THE BRAIN:
A SYSTEMS NEUROSCIENCE PERSPECTIVE

Vikas Rai

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The Brain: A Systems Neuroscience Perspective

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PREFACE

It is 'the brain' that stops functioning at the end of the journey of a living entity. The brain is a complex system. It is made up of many subsystems. A complex system means 'whole' is not a sum of the parts. It is characterized by emergent behavior. Therefore, there is an urgent need to understand it as it is. Reductionism of basic sciences does not apply to the human brain. The book is prepared for undergraduate students and instructors working at that level. It is organized as follows:

The first chapter describes the subsystems mentioned in the first paragraph. The central nervous system, sympathetic nervous system, and parasympathetic nervous system are discussed first, as these are the most crucial for the functioning of the brain. Concepts such as cerebrospinal fluid, blood-brain barrier, and blood-cerebrospinal fluid barrier are presented in such a way that even a novice in neurosciences would be able to grasp the fundamentals easily. Neurons and glial cells are discussed next (Chapter 2). Imaging techniques that are employed in the diagnostics of brain disorders and neurodegenerative diseases are also presented in this chapter.

The subsystems of the brain are made of neurons and glial cells. These cells participate in cellular signaling. Thus, cross-talk between different subsystems becomes a reality. This happens either electrically or chemically. The information transport in the brain is discussed in Chapter 3. Spatial navigation is an essential part of life. A living entity executes it for different purposes, *e.g.*, to search for food or better habitat. Therefore, a complete chapter (chapter 4) is devoted to this topic.

Chapter 5 presents a mathematical theory of Alzheimer's disease. This theory posits amyloid β in a new light. It introduces femto particles for the first time. Femto particles are proton–antiproton entangled pairs. It has been shown that these particles have the potential to revolutionize research on Alzheimer's disease, both with respect to detecting the disease at an early stage and discovering drug molecules that could cure the disease. At the end of this chapter, a set of parameters is given that a clinician can use to detect Alzheimer's disease, which is known to be a silent, deadly disease. The last chapter presents the neuroscience of romanticism, a literary movement that has influenced the literature of almost all languages. It resolves to define and refine the idea of beauty for Homo sapiens.

I hope the book fulfills its purpose.

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CHAPTER 1

Elements of Organization

Abstract: The lives of species are trapped within '**cooperation and conflict'**. They compete with each other to win the '**survival of the fittest'**. In **cognitive neurosciences,** action and perception are the most crucial. Perception guides action by selecting targets and correcting errors. This entire process is stored in the memory. It is an essential part of learning and creates the basis for new knowledge by association. Neural circuits that control metabolism and food intake are housed within the **hypothalamus**. It is small in size but plays a crucial role. Temperature, sleep, eating, and social interactions are its responsibility. **Emotion** and learning are related *e.g.*, positive emotion (simply feeling good) motivates students to perform better. **Emotion,** as the present state of knowledge stands, is taken care of by the **amygdala.** Should we consider it the '**heart of the brain'**?

The purpose of this chapter is not to cover all systems or subsystems but to discuss only a select few. This decision has been taken to reduce the complexity of the brain's **neurovascular structure**. Capillaries in the neurovascular structure hold back certain molecules, RNA viruses, and other disease-causing agents (ions, molecules, *etc*). The blood-brain barrier, cerebrospinal fluid, and blood-cerebrospinal fluid barrier are three key elements of the organizational structure of the brain.

Keywords: Amygdala, Adrenergic receptors, Action, Blood Brain Barrier, Blood Cerebrospinal Fluid Barrier, Cerebrospinal Fluid, Cholinergic receptors, Central Nervous System, Emotion, Free Energy Surface Functional, Fluctuations, Hypothalamus, Hidden Environmental variables, Mossy Fiber Synapse, Perception, Parasympathetic Nervous System, Sympathetic Nervous System, Sleep, Statistical Physics, Temperature.

INTRODUCTION

Life is full of rhythms. Pulsations in the heart are represented by the **Van der Pol Oscillator.**

$$\frac{d^2x}{dt^2} + (x^2 - 1)\frac{dx}{dt} + x = 0 \quad (1)$$

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x represents the cumulative charge in the **blood** that the heart pumps. The limit cycle of this oscillator represents robust electrical oscillations of the heart, which continue till the doctor pronounces the patient '**brain dead**'.

The blood-brain barrier (BBB) controls the influx and efflux of biological substances essential for ***homeostasis*** of the brain's microenvironment represented by the neurovascular unit. Blood vessels in the brain capillaries form the vascular structure, which controls the movement of ions, molecules, and viruses of various kinds.

Paragraphs that follow discuss key elements of the organization.

CENTRAL, PARASYMPATHETIC AND SYMPATHETIC NERVOUS SYSTEMS

Electrical signals are responsible for transferring information over long distances within neural systems. Chemical signals are involved in the transmission of information between neurons. Synaptic and action potentials are caused by transient changes in current flow into and out of the neuron. This flow of current in and out of the neuron drives the electrical potential across the plasma membrane away from its resting condition. The transient current flow is caused by ion channels, a class of integral proteins that traverse the cell membrane. The purpose of the nervous system is to transfer information from the **peripheral nervous system** (PNS) to the CNS and send back the information to the PNS. The transfer of information from the external environment and back again is known as **neuronal signaling**.

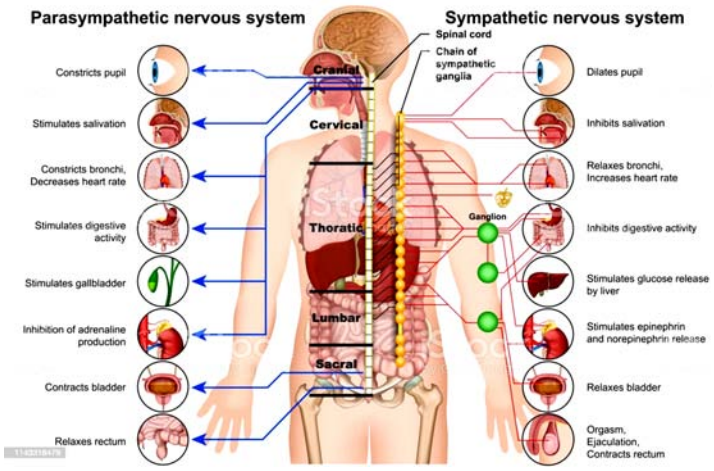

Fig. (1). Central, parasympathetic, and sympathetic nervous systems. The cross-talk between these systems is crucial for the functioning of the brain.

The **central nervous system** (cf. Fig. **1**) is a part of the nervous system that consists of the brain and the spinal cord. The peripheral nervous system connects the CNS to sensory organs such as the eye and ear, other organs of the body, muscles, blood vessels, and glands. The peripheral nerves include the 12 cranial nerves, the spinal nerves, and the roots and autonomic nerves, which are concerned specifically with the regulation of the heart muscle, the muscles in blood vessel walls, and '**glands**'.

The parasympathetic nervous System (PNS) contains both kinds of fibers. These fibers provide sensory input and motor output to the CNS. PNS is a component of the autonomic nervous system that participates in the regulation of bodily functions at rest and during non–stressful situations. It slows down heart rate, decreases blood pressure, and promotes digestion. Conservation of energy, relaxation of muscles, and maintenance of bodily equilibrium after stress or physical activity are its primary responsibilities. The sympathetic nervous system functions to produce **localized adjustments**, such as sweating, as a response to an increase in temperature, and reflex adjustments of the cardiovascular system. Under the conditions of stress, the entire sympathetic nervous system is activated and produces a fight-or-flight response. **Autonomic nervous system** (ANS) refers to collections of **motor neurons (ganglia**) situated in the head, neck, thorax, abdomen and pelvis and the axonal collection of the neurons. The CNS components of the ANS include brain stem and spinal autonomic pre-ganglionic neurons that project to the autonomic motor neurons in the peripheral ganglia.

ENTERIC NERVOUS SYSTEM

It is the largest and most complex component of the peripheral nervous system, with approximately 600 million neurons. These neurons release neurotransmitters to facilitate the motor, sensory, and secretary functions of the gastrointestinal tract. The enteric nervous system interacts with the gut-brain axis. CNS communicates with ENS *via* the **vagus nerve** and **pre-vertebral** ganglia. The functions of ENS are affected by CNS in relation to emotional and cognitive factors. The control of gastrointestinal motility and secretion is mediated through a communication link between smooth muscle cells and glands. The sensory information from the gut is relayed to the CNS, affecting the digestive processes. The neurotransmitters used by ENS are acetylcholine, dopamine, and serotonin.

In the next two sections, limbic and reward systems are discussed.

Limbic System

It is present at the border of the cerebral cortex and subcritical structures of the diencephalon (cf. Fig. **2**). It participates in emotion, pleasure and reinforcement;

CHAPTER 2

Neurons, Glial Cells and Imaging

Abstract: Scientists at the European Molecular Biology Laboratory have investigated how embryonic stem cells become mature nerve cells. They assessed the complex interplay of molecules during the differentiation process. Consequently, new insights into the role of a protein called SOX2 in neurons emerged. This protein is expressed by a gene, SOX2, located on chromosome 3 in humans. This gene is a sex-determining Y-related HMG box2 and serves as a marker for neural stem and progenitor cells [1]. Progenitor stem cells become neurons and glial cells. The ratio of glia to neurons in the human brain is 10:1. This suggests that glial cells play significant roles in cognitive functions. Glial cells of CNS are divided into ***microglia*** and ***macroglia***. The microglia are macrophage-like cells, which function as a phagocyte. Macroglia consist of **astrocytes** and **oligodendrocytes**. Oligodendrocytes act as CNS equivalent to myelinating Schwann cells in the peripheral nervous system (PNS).

Neuroimaging is a branch of medical imaging that focuses on the brain. Among all imaging techniques, magnetic resonance imaging (MRIs) and MEGs (Magnetoencephalographs) are favorites of medical doctors. MRI has two variants: **functional MRI** and **structural MRI**. In this chapter, both of them are discussed. Detection and monitoring of the progression of neurodegenerative diseases are performed with MEG by analyzing neural complexity and the Grassberger-Procaccia correlation dimension. Lempel-Ziv complexity is a better option. Positron emission tomography (PET) is a useful procedure to measure the metabolic activity of the cells of body tissues. PET helps monitor biochemical changes in the body. Electroencephalography is used to characterize states of consciousness of the brain. EEG is not discussed in the present chapter since the aim of the chapter is not to present all neuroimaging techniques but to cover a select few depending on the author's own background and experience.

Keywords: Action Potential, Astrocytes, Computed Tomography, Embryonic development, Functional Magnetic Resonance Imaging, Heat Shock Proteins, Inter – neurons, Motor Neurons, Magnetic Encephalography, Magnetic Resonance Imaging, Oligodendrocytes, Positron Emission Tomography, Resting potential, Regeneration of Cancer Cells, Stem Cell, Structural Magnetic Resonance Imaging, Synapse, Sox2, Sensory Neurons, Spontaneous Differentiation, Transcription Factor.

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INTRODUCTION

Brain functions are executed through the neural systems consisting of neurons of various shapes and sizes. Glial cells assist them in their duty. They also perform a few crucial functions. A modern view of these cells is given in this chapter. Neural activity in the brain is studied through different imaging techniques. A brief description is provided in this chapter.

NEURONS

Neurons are basic units of the brain and the nervous system. These are the cells responsible for receiving sensory input from the 'environment', which is a neuron's surroundings or agents outside the brain and the external world. Motor commands to our muscles are sent by another type of neurons. These are called ***motor*** neurons. Nearly 100 billion neurons interact with glial cells, which outnumber neurons. A neuron has three parts: **dendrites**, **an axon**, and **a cell body** (cf. Fig. **1**). A neuron receives an input signal from other cells at the dendrites. Leaf-like structures on dendrites are called spines. These leaf-like structures are the result of the branching process, which dendrites undergo while moving towards their tips. An electrical message (an **action potential**) is sent to another neuron through the entire axon when an individual neuron interacts with other neurons [2]. It is shown in Fig. (**2**).

Fig. (1). Embryonic stem cells become nerve cells. Dendrites, axons, and the cell body are key elements of the structure of a neuron.

Embryonic stem cells are derived from the inner cell mass of a blastocyst, an early-stage pre-implantation embryo. Scientists at the European Molecular Biology Laboratory have figured out how early cells called '**stem cells'** develop

into mature neurons. It is a complex interplay of molecules during the differentiation process. New insights emerging from recent investigations suggest that the protein Sox2 acts as a transcription factor. The role of this transcription factor is to hold **spontaneous differentiation** [Oswald, EMBL]. An action potential causes the release of the neurotransmitter into the ***synapse***. This is the way a neuron communicates with other neurons. Soma is the house of the neuron's DNA. Proteins made herein are transported throughout the axon and dendrites.

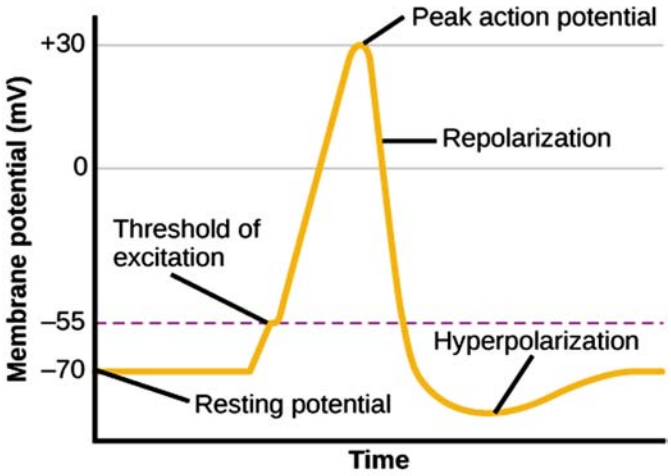

Fig. (2). An action potential. The threshold of excitation is the point beyond which a neuron fires.

Types of Neurons

Based on functions performed by them, neurons are classified into three categories.

1) Sensory

2) Motor

3) Interneurons

Sensory Neurons

When we feel pain, the flow of electrical impulses is directed from the source of pain along nerve fibers connecting to sensory neurons. Complex movements, *e.g.*, picking up a pen, are supported by sensory neurons. These neurons enable precise movements by providing feedback messages to our muscles and joints.

CHAPTER 3

Neural Systems in Learning and Memory

Abstract: In this chapter, theories of learning are not discussed at all. Numerous texts exist where they can be found. It would be enough to note that behavior has two aspects: 1) explorative and 2) exploitative in ***active inference***. The former is sensitive to **ambiguity,** and the latter is sensitive to **risk**. In the absence of ambiguity, active inference reduces to a Bellman scheme [1]. Bayesian inference is integrated with active inference in free-energy formulation. Actions are guided by predictions and are refined by sensory feedback. The variational free energy is a function of observations and a probability density over their hidden causative agents. The time average of energy is action. Minimum variational free energy corresponds to a principle of least action. **Perception can be regarded as a minimum of free energy with respect to inbound sensory information and action as a minimization of free energy with respect to outbound action.**

Synaptic modification is a prerequisite for learning to occur. What one learns must be preserved for future use. Therefore, it needs to be stored. That storage is memory. Neural plasticity is the basis for memory formation. Information about biologically important events (Pavlovian conditional fear, Pavlovian conditioned eye-blink) reach centers in the amygdala and cerebellum through circuitry, which depends on the modality of stimulus and its complexity. In the present chapter, memory systems are introduced to the reader, starting from the Baddeley-Hitch model of working memory. Working memory is also known as **short-term memory** (STM). Certain information stored in short-term memory is transferred to a memory system known as **Long-term memory** (LTM). The brain makes decisions as to which information is to be transferred to LTM. The role of brain oscillations in memory formation is also discussed. 7±2 rule states that STM in humans can store only 5 pieces of information when it is complex; on the other hand, it can store 9 pieces when information is simple. A method to characterize the complexity of information is given. Information transport in the brain is thoroughly discussed. The chapter ends with a discussion on the discovery of **engram cells,** which participate in **systems consolidation of memory**.

Keywords: Active Inference, Bursting, Brain Dynamics, Cellular Signaling, Cognition, Declarative Memory, Excitability, Energy Efficiency, Emotion, Episodic Memory, Free Energy Principle, Functional Connectivity, Global Sate Interactions, Information Transport, Information Complexity, Long-term memory, Neurocognitive networks, Protocol, Perception, Solution of a Task, Sensory Memory, Short-term memory, 7±2 rule.

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INTRODUCTION

Learning and memory are related. Learning is the acquisition of knowledge, and memory is the representation of acquired knowledge. Together, they refer to the processes of acquiring, retaining, and retrieving information in the central nervous system. Emotion has an appreciable effect on cognitive processes (perception, attention, learning and memory). It has a dominant influence on attention, while it motivates action and behavior. In this chapter, the goal that is to be achieved is to produce study material that is brief, concise and easy to be grasped by a broader readership. Therefore, for theories of learning, the reader is referred to books by Parr *et al*. [2] and Pessoa [3]. Let us focus on the memory systems in the human brain.

The activity of a specific group of neurons participating in the formation of a memory undergoes phases of action and inaction. The strength of connections (synapses) between neurons witnesses persistent change. This change depends on the frequency of occurrence of activation in the past. This persistent change in the strength of connections is known as ***synaptic plasticity***. Exercises increase the volume of the hippocampus. The birth of new neurons improves the performance of a memory task. The stimulus triggers a particular pattern of neuronal activity. A memory recall involves the reactivation of a particular group of neurons. The control or deregulation of translational initiation in eukaryotes has been implicated in memory and involves about a dozen initiation factors that bind to the small subunit of the ribosome at various stages, allowing it to scan along mRNA and eventually associate with the large subunit (MRC laboratories of molecular biology at the University of Cambridge).

Synaptic modification is a prerequisite for learning to occur. Neural plasticity is the basis for memory formation. Information about biologically important events (Pavlovian conditional fear, Pavlovian conditioned eye-blink) reach centers in the amygdala and cerebellum through circuitry, which depends on the modality of stimulus and its complexity. Convergence of stimuli and associated biological information causes neural plasticity. A coordinated interplay between pre- and post-synaptic regions decides the outcome of the learning exercise. Learning and gene expression are intimately related [4]. In the following section, forms of memory are discussed in detail.

MAIN FORMS OF MEMORY

1) Sensory

2) Short-term

3) Long-term memory

Sensory Memory

It is a piece of data that contains details about the external world.

Vision

Sensory information received by multiple layers of the retina is converted into electrical signals that travel through the optic nerve. These signals are processed in the thalamus and visual cortex.

Hearing

Vibrations picked up by ears are converted into electrical signals in the cochlea. Signals travel through the cochlear nerve to the auditory canal and cortex.

Touch and Balance

Mechanoreceptors are required by the ear to receive sensory information. Touch receptors, found all over the body, collect information about touch and balance.

Taste and Smell

Taste and smell are processed simultaneously. Food broken down by chewing produces gaseous particles, which enter the olfactory receptors. The information is converted into signals, which travel through the facial nerve, vagus nerve, and glossopharyngeal nerve.

Where is the sensory memory stored? It is stored in the mind for less than a second or so.

Sensory memory is divided into the following subsystems: 1) asiconic, 2) echoic, 3) haptic, 4) olfactory, and 5) gustatory. If a person's attention is focused on one of the sensory stores, then the data is transferred to short-term memory.

Short-Term Memory

Information from the external world is stored in sensory memory for future use. Short-term memory corresponds to information processed in a short period of time. Long-term memory is the stored information for a long period of time. This information can be retrieved on demand (explicit memory) or unconsciously (implicit memory). A proposal advanced by Baddeley and Hitch [5] considered a multi-component memory in place of a storage unit in the short-term memory [6]. This proposal considered three subsystems: the central executive, a phonological

CHAPTER 4

Geometry of Navigation in Space: Neural Maps

Abstract: A cognitive map guides spatial navigation in mammals. Pyramidal neurons in the hippocampus become active only in a particular region of the environment. These regions are called 'place fields', and these neurons are called **place cells**. Many brain regions are involved in the cognitive mapping of the environment. Grid cells in the medial entorhinal cortex organize themselves on a regular grid of triangles covering the entire surface of the environment. The firing pattern of grid cells represents the distance between spatial locations. These distances provide spatial metrics for the cognitive map. Other neurons that participate in spatial navigation are **head direction cells, border cells, speed cells, goal cells, reward cells, *etc.***

Hippocampus-entorhinal circuit provides a 'coordinate system' for on-line measurement of distance and direction of landmarks defining a path leading to a goal. Navigation of an animal toward a goal depends on synaptic plasticity. Functional synapses are chosen from a set of anatomical synapses based on the interaction of Hebbian learning rules, sensory feedback, attractor dynamics, and neuromodulation. Artificial neural networks, which emulate biological neural networks, can be derived from complete connectomes of an organism. Design and control principles underlying intelligent autonomous control systems can be understood based on an analysis of these ANNs.

Keywords: Border Cells, CA1 pyramidal cells, Cognitive map, Coordinate System, Connectomes, Direction cells, Goal Cells, Grid Cells, Hippocampus, Hippocampus – Entorhinal Circuit, Intelligent autonomous control systems, Medial Entorhinal Cortex, Macaque monkey, Neuro - modulation, Place Cells, Rodents, Spatial Navigation, Speed cells, Theta Cycle, Theta Phase Precession.

INTRODUCTION

Place cells were discovered by O'Keefe [1 - 3]. These cells reside in the dorsal hippocampus located at the peak of the cortical hierarchy, far away from the sensory inputs. Cells in the entorhinal cortex have very regular firing fields with a periodic hexagonal structure. A hexagonal pattern gives the highest possible spatial resolution with the fewest cells. Each cell generates its own grid. An animal recognizes location and direction through the matching of patterns. **Phase Precession.** The time of firing of action potentials by individual neurons is in

precession in relation to the phase of the local field potential (LFP) oscillation with each successive cycle. Phase precession in theta cycle characterizes the navigation of an individual agent in space.

Grid cells in a periodic hexagonal lattice represent **space.** Grid cells with similar properties have been found in bats, monkeys, and humans [4 - 7]. Grid cells have at least three dimensions of variations: phase, scale and orientation. While phase is mapped non-topographically, scale is measured from dorsal to ventral topographically. Steps in grid stepping are discrete. This suggests that grid cells are organized in modules. Grids of different sizes exist. Grid modules are functionally independent. These cells intermingle with speed cells, cells with firing rates that follow an animal's running speed.

Place cells in the hippocampus and the EEG θ rhythm have a unique relationship. The firing of complex spike cells follows a bursting pattern with an inter-burst frequency in the range of frequency of θ rhythm (cf. Fig. **1**). Keefe and Recce [2] studied the phase of the theta wave at which place cells fired. It was found that it started at a particular phase when the rat entered the field. But, there was a systematic shift as the rat traversed the field. The phase shifted in a forward direction on each θ cycle. The range of precession of the phase was 100 to 355 degrees. The ability of cortical microcircuits to integrate information about place, distance and direction depends on topographically organized neural maps of the spatial environment. A series of grid cells represent the space around the animal. Each grid cell fires when the animal's position coincides with a vertex on a grid of equilateral triangles that span the surface of the environment [8].

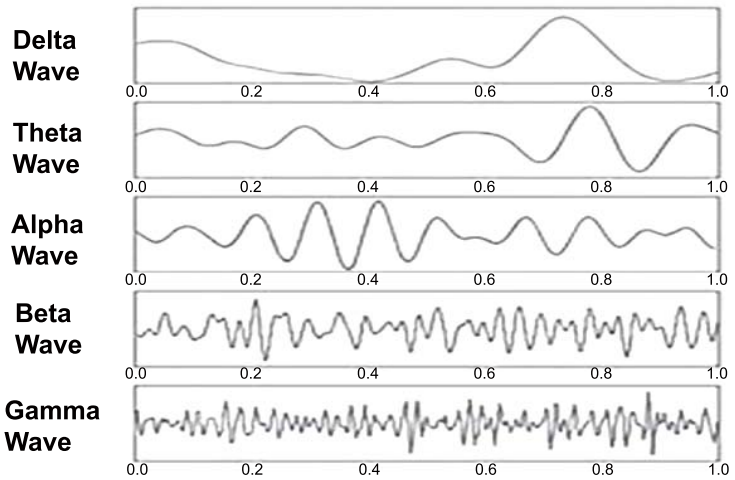

Fig. (1). Waves in Human Brain Theta Cycle (6.5 HZ - 9 HZ). High-velocity movements *e.g.*, jumps along high gaps correspond to higher frequencies.

O'Keefe [9] proposed that each place cell receives two different inputs. One contains information about environmental stimuli, and the other from a navigational system that computes an animal's location in an environment independent of the stimuli. The navigation system works on the basis of information about how far and in which direction the animal has moved. Grid cells in layer II of the rat medial entorhinal cortex (MEC) [8] provide input to the place cells. The dorsal half of the hippocampus is more important for spatial learning than the ventral half. The amount of damaged dorsal hippocampal tissue is a determining factor for the ability of spatial learning [10]. Brain tracks spatial orientation with head direction cells in the rat postsubiculum [11, 12]. An HD cell's firing reaches its peak when an animal's head points in a preferred direction.

OSCILLATORY INTERFERENCE MODEL FOR PLACE CELL FIRING

O' Keefe and Recce [2] proposed that the θ phase precession effect in place cells can be thought of as a result of interference between two oscillatory signals: one somatic with angular frequency ws and the other dendritic with angular frequency wd, related to each other by the relation

$$w_d = w_s + \beta s \quad \textbf{(1)}$$

The cell will cross the firing threshold at the peaks of the resulting interference pattern. The firing pattern will contain a 'carrier' at the mean frequency of the two oscillations, modulated by an 'envelope' at half of the difference of frequencies.

OSCILLATORY INTERFERENCE MODEL OF FIRING IN GRID CELLS

The hippocampus receives cortical inputs from both the medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC). LEC cells encode information on the non-spatial content of the environment [13]. The entorhinal cortex is a narrow strip of tissue running vertically up the lower back of the rat's brain. A characteristic feature of grid cells in the medial entorhinal cortex (MEC) is the regular spatial firing pattern. Grid cell firing at a single cell level can be understood in terms of constructive interference between two oscillators. One of the oscillators has a constant baseline frequency, and the other is assumed to have a frequency that varies linearly with the speed of the movement. This latter oscillator is called a "velocity-controlled oscillator".

$$\boldsymbol{V_{vco}}(t) = s(t) + COS\big(\varphi(t) - \varphi_{vco}(t)\big) \quad \textbf{(2)}$$

$$f_{vco}(t) = f_{base} + \beta\ \mathbf{V_{vco}}(t) \quad \textbf{(3)}$$

CHAPTER 5

Alzheimer's Disease: Diagnosis and Cure

Abstract: Causative agents of Alzheimer's disease are 1) amyloid β foldings, 2) neurofibrillary tangles, and 3) reactive gliosis. Interaction of Aβ with the prion protein within neurons has recently been suggested to be the basis for drug discovery. **Prion protein** is a membrane protein found on cell surfaces of diverse types [1]. The accumulation of misfolded and unfolded proteins (UP) generates stress in the endoplasmic reticulum. This stress worsens the health of the regular function of neuronal cells. The role of unfolded protein response in T cell development and function has also been acknowledged [2]. The induction of Femto particles (Fps) is proposed inside G protein-coupled receptors at an appropriate point in time to monitor the accumulation of unfolded proteins and to control the misfolding of amyloid β. These new particles of 10^{-15}m are proposed to be produced in neurons of the blood-brain barrier (BBB). Protons released by hemoglobin can be glued to their antiparticle, *i.e.*, antiproton, in the conformational space of partially folded amyloid β polypeptides. Portable Penning antiproton traps are now available at CERN. Gluing of protons and antiprotons to form a **femto particle** is mediated by dopamine, a neurotransmitter in the excitatory synapses.

Intraneuronal *oxygen homeostasis* also contributes to the control of the progression of the disease. **Quantum entanglement** between two fps (cf. Fig. **8**), one in the neurons of the neurovascular system (NVU) and the other in cerebrospinal fluid (CSF), may be used to assess the efficiency of the process in a patient with AD. Our approach to the discovery of a drug for AD is based on monitoring and controlling the misfolding of amyloid β and the initiation of folding of unfolded proteins by the intervention of femto particles.

Keywords: Amyloid beta Foldings, AD patients, AD therapy, Blood Brain Barrier, Blood Cerebrospinal Fluid Barrier, Drug Discovery, Femto Particle, G Protein Coupled Receptors, Gamma waves, Holding the mis – folding, Modulation of GABAergic Function, Mathematical Modeling, Neurovascular System, Oxygen homeostasis, Portable Penning anti - proton traps, Prion Protein, Quantum Entanglement, T Cells, Tau protein.

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INTRODUCTION

Dementia is a degenerative brain disorder causing neuron connections to deteriorate within the brain and the eventual death of neurons. In 2015, official death certificates recorded 110,561 deaths from AD, making AD the sixth leading cause of death in the United States and the fifth leading cause of death in Americans of age ≥ 65 years. The recent estimates indicate that the disorder may rank third, just behind heart disease and cancer, as a cause of death of older people. Healthcare costs for AD are massive; in the US alone, the estimated healthcare costs are $172 billion per year. Despite these striking numbers and the extensive amount of research being conducted on AD, its exact pathological mechanisms remain to be determined. Risk factors for AD development include genetic factors, traumatic brain injury, hypertension, obesity, and smoking. Inheritance of Alzheimer's disease can be inferred from regional localization of the gene by both physical and genetic mapping. Over-expression of a gene in the brain tissue from fetuses with Down syndrome (trisomy 21) as the locus encoding the beta protein maps to Chromosome 21 [3]. Researchers are conducting studies to learn more about plaques, tangles, and other biological features of Alzheimer's disease. Advances in brain imaging techniques allow researchers to see the development and spread of abnormal amyloid in the living brain. Changes in brain structure and function have also been revealed. Scientists are exploring the earliest steps in the disease process by studying changes in the brain and body fluids that can be detected years before Alzheimer's symptoms appear.

In Alzheimer's disease (AD) patients, η-secretase processing of APP inhibits neural activity in the hippocampus. The causes are a combination of genetic, environmental, and lifestyle factors. It is a progressive disease of the brain that manifests as an impairment of memory. **The eventual symptoms are disturbances in reasoning, planning, language and perception.** Amyloid β-induced synaptic and memory deficits have been found in mouse models of familial Alzheimer's disease (FAD). Neuro-fibrillary tangles, which are aggregated forms of hyper-phosphorylated tau proteins driven by the accumulation of amyloid beta peptide, could not be seen in human neurons derived from AD patients. Choi *et al* . [4] demonstrated the ability of mutations in amyloid precursor protein and presenilin 1 to induce the deposition of amyloid beta in the extracellular space of human stem cell-derived culture. Mutations with FAD-associated genes account for 50% of the early onset of familial AD. On the other hand, epsolin 4 and epsolin 2 variants of the APOE gene account for late-onset AD [5]. Recent studies have opened up a new possibility that assigns Aβ deposition a protective role as an innate response of the brain's immune system to an invasion by an infecting agent, *e.g.*, herpesviridae [6, 7]. Specific conformation of the peptide determines the profile of primary microglia activation by Aβ

oligomers and fibrils [8]. Vascular dysfunction is an early event in AD pathophysiology. A biomarker-based definition of AD has been given. Amyloid, τ, and neuronal injury form the basis of this definition [9]. It is proposed that dancing protein clouds of *Aβ* and *α*-synuclein receive guidance from entangled states of anti-proton-proton pair. These macromolecules allow N ACP to be expressed in suitable quantity by associated genes. mRNA plays a role here. *Aβ* , *α*-synuclin, and *β*-synucleinare intrinsically disordered proteins. Interactions between *α*S and *β* S take place at the levels of monomer, oligomer and surface. *β* S regulates *α* Saggregation at different stages by controlling the process of inhibition. Intramembraneous cleavage of transmembrane protein APP by *α* - and *β* secretases is accompanied by the release of numerous soluble ectodomains. The APP intracellular domain is released after the cleavage of membrane-bound C-terminal fragments by *γ*-secretase. Biochemical events that take part in the deposition of *Aβ* lead to a different pattern of expression for the gene encoding APP from the one reported earlier [10]. Meta-analyses have unraveled that 20 loci have an influence over the AD risk. Associated biochemical pathways are discussed by these authors in detail in this review.

A receptor exists in multiple conformational states. Glucagon receptor (62 kD) is a member of the class B G protein-coupled family of receptors. It is encoded by the GCGR gene-control cortex. It has an extracellular domain (ECD) and seven transmembrane domains (7 TD). A conformation selection mechanism enables the binding of glucagon to GCGR [11]. GCGR exists in both open and closed states. These states transit along a dynamic equilibrium of open and closed conformational states.

Outer membrane protein G conformational dynamics at time scales of domain and loop fluctuations were explored by Reddy *et al* . [12]. A correlation between the functional and conformational dynamics of this protein was examined by HS-AFM height microscopy. Sub-millisecond loop 6 conformational dynamics was the focus of this study. It was found to be pH-dependent. Rapid transition takes place between different conformational states.

Factors that influence the conformational spectrum are:

1. Genetic variation in PS1, APP, and other members of γ-secretase enzymatic complex
2. Environmental stress
3. Pharmacological agents

The presence of a 35 amino acid fragment of αsynuclein in amyloid plaque in DLB patients suggested the possibility of interaction between two intrinsically

CHAPTER 6

Brain and Beauty: Neuroscience of Romanticism

Abstract: The meaning of the word "**romantic**", according to Oxford Dictionary, is **having a quality that motivates emotions**. It makes you think about love. One would find the meaning of love either in the poetry of Ravindra Nath Tagore or in the poems of Rumi. W. B. Eats defined beauty as a thing of eternal joy, which keeps on increasing. It has no upper bound. The branch of neurosciences that connects us to the study of literature, paintings, and movies is **cognitive neuroscience**. Cognition is the process by which knowledge and understanding are developed in the mind, i.e., how does the brain enable the mind? Now, what is mind? Mind is reflected in occurrences such as sensations, perceptions, emotions, memories, desires, and many more. The aim of this chapter is to elucidate the link between neuroscience and romanticism.

Language plays a central role in cognition. The effects of language on visual perception were explored by Lupyan *et al.* [1]. Our ability to recognize perceptual stimuli is dependent on the physical features of the stimuli and our prior experiences. Language influences visual processing both offline and online. These effects are the result of a predictive processing approach to perception. The history of English (both British and American) literature is discussed. Poets from South Asia and the Middle East are also covered. The chapter impresses upon the reader that poets such as Rumi, Khalid Gibran, Mirza Ghalib and others guide us to the path of **eternality.** The reader will find a few stanzas from their poems in this chapter.

Theories of action and perception are discussed in Chapter 1 under the heading '**Reward**'. Sensations, emotions, desires and **empathy** are the subject matter of this chapter. This chapter will attempt to establish a link between the occurrences and the quality, which is known as **empathy**. A piece of literature devoid of this quality does not qualify to be literature. Some recent developments in neurosciences are reviewed. Free-energy formulation of inference and learning schemas based on generative models of the world is given. The free-energy principle provides a useful framework to investigate neural computation and probabilistic world models.

Keywords: Action, Beauty, British Literature in English, Cognitive Neuroscience, Empathy, Forgetfulness, Free energy principle, Free energy of sensory samples, Human behavior, Learning, Literary Histories, Love, Mental Model, Minimization, Memory, Perception, Psychology, Plasticity – stability cycle, Poetry, Psychiatric Disorders, Sensations, Systems Neuroscience.

Vikas Rai

INTRODUCTION

Jalāl al - Dīn Muhammad Rūmī a Persian poet, has given many pearls of poetry to society. Following is an English translation of his **Persian** verse as an example:

Slience is an Ocean

Speech is a river. when

the ocean is searching for you,

Do not walk into

The river, Listen to the Ocean.

The **meaning** of this text is simple. It would not change. On the other hand, couplets by an Urdu poet, Mirza Ghalib, have several meanings depending on the reader's personal experience. The author presents a select few later in the chapter. First English Literature (both British and American), then Persian, Arabic, Urdu, and at the end, Hindi verses will be quoted. Their meanings will not be discussed but will be left to the reader to decipher. Not all the literature is in the form of poetry. An example of a famous quote from the German Philosopher George Hegel is as follows:

"**We learn from History is that we do not learn from History.**"

It is a piece of prose. The philosopher points towards an essential aspect of human behavior. Sometimes it appears that we keep on repeating the same mistakes that we committed in the past. Committing mistakes is natural to human beings. However, repeating the same or similar mistakes tells us that we are poor learners. Intelligent systems are efficient learners. Forgetfulness is an essential attribute of the human brain. In what follows, the characteristics of literature are covered. The purpose of this chapter is not to cover all of them but to discuss essential aspects of these characteristics.

German Psychologist Gustav Fechner provided evidence for people's preference for rectangles with sides in proportion to the golden ratio (1: 6:1). Fechner's experiments with the golden ratio are famous. Inner psychophysics, relating the states of the nervous system to the subjective experiences that accompany them, is an old discipline.

In the next paragraph, the characteristics of the literature are discussed.

CHARACTERISTICS OF LITERATURE

Harmony and Dissonance

Harmony is a broad category in the art of combining tones, which sound simultaneously. Dissonance is a category within 'harmony'.

Intertextuality is the relationship between two texts. A text is a written or visual work, like books, paintings, movies, *etc.*

Self–reflexive abilities

Self–reflection involves thinking about and reflecting on one's own mental processes [2]. The following three skills are needed:

1) **Openness:** Becoming free from inherited beliefs and stereotypes about the world and ourselves

2) **Observation:** Analyzing your own mind and behavior

3) **Objectivity:** It is a quality of an individual not being influenced by personal beliefs or feelings but being based on facts.

MEANING AND INTERPRETATION

The meaning of a piece of literature is dependent on the reader's experience. Variability of interpretations exists for a few texts while others have simple meanings, *e.g.*, the novel by American author Harper Lee. The plot and characters are loosely based on the author's observations of her family, her neighbors, and an event that occurred near her hometown of Monroeville, Alabama, in 1936, when she was ten. Mockingbirds make music for us to enjoy.

How are mental processes connected with brain dynamics?

PREDICTIVE FRAMEWORK AND CODING

The free energy principle is used as a means of minimizing the conditional entropy of an agent's states. The agent's states are guided by action in an unknown environment. The free-energy principle assumes that both the action and the internal states of an agent minimize the surprise (minus the log of likelihood). Internal states correspond to conditional expectations about hidden states and parameters, in the present context, neuronal activity and connection strengths. Optimizing the conditional expectation about neuronal activity corresponds to ***perceptual interference***. Optimizing conditional expectations about neuronal

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Vikas Rai

Prof. Vikas Rai did masters in physics from Banaras Hindu University in 1985. In the month of August of the same year he joined a group of researchers, in the School of Environmental Sciences, Jawaharlal Nehru University, New Delhi, India, who focused on causes and consequences of current environmental problems. His research thesis "Order and Chaos in Ecological Systems" earned him a Ph. D. in 1993. Since then he has been working on applications of nonlinear dynamics to ecological systems, brain dynamics, and neuro – degenerative diseases. This is the first time that a book at the undergraduate level presents a mathematical theory of Alzheimer's disease. It is based on ideas from quantum theory; e.g., quantum entanglement, superposition of states, etc.