: the epidermal (skin temperature) response, urine, blood, whole body temperature, physical rigor (energy to do work), weight, heart rate, blood pressure, respiratory peak flow, Growth Hormone levels, and even Plasma ACTH (stress hormone levels). Studies have also shown that body's response to drugs (such as pain killers) also differs with the time of the day, implying the smaller or larger dose may be necessary for the therapeutic effect.

The Circadian Rhythms are controlled through the Suprachiasmatic Nucleus (SCN) located in the medial hypothalamus. Lesions in the SCN breaks down the behavioral circadian rhythms in rats drinking and adrenal cortisone responses were affected in SCN lesioned rats (Zucker 1972). In hamster, the estrus cycles (female's ovulatory cycles) are also disrupted.

How can our circadian rhythms be changed or influenced: by phase shifts (day and night shift workers have not just sleep to take care of but their body adjusts by making changes in the other cycles as well. Studies on changes in 12 hour shifts have shown that adaptation of shifts to heart rate, Norepinephrine, epinephrine levels, body temperature, stomach enzyme production, and performance peaks also were affected (Higgins 1975),

Menstrual cycles of women were also found to be disrupted if they were traveling across continents and their sleep/awake cycles were disrupted (jet lags?)

Day/Night and dark light cycles also affect mental health. In countries where there are long dark winters, there is behavioral syndrome known as the winter blues.

Circadian and other biological rhythms are important modulators of behaviors in man and animals.

Body Temperature and biological cycle: circadian (of a day)
The body temperature is not constant throughout the day. Depending on the type of species, whether these are nocturnal (night foragers: night hunter) or day forager, their body temperature would rise and fall accordingly. The temperature peaks whenever the animal is most active, therefore for the humans, horse and other day animals it would peak during the mid afternoon. The rodent rat is nocturnal therefore its temperature peaks at night. Similarly the lowest temperature would be at night for the day foragers and during day for the nocturnal animals. The set point for the body temperature is set by the light /dark cycles which set the biological clock which in turn sets the biological metabolism (faster during awake and slower during sleep- to save on energy) Temperature lowest during sleep, because metabolism is lowered. Sleep reduces demand on metabolic heat production

Therefore, the L/D cycles-set the biological clock which in turn sets the temperature-set point? In some species the thermoregulatory behavior is modulated for longer cycles such as Hibernation. Hibernation is when the animals moves into a state where the body temperature is reduced and metabolism slowed to particular level. There is limited requirement of fats etc, and the body can go a long way on the stores of fat. There are bears and other animals which hibernate in winter and others such as birds which fly away for winters (the Siberian birds migrate towards the Arabian Sea coastal areas for the winters)
Among the other important biological systems which have an autonomic modulating mechanism, one of the most important ones is hunger through which energy and nutrition is provided to ensure the survival of the organism's systems

Hunger/Feeding

Feeding is an essential behavior as provision of nutrients, energy for survival for heat production for metabolism all depend on what is eaten by the animal. Animals must eat enough to maintain their requirement and to maintain body weight. If they exceed the input and not sue it – it would lead to obesity, and if they do not take what is required in sufficient amounts it would lead to starvation. The seeking of food is hunger- and a very strong motivating behavior. Humans and animals spent most of their awake hours in foraging for food. Food Seeking is part of the homeostatic systems to regulate the organism internal needs.

Hunger/feeding as a motivated behavior

Food intake/feeding/hunger is motivated behavior, because feeding behavior

a) Periodic: it is tied with the body's energy consumption, metabolism, its needs, the external environment (temperature etc).the signals for onset of feeding and of stopping eating increase and decrease with the internal and external signals and clocks.

b) Priority: Feeding has high survival value therefore it takes priority over other behaviors such as mating. Animals would seek food over seeking others. A hungry man would see the moon as roti, and the man whose stomach is full can think of the beloved face like the moon.

c) Purposive: very much goal directed when food is sought and animal is hungry. The behavior would continue till hunger is sated.

d) Persistence: Food seeking is persistent. It would continue till the goal has been achieved and enough food taken in.

Although there are many set points within the feeding cycle, there are two major set points which have to be maintained by the feeding behaviors

a) Body weight set point. This set point ensures that the body weight is maintained at a constant so if you are 120 or 200 pounds your body works to maintain that weight

b) Body energy and fat content. Within each organism there is a glucose set point and a lipid set point which the body works to maintain and monitor.

However, remember if the Energy intake is equal to the energy expenditure, i.e. Intake= output, there would be no weight gain. The body weight would be maintained at a constant level. Weight gain and weight loss would occur if the equation is imbalanced either for input or output of food.

What are the factors regulating food intake.

This is an interesting question as feeding may occur in the absence of hunger signals. For example, when we see cakes in a bakery window, or smell samosas frying, there is an urge to eat, an immediate desire which overrides the full stomach signals!! Or we may defer eating because there is a high priority for some other activity (run for life, or prepare for exams--- food becomes a low priority)

"Feeding is under a multifactor control and the multiplicity if signals means that there are a number of feedbacks loops for the initiation and termination of food intake" (Mogensen and Carlson 1977, p10, cf Mogensen 1980). This can be understood if we look at the body's requirements, that even though glucose and fats are the main sources of energy and metabolism, there is also need for proteins for growth, maintenance (and for NT systems).

If we analyze them intuitively we can identify several possible reasons why we eat and what sets our hunger signals: we feel hungry because

a) We salivate (Pavlovian dogs!) or our stomach sends signals (rumbles), or we smell food, or because the body sends signals. These can be classified into the following categories.

Oral, /Peripheral, (also odor) Gastric and Metabolic (neural)

Oral/ peripheral factors: The taste odor, sight and texture of food has role (though small) in the control of food intake. Animals eat more if the food looks and tastes good, and less if the food tastes bad. Mouth palatability (how good it tastes and looks) and variety: increases food intake in rats and humans alike. Palatibility is a very important source of obesity– eating when not required by the body

Rats like high fat foods very much, and increased total feeding response, and become obese, the same for mice. Rats would eat quinine adulterated food only if they are starving (wouldn't anyone else?)

Teitlebaum and Epstein (1962) inserted a nasopharyngeal gastric tube which by passed the mouth region. Rats were trained to send food through tube to stomach- their intake is only how much required to maintain body weight

Therefore more than mouth and the stomach region are involved in feeding. Snowdon (1969) report that rats maintain lower than normal weight levels if food is not routed through mouth (oral). There are some signals from the mouth, (odor and taste).

Another study of eliminating oral factors on food intake is to administer nutrients through intravenous infusions. Experiments by Nickoliadis and Rowland (1976) "When infusion equaled or was greater than the normal daily intake, there was an increase of oral intake of the diet…" indicating that there were some oral factors involved in feeding.

Sight of Food stimuli also leads to an initiation of and increase in eating response even when sated or full.

In man and higher mammalians, the experience and cognitive factors are important in feeding behaviors. Therefore, eating different foods, raw or cooked, liking Chinese, Japanese, Thai, Greek, Ethiopian food is learnt, using different cooking spices are also learnt. The taste aversions are also learnt such as cultural, religious and other constraints. There are some animals such as snakes, frogs and lizards not thought edible in majority of the developed world but there are some cultures where these are relished! We may like the head of the goat and trotters (siri paiy), but they may not be the food of choice in most countries. What we eat, how we eat (chopsticks/ knives or forks or banana leaves and hands), cooked or uncooked vegetarian or meat depends on our region. Therefore, human food and eating is determined by cultural, religious and regional factors,

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LESSON 39

BRAIN AND MOTIVATIONAL STATES

Objectives:

To familiarize the students with the

- Brain and motivational states
- Homeostasis, include temperature regulation, Cellular and brain controls of Thirst, Reward systems and addictions, Fear, aggression, attachment
- Hunger, Body weight set point (Theories), Obesity, Anorexia Nervosa, thirst, bio-rhythms, Sleep and awakening.
- Pathology related to sleep cycles
- Sleep disorders and treatment
- Neurophysiology and biorhythms, Sleep and awakening cycles, Dreams, Sleep disorders

Factors that control Food Intake behaviors (continued)

In the last lesson we have discussed the contribution of the oral factors, (palatability etc) and the smell and sight of food, cognitive and learning influences on what we eat and how we eat. Now we will find out if the gastric factors (stomach, the alimentary canal, the digestive system), contribute to feeding behaviors.

Gastric factors:

The gastrointestinal tract is important in digestion and breaking down of food into nutrients needed by the body. The stomach seems important intuitively because we eat when the stomach is empty and stop eating only when there is feeling of fullness in stomach. But this is not true!

Let's find out through the evidence from experiments carried out to isolate the stomach factors.

If the feeling of fullness comes from the stomach as a signal to stop eating, what if we preload the stomach in some way, and the stomach is distended or expanded (remember that the stomach has the capacity to flex and contract)? The first experiment of balloon preloading of the stomach was carried out by Cannon and Washburn (1912 cf Pinel 2002), Cannon was the experimenter and Washburn the subject, he had to swallow the balloon) and reported whenever hunger pangs felt. As he reported the pangs Cannon measured electrical activity of stomach contractions through a mechanism placed beforehand. The hunger pangs were found to be correlated to stomach contractions, leading to the view that stomach was important in hunger control. When there is preloading of the stomach with water or some other substance, there is decrease in food intake

But this theory was not supported by the following:

1. The stomach is almost always full; it is never completely empty except in long fasting or starvation.
2. When we are full and have eaten enough, if required or asked to eat even on a full stomach we can add some more good food (think of the Pakistani hospitality!)
3. In human patients when the denervation or removal of stomach takes place and the esophagus is connected directly to the duodenum they still report pangs of hunger and feelings of being full, and continued to eat to maintain their body weight, although their meals were smaller. This is similarly true of animals as well.

However, Koopmans (in 1981) carried out an experiment on animals where he attached another stomach and connected the blood vessels through the additional stomach. In this procedure, the food was passed from the additional stomach to the real stomach (measured), but blood vessels only passed through the new stomach--- interestingly the animals stopped eating in response to some

signal from the blood. It appears that there must be some chemicals not found in the food, but which stimulated signals for stopping of eating.

Keeping this evidence and the fact that one stops eating even before the process of digestion and absorption of food starts taking place (as this requires time), there appears to be some role for gastric cues. Feeding ends even before the nutrient-deficiency signals are terminated, therefore there has to be another signal to terminate feeding, coming from the gastric region.

Smith, Gibbs and Young in their studies (from 1973-1976 onwards) suggest that there may be peptides (short amino acid chains) i.e. hormones or neurotransmitters which signal the satiety signal. The ingested food may be triggering the release of hormones into the bloodstream. One of these gut peptides cholecystokinin (CCK) when injected led to rats eating smaller meals- or inhibit feeding without causing any illness or pain. Administration of this peptide directly into the brain is not as effective as injection into the blood stream. However, later studies by Mineka and Snowdon (1978) have shown that this effect does not last very long—therefore there are other controlling factors for food intake.

Thus we have found out that the oral and gastric are important in feeding but not enough, therefore we now look at the metabolic, energy and neural controls to see if those are important in the initiation and termination of feeding signals.

Metabolic Factors:
If Glucose level in the blood decreases it leads to initiation of eating, increases in blood glucose would lead to cessation of eating. More recently Campfield and Smith (1990) have shown that rats with free access to food and water were monitored for blood glucose through a catheter. These rats had constant level of blood glucose at about 2%, but just before eating, the blood glucose levels dropped to about 8%, indicating that blood glucose levels may be a signal for food intake. This takes us to the now classic assumption of set points in the body of glucose and of lipids. The set point means that there is an energy set point which determines how much is eaten and when. This has three basic components: the set point mechanism (assumption is that these are neuronal receptors), the detector mechanisms (which detect differences from the set point), and the effector mechanisms which are to bring about a change so that the set point level is met. Thus, there is a set point for glucose levels, a set point for fat levels, a set point for weight etc. We will discuss the theories which propose the first two.

Glucostatic Theory proposed by Mayer
This theory suggests that feeding regulatory system is actually keeping the glucose set point in the blood at a constant level. There are glucostatic set point monitors. Gluco-receptors in the hypothalamus constantly gauge the level of glucose in the blood. This is a short term mechanism for initiation and cessation of feeding.

If the glucose levels in the blood fall then the glucose from pancreas is released in blood stream leads to an increase in eating, glucogen injection lead to decreased eating and reduced stomach contractions. Further, Insulin injections lead to marked hypoglycemia (reduced glucose levels in the blood).This lead to increased eating as insulin increases the entrance of blood glucose into the cells. In an experiment, this injection was followed by
a) Glucose injection
b) Fructose or mannose (types of sugars: fructose cannot cross blood brain barrier but can be utilized by the liver, mannose can be used by both brain and liver) or ketone bodies (fuel used by the brain not the liver). All animals given some nutrient after the insulin injections showed a drop in

feeding, indicating that it is not the brain signals but some controls of the periphery which monitor feeding.

Lipostatic theory:
Lipostatic theory states that there is a body set point for lipids and any deviation decrease in the body stores of fats would lead to initiation of feeding. This is long term mechanism body weight maintenance

(Remember in cases of starvation, stored body fats are broken down for providing glucose).

The difficulties with the set point theories are:
a) That these are not consistent with the evolutionary perspective--- when man didn't know if he would be able to eat next—(if hunt successful only then food would be available right?), how is possible to have a set point sending out signals to regulate food.
b) Hunger and feeding are not just following glucose patterns, people around the world have culturally varied food patterns. How can this be explained in glucostatic or lipostatic theory.

Neural Control of feeding:
Research into the neural controls of hunger has been ongoing since the 1940's. There are two brain areas the Ventromedial Hypothalamus (VMH) and the Lateral Hypothalamus (LH) which have become more important from the 1940's- 1980's

Hypothalamus is important in eating and drinking. We know hypothalamus is important in motivational and survival behaviors. If there would be no hypothalamus there would be no feeding, and no drinking controls. There is specialization within hypothalamus where each region works in coordination with the bodily needs, and other regions

- **Ventromedial hypothalamic** damaged rats become obese rats. This was first demonstrated by Anand and Brobeck in 1943! VMH lesions to hyperphagia (overeating), and LH lesions lead to aphagia (no eating).These have been shown to be the same effect in rats, dogs and monkey—also humans. The following are the similarities in VMH rats and human.

1. Food Nutritive Content Challenge: If the nutritive content in food is decreased then the normal would increase food intake to compensate but VMH are finicky eaters. The VMH cannot respond to these challenges
2. Palatability is important for VMH rats and humans. If we increase the palatability, it leads to increased eating in VMH animals and human, whereas normals stop eating in response to body's signals (The VMH become obese as a consequence)
3. Work for food: if effort is involved to work for food, the VMH damaged rats and fat humans would do minimal work for food. In an experiment, normals and VMH animals and fat humans were given peeled and unpeeled almonds. Fat humans and the VMH rats ate more unpeeled whereas the normals ate about 50% of the peeled and unpeeled almonds.

There is a hypothesis that VMH may be the satiety control this areas controls the signals for stopping of feeding- which is why if VMH is damaged the inhibition is gone, and the animals continue eating!
LH damaged animals are starving rats. These animals are aphagic (do not eat), adipsic (do not drink water) if they are not tube fed they die. Recovery is slow and takes place in phases. These animals can recover eating but not drinking. Eventually they start drinking condensed milk but no water. Their recovery reaches almost normal levels of eating, but these animals cannot respond to challenges. The LH animals also cannot eat to compensate for initial weight loss. These animals cannot fully recover their normal weight. It is said that the LH is the center for initiation of eating which is why lesions

lead to the starvation like state (no LH no signals to eat). However it is difficult to interpret as many NTs passing through it, NE DA may also be involved.

It is Possible that this damage causes motivational deficit/inertia that animals don't want to eat or drink. This is supported by the fact that there is no spontaneous activity of these animals. Further there is sensory neglect (lack of response to visual. Tactile and other stimulus.

Other factors such as Neurotransmitters and hormones have also been found to be important:

- The role of Norepinephrine has been highlighted by studies by Liebowitz and her colleagues especially in the area of LH as stimulation of NE rich neurons leads to initiation of eating.
- More recently role of gut peptides have also emerged as important, in the initiation and controlling feeding.
- We have already studied that there is a large amount of serotonin in the gut. There appears to be role for the chemical in the signals for feeding.

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LESSON 40

BRAIN AND MOTIVATIONAL STATES

Objectives:

To familiarize the students with the

- Brain and motivational states
- Homeostasis, include temperature regulation, Cellular and brain controls of Thirst, Reward systems and addictions, Fear, aggression, attachment
- Hunger, eating, satiation: brain+ NT control, Body weight set point (Theories), Eating Disorders Obesity, Anorexia Nervosa.

If we look around us disorders of eating, whether it is obesity or anorexia nervosa, anorexia bulimia seems to have overwhelmed especially our younger generation (mostly females). To understand why feeding behaviors goes wrong, there must be some mechanism which ensures that weight remain stable and when that mechanism breaks down the eating disorders are seen.

Obesity is a major problem of the fast food advanced world. In the US 34 million people are overweight and 12.5 million people are severely overweight. It is now catching up and China where American fast food was introduced to Chinese culture (where the body and system was not used to the cooking or the food) led to an emerging obese younger population. Chinese children are actually being sent to camps to reduce weight!

Obesity is also genetically linked but this does not explain why or how it has become a disorder of epidemic nature, with more than double the number of obese people in the world in the 20th century. The reason may be many a) during evolutionary development as hunters man needed to store fats, plus man walked many miles, had a lot of physical work which did not fat accumulate. As life became more and more sedentary this stored fats became unhealthy. Similarly changes in style of cooking, storing food (now you get frozen foods) earlier women used to spend all day grinding corn or wheat for one meal. Changes in life styles also made a huge difference—the older generation ate healthy foods and had a healthy life style, the younger generation prefers to eat fried and fast food and very little exercise! These are actual findings of a survey that a Behavioral Sciences class I taught carried out: to compare four generations (their grandparents, parents, themselves and their younger brother and sisters).

Eating Disorders: could be acquired, learnt biological, metabolic, acculturated Acquired:
Children are taught to eat what was given to them and to finish their food. Further they learn to associate eating with reward (parents promise candy for good behaviors!). Nutrition is not the focus at the growing age. As people grow older they continue to eat the same kinds of food s that as children/ teenagers/ young adults, even though there is reduced nutritional requirement (and still eat as much!) Then they tend to store fat. Why don't people stop (check out animals, they do stop!). Because in humans the inhibitory signals are over ridden, and we continue to eat as the food looks good or tastes good.

The Psychological variables which lead to overeating have been identified as: field dependence, reduced impulse control, eats food too fast (too much), maladaptive controls, depression, tension etc.

Innate: obesity is a metabolic disorder. It has been reported by researchers that the reason why it is difficult for fat people to loose weight is because of metabolic factors. There is basal metabolic rate difference (some have a higher metabolism rate than others). This is supported by the findings that the food intake of normals and obese people has not been shown to be significantly different (Rodin et al 1989,). However, there may difference in energy expenditure rates and metabolic states

Resting metabolic state: diet resistant difficulty in losing weight, even after decreased caloric intake. Those who diet and binge are setting their bodies at a different metabolic rate. The metabolic rate slows down with each diet--- making it difficult to lose weight after every diet.

However, there are other factors such as underreporting, underrating eating: "I don't eat a thing, but I keep gaining weight is something familiar we hear from people who have gained weight.

The simple formula is that if food and fat input= energy expenditure output: balance and weight is maintained at a constant

Interestingly, 70-80% of a person's energy expenditure is through resting metabolism (Thermogenesis, fidgeting and maintenance of posture/muscle tone: Non exercise thermo genesis)

Metabolism and energy needed to digest and assimilate food: exercise does not reduce weight but only facilitates aerobics, and toning of body.

Fasting sends the body into the diet induced thermogenesis

Diet binge- Sporadic Dieting affects body's metabolism by setting it into a starvation mode. The starvation mode means "we need to save what we have on the body" therefore signals and mechanisms to store food, store fat come into operation. Once the alteration in metabolic efficiency of the body takes place, it starts storing fats. Therefore diet binges do not work, if anything they slow down the metabolism.

Individual differences: Why do some people put on weight more easily than others/ Research ahs shown that there are special brown adipose tissues which may carry the clue. These convert calories directly into heat. These are important in animals which hibernate. These animals need this to wake up in spring. This is known as the Non shivering thermogenesis. These cells rich in mitochondria (explains why they are high metabolic rate cells!) The mitochondria give these cells the brown color which is why they are known as brown adipose cells. The B adrenergic receptors control the metabolism of these cells. Increased Norepinephrine levels lead to increased non shivering thermogenesis leading to heat production. This mechanism is controlled by the medial hypothalamus. Defect in brown adipose tissue metabolism leads to defects in the breakdown of fat. It has been reported that in normal rats the increases in metabolism of brown adipose tissue rises by 200% occurs after a meal, whereas in obese rats this does not happen. This indicates that deficient meal induced thermogenesis may be involved in eating disorders.

If each meal increases metabolism, then increase in number of meals would burn more through this process. This has been suggested and been used as a mechanism for weight reduction.

In extreme cases the relevant therapy for treatment of obesity has been a) jaw wiring: to stop the patient from eating, or intestinal surgery, which reduces the length of the intestines, or reducing the stomach size by stapling the stomach (gastroplasty)

Reducing the length of INTESTINES lead to reduced gastric activity, but this can cause a great deal of discomfort!

We have been talking so far of people who overeat, but there are some people who under eat to the point of starvation. This is especially true of young women who see models and film artists who have become thin to be fashionable. This disorder is called Anorexia nervosa. In another form of this disorder young women eat very little and then binge and throw up forcibly. This disorder is known as

Anorexia/ bulimia. Their focus is on food- but in a different way. They like to cook, they like to feed people, they like to talk food, collect recipes—but they do not eat.
Anorexia: Is it hereditary or enlarged sulci in the brain (return to normal after recovery), enlarged ventricles (permanent damage), defect in Dopaminergic, noradrenergic, and brain opioids levels- these may the biochemical/structural defects which lead to Anorexia? Psychotherapy is not effective but the anorexic drug Fenfluramine is successful in treating anorexics

Self starvation- This has become part of the modern cultural norms? There have been many famous cases. One such case is that of a famous American popular singer of the 70's, Karen Carpenter who died of Anorexia. A bright talented young woman who kept starving herself because she thought she was fat. More recently cat walk models have been required to go through a weighing process in various shows around the world to ensure that they are not below required levels of Body weight and Mass.

Thus we have seen that feeding though important for survival can be strongly controlled by social and other factors in humans.

Thirst: fluid intake
Have you ever thought why do you drink fluids/water, you might answer you do so because you get thirsty, but then ask yourself where do you feel thirst? In our mouth you would reply, because you feel dryness in your mouth. Then the question is what would cause this dryness? Dry Salivary glands, you would answer obviously. The salivary glands dry out because of lowered water level in blood leading to dryness leading to thirst which would lead to drinking.

Thirst is motivated behavior—it is purposive- animals would continue to seek water when thirsty and only stop when they have taken water. It is periodic as it appears several times (when the animal eats). This is almost constant seeking of water as water cannot be stored like fats on our body- there is greater depletion of fluids

Lets think like a researcher,
1) What if water is injected directly into mouth? It leads to reduced drinking.
2) What if we remove the salivary glands? This leads to dryness of mouth, but no increase in drinking. So what is drinking or fluid intake controlled by.

For survival, every living organism needs water because each cell in the body and all processes need fluids for maintaining and cleaning the system one of the most important motivated behaviors is thirst. For average human adult daily water intake and output equals about 2500 milliliters. Water is lost through the lungs (vapor), through skin (perspiration) through kidneys (urination) and we input it through drinking, eating foods with high water content (think of melons, or oranges, even meat is 70% water). The human body is 50-60% water Sources/mechanism to measure fluid level

It is interesting to note that there are two different mechanisms by which fluid is regulated: the intracellular and the extracellular.

Intracellular monitors the vascular (blood) and nonvascular (Tissue) fluid components. There are saline levels of the body fluids in addition to the level of water which is needed to be maintained therefore constant monitoring of
1) Fluid level
2) 9 % level saline in blood and CSF.

If you recall the sodium levels of ions is high on the extracellular membrane and low in the intracellular membrane. If sodium ions increase in the intracellular membrane, fluid passes through the cell walls to dilute salt– inside the same would happen if the sodium concentration increases in reverse. Immediately fluid forms one compartment move to equalize the fluid and osmotic balance on both sides of the membrane. If fluid is lost form the intracellular membrane it is known as cellular dehydration, and if it lost from extracellular compartment it is known as hypovolemia. Both lead to thirst and drinking

Hypothalamic mechanism of fluid works regulation and drinking. Wayner and Carey (1973) have shown that two separate regions of the hypothalamic receptors are involved in detection or monitoring of fluid levels.

Cellular dehydration and Osmoreceptors:
For detection of changes in intracellular fluid level, the lateral hypothalamus is involved, and for detection of changes in the extracellular fluid level the anterior hypothalamus is more sensitive. Fluid levels in extracellular more important. The fluid level is constantly monitored

When the cellular dehydration takes place the pituitary releases Antidieuretic Hormone and the animal starts drinking. The Kidney and hormones produced by kidney become important Renin acts on Angiotensinogen- which produces Angiotensin II- which acts directly on thirst receptors in Hypothalamus. The Anti diuretic hormone (ADH) released by Anterior Hypothalamus via posterior pituitary. Increased release of ADH acts on kidneys to retain fluid/decrease urine volume (excretion of water) and the decreased ADH is a signal to retain fluid output from the body (save body's water). The water intake help reduce the osmotic pressure and the water is then absorbed by the intracellular compartment

The Osmoreceptors are located around the Lateral Pre Optic area of the hypothalamus, which can then send out signals through cellular mechanism and the neural systems.

There are mechanoreceptors which monitor the hypovolemia (extracellular dehydration) and these monitor the vascular walls for tonic rate of discharge. Some of these are located near the heart and can monitor the changes in blood pressure (sound familiar?) which results from hypovolemia

There are two mechanisms of thirst and both these are important for maintaining the fluid levels of the body and ensuring survival and working of the cells.

Loss of fluid from either compartment lead to primary drinking or this is to restore loss of fluid. But there is drinking in the absence of water loss which is called secondary drinking. This is not in response to cellular dehydration but dryness of mouth or psychogenic or other pathological reasons

Drinking is therefore one of most important needs of the body's system and research is ongoing for the NeuroChemicals and hormones that are involved in this behavior.

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LESSON 41

BRAIN AND MOTIVATIONAL STATES

Objectives:

To familiarize the students with the

- Brain and motivational states.
- Neurophysiology and biorhythms, Sleep and awakening cycles, Dreams, Sleep disorders.

Sleep and Dreams

One of the most important motivated behaviors (ask someone who has not been able to sleep. Eminent researchers such a Moruzzi and Magoun, Jouvet, Asertinsky and Klietman, Dement and Klietman have contributed to the study of sleep and have tried to answer the questions of the enigma called sleep.

What is sleep? What is the function of sleep?

Sleep is certainly one of the most interesting and intriguing behaviors (or lack of it). Sleep has very species- specific behavior patterns. Some animals sleep for 2/3rds of their life like the cats, and some animals are light sleepers (the horse and the cows). Further the birds sleep with their beak tucked in their feathers, and the dogs and cats sleep all curled up.

Sleep is cyclic (it follows a circadian rhythm: a day/light cycle). And you feel sleepy the same time every night and wake up same time every morning.

Sleep is purposive- It has survival value and fulfill the system's needs (try sleep deprivation to see how bad one feels and performs)

Sleep is also purposive that each time an animals needs to sleep it would seek its own location (or bed, or pillows or direction)

Sleep has a high priority for survival

Sleep is one of the Circadian- Zeitgebers one of the biological rhythms which has an important influence on behavior.

Our sleep is governed by our Internal clocks and each one of us has a unique Rhythm there are day persons who are early to bed and early to rise and then there are the evening types who like to go to sleep late and then wake up late. Their functional and behavioral peak is at around afternoon. How does one determine their clock or is it biologically determined?

Though we do have a strong focus on the day training where everyone ahs to start working in the morning- going to school and then sleep early for school net day. It appears that these external cues do place a restriction on the biologically preferred (entrained) clock.

An experiment was carried out on volunteer students to a sleep study. These students had to live on the site and each one was assigned a sound proof room with no windows or any other cues as to the time of the day. There were no clocks, no newspapers delivered, and no breakfast, lunch and dinner timings. The students could ask for the newspaper and breakfast or other meals when they so wanted. The aim was to allow each to have free floating sleep periods. Their sleep patterns/cycles were noted before the experiment began and during the experiment. It was noted that at the end all except one or two had 24 hour cycles, these two exceptions had cycles of >24 hours! Most interestingly there were some who had entirely reversed during free cycles! These had a cycle in which they stayed alert and awake during the night and slept during the day—indicating that this was their natural cycle.

The Question still remains, why spent 1/3rd of life in sleep? About 25-30 years
It appears that sleep is non adaptive. It leaves you vulnerable for predators and enemies. It is well known that hunters sleep deep while the hunted cannot do so.

However, sleep deprivation affects cognitive and emotional responses. It reduces attention to stimuli, affects memory and sleep deprivation has been used as torture (by not allowing them to sleep). We would keep coming back to this question again and again!

Characteristics of sleep
Sleep is species specific all animals are similar in some cases and different in others when they sleep: though similar still different (birds, horses, lions)

Home territory important for sleep for all animals why? The home territory is important for sleep. Even humans like to have their own bed, or bedding or own direction, animals have their own nests, and dens or anywhere which is home to them? Why? It has survival value- safety and security of home would ensure that falling asleep would be safe and comfortable and not get you killed.

Periodicity: cyclic nature of sleep. As we have already seen, sleep has a very formal cycle of 24 hours and within this cycle are several cycles per night. This is the same for all animals. However, infants have sleep which is polycyclic and polyphasic (they sleep and awake during the day and night- this is because their circadian rhythm has not been trained yet), and adults are monocyclic and monophasic. One time day (however there were many like Einstein and Leonardo Da Vinci who were polycylic and had short sleep cycles – but many of them).

Function of sleep:
The most obvious answer is to rest because you get up refreshed after a good nights sleep, or even a nap– but brain never rests!

There are many explanations given as to why one sleeps. There is the memory consolidation theory which states that we sleep so that consolidation of memories can take place, especially during the REM period. For young infant and growing children (especially) there appears to be sensory motor practice during REM sleep. It also seems that REM sleep is important and needed for repair of any damage to cells. This is continual work ongoing

Electrophysiology of Sleep.
Asertinsky and Klietman, Dement and Klietman, Jouvet, and earliest reports by Hess (1931) showed that the sleep has very formalized stages which can be distinguished on the basis of the electrical activity of the brain

Asertinsky and Klietman recorded EEG, EMG, and Oculomotor (EOG) movements and reported the following changes in brain and muscular electrical activity where a person was set up with electrodes to sleep in a sleep laboratory, and these electrodes were attached to an oscilloscope and a polygraphic recording device which recording the stages through which the brain electrical changes moved. Interestingly, this is a consistent pattern seen across all animal species

Based on EEG patterns we can see the distinct stages and how the sleeper moves form one stage to another.

- In the Awake state the brain has -Beta-waves which are very high frequency low voltage low amplitude. This means these are highly active state-the height of the waves is short and there is 12-18 cps.

- As awakes person relaxes and slows down, the brain enters Stage 1-- Alpha—waves start emerging these are slower with lower frequency and the voltage is higher, these are about 8-12 cps.
- As the person goes into a deeper state of sleep he enter Stage II-comprising of Delta waves are about--1-4 cps really slow but high voltage waves (even slower, low freq, height of waves increased) these are interspersed with sleep spindles of 13-15 cps and K complexes). So every now and then there is a spurt of high frequency low amplitude waves.
- Following this stage the person goes into a deeper stage the Stage III—this is known as deep sleep. Here we see delta wave largest and slowest of slow waves 1-2 cps. It is difficult to wake a person up in this stage. The sleep waves are really slow, with high amplitude/voltage.
- The Stage IV of sleep waves slow waves and more and more Delta waves which are really slow and large in height. It appears as if the person is in a coma
- Suddenly there is change in electrical activity. If we just look at the brain EEG we see Awake like pattern of Stage I sleep with theta waves but there is loss of muscle tone in the neck, and there is rapid eye movement: This is REM sleep or Rapid Eye Movement sleep. It is also called PS or paradoxical sleep disappearance of tonic activity in muscles especially neck. The person appears paralyzed, except for the eyes (there is a good reason for this : If you were doing all the things you were dreaming about, you would hurt yourself… therefore the body is under the control of the pons and there inhibition of all movement).

This is a 90-minute cycle and there are repeated cycles of 90 minutes. Every 90 minutes the person wakes up and then goes to sleep again however, there is more and more REM sleep towards morning (out of the 90 minutes REM is for a few minutes towards the early part of the cycle, but towards the morning it increases.

The REM sleep is the sleep during which you dream. When people are woken up during this stage, 80% report that they have been dreaming (Hartmann 1967).

Dreams are difficult subject: but there have been theories of why dream occur and during REM sleep. Freud talked about dream expresses unconscious desires, but there have been primitive tribes who actually train their young to fight their foes in dream (face an anaconda). The research on dreams is an active area (please refer to Dreaming: Journal of the association of the study on dreams)

What if you deprive someone of sleep? You know that this has an adverse effect on functioning. But REM sleep if deprived has disastrous consequences to the point of psychotic like features.

Can you train to sleep more or less? Yes you can. Da Vinci was a very prolific artist, architect, and scientist, writer he had trained himself to sleep every 4 hours sleep for 15 minutes and then he would wake up fresh to work

Napping it is polyphasic (similar to the sleep of babies and young children) Einstein used to take short naps and his sleep need was satisfied

Sleep disorders:
There are several sleep disorder, the most common of which is insomnia (which we all have gone through at some point in time), or hypersomnia where you want to sleep (and I know many young people who go through these stages. This is related to hormonal states and even body energy levels

Sleep apnea:
People suffering form this disorder keeps waking up during the night because they cannot breathe. They stop breathing and therefore wake up repeatedly. This is due to loss of contraction of the diaphragm which occurs when involuntary control of sleep takes over (remember in REM all muscles are paralyzed!). One patient woke up 360 times a night—n o wonder he reported being tired during the day!! There are surgical procedures such as tracheotomy which help patients who have a severe form of this disorder
Nocturnal myoclonus: is the twitching of legs at night or Restless legs where one person keeps waking up because of the legs twitching involuntarily
Narcolepsy: is also known as REM attack. This is a very serious as well as an interesting disorder. In this disorder, the person moves directly form the waking state into the REM sleep. The body loses tone and the person becomes flaccid-REM attacks are sudden and can be dangerous. Especially if the person is driving a car or doing some heavy machinery work. Amphetamine is used for treating patients suffering form this disorder
Sleep paralysis:
When you wake up but feel unable to move upon waking up. The muscles are still under the inhibitory control of pontine gigantocellular nuclei which stop the body from moving during REM sleep.

Brain correlates:
Jouvet has identified the Raphe nuclei as the critical are in sleep. Jouvet lesioned the Raphe nuclei of cats, destroying about 80% of serotonin. This led to Insomniac cats. Similarly PCPA also reduced sleep of cats for over 200 hours.

Moruzzi and Magoun (1949) showed that if the Reticular Formation (now known as the Reticular Activating system) of animals are electrically stimulated it leads to desynchronization of all electrical activity of the brain. Sleep animals wake up, awake becomes alert

The Locus Coeruleus containing Noerepinephrine is also important in sleep and awakening. Animals with Lesion in the locus coeruleus– spent more time in sleep

The Pontine nuclei are important because of their involvement in REM sleep. There is a group of cells known as the Gigantocellular Tegmental field (FTG: Giant cells of the tegmentum) which control the D sleep. Animals can sleep but the sleep is restricted to slow wave sleep.

Thus, we have seen that sleep is very important, and we are still waiting to find out why we sleep! Sleep is an important motivated and survival behavior

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LESSON 42

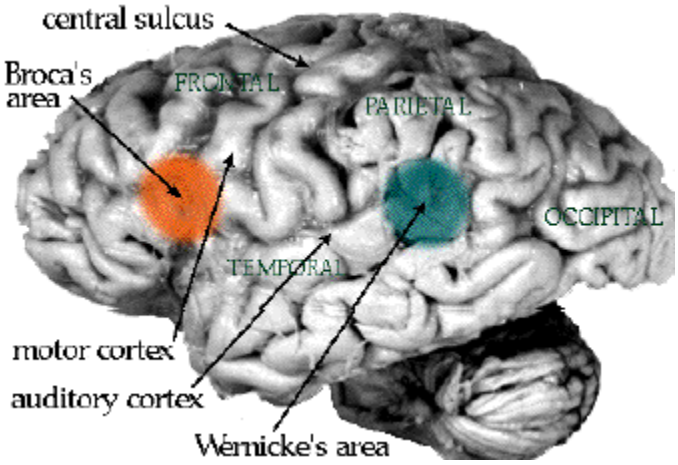
HIGHER ORDER BRAIN FUNCTIONS

Objectives:

The students would be familiarized with the role of higher order brain functioning. This is the role of the highly evolved areas of the brain, the cerebral cortex.

Brain correlates

- **a)** Language Speech Production Comprehensions, Aphasias
- **b)** Visuospatial, The man who mistook his wife for a hat?
- **c)** Apraxias.(Neuropsychological tools)
- **d)** Brain correlates of Learning and Memory, Amnesia, Verbal, Non verbal memory,
- **e)** (Neuropsychological tools)



When we refer to the higher order functioning we are focusing on the cortical control of major functions. As we stated in our earlier chapters, the higher the animal on the evolutionary scale the more the cerebral cortical control over these functions and development of newer functional connections.

Behavioral neurosciences is attempting to

- Understand functions such as language, emotions, learning, memory and psychopathology,
- Develop models to explain the function of cortical areas as they relate to behavior

We would discuss language which humans have evolved as specialized communication. This is not just communication but language is intertwined with development of healthy and pathological behaviors

Language

This is among the most important higher order function, and is uniquely human but not so, because if we look around us we can see examples of communication in other animals as well. For example, Bird songs dog's growling are complex communication system, with the variation - which can communicate the state of one dog to another – even across species communication can take place through these signals.

In the squirrel monkeys language comes under limbic control, in humans vocalization is both limbic (non verbal: cries, groan, gasps,) and cortical (: verbal, and symbolic). The development of language is based on capabilities already present in the nervous system.

Therefore the evolution of language involves

- Appropriate development and evolution of cognitive and communication abilities and apparatus. The abilities of primates are limited with categorization of calls i.e. the alarm calls are different from the mating calls. These do not have the sophisticated mechanism for variation as humans have.
- A structure of language in a formal system of signs and symbols
- Development of the language in children who have the capability of doing so

Speech is difficult (fairly impossible) for a non human primate and young humans as the appropriate mechanisms have not developed physically. It is only about 50,000 years ago the tracts and physical apparatus for language evolved (this is controversial and the brain and language capabilities must have evolved together).

Language in Non Human Primates

Communication Non human primates: primitive, gestures, postures, (more non verbal) calls of different types: alarm, distress, territoriality threat but not complex communication such as, how are you today? This is not possible for animals even the higher order primates (except for humans).

In innovative experiment carried out by Gardiner and Gardiner where they trained a chimpanzee Washoe to communicate with humans using the American Sign Language. The chimpanzee learnt over a hundred signs and exhibited capability of communication equivalent to two years (human) with "slot grammar" such as a human child would use: long darkness for tunnel. However this chimpanzee was not able to verbalize.

In primate's one call, one sound is communicating one message, whereas human language uses a combination of a few sounds to lead to thousands of words (with intonations entirely different interpretation, grammatical limitations and boundaries. The same sound uttered in different ways in different situation leads to a different interpretation

However, many experimenters such as Premack and Premack have led us to rethink. First and foremost man and chimpanzee share 96% genes it is possible that chimpanzee can develop language as humans did.

Lana, a chimpanzee at the Yerkes Primate Institute, developed grammatical relationships on her own such as saying "Lana wants banana" and connected novel strings of symbols using computer and other symbols, innovation in picking up and expanding on the learnt words demonstrated that there were capabilities in the primates closest to humans. There was not much learning by interaction and socialization

We must understand that language development requires learning by interaction and socialization. How does a child learn a language? Through imitation and reinforcement of the words expressed till they become meaningful and can get the desired objects such as candy or food. Even human children if brought up without such stimulation do not develop language even though they have the capability of doing so. For example children reared by wolves don't have the human language; they can only communicate like the wolves by snarling, growling or barking.

Speech Production and Comprehension

In order to understand speech we move through the absence of speech. Stroke, accident or any other traumas which lead to loss of speech.

One of the disorders of speech is Aphasia which is disorder of comprehension or production of speech

Speech production: is based on several abilities: sensation and perception of the surrounding, memories and imagination; connection between past and present, vocal capabilities, articulation musculature.

Paul Broca a French neurologist described a patient who had great difficulty in producing speech. Broca described the cases of 14 patients at a conference – and his paper went unnoticed. These were stroke patients who had middle cerebral arterial supply of blood to the Sylvain fissure affected leading to similar difficulties. He then identified this area as inferior prefrontal cortex

Broca's aphasia(Aphasia: Greek word, A: without, phasia: speaking out): Broca's area in the frontal lobe controls the musculature and other mechanisms (air vibrating in the vocal cords) and damage to inferior left frontal lobe, The Broca's area contains motor memories of tongue, lips, jaw, coordinated and sequenced movements. It lies adjacent to the controls of face and lip, though the posterior parts of Cerebral Cortex want to say it but the frontal damaged area makes it difficult

Brocas aphasia: is mainly a disorder of expressive speech. This results in slow laborious and non fluent speech. Broca's aphasics make an effort to locate words to express what they want to say, they mispronounce words but usually come out with meaningful sentences. These aphasics have difficulty in small grammatical mistakes such as the use of a, the, some, in, about (linking words)

They can articulate little words with grammatical meanings: Function words are difficult, but content words come easily, as they can convey what the patient is trying to say, "Ah Monday, Ah DAD, Paul and Dad, hospital… Wed…. 9p.m. (Goodglass 1976, p 278 cf Carlson 1994 and Bridgeman 1988)

Their speech is telegraphic, and there is no impairment of speech comprehension

A series of Neuropsychological tests which can assess Broca's aphasia are for example:

A picture is shown to the patient where a horse and a cow are standing in the same posture. In one picture the cow is kicking the hind leg of the horse with its hind legs, and the second picture the kicking is reversed. There are questions of what is happening who is kicking who and where? The correct grammatical order is required (Shwartz, Saffron and Marin 1980)

Task sequencing commands are also given, word order is disrupted because they difficulty in carrying out a sequenced response. If this area is stimulated it leads to a coordinated movement, lesioning blocks the coordinated sequence. Questions can be "Pick up a red ball and touch green circle," difficulty in saying it is difficulty of muscles of speech production.

Speech Comprehension

In Speech Comprehension the areas in the auditory lobe are involved. Wernicke's area is located in the Middle and Posterior region of Superior Temporal Gyrus.

The speech comprehension area collects information, matches, recognizes, and analyzes it and sends it to the articulation areas (through the arcuate fasciculus). Recognition of a word involves

a) Sensation,
b) Perception
c) Memories of the sequencing of sound articulation.

Damage to this region leads to receptive speech disorder

Primary characteristic of Wernicke's aphasia is that the speech appears better than Broca's fluency rhythm as the articulation intact but what they say does not make sense. However, they cannot recognize the deficit. Poor speech comprehension and production of string of meaningless words characterizes Wernicke's aphasia. Wernicke's patients are not aware of their problems with speech. Wernicke's patients not aware of their problems are speech. They are not aware that people don't understand them, or they are having any difficulty. What they say or hear is incomprehensible to them and others

Speech appears correct to a foreigner but to those who know the language it is nonsensical. As an example,

When asked what do you do?

The patient replies, "Mista oxycge,wann tell happened when happened, herent, kell, cam ho, renrapiers" and the patient is satisfied that he was answering the question

The neuropsychological tests for speech comprehension e.g. the Patient tested through questions of receptive speech: point to pen, your nose,

The deficit is at the semantic level (meaning of the words) their deficit is in understanding speech and its meaning

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LESSON 43

HIGHER ORDER BRAIN FUNCTIONS

Objectives:

The students would be familiarized with the role of higher order brain functioning in disorders of speech, motor and sensory apraxias, memory and amnesias.

Brain correlates

- **a)** Language Speech Production Comprehensions, Aphasias
- **b)** Visuospatial, The man who mistook his wife for a hat?
- **c)** Apraxias. (Neuropsychological tools)
- **d)** Brain correlates of Learning and Memory, Amnesia, Verbal, Non verbal memory,
- **e)** (Neuropsychological tools)

Aphasia and Dyslexia:
Aphasias and Dyslexia are related because the spoken words are transferred to written language. Reading and writing is closely tied to listening and speaking auditory modality). Wernicke's aphasia is accompanied by dyslexia.

Interestingly, there are more dyslexics with Wernicke's aphasia in English and other western language, but not so in Chinese where each word is represented individually or where the sign language (spatial not auditory modality) is used.

Chinese aphasics retain ability to write accurately. The Japanese language comprises of two forms the Kanji and the Kana. The Kanji symbols are the pictographs adopted from the Chinese language. These are the visual representation of concepts, thus a house would be shape of a Pagoda. On the other hand the Kana symbols are acousitic or Phonetic representations. Thus Kana (sound, auditory mode), and kanji (visual mode) Sasanuma (1975) reported that left temporal lobe lesions affected the writing of the Kana symbols but not the Kanji where visual cortex is involved).

The Japanese language:	3 phonetics and 1 pictograph	
Mode:	Kana	Kanji
Brain areas	left temporal lobe	Visual cortex

Generally most languages use sound and acoustic signals and cues to write (look at how recite our nursery rhymes and how we remember the correct spelling of words). The question is if we are so dependent on the sound for language what about the deaf? Interestingly the deaf are not dyslexics with receptive aphasia (as they read without phonetics (Braille, the language script of the blind is a touch language)

Aphasias related to speech
A wide range of disorders even within the major aphasias, the characteristics differ with areas of damage. We will disucss some of this aphasia in brief.

a) Conduction Aphasia: is produced when damage to inferior parietal zone disconnects the axonal fibres connecting the Brocas and the Wernicke's areas. Conduction aphasics have meaningful, paraphrasic speech, somewhat fair comprehension, but poor repetition (they can repeat single and meaningful words, but not non-meaningful words)
b) Anomic Aphasia: This is aphasia specific to names. They have difficulty in finding the right word, so they use circumlocution going the round about way

I had a patient who had anomia after a stroke

When asked to identify a stapler in a picture: What is it?

He replied, it is used in the office.
Yes, but what is it?
It is used to pin papers together
Yes, but what is it?
He showed how it worked
Yes but what is its name
He could not give the name even after several attempts.

This illustrates that he knew what it was, what it was used for, but could not name it.

There are cortical aphasias and Trans cortical aphasia, and sub cortical aphasias, but we would not be discussing the whole classification, this should be enough to give you an idea.

Dyslexia: (Reading, Writing, Mathematics)
Reading and writing disorders are related to the kind of aphasia that patients have. The patient with Wernicke's aphasia would have difficulty reading and writing as they do comprehending speech. Broca's aphasics have difficulty in reading out aloud; their writing and speech both are agrammatical

1. **Alexia with Agraphia:** This is a difficulty in which the person has difficulty in reading and writing. This is caused by damage to the left angular gyrus in the parietal lobe (angular gyrus is at the borderline of visual, auditory and somatosensory cortices therefore it may affect skills involving all three modalities
2. **Pure Alexia:** This is actually word blindness, where alexia occurs without agraphia: patient can write but cannot read what he writes. Although they cannot read, they can recognize the words if they are spelled out to them. Pure Alexia is a perceptual disorder, similar to pure word deafness only it is visual not auditory.
3. **Agnosias** are disorders related to sensory modalities either auditory or visual

Disorders of auditory perception Agnosias:
An auditory agnosia is the impaired capacity to recognize auditory stimuli, perhaps due to a disturbance of perceptual processes more than sensations. There appears no problem with the input of information but of giving it meaning and of recognizing it.

We will discuss only two of these here
a) Amusia
b) Agnosia for Sounds

1. Amusia: subdivisions of this disorder are tone deafness: inability to discriminate various tones of musical scales, and Music deafness: impaired recall or recognition of a melody, tune) as well as rhythm, measure, or tempo (beat), and Receptive amusia; difficulty in discriminating basic notes of music or series of notes of pitch, rhythm etc

2. Agnosia for sounds: inability to identify what the different nonverbal sounds mean (classification difficulty? For example if there are different kinds of bells ringing —church, school, telephone, the patient cannot tell the difference. These sounds may sound all alike, or may be confused for each other. So basically it's discrimination and categorization deficit.

For these disorders it appears that the bilateral temporal regions are involved

Visual deficits: These are deficits related to integration or processing of visual information. Agnosia is a failure of recognition, not due to sensory (the input is all right) or intellectual problems (the patient does not have any intellectual impairment).

Visual Agnosia: is Agnosia for visual stimulus. It is not a seeing deficit, as the patient can see but cannot put the pieces of visual input together in a coherent form.

Very interesting deficit: **Prosopagnosia**

Prosopagnosia is Visual Agnosia: Faces is the first key you have to other people- friend or foe? There is a dictionary of features of faces where every face is immediately matched. Prosopagnosics have difficulty recognizing a face know it is a face but who?

The patients report seeing parts such as nose, eyes, lips but cannot put it together. In order to recognize a face you have to match and put together the entire feature in a coherent face. In extreme form of this deficit patients cannot even recognize themselves in the mirror. This is due to damage to the Inferotemporal region. There are some patients who have difficulty recognizing only the familiar faces, while others have difficulty in recognizing unfamiliar faces. They can sometimes use a cue such as a mole or a scar to recognize a face. It is a visual-limbic disconnection (especially for familiar faces) of the Right hemisphere region

Apraxia is movement or motor difficulties when required to perform at a verbal command. Though these tasks can be performed spontaneously (can be copied) without problems. Apraxias are bilateral but usually produced by the left hemisphere lesion. This deficit was first described by Hughlings-Jackson

Apraxia: Greek word praxis: no action. The missing or inappropriate action is not due to paralysis or difficulties of motor movement, or of understanding of instructions, or motivation, but difficulty in carrying out the action required.

Construction Apraxia: is tested by asking the patient to copy or draw or build blocks in a given design. There is both left hemisphere and right hemisphere damage. LH is oversimplification, very little details, whereas RH damage leads to loss of overall gestalt

We have seen some of the deficits which are caused by damage to the cortical areas. This requires complex neuropsychological examination and rehabilitation strategies can be developed keeping each patients individual deficits in mind

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LESSON 44

HIGHER ORDER BRAIN FUNCTIONS

Objectives:
The students would be familiarized with the role of higher order brain functioning in learning, memory and amnesias.

Brain correlates:

- Brain correlates of Learning and Memory, Amnesia, Verbal, Non verbal memory,
- Famous case of Amnesia, H.M.

Memory is one of the puzzles where biologist, physiologists, neurologists started working early on Krech (1973) spent a lifetime investigating memory believes that memory is one of the most intriguing phenomenon. There are many hypotheses and there are many frustrations for those working in this field. Lashley was pioneer in the area of locating engrams- basically he was a zoologist trying to locate where memories are " I sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning is just not possible. (Lashley 1950)

Memory is defined as information stored in the brain because of sensory and other experience (Bridgeman 1992, p324) and learning is the acquisition of new memories. However, where exactly is happening and how? Is there a specific location or diffuse connection and locations?

Lashley formulated two principles: the Principle of Equipotentiality and Principle of Mass Action

Principle of Equipotentiality:
Lashley trained rats to run the maze. The animals learned to discriminate between the light and dark alleys. They were rewarded for light alleys and punished forgoing into the dark alleys. Lesioning various parts of the brain, he found that disruption of learning took place after lesions of the visual cortex. He reported that for retention of visual tasks Visual cortex important. Various parts of cortex contribute to memory at least for complex behaviors. No one part is more or less specialized than other" Neurons within a given sensory area is capable of participating in memory formation- all are equipotential in contributing to the retention of a task. Memories are also discretely located within each sensory cortex (though diffusely spread in that area) There are also memories for the specialized sensory function.

Principle of Mass Action:
Lashley's rats were trained on complex tasks utilizing information from various sensory modalities, requiring visual cues, somato-sensory cues, kinesthetic and even auditory cues. This involves mass action. Thus, information from all cortical areas is integrated to form complete memories. After the learning had taken place Lashley lesioned parts of the cortex and found that the greater the extent of the lesion, the greater the deficits in memory. Retention is related to the size of the cortical areas removed. Thus, it appeared that cortical area is not important only the extent of damage. Therefore, cortex works as a whole, the more cortex involved in learning the better it is. The same principle holds for man and for rats. As an example, soldiers with head bullet wounds exhibited lower IQ on tests performance, and the lowering of I.Q depended upon the overall amount of brain damage. The amount of remaining cortex is more important than the region states Grafman and his colleagues 1986)

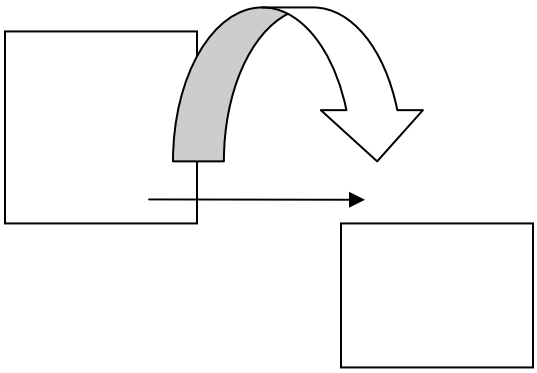
There are many more questions to memory. It is intriguing to how we learn, forget, how we remember friends, their faces, spellings of names or generally, telephone numbers etc. The question is also why older people remember events long past better than immediate past, where are our memories located?

There are many such questions.

- Why do different areas store different part of the memory picture, how does it get integrated. One piece missing how the defect is covered, or compensated.

In the 1950's two different memory storage systems, the Short Term Memory (STM) and the Long Term Memory (LTM) were hypothesized. Memories are retained in the STM(stored temporarily) when the physiological changes to store in the long term memory are taking place, the STM memories are transferred to LTM.

Short-term memory **repeated thinking and reviewing**



Long-term memory

Hebb one of the pioneers of neurosciences and of memory research stated that memories remain in STM temporarily. The reverberating neural activity (neural activity, which goes, round and produces structural changes in synapses) leads to LTM storage. Thus, the changes in neuronal biochemical structure are the basis of LTM storage. He proposed a Two-stage memory theory is supported by everyday evidence that unless you keep repeating telephone number it becomes difficult to recall it!

Cross modal transfer:
It is possible to learn with one sensory mode and use what is learnt and retained, in another mode. For example, the visual scanning of mazes takes place, then one can go through it using the kinesthetic mode. Humans and higher primates can do that easily but lower animals cannot transfer information from one modality to another. If memories were diffusely stored then lower animals should also be able to do the same

Problems and Issues in testing memories:

a) There is no adequate method to identify where memories are stored, where memories stored not known effectively even after so many years of research,
b) Performance not memory may be affected (if you remember there was a famous joke that if you cut frog legs the frogs forget to hop across lines--- performance not memory was affected by cutting the legs)
c) How do we know that connections of other areas are not damaged by lesions to one area? Lesion in one area may alter connection in other,
d) Lastly, is what we assess if the loss of memory or the loss of retrieval of memory?

Biological Systems and Memory:
Researches using single cell recordings have shown that learning changes single cells. There are measured increases in calcium in neurons, decreases in potassium flow, increases in number of certain synaptic receptors, changes in RNA and proteins. Impaired learning may be due to the deficits in biochemistry.

RNA:
These are the memory code molecules. There are qualitative and quantitative changes in measures of RNA and protein synthesis in animals, which have learnt a task. Heredity is memory passed on from one to another generation. The DNA is the template for RNA-, which determine the structure of proteins. Hyden and Colleagues (1962) trained rats to walk on a tight rope as compared to normals. There was increase in increase in RNA in brain cell nuclei. Glassman and colleagues (1974) showed that changes in RNA and proteins were found after learning a shock avoidance task. Shock avoidance where the rats had to jump onto a platform at the sound of a buzzer, whereas the controls had a buzzer but no shock/ and or no platform to jump. These rats were injected with labeled Uri dine (precursor for RNA), or labeled lysine (precursor for protein), 30 minutes before the experiment. The amount of Uri dines incorporation decreased with time i.e. RNA synthesis decreased after training and lysine increased after training. RNA coding for new protein. Labeled Lysine injected carried into cortex and hippocampus with acquisition. Interesting experiments have also been carried out where rats, chicks and other species were trained and learnt a task, these animals were decapitated and their brains homogenized and injected into the normal rats. It was found that the injected animals learnt faster than untrained or un-injected rats.

Protein synthesis:
Researches on single cell basis of learning have indicated evidence that Proteins synthesis is a necessary step in long-term memory. Proteins synthesis modifies characteristics and properties of neurons. Drugs that inhibit protein synthesis impair LTM storage but not STM. The increased inhibition leads to increased deficits in learning (Bennet et al, 1977). Anisomycin blocks protein synthesis blocked rats memory of location of the shock but not the memory of location of food!

Other important bio-chemicals are Cyclic Amp, ACTH, Vasopressin, Acetylcholine and NE

Other Influences on Learning and memory:
Stress interferes with learning and retrieval of information. We all are familiar with Blockade before important paper! Electroconvulsive therapy blocks protein synthesis

Hebb's consolidation theory time required for STM to LTM any interference with consolidation would result in disruption of long-term recall. If there is a head injury then memory of events prior to injury lost (retrograde amnesia), destroyed as evidence indicates that a small reminder brings back memories .In head trauma memory returns after delay or under tranquilizers.

ECT affects both long term and short-term memories: Kalat (1980) "ECT interferes with memories that are active at the time of ECS regardless of the fact whether formed recently or long ago"

Plasticity and the nervous system
Experiments by Hubel and weasel have shown that anatomical changes take place in the visual cortex with experiences. Horizontal goggles worn by kittens during early period of development lead to firing of neurons when horizontal stripes are seen as adults.

Similarly, if one eye receives more stimulation, the brain area for that eye is enlarged (more neurons respond)

Shock to the foreleg of young kittens led to a greatly enlarged somato-sensory cortical area (Increased stimulation led to increased areas for responding).

Merzenich carried out an experiment where he joined the third and index finger by sewing them together, the area for this "one" finger becomes large. If the thumb is removed the areas for thumb in the cortex becomes smaller. MRI's studies of violinist's brains showed that their cortical auditory areas were enlarged as compared to normals.

Super Plasticity in growing Brain?

There have been studies which have shown that an early start e.g. for musicians, for language proficiency, for players, for gymnasts, there is need to start early. As the information, being sent to the sensory cortices when learning is taking place. In language learning, the left hemisphere growth spurt is recorded on EEG between 2-4 years of age, and another 12-15 years again only in the left hemisphere.

There is increasing research in the early development and the neuronal stimulation, nerve growth factor, and stem cell research.

Brain correlates of Learning and Memory, Amnesia, Verbal, Non-verbal memory, tests

Amnesia is a memory disorder, and patients suffering from Amnesia have been studied to find out more about how memory works. One of the most famous cases of amnesia is

H.M: pure amnesic: H.M. had severe epileptic seizures and for treatment of epilepsy, surgery was carried out when he was 27 years old. In addition, after the surgery he has been in the time freeze of being stuck at 27 (even 40 years later) HM has amnesia for events prior to surgery, and has no LTM. He actually lives in the present, in STM. He ahs no IQ loss as assessed by IQ tests. He has been tested for memory using the mirror drawing task, the digit span test, Block tapping memory span test, Incomplete pictures test, and even eye blink Pavlovian type conditioning response. He has damage in the temporal region and this has provided evidence of the importance of temporal lobe (and hippocampus) in memory.

Amnesia

- Anterograde:loss of ability to learn new information. The amnesic can remember events before surgery or injury. The complex perceptual motor learning abilities however are intact in these patients. Karsakoff's syndrome is the severest form of Anterograde Amnesia, where damage is to the mammilliary bodies and temporal lobe
- Retrograde. This form of amnesia is inability to remember event, which had occurred before brain damage. Confabulation is creation of pseudo memories to fill gaps.
- Alzheimer's disease is one of the major diseases, which leads to severe memory loss. This is the most common cause of dementia (memory and intellectual impairment) research has provided evidence of Neurofibrils, amygdloid plaques, neural degeneration, also reduction in ACH as the underlying pathology in Alzheimer's Studies on amnesiacs have shown:

1. Hippocampus is not the location of Long term memory nor is it important for retrieval of long term memories
2. It is also not the location for immediate memories
3. Hippocampus is involved in transforming STM to LTM

Studies have also shown the importance of mammilliary bodies, and the Dorsomedial Thalamus in memory.

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LESSON 45

HIGHER ORDER BRAIN FUNCTIONS

Objectives:

The students would be familiarized with the Brain Hemispheric differences, Laterality, specialized role of higher order brain functioning. Brain Damage and behaviors. Neuropsychological testing would also be discussed

Brain correlates:

- Brain correlates of Learning and Memory, Amnesia, Verbal, Non verbal memory, (Neuropsychological tools)
- Split Brain studies, Brain Hemispheric differences, laterality One brain/Two Brains? Brain Damage and Plasticity
- Neuropsychological Tests
- Cerebral hemispheric specialization

Have you ever wondered why we have two lobes instead of one? Do they work as one brain or two? Are they independent or do they communicate with each other. Is there any hemispheric specializations (doesn't seem possible if you know that all neuroanatomical areas are bilaterally located, right?). But did you know that brain areas are not exactly alike, and that each command center deals with the opposite hemisphere. All fibers cross over except for the visual pathways, which are partially crossed. This makes for a very complex research area, which was only focused in the last few decades.

Fact: The two lobes are connected by commissures.

Fact: There are specializations of functions.

Fact: There is cooperation as well as competition between the two hemispheres.

The earliest study reported on the "specialization" of brain hemispheric specialization was reported by a French Neurologist Marc Dax. Dax presented his report on the findings of brain autopsies in a conference in 1836. The interesting findings were that patients with strokes, who had speech problems brain damage, all had damage to the left (none in the right hemisphere). Not until 25 years later did some one bring this to the attention of the world obvious functional specialization is speech and language abilities. In the mid-1800s, Paul Broca (a French neurosurgeon) reported two cases of aphasia where the left hemisphere damage and speech production was identified. This is now known as **Brocas area** (for speech articulation. Shortly afterwards, a German neurologist, Carl Wernicke, identified another part of the left hemisphere primarily concerned with language comprehension **(Wernicke's area)**

Two studies in 1959 and 1961 produced evidence that unilateral lesions produced deficits which were evidence for brain hemispheric specialization.

Roger Penfield and his colleague Ebert (1959) reports on neurological patients and Russel and Sapir (1961) on military personnel. Their results indicated that language was dominant in left hemisphere for both the left and the right hemispheric dominant persons. (Remember: If you are right hemisphere dominant, you are left handed, if you are left hemisphere dominant then you are right handed)

Brain Hemispheres: Two Brains or One?
The interest in further research in this area was stimulated accidentally. The major names in this area are Penfield, Sperry, Gazzaniga, Milner, and many others who were pioneers in this area

These studies used Commissurotomy, or Split Brain Procedure. This procedure uses a knife cut to sever the commissures (including the Corpus Callosum) so that the two hemispheres cannot communicate with each other. Interesting things happened. Outwardly these individuals seem normal, but sensitive neuropsychological tests revealed that there were deficits. These tests were visual tactual verbal etc. These tests were devised so that information could go to only one hemisphere. When words were presented to the right visual field to reach the left hemisphere, the person could read it out loud (and also write it). But then when it was shown to the right hemisphere the person reported he saw nothing. The right hemisphere did not comprehend? Or perceive? It was thought that the left hemisphere did all the work, and the right only was in a supportive role. It could not talk about what it saw, but when the methodology was changed and the person was asked to pick out words from a group of alphabets or objects form a group of objects, he picked the right ones!

When **HEART** was flashed on the screen in such a way that **HE** was in the right visual field so that it input only the left hemisphere and **ART** input to the right. When asked what he saw, he stated **HE**, but when asked to pick out words form a bloc of words given, he picked **ART**!

In other studies, when a split brain patient was walking through the room he acted as a blind man not able to see while he walked, but he could identify objects in the areas when asked verbalize.

Thus do we have two brains or one, this is the question researchers asked, and what is the role of each

Brain Lateralization exists and the two halves of the human brain are not exactly alike. Each hemisphere has functional specializations: some function whose neural mechanisms are localized primarily in one half of the brain.

Handedness:
Handedness as
(a) The hand that performs faster or more precisely on manual tests, while others define it as
(b) The hand that one prefers to use, regardless of performance.

Majority of us are right handers (left hemisphere dominant), but there are reasonable number of people who are left handed, and a small number is ambidextrous. Famous left handers are Leonardo Da Vinci, Michelangelo, Napoleon, Alexander the great, and Baden Powel (ambidextrous: means can use both with equal proficiency)

We also have dominance for foot (which foot used for kicking a ball or stepping on a stair first), eye (if you are to use a telescope which eye would you use), ear (which ear do you use for listening to the telephone). Dominance can be assessing by tests such as the **Harris Tests of Lateral Dominance.**

Asymmetry in faces is also reported, and Sackheim, Gur and Saucy (1978) took photographs of expressed emotions and cut them and made composites, left-left (left half face) composite, right-right composite (right half face composite), and had subject compared it with normal pictures for intensity of emotions. They found that subjects reported the left-left faces more intense as compared to the right –right (why? Because the right hemisphere cannot speak, so images have to be more intense for the visual input, whereas the left hemisphere can express itself through words.

How do we explain asymmetry?
There are two schools of thought a) one which believes that the: brain is equipotential for specialization and at around 2 years of age the division of labor and specializations of the two hemispheres is completed. The two hemispheres compete for control e.g. when both try to speak at the same time stuttering occurs, Orton (1939).

The other view point is that it is inborn and innate. This is even before any cultural or learning influences can take place. For example, the planum temporale in the left hemisphere is larger in the fetus. Therefore language is programmed to be in the left hemisphere

Tests for Language and Other Functions.

1. **The WADA test:** In this test Sodium Amytal, a barbiturate is injected through the carotid arteries (main arteries which carry blood to the brain). This injection is made unilaterally (to one hemisphere only) and the patient is required to speak a list of words. When the language hemisphere is anaesthetized, the patient's speech becomes slurred, till it is blocked completely. Milner branch and Rasmussen (1966) studied 212 patients like this to identify hemispheric dominance for speech.
2. **Zeidel lens** (a specialized tachistoscope) was used to project images only to one hemisphere to test verbal, visual, language and other asymmetries.
3. Dichotic listening tests: this is a test which sends out two different types of auditory signals to the left and the right ear. For example, it can send alphabets to the left ear and simultaneously send out numbers to the right ear. The subject is asked to repeat what they hear. The dominant ear would hear, and therefore the list given by the subject would be of what the dominant ear heard.

At present research is ongoing and it has been recognized that each hemisphere is specialized to work alone and to work together.

Unilateral neglect, unilateral sensory neglect
This is very special disorder affecting response to one side of the body, somato-sensory, or visual field. It is characterized by the patient not attending to one side only. This occurs as a consequence of damage to either hemisphere in the spatial recognition the **parieto-occipital** area. This is a lateralized deficit i.e. the patients don't respond to the side/ visual field opposite to damaged hemisphere. How can we assess this simply by asking the patient to draw a clock face with numbers and showing a specific time – let's say 10 to 11 o'clock. And the patient draws only one half of the clock. In extreme cases the patients eat from one side of plate, or shave one side of face, put lipstick on only half the face, interestingly if we move them around they are able to describe the whole as their body moves.

More interesting and intriguing is the finding that we may have our frontal cortex controlling the rest of the body and brain, as the Chief executive.

Frontal lobe
Orbit frontal: there is an interesting paper entitled **No Longer Gage**. This is about a person named Phineas Gage who was a railway laborer. During construction, he had a major head injury where the rod he was holding went right through his head. He survived but he changed personality, he was no longer the same person. His family and friends said- he was no longer Gage. It was found that his injury to the Orbito frontal areas changed him. There is now much research which indicates that judgment, personality, fore sight, "conscience" reduced impulsivity are all located in this area. As a child grows, inhibitions of the society and culture learning are all programmed in this area. Similarly control of all emotions also resides here.

- **Neuropsychological tests:**

a) Luria, the father of Neuropsychology developed a series of tests to assess all abilities, but holistically and by varying the tasks. For example to test handed ness, he would give the same task but use different modalities (visual, somato-sensory: touch, language command etc) different tests). These have been incorporated in the Luria Nebraska Nueropsychological test Battery

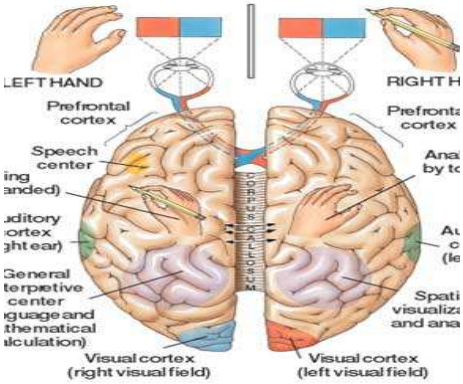
b) Halstead Reitan Battery also tests such as the grooved pegboard, the tapping tests etc.

- **Harris tests of laterality**

Research ongoing but both hemispheres work and compete, they are working together, sharing information through corpus callosum this gives ones behavior a holistic, and a gestalt. Each hemisphere needs the other, to provide back up information.

What if one hemisphere only? There have been cases where through surgery or brain injury or even birth or developmental trauma, one hemisphere has been lost

If there is only one hemisphere, the remaining hemisphere can take over functions- without any visible or other deficits. The earlier the traumas the more easily can the functioning take place. In later life, it becomes difficult for the hemisphere to relearn.



Neuropsychological Tests

Neuropsychological assessment of cognition and other functions is carried out by trained neuropsychologists (brain-behavior relationship specialists).

A formal interview is carried out initially followed by review of all medical and other history taking records (whether they have been treated, birth traumas school records,) interviews of parents, or relatives and neuropsychological testing using formalized procedure and tests

Neuropsychological testing aims to assess a patient's higher order functioning of attention, memory, speed of information processing, language, visual-spatial ability, sensory processing, motor ability, executive and intellectual functioning. This is based on the referral questions and also the previous history of the patient. This also helps in developing a rehabilitation strategy.

The referrals for neuropsychological assessments are
a) Stroke patients
b) Head injury patients
c) Children with slow development or difficulties in speech, attention or learning
d) Chronic alcohol or substance abusers

Some neuropsychological tests
There are several protocols available, the two well known batteries are a) The **Halstead Reitan Neuropsychological Battery** is older and which takes about 8 hours for a patient to complete. The second battery is the **Luria- Nebraska Neuropsychological Test Battery** which is developed by American Neuropsychologists based on Luria's techniques. This is has a series of subtests but takes less time and has more flexibility (qualitative information). These tests assess motor, sensory, visual language, kinesthetic, attention, memory, receptive and expressive speech (speech sounds rhythm) tests.

Test also assess if the patient is following instructions through different modal tests

Two of the simplest tests which I have used which provide rich information are the **Trails making A and B:** these are part of the Halstead Reitan Battery. They appear simple where the patient has to join lines of various numbers in Part A and numbers and words in alternating sequence in Part B. Spatial organization, grapho-motor speed, recognition of numbers, visual pursuit, vigilance and number sequences is measured by this. **Part A** evaluates visual motor coordination and visual scanning as well as short term memory. **Part B** measures higher order functioning as it requires alternating between numbers and letters, ability to learn an organizing principle and apply it systematically, also verbal problem solving, and planning action beforehand.

Thus, the Neuropsychological tests are effective tools for a trained person. These tests are used for diagnosis, to identify deficits due to illness or injury, to assess learning problems, reasoning and problem solving abilities, ability to understand and express language, memory and attention especially post trauma, visual-spatial memory and organization, visual-motor coordination, and higher order planning and organizing abilities.

Course Recap
We have completed the course today, and if we look where our lessons began.

- **a)** We learnt about the development of behavioral Neurosciences as a discipline, the major contributors to this discipline, and how it is made up of specializations from various field of the hard sciences Chemistry, biochemistry, physics, biology and of course this is incorporated to help us understand behavior- both at the lower level (of animals) and of humans
- **b)** We learnt of the various stages of evolutionary development, of commonalities and differences between man and other animals. We also learnt of how the brain developed form a single cell layer to the complex form we have. The developmental journey with nature-nurture interaction, where things can go as programmed if only the right environmental stimulation is given
- **c)** You also learnt about the various neuroanatomical sites and their contribution to behavior, NeuroChemicals and their effect (in some cases very serious psychopathologies and physiological deficits can take place with a single molecule
- **d)** We have learnt how motivational states are neuro-anatomically, neuro-chemically driven. Hunger, thirst, sleep, without which we may not be able to survive let alone function

e) The journey into higher order functioning, language (its deficits) learning and memory (amnesias), disorders such as apraxias, agnosias, aphasias, were also discussed giving you and insight into the neuropsychological area

f) It has always been interesting to teach the brain-behavior relationships, I do hope this course would help you understand your behavior as well as behavior of others better.

There are excellent sites on the web for you to visit and learn more. Some of them are given in the handouts, but others are as follows:

Central Nervous System Overview
Learn about an astonishingly complex system of creases, projections, fibers, branching cells, colors, and connections known as the human nervous system.

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