

## **Cutting-edge applications of Neural System Engineering in the Treatment of Neuromuscular Disorders**

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### **Abstract**

The growth and muscle-nerve communication of the neuromuscular junction depends on acetylcholine receptor clustering. Acetylcholine clusters affect neuromuscular diseases such as Myasthenic Syndrome, Lambert Eaton Syndrome, and Neuromyotonia. Acetylcholine receptor clusters, Lrp4, Musk, and Agrin form a motor end-plate complex. After binding to Lrp4; Agrin stimulates the kinase domain of musk to self-phosphorylate Musk and CK2 in the neuromuscular junction signal pathway. This enters the cell membrane and form the clusters of acetylcholine receptors. Neurotrophic factors rise during exercise. Exercise alone increases skeletal muscle Brain-derived Neurotrophic Factor (BDNF). Muscle force production and atrophy prevention are improved by exercising. Neuro stimulation is one of the method of neural system engineering with the help of which muscles can be stimulated by using electrical stimulating devices such as electrodes that eventually boosts the muscle strength. These devices send electrical pulses to muscles from signal generators and skin electrodes. These pulses triggers the user's limb through involuntary muscle contractions. These electrodes can be used to trigger the wrist, shoulder, biceps, triceps, legs and other body parts. Electrical muscle stimulation targets hard-to-reach areas. Exercise training along with the electrical muscle stimulation increases the protein levels in neuromuscular junction. Various Proteins increases acetylcholine receptor clustering, which helps muscle and nerve cells interaction. Contact between nerve and muscle cells prevents neuromuscular diseases like Myasthenia gravis and others.

**Key words:** Neuromuscular Disorders, Neuromuscular Junction, Neurological Devices, Signaling Pathways, Electrodes, Acetylcholine receptor clusters, lrp4, musk, and Agrin.

### **Introduction**

A complex network of specialized cells that can carry messages to and from the brain and spinal cord to various parts of the body called the nervous system. This organ system receives stimuli

from the environment and accordingly regulates the action of our body. The regulation of activity is mainly associated with the Muscular System secretion of various gland sensations and thinking **etc.** The specialized cells found within the nervous system are called Neurons or neural cells. There are three types of neurons: (a) Sensory neurons (b) Motor neurons and (c) Interneurons. Sensory neurons are those neurons that get electrically activated by any environmental stimuli such as sound, touch, heat and light **etc.** (Vandergriendt & Zimlich, 2022) Motor neurons are the communicating neurons that allow the organs of the nervous system such as the brain and spinal cord to communicate with other organs and glands of our body (Vandergriendt & Zimlich, 2022) Interneurons are the interlinking neurons that interlink the sensory neurons to the motor neurons and pass the signal sensed by the sensory **neuron** to the motor neurons. Neurons can be bipolar, multipolar, pseudo unipolar and anaxonic. (Vandergriendt & Zimlich, 2022) Neurons have three main parts: Dendrites, Axons, Cell body or Soma. The dendrite is meant to receive the incoming signal called afferent signal; the axons carry the signal which has to reach the other neurons while the Soma contains sensory organelles for neuronal function. The Nervous System performs its function by releasing neurotransmitters on receiving sensitive signals. The brain has four main parts (a) Brain stem (b) Cerebellum (c) Diencephalon (d) Cerebral hemisphere. (Ludwig et al., 2023) The brainstem has further been divided into three main parts: Medulla, Pons and Midbrain. (Ludwig et al., 2023) It mainly regulates some body functions such as breathing, heart rate, reflex action **etc.** Pons control the body's posture, balance and breathing. It also carries the information from the cerebrum to the cerebellum. (Ludwig et al., 2023) The midbrain is mainly involved in movement and it controls the hearing and visual signaling pathways. (Ludwig et al., 2023) The cerebellum of the brain is mainly involved in, controlling, walking, posture, balance, coordination, eye movements and speech. (Ludwig et al., 2023) The diencephalon involves two main parts thalamus and the hypothalamus (Ludwig et al., 2023). The thalamus is mainly involved in taking the information from our sensory organs and sending it to the brain, transmitting the information to its related area within the cerebral cortex, plays a significant role in keeping us awakened, helps in focusing on the particular signal among the bunch of Signals, and involve in processing and regulating\_\_emotions, formation **and** storage of memories and learning **etc.** (Ludwig et al., 2023) The Hypothalamus of the brain maintains homeostasis appetite and **body weight balancing body fluid controls pituitary gland secretion etc.** (Ludwig et al., 2023). The secretion of antidiuretic hormones and oxytocin is also controlled by cell bodies located in the hypothalamus (Ludwig et al., 2023) The cerebral Hemisphere is one-half of the cerebrum which is the center of thinking **and** memory writing, reading and learning (Ludwig et al., 2023).

On the other hand, the muscular system is composed of a complex network of bones (presented as nodes), muscles (presented as hyper edges), and other connective tissues. (Murphy et al., 2016) These hyper edges connects multiple nodes and muscles to multiple bones through the point of origin and the point of insertion. The muscular system controls the function of various muscles connected together as a network in human body. Muscular systems are the organ systems consisting of skeletal (Voluntary Muscles), smooth and cardiac muscles (Involuntary Muscles). These muscles are responsible for regulating the body's movement, posture, and blood circulation throughout the organism. In vertebrate organisms, the nervous system is responsible for the regulation of muscular systems, although certain muscles (such as the cardiac muscle) can be completely independent. In addition to the skeletal system, a muscular system also forms the musculoskeletal system, which is responsible for movement of the body. (*International Online Medical Council (IOMC)*, n.d.) The three-dimensional nature of muscle and skeletal networks distinguishes them from other physical networks. (Barthélemy, 2011) Muscle tissues shows

various physiological characteristics. These physiological characteristics consists of Excitability (irritability) a property that both the nerve cells and muscle cells possess which enables them to respond to a certain stimuli and produce the action potential (impulses), other physiological characteristics possessed by the muscle tissues are Contractility, Extensibility and Elasticity.

The primary function of the muscular system is to move the muscles; however, it also aids in joint stability, posture maintenance and the generation of heat during exercise. Movement may be voluntary and facilitated by skeletal muscles or involuntary and facilitated by smooth muscles. (*Muscular System / Peer Reviewed Journals*, n.d.) The contraction of skeletal muscle necessitates the release of ATP, which is broken down into ADP and Pi. Some of this energy is used to transport the cross bridges, while the remainder is released as heat. But, sometimes muscle fatigue can also occur, when ATP is used during muscle contraction faster than it can be produced in the muscle cells, and lactic acid builds up faster than it can be removed. As a consequence, ATP levels are too low to sustain cross bridge movement and the contractions become weaker and weaker. Mainly muscle contractions are of two types: (a) Isotonic, during this contraction, the amount of tension generated by the muscle remains constant, however, the length of the muscle is altered; (b) Isometric, in this contraction, the length of the muscle remains the same, but the degree of stress is increased during the contraction. (*Ln\_human\_anat\_final.Pdf*, n.d.) Muscular system also controls the function of nervous system as the Muscle cells and the Nerve cells interaction at the neuromuscular junction. This interaction of nerve cells and the muscle cells affect the functioning of neuromuscular junction, as they directly interact with the number of proteins present.

Muscular function such as Relaxation and contraction is highly controlled by the nervous system (Hines, 2013) The neuromuscular junction is considered to be the communicating junction between the muscles and the nerves, where the cross-talk between the muscles and the motor neurons takes place in response to which neurotransmitters are released. The release of neurotransmitters will regulate the reflex action of muscles. The neurotransmitters can be excitatory, inhibitory and modulatory. The release of excitatory neurotransmitters such as epinephrine, norepinephrine and acetylcholine will pass the information to the muscle cells which will play a key role in regulating muscular function such as muscular contraction. In the case of skeletal muscles, the Acetylcholine released by the motor neurons will bind to the nicotinic acetylcholine receptor which leads to the activation of voltage-gated Na<sup>+</sup> Ion channels. On confirmation changes\_\_the L-type voltage-gated Ca<sup>+2</sup> channel gets activated. **The activated and type voltage gets it calcium** and the channel will subsequently activate the Ryanodine receptor (RyR), From the opened RyR receptor the Ca<sup>+2</sup> will be released continuously which leads to muscle contraction. In the case of smooth muscles, a small number of the L-type channel is always open due to the overlapping membrane potential i.e. (-50mV & -40mV). (Kuo & Ehrlich, 2015) The Ca<sup>+2</sup> release by the L-type Ca<sup>+2</sup> channel causes contraction. On the other hand in case of hormonal release, the GQ-coupled receptor gets activated. The GQ-coupled receptors will initiate the GPCR signaling pathway in smooth muscle; where the activated GQ protein releases PLC. The PLC will change the PIP2 into IP3 and DAG. The IP3 released will bind to the IP3 receptor and the receptor gets activated. The activated RyR receptor will activate the L-type Ca<sup>+2</sup> channel. The activated Ca<sup>+2</sup> channel will bring changes in the action potential of the SR that lead to the release of Ca<sup>+2</sup>; further to the contraction. In the case of cardiac muscle, muscle contraction occurs as a consequence of Ca<sup>+2</sup> entry through the L-type Ca<sup>+2</sup> channel, which activates the RyR channel in the SR. Alternatively, the β Adrenergic receptor on the cell membrane leads to the activation of Adenylyl Cyclase, which stimulates protein kinase A (PKA). The PKA phosphorylates the RyRs

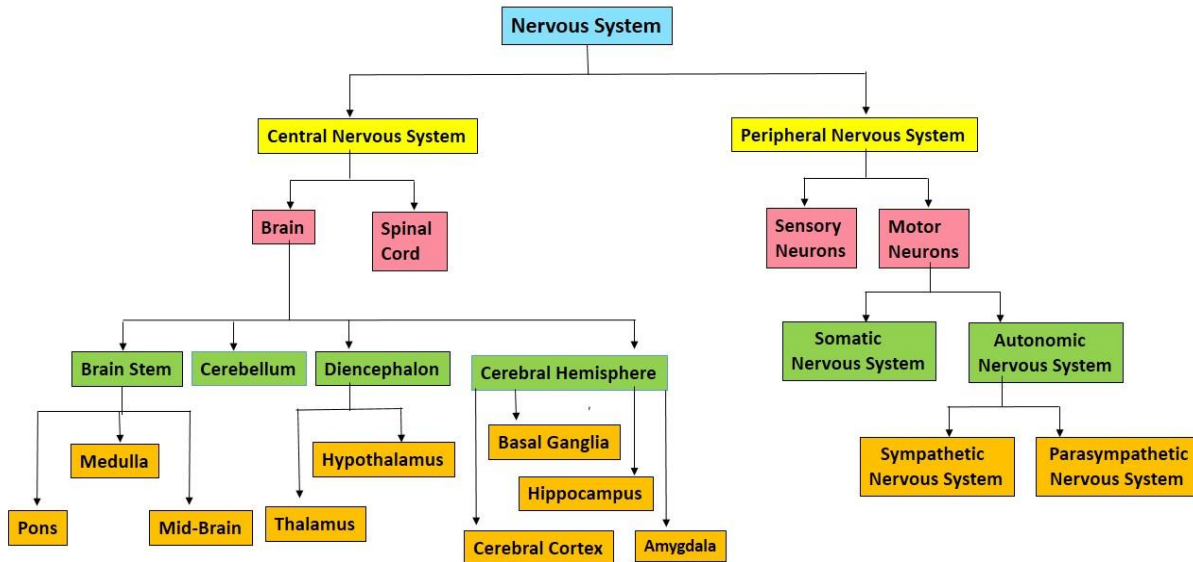
and L-type  $\text{Ca}^{+2}$  channels which leads to the release of  $\text{Ca}^{+2}$ , further causing cardiac muscle contraction.

Neural system engineering is the interdisciplinary approach involving computational tools to explore the functioning potential of neurons. Some of the models have been proposed to describe the internal operations involved in neural system engineering such as the point neuron model, spike response model, the Hawking-Huxley model, the Izhikevich model *etc.* (Furber & Temple, 2007) Neural system engineering approaches mainly involve brain imaging, neuro estimation, neuro-modulation, neural prosthesis and brain-machine interface. The brain imaging method mainly focuses on (a) Structure-mapping and (b) Function analysis. The structure mapping is done through a **CT** scan and **MRI**. The functional analysis mainly requires single Positron emission computed tomography. It is used to collect information about the metabolic function of the brain, anatomy of the brain and mental status of an individual such as cognitive function, emotions and function of motor neurons. Neuromodulation is the modification in the neurons which will bring changes in the nerve function (Karems et al., 2018). **It is used to know neural positioning in case of pain.** In case of severe pain/headache, the position of neurons can be changed which **can** give relief to the patient. Neurostimulation is the method in which neural cells are stimulated by using some of the electrical internal and external devices. (Christine A Edwards et al., 2017) Neurostimulation aims to reduce the changes in the behaviour movement fillings and the level of concession is called a seizure. There are two methods of stimulation (a) Direct brain stimulation and (b) transcutaneous stimulation (Christine A Edwards et al., 2017). Neurostimulation is done in two ways by; implanting electrodes into the brain called the direct brain method and by placing electrodes on the skin called the transcutaneous method. In response to neurostimulation, an electrical impulse will be released which can lead to reduced seizures. There are two types of Neurostimulation (a) Invasive neurostimulation (b) Non-invasive neurostimulation (Christine A Edwards et al., 2017). In the case of invasive stimulation, **the electrical devices are placed via surgical means into the brain**, for example: Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS), Responsive Neurostimulation (RNS) and Cervical Spinal Cord Stimulation (CSCS). The non-invasive stimulation does not require implantation but the stimulation is done by external means. (Christine A Edwards et al., 2017) Neuromodulation is the method of ordering nerve function by invasive and noninvasive means. Some of the methods of neuromodulation are Vagus nerve stimulation (VNS), Transcranial Direct Current Stimulation (TDCS), Deep Brain Stimulation (DBS) and Spinal Cord Stimulation (SCS). (M. D. Johnson et al., 2013) Neuromodulation is mainly done for the treatment of neuromuscular dysfunction, epilepsy and chronic pain. The SCS method is well established and used to reduce the intensity, frequency and duration of pain. The brain-machine interface is a new technology that helps in the treatment of disabled people such as paralytic patients and patients suffering from brain stem stroke and sclerosis. (Lebedev & Nicolelis, 2006) It involves hardware and software systems that can record the brain activity which **can** further control the external devices. **Through this technology, the words of disabled people can be communicated and understood.** Neuroprostheses are a group of devices that can replace defective neurons (motor and sensory) and cognitive function with new and effective neurons.

## 1. Nervous system

The nervous system is a complex network of neurons; signaling within these networks of neurons is meant for thinking, language, feeling, learning *etc.* In the case of vertebrates, the nervous system

is broadly divided into two types (a) central nervous system and (b) peripheral nervous system. The types and parts of nervous system has been shown in fig. 1.



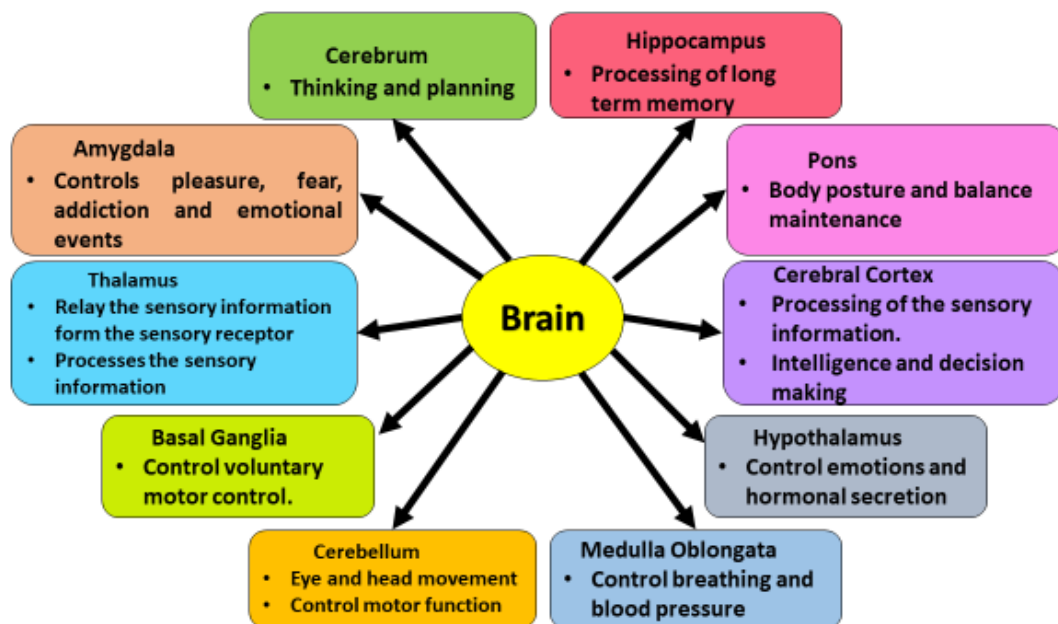
**Fig. 1: Showing the types and parts of the nervous system:** the nervous system is of two types: the central nervous system and the peripheral nervous system. The central nervous system mainly includes the brain and spinal cord, while the peripheral nervous system includes sensory neurons and motor neurons.

#### (a) Central nervous system

The central nervous system comprises the brain and the spinal cord. The brain is divided into 4 main parts (a) Brain stem (b) Cerebellum (c) Diencephalon (d) Cerebral hemisphere. (Ludwig et al., 2023) The brain stem consists of the medulla, pons and midbrain. The diencephalon consists of the thalamus and hypothalamus. The cerebral hemisphere consists of the cerebral cortex, basal ganglia, hippocampus and amygdala. The pons are found in between the medulla and midbrain; the medulla is found near the rostral part of the spinal cord. The medulla controls breathing and blood pressure. The pons maintain the body posture and balance; they also carry information from the cerebrum to the cerebellum through the corticospinal tract. The cerebellum is found in the posterior fossa of the brain. Eye movement and head movement are maintained by the cerebellum, it also involves posture maintenance, control of motor function and speech recognition. (Ludwig et al., 2023) The thalamus and hypothalamus are located between the cerebral hemisphere and brainstem, which controls the sensory information transferring to the cerebral cortex and motor information to the spinal cord and brainstem. (Ludwig et al., 2023) The hypothalamus controls hormone secretion into the hypothalamic portal blood which will further regulate the anterior pituitary hormones and posterior pituitary hormones e.g. antidiuretic hormone and oxytocin. The thalamus relays the sensory information from the sensory receptor and processes the



information. The basal ganglia **control** voluntary motor action such as quick movement in the response to a command. It receives the signals from the cerebral cortex that need to be transmitted to the muscle to perform the motor action in a loop fashion; whereby the signal received by the basal ganglia will be again sent back to the cerebral cortex and once enough amount of signal received\_\_ then the signal will be transmitted to the muscle. (Reynolds et al., 2023) The outermost layer of our brain is called the cerebral cortex. It has been divided into four lobes: (a) frontal lobe, (b) parietal lobe, (c) temporal lobe, and (d) occipital lobe. The frontal lobe is mainly associated with intelligence and decision-making; the parietal lobe is associated with the processing of sensory information; the temporal lobe helps in the interpretation of speech into visual images; **while the function of the occipital lobe is recognition of the object** (*Cerebral Cortex: What It Is, Function & Location*, n.d.). The Amygdala has a strong control over the action in response to emotional events; it also controls pleasure, fear and addiction. The function of the hippocampus is mainly associated with processing long-term memory and evaluating the change in the behaviour and thinking of the person. (Dutta, 2019) The functioning centers of brain and their functions has been mentioned in fig.2. The spinal cord lies within the spinal column and extends from the brain to the lower back; involved in the transferring of the signal between the peripheral and central nervous system and vice versa.



**Fig. 2: Showing the functioning centers of our brain:** The functioning centers of our brain mainly include the cerebrum, Cerebral Cortex, Pons, Thalamus, Hypothalamus, Cerebellum, medulla oblongata, Basal Ganglia, hippocampus, and Amygdala.

The central nervous system follows two pathways (a) Ascending sensory pathway and (b) Descending sensory pathway. (Ludwig et al., 2023) Ascending sensory pathway: through this pathway, the information or signal sensed by the receptor in the periphery of the brain will be transferred along the ascending neural tracts in the spinal cord. (Wang et al., 2022) The ascending sensory neurons arise from the spinal ganglia. There

are three types of ascending sensory pathways (a) Spinothalamic tract (b) Dorsal Column Medial Lemniscal Pathway and Spinocerebellar tract. Spinothalamic tract: This is the sensory tract found within the brain which can sense temperature, crude touch, and pressure. (Al-Chalabi et al., 2023) It is subdivided into two tracts (i) Anterior spinothalamic tract and (ii) Lateral spinothalamic tract. The anterior spinothalamic tract senses the touch while the lateral spinothalamic tract senses the temperature and pain. The spinothalamic tract reaches the spinal cord; and consists of pseudo unipolar neurons, which have no dendrites. The sensory signal received by the dorsal root ganglion that at first receives the sensory information is called a first-order neuron. The information is passed to the grey matter of the spinal cord through the Lissauer tract and synapses which are found near the lateral dorsal root, called the second-order neurons. From the second-order neurons, the signal will be carried to the anterolateral portion of the spinal cord and then enter into the brain stem. Now the signal will be carried by the ventrolateral part of the white matter of the spinal cord, across the length of the spinal cord. The tract will finally carry the signal to the ventral posterior lateral nucleus of the thalamus called the third-order neuron where the pathway terminates and the signal is processed.

Dorsal column medial Lemniscal pathway: Through this pathway, the sensory information is carried from the peripheral nerves to the cerebral cortex. Through this pathway, the fine touch and vibration can be sensed and the signal can be carried to the cerebral cortex. The periphery of the brain contains two receptors: a mechanical receptor and a conscious receptor. The **single** will be carried by the central axons of the dorsal root ganglia and passes through the medial dorsal root to the spinal cord. The signal will be carried to the grey matter of the spinal cord where the information is processed and the reflex action is initiated in response to the signal. (*Dorsal Column Medial Lemniscal Pathway - Physiopedia*, n.d.) The signal will enter into the fasciculus Gracilis or the fasciculus cuneatus, which are a bundle of axon fibers in the dorsomedial spinal cord. The fasciculus Gracilis carries sensory information from the lower extremities such as hips, knee, toe, leg **etc**. The information from the higher extremities such as arms and hands to the fasciculus cuneatus nucleus in the caudal medulla will be carried by the second-order neuron. The second-order neuron will cross over at the midline of the medulla and travel up to the medial lemniscus tract to the end at the ventral posterolateral nucleus of the thalamus. Now\_\_the second-order neuron will synapse with the third-order neuron\_\_which is the ventral posterolateral (VPL) neuron. The third-order neuron will carry the information in a highly specific way to the regions of the primary somatosensory cortex which represents the leg. (*Dorsal Column Medial Lemniscal Pathway - Physiopedia*, n.d.) Spinocerebellar tract: It carries the unconscious information from the muscle spindle, ganglia tendon, organ and joint capsules to the cerebellum. There are three types of spinocerebellar tract (i) anterior (ii) posterior (iii) curios cerebellar.

## **(b) Peripheral Nervous System**

It is another type of nervous system that connects the **CNS** to the different tissues and organs of the body. It consists of sensitive neurons, which carry the signals from the body to the CNS called the afferent neuron while the motor neuron connects the CNS to the skeletal muscle. The motor neurons are further divided into (i) The autonomic nervous system and (ii) The somatic nervous system.

The autonomic Nervous System includes two main pathways: parasympathetic and sympathetic pathways. The autonomic nervous system controls the daily function or normal functioning of the organ, tissue, and cells. Two types of neurons **pre** and postganglionic neurons found in the parasympathetic nervous system. (Wehrwein et al., 2016) The preganglionic neurons initiate from the brainstem and reach the CNS through cranial nerves. It mainly acts on the eye, lacrimal gland, salivary gland, **viscera** of the abdomen and Thorax. The **PNS** consists of 5 types of G protein-coupled receptors called muscarinic receptors such as M1, M2, M3, M4 and M5 (Tindle & Tadi, 2023); which are located on different effector organs. The muscarinic receptors involve two pathways (i) the IP3 pathway and (ii) the cAMP pathway. (Haga, 2013) The IP3 pathway is mainly followed by M1, M3 and M5 receptors while the cAMP pathway is followed by M2 and M4 receptors. (Haga, 2013) The M1 receptor is found in the salivary gland, and its activation causes the excess secretion of water, **K<sup>+</sup>** ions, and amylase. The M2 receptor is found in the heart, its activation causes a reduction in the heart rate. The M3 receptor is found in the lungs, gallbladder, pancreas, kidney, eye **etc.**; The activation of the M3 receptor causes bronchial secretions and bronchoconstriction; stimulates contraction to release the bile juice; activation causes release of digestive enzymes and insulin; peristalsis of ureters, contraction of the detrusor muscle; relaxation of internal urethral sphincter aiding in the flow and excretion of urine; respectively. Sympathetic nervous system: It is one of the types of two divisions of the autonomic nervous system which consists of **pre** and postganglionic neurons. (Wehrwein et al., 2016) The preganglionic neurons will originate from the thoracic and lumbar regions of the spinal cord, while the postganglionic neurons will carry the message to the effector organs where they release neurotransmitters such as epinephrine, norepinephrine and acetylcholine. The effector organs contain the adrenergic receptor which can be excitatory or inhibitory. The adrenergic receptors are **Alpha1, Alpha2, Beta1 and Beta 2**. They follow the G protein-coupled receptor signaling pathway; the **Alpha one** is found in a bound state with the Gq protein and works through the IP3/Ca<sup>2+</sup> ion pathway, and the **Alpha 2, Beta 1 and Beta 2** are found in the bounded state with the Gi protein and follow the cyclic AMP pathway (Haga, 2013).

Somatic Nervous System: The type of peripheral nervous system whose function is mainly associated with the control action on voluntary movement such as movement of arms **legs** and other parts of the body called somatic nervous system. It consists of both afferent neurons with sensory information from across the body or **periphery** of the brain while the efferent neuron will send the information to other parts of the body. It consists of 12 pairs of cranial nerves and 31 pairs of spinal nerves. The cranial nerves carry signals to the brain and from the brain to the **Periphery**; while the spinal nerves carry the somatosensory information to the spinal cord. (Akinrodoye & Lui, 2023) The function of the somatic nervous system involves collecting information from the **periphery** to the central nervous system information and from the central nervous system to the rest of the body parts. (Akinrodoye & Lui, 2023)



## 2. Muscular system

### 2.1 Voluntary muscle

Voluntary muscle also called skeletal muscle is a vigorous tissue. It holds around 40 % of the total weight. (Wolfe, 2006) In skeletal muscles, there is a well-established arrangement of myofibers (muscle cells) and connective tissue is present. The size of muscle fibre plays a vital role in the size of muscle. (Javan et al., 2013) (Fortin et al., 2014) The cells in muscles are multinucleated and these myonuclei (nuclei of a muscle fiber) are found peripherally in the cylindrical myofibre. The myonuclei are not capable of doing mitosis and eventually cannot perform regeneration. (Hikida, n.d.) Which commands the synthesis of proteins in the specific region of the cell. This particular region is known as the nuclear domain. (Macaluso & Myburgh, 2012) Along with the muscle cells, there are satellite cells (resting myoblasts) present (Raven et al., 2012) between the sarcolemma and basal lamina which play a vital function in muscle growth and repair. (Macaluso & Myburgh, 2012) (Sherwood, 2013) There is an epimysium, a thin layer of connective tissue is present around each muscle. (Valentine, 2017) (Thomas, 2013)

Myofibers are arranged into fascicles which are further surrounded by another layer of connective tissues called perimysium. This overall skeleton of connective tissue has a crucial role in muscle contraction. (Valentine, 2017) There is also a single muscle fibre present which is surrounded by the cell membrane called sarcolemma. There are several proteins present in internal myofilament, such as Actin protein in the thin filament, these proteins are initially connected with the sarcolemma. Any abnormality in such proteins leads to muscular disorders. Hence these are crucial. (Williams & Rubin, 2018) Skeletal muscle plays a major role in maintaining body movements and overall body posture. This muscle can potentially regulate the body temperature hence, it holds a major role in body homeostasis. Skeletal muscles are also involved in the process of glucose metabolism. (Hafen & Burns, 2023)

### 2.2 Involuntary muscle

#### 2.2.1 Smooth Muscles

Smooth muscle is a component of the human body that supports digestion and facilitates the absorption of nutrients. It is distributed throughout the arteries and veins of the body and is responsible for the regulation of blood pressure and the oxygenation of tissues. The nervous system utilizes smooth muscle to control a range of subsystems throughout life, but the primary function of the nervous system is the regulation of hormone and neurotransmitter levels in smooth muscle. (Pogoda et al., 2019)

The mesoderm lineage is responsible for the development of smooth muscle tissue, while the neural crest lineage is involved in the regulation of blood vessels in the body. (Chokhavatia & Anuras, 1991) Smooth muscles play a vital role in muscle contraction. Single-unit smooth muscle, one of the two types of involuntary muscles, contains a large number of cells attached with connexins which allow cell-to-cell communication in the muscles. (Maruhashi et al., 2020) On the other hand, each muscle cell receives

its synaptic input in multi-unit. Involuntary muscle helps regulate the urine and blood flow. (Chokhavatia & Anuras, 1991) Smooth muscles also play a vital role in the motility of gastrointestinal tracts. Sometimes, there is a condition called Gastroparesis happens when there is damage to the smooth muscle of the intestines. (David Ginsberg, 2013) Abnormalities in the vascular smooth muscles are also connected with chronic kidney disease. (Calvert & Lefer, 2012) Also, when there is damage to the ureters it eventually leads to the dysfunction of smooth muscles and ureters. This condition is known as Nephrolithiasis. (Pinnell et al., 2007)

### **2.2.2 Cardiac muscles**

The cardiac muscle also called the myocardium is very similar to the skeletal muscle. Both muscle types are composed of single-celled muscle fibres, each of which is composed of a multitude of alternating thin and thick contractile fibres, which contribute to the distinct striated appearance of each cell type. (Rehman et al., 2023) The cardiac muscle cells are encircled by a cellular membrane called the sarcolemma, which contains a single nucleus. Mitochondria are also present in the cardiac muscle cells to provide energy for cardiac contraction. As it is mentioned earlier about the similarities between muscles, in coordination with that, there are contractile proteins which are Actin, the thin filament and Myosin, the thick filament along with Troponin and Tropomyosin, the regulatory proteins are present. (Rehman et al., 2023) Three layers together make the heart, which are the pericardium, myocardium and endocardium. There a squamous epithelial cells present in the endocardium which form the lining of the chambers of the heart and valves. Pericardium refers to the fibrous sac that encircles the heart, which is composed of the epidermis (the heart's major blood vessel), the sub ventricular space (the small blood vessel located in the heart's heart), the parietal (the side of the neck) and the fibrous (the outermost layer of the heart). (Jones et al., 2017) Cardiac muscles along with the electrical impulses are involved in the process of contraction. Although primarily, the cardiac muscles hold a vital role in the pumping of blood into the circulation via generation of force. (Wood & Slater, 2001)

## **3. Impact of the Neural System on Muscular System**

### **3.1 Neuromuscular junction in muscle disorders**

#### **3.1.1 Neuromuscular junction**

There is a synapse between the surface of the muscle fiber sarcolemma and the motor nerve terminal this is known as a neuromuscular Junction. The overall structure of the neuromuscular junction is very compact in comparison with the muscle fibre they interact with. The neuromuscular junction present in humans is less complex and smaller. There are three divisions in the neuromuscular junction and these are:

1. Pre synaptic terminal
2. Synaptic cleft
3. postsynaptic muscle membrane (Desaki & Uehara, 1981)

Neuromuscular junction plays a functional role in the transformation of a temporal series of action potential signals from motor neurons into muscle fiber. (Lai et al., 2017)

### **3.1.1.1 Pre-synaptic terminal**

There is a digital axon termination that is specifically designed for neurotransmitters. It releases varicose axon terminations along the axon path that have similar specialized functions and also release neurotransmitters, this include Presynaptic terminals of both central nervous system and peripheral nervous system. Within the pre-synaptic terminal motor nerves break into terminal branches at the skeletal muscles after transverse from the spinal cord and further form synaptic swellings that touch the muscle tissues. (Ratliff et al., 2018) These synaptic swellings contain vesicles filled with the neurotransmitter acetylene that proceeds vesicle exocytosis. (Hirsch, 2007) These synaptic (also called nerve terminals) membranes have active zones located on them (these active zones are the membrane thickening). In addition to the presence of potassium channels on the membrane of a nerve terminal, it also includes mitochondria, the endoplasmic reticulum and synaptic verticals (SVs). These synaptic verticals are centered on the active zones. There are few proteins present on the synaptic vesicle membrane and these proteins help in the Fusion and docking of synaptic vesicles at actor zones. The docking processing is led by the calcium which is inserted through the calcium channels and it also causes the exocytosis of the acetylcholine from synaptic nerve (Slater, 2017) vesicles into the synaptic cleft. (Slater, 2017) (Sanes, 2003) (Ohno et al., 1998)

### **3.1.1.2 Synaptic cleft**

A synaptic club is a gap between the nerve and muscle components of the nerve-muscle Junction. This gap between the pre-synaptic and post-synaptic terminal membrane is filled with the synaptic basal lamina which is an extracellular matrix. (De Harven & Coers, 1959) Synaptic cleft contains an enzyme called acetylcholine-esterase, which stops this synaptic transmission through the breakdown of acetylcholine into acetyl and choline and none of these can activate the acetylcholine receptors. (Kong et al., 2004)

### **3.1.1.3 Postsynaptic terminal**

The postsynaptic terminal or muscle membrane is a complex structure and this part of the neuromuscular junction is formed by the motor and plate. (Barik et al., 2014) In this post-synaptic membrane there are functional folds present which is formed by sarcolemma. This functional folds broadens the surface area of the post-synaptic membrane, which contains the acetylene receptor in them. These acetylcholine receptors helps acetylcholine bind to them which results in the opening of the channels present. This transfers the end- plate potential or action potential to muscle membrane. (Ohno et al., 1998; Sanes, 2003; Slater, 2017)

## **4. General mechanism of regulation of the Muscular System by the neural system**

Pathways involved in the regulation of the Muscular System by the neural system

### **4.1 The AGRIN- LRP4-MUSK signaling pathway**

The Agrin- LR- Musk signaling pathway is one of the important Pathways for maintaining neuromuscular Junction. (Tezuka et al., 2014), (Eguchi et al., 2016), (N. Kim et al., 2008), (Okada et al., 2006) The acetylcholine clustering and dispersal Pathways are thought to be driven by two mechanisms. When Agrin is released from the nerve Terminal, it attaches to LR P4, resulting in the activation of Musk (Muscle-Specific Kinase) (Chen et al., 2007) and the recruitment of Dok-7 (Docking Protein- 7) and CRK / CRKL . (Patrick et al., 1999). This signal is then transmitted downstream, resulting in the clustering of acetylcholine receptors by cytoplasmically anchored Rapsyn. Conversely, Acetylcholine discharges acetylcholine receptor clusters that are not stabilized by Agrin Signaling. The mechanism of this Pathway is thought to be mediated by receptor-associated protein of the synapse (Rapsyn) interaction with the calcium-dependent PlugIn - 3- CDK 5, Known as Calpain. (Schaeffer et al., 1998) Calpain activity facilitates the cleavage of P35 to P25, Activating Cyclin-dependent kinase -5 (CDK 5). (Rodríguez Cruz et al., 2020). Rapsyn, On the other hand, is thought to act as a calpain suppressor, thereby stabilizing the acetylcholine clusters. It is proposed that, upon Synaptogenic induction and delivery to the Nasophosphonate postsynaptic sites, acetylcholine receptors are endocytosed along with the spontaneous acetylcholine receptors.

Synapse specific transcription in sub synaptic nuclei by various transcription factors and specific promoter elements in synapse genes, GA-binding protein (GABP) (Bezakova & Ruegg, 2003) and ERM (Ezrin/Radixin/Moesin) proteins are essential for the attainment of a high concentration of autonomic cholinergic reuptake responses (acetylcholine receptors) in synaptic sites. Volgated - Gated Na<sup>+</sup> Channel (VG Na<sup>+</sup>C). Agrin is of 400dka molecular weight, similar to heparan sulphate proteoglycan. Agrin is present in a variety of tissues and cells of the immune system. (Lemmon & Schlessinger, 2010) Agrin Is believed to play a role in the development of excitatory synapses. (Hopf & Hoch, 1998) On the other hand, Musk is classified as a member of the RTK (Receptor Tyrosine Kinase) Superfamily. (Xie et al., 1997) Antibodies play a vital role in the activation of acetylcholine receptors present on the post-synaptic membrane. Also, antibodies help in the auto-phosphorylation of Musk, this process is believed to be similar to the RTKs. (Zhang et al., 2008), (N. Kim et al., 2008). LRP4 is the protein that interlinks Agrin LRP with Musk. (Weatherbee et al., 2006), (Lemmon & Schlessinger, 2010), (Ahmed & Simmons, 2015) Along with the soluble Agrin ligand receptor. LRP4 is a major requirement for the activation of Musk. (Phillips & Vincent, 2016)

#### **4.1.1 Role of AGRIN-LRP4-MUSK signaling pathway in neuromuscular disorders:**

There are several autoimmune neuromuscular junction disorders which include Acquired Neuromyotonia (ISAACS syndrome), (Phillips & Vincent, 2016) myasthenia gravis (MG) (Ohno et al., 2016) and Lambert Eaton Myasthenia Syndrome (LEMS). (Engel et al., 2015) Particularly in Isaacs syndrome, the antibodies are activated against the voltage-gated potassium channel of the pre-synaptic neurons. Voltage-gated Calcium channel (VGCC) and voltage-gated potassium channel (VGKC) won't lead to an acetyl choline deficiency in the motor and plate. Congenital myasthenia syndrome (NMJ) is a collective term used to refer to hereditary neuromuscular junction diseases. (Hoch et al., 2001), (Kawakami et al., 2011) Where Lambert Eaton myasthenia syndrome there is a P/Q type calcium channel, is a pre-synaptic VGCC in which autoantibodies are produced. On the other hand,

myasthenia gravis detects antibodies directed against the following receptors: Acetylcholine receptors (AChRs), Muscle-Specific Receptors (Otsuka et al., 2015), (Higuchi et al., 2011), (Zhang et al., 2012), low-density lipoprotein receptor-related protein 4 (LRP4) (Pevzner et al., 2012), (Gasperi et al., 2014), (Gasperi et al., 2014) and Agrin. (Inoue et al., 2009) (Okada et al., 2006)

Mainly germline mutations in motor end plate expressing genes and glycosylating enzymes and coding genes of the congenital myasthenia syndrome subtype demonstrate a deficiency of acetylcholine receptors, while the remaining congenital myasthenic syndrome subunits do not display any deficiency. These diseases that occur in the neuromuscular junction can be prevented by increasing the signal transduction in the neuromuscular junction which eventually enhances the clustering of acetylcholine receptors.

## **5. Intracellular Pathway downstream of Musk (a Receptor tyrosine kinase)**

In the downstream signaling of the MuSK, the Docking protein-7 (Dok-7) plays a vital role in activating the MuSK. (Beeson et al., 2006) The molecular structures of Dok-7 are characterized by the presence of amino acid homology at the amino terminals of Pleckstrins as well as the Phosphotyrosine-binding domain. These domains are vital for the binding of PY553 MuSK. The Dok-7 also contains a carboxyl-terminal domain. (Hallock et al., 2010) Mutations in the Dok-7 in neuromuscular junction is the basis of congenital myasthenic syndrome (CMS). (Hallock et al., 2010) Dok-7 indirectly regulates the formation of synapses by controlling MuSK activity. (Hallock et al., 2016) In the C-terminal domain of Dok-7, adaptor proteins CRK and CRK-I are formed through the phosphorylation done by Agrin. There are two main Pathways involved regulated by the C-terminal and N-terminal domain which mainly regulates the function of Dok-7. (Weston et al., 2003) (Dai et al., 2000) The downstream signal in the pathway from musk involved RAC Rapsyn, actin, RHO. The RAC and RHO are associated with Agrin signaling and the clustering of acetylcholine receptors. (Weston et al., 2000) (Burden, 2011; Evoli et al., 2008; Ramarao et al., 2001; Vincent et al., 2008)

### **5.1 Role of intracellular Pathway downstream of musk in neuromuscular Junction**

The main cause of autoimmune myasthenia gravis is intermittent muscle weakness. Another cause is the auto anti-bodies to the acetylcholine receptors. Some of the cases of Myasthenia Gravis have antibodies to MuSK. (Higuchi et al., 2011) (Pevzner et al., 2012) whereas on the other hand, very few cases of myasthenia gravis have autoantibodies to LRP4. These autoantibodies inhibit or prevent the LRP4 and Agrin binding (Chevessier et al., 2004; Miyoshi et al., 2017; Zhang et al., 2012)

In a study of congenital gene mutation, gene mutation is the primary determinant of this condition, Mutations in MuSK is not the primary contributing factor to this condition, however, the mutation in Acetylcholine Receptors is the primary determinant. (Hardiman et al., 2017) MuSK holds vital importance in amyotrophic lateral sclerosis. The activation and over-expression of MuSK enhances the stability of neuromuscular junction. The expression of MuSK by adeno-associated virus vector can potentially reduce the loss of nerve terminal at the neuromuscular junction (Taylor et al., 2016) which is the root cause



of amyotrophic lateral sclerosis. (Hoch et al., 2001; Koneczny & Herbst, 2019) Also in myasthenia gravis, development of autoantibodies against acetylcholine receptors is the major cause of this condition, whereas very less caused by the autoantibodies against the Musk. (Klooster et al., 2012) In this particular condition the interaction between musk and LRP4 is affected which eventually decreases the acetylcholine receptors at neuromuscular Junction. (Koneczny et al., 2013; McConville et al., 2004; Otsuka et al., 2015; Takamori et al., 2013; Tan-Sindhunata et al., 2015; Wilbe et al., 2015). On the other hand, MuSK mutations can potentially interfere in the functionality of neuromuscular junction then it's not prerequisite but causes congenital myasthenic syndrome. (Finck, 2006; Knutti & Kralli, 2001)

## 6. Signaling pathways for muscle activity

### 6.1 PGC-1 $\alpha$ signaling in muscles

The presence of PGC-1 $\alpha$  (Poly Glycine-Coagulase-1) is detected in tissues rich in mitochondria including the tissues of the brain, kidney and skeletal muscle. (Russell, 2005) During the process of mitochondrial biogenesis PCG-1 $\alpha$  is associated with various nuclear transcription factors. Some of them are nuclear respiratory factors, myocyte enhancer factors and others. (Lin et al., 2002; Wu et al., 1999) This interaction of PGC-1- $\alpha$  with nuclear transcription factor enhances the levels of mitochondrial DNA (mtDNA) which eventually increases the oxygen utilisation. (Michael et al., 2001) and also lipid utilization in skeletal muscles. (Disatnik et al., 1998; Geering et al., 2013; Jagoe & Goldberg, 2001)

PGC-1 $\alpha$  also contributes to inflammation which in response helps in the development of a particular immune response. (Eisele & Handschin, 2014) (Tran et al., 2011). In many skeletal muscle disorders, the body is able to inhibit the production of Poly Glycine-Coagulase-1 (PGC- 1) and its related inflammatory responses. (Feingold et al., 2004) It has been found that Lipo- polysaccharides can potentially repress the PCG-1 $\alpha$  mRNA expression. (Arnold et al., 2011; Handschin, 2009; M. S. Kim et al., 2005). The mechanism of action of PGC- 1 $\alpha$  is to modulate inflammation at the local or systemic levels and may also modulate the production of inflammatory cytokines and inflammatory biomarkers such as Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and Interleukin-6. (Aslam & Ladilov, 2022; Lin et al., 2002). PGC -1 $\alpha$  holds a great role in the prevention and control of inflammation conditions. Also when it comes to PGC-1 $\alpha$ , it is at its strongest in muscle beds that have a lot of oxidative Type 1 and Type 2a fibers like soleus. PGC-1 $\alpha$  has been demonstrated to stimulate mitochondrial biogenesis and muscular fibre-type switching. (Garcia-Roves et al., 2008)

### 6.2 cAMP / AMPK signaling

In the cAMP (Cyclic adenosine monophosphate) / AMPK (AMP-activated protein kinase) signaling, the catalytic sub-unit of adenosine monophosphate -activated protein kinase (AMPK) is alpha while the regulatory sub-units are Beta and Gamma. The induction of AMPK activity by cAMP may be mediated by either Exchange protein activated by cAMP (EPAC-mediated activation) (CAMKK2) or

by Protein kinase A (PKA) -mediated activation LKB-1 (Liver Kinase B1). The increase in cAMP may also result in the increase of AMP product of degradation of cAMP that results from Phosphodiesterase (PDE) activity. By increasing the ratio of AMP to ATP, AMP may stimulate AMPK activity. (Jäger et al., 2007) The vital mechanism of action of AMPK is to promote the activation and expression of peroxisome proliferator-activated receptor coactivator 1 Alpha. That helps in the regulation of the expression of mitochondrial proteins. (Chung et al., 2017; Lv et al., 2017)

Also, mitochondrial homeostasis is significantly supported by the cAMP /AMPK axis, which encourages the biogenesis functioning and clearance of Mitochondria. cAMP plays a functional role in the regulation of metabolic function. The expression of genes that are involved in the oxidation of fatty acids in hepatocytes is enhanced by the activation of the cAMP/AMPK signaling which facilitates the metabolism of fatty acid. (Yimlamai et al., 2005) According to the study have been done on the adipose tissue of PDE3B knockout mice it has been observed that the cAMP/PKA and AMPK signaling has been increased and this enhancement in the cAMP / PKA and AMPK signaling contributed to the reduction of fat accumulation and enhancement of the beta-oxidation in high-fat diet Mouse models. This clearly shows that the cAMP mediate AMPK activation in the regulation of lipid metabolism. (Gonçalves et al., 2012)

This particular pathway has potentially affect the muscle atrophy condition. Muscle atrophy may be reduced with the use of Beta 2 adrenergic agonists by the inhibition of the Ubiquitin-Proteasome System. (Kline et al., 2007) (Gonçalves et al., 2009) The mechanism of this action is depend upon the interaction between cAMP and Protein kinase B (Bodine et al., 2001; Centner et al., 2001; Gonçalves et al., 2012), then Forkhead Box Protein O3 (FOXO-3A) is phosphorylated resulting in a decrease in the production of two proteins that are associated with muscle atrophy that is ATRIN-1 (Attractin) / MAFbx (Muscle Atrophy F-box gene) and MURF1; (TRIM63) (Muscle RING-finger protein-1). (Health, 2021; K. T. Johnson & Picard, 2020; Lecker et al., 2004; Sandri et al., 2004)

## 7. Neural System Engineering and its application

Neural system engineering is a cutting-edge application involving computational tools and mathematical tools that are being applied to the nervous system to improve neural functioning. Some of the ways of neural system engineering are (a) brain imaging, (b) neuromodulation (c) neurostimulation (d) brain-machine interface.

### 7.1 Brain Imaging

The neural system engineering technique through which the live images of the brain can be obtained is called brain imaging. This technology is mainly performed for structural mapping and function analysis. The imaging of the brain can be done by x-ray computer tomography, positron emission tomography, near-infrared Spectroscopy, Magneto encephalogram, electroencephalography and fMRI.

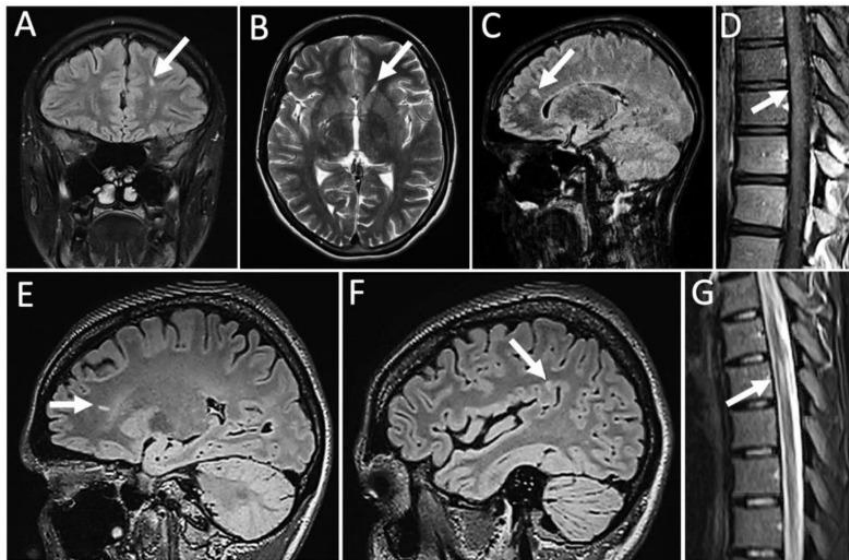
**7.1.1 X-ray computer tomography:** It is also called CT scan. In this method, the motorized X-ray is passed through the X-ray machine on the head of the patient where the X-ray rotates around the head of the patient. (XUE et al., 2010) The X-ray will create the cross-sectional images with the help of computer processing. The CT images are more detailed as compared to the conventional X-ray images of bones, organs and tissue. (Patel & De Jesus, 2023) The specialized set of detectors are present on the opposite side of the rotatory X-ray which can pick up the X-ray which will pass through the head. The transmitted x-ray will be passed on to the computer and the images can be displayed individually in 2D form or all the images are stacked together to find the 3D images. (Kulathilake et al., 2023) The 3D images are used by physicians for monitoring or treatment.

**7.1.2 Positron emission tomography:** In the PET scanning, the patient is injected with radioactive substances that have been carried to the particular protein or sugar by the carrier molecule. These radioactive substances emit small particles called positrons which interact with surrounding electrons. This interaction results in the complete annihilation of both particles; releasing two photons that speed in the opposite direction. The detectors in the PET scanner measure these photons and use this information to create a 3D image.

**7.1.3 Functional Magnetic Resonance Imaging:** It is the most recently developed method for brain imaging. It is one of the highly advanced techniques with more acceptance and having less side effects. It is of three types (I) fMRI, BOLD (II) perfusion fMRI and (III) contrast fMRI. fMRI, BOLD: Functional Magnetic resonance imaging blood oxygen level-dependent. The most important component of our blood which is blood has a red color called hemoglobin. It also maintains the pH of our blood. In the oxygenated condition, the hemoglobin shows diamagnetism while in the case of deoxygenation, the hemoglobin shows Para magnetism (XUE et al., 2010). The fMRI BOLD can bring the changes in the magnetism of the hemoglobin (XUE et al., 2010). The changes in the oxygenated state of the hemoglobin and subsequently the change in the magnetism occurs mainly due to the change in the blood flow. The change in the blood flow is followed by changes in neuronal activities (Logothetis et al., 2001). The blood oxygenation level gets enhanced by an increase in the blood flow, causing the number of oxygenated hemoglobin to increase and as a result, the fMRI BOLD response gets enhanced (XUE et al., 2010). Contrast MRI: Another method of MRI in which the contrast reagent is being used. The Contrast agent can be iron oxide coated with sugar or starch. The contrast reagent will be distributed across the blood volume. The signal emitted by the contrast agent will indicate the cerebral blood volume (XUE et al., 2010). Perfusion fMRI: In this method of fMRI, the hydrogen nuclei found in the blood artery were labelled with the “arterial spin labelling” (XUE et al., 2010). The signals transmitted by the nuclei will project the image of the brain. Periventricular and Juxta cortical Lesions in Neuromyotonia can be visualized with the help of MRI technique. The MRI image of Neuromyotonia have been shown in fig.3.

#### **7.1.4 Application of brain imaging**

1. The fMRI BOLD greatly helps in collecting information about blood flow (XUE et al., 2010).
2. The fMRI BOLD provides information about the metabolic activities of the brain for the nervous system (Glover, 2011).
3. It helps to know whether the red pigment called hemoglobin, of our blood, is in an oxygenated state or a deoxygenated state (XUE et al., 2010).
4. The contrast MRI signal can reveal the overall cerebral blood volume.
5. The neuronal activity can be better revealed by the perfusion fMRI as the hydrogen nucleus is magnetically labelled across the blood artery and then the images of their distribution in the brain will be framed.
6. With the help of Neuroimaging we can know about human behaviour with changes in metabolic neuronal function.



**Fig.3. MRI image of Periventricular and Juxta cortical Lesions in Neuromyelitis Optica.**

## 8. Neuromodulation

The method of needle system engineering in which the nerve function is modulated is called neuromodulation. It can be done by activating the neurons or deactivating the neurons by changing various cellular parameters. Modulation of nerve function can be done by either extensive or intrinsic means. Intrinsic modulation includes a change in the nerve function by releasing the modulating substance from the neural circuit itself. However, in extrinsic neuromodulation, the nerve function is changed by the

implementation of any component that is not part of the neural circuit. The changes in the nerve function by the cotransmitters which are released by neural cells can cause intrinsic neuromodulation. The Cotransmitters can readily stimulate or excite the postsynaptic target which can be an ionotropic receptor or a metabolic receptor. (Cropper et al., 1987) (Eve Marder, 2012) However, if the neural glands release any hormone that can travel from one part of that neural circuit to another part of the neural circuit and can bring changes in the nerve function it is called its extrinsic modulation. (Christie et al., 1995) The neuromodulation can be done by (a) direct electrical stimulation (b) magnetic stimulation (c) thermal stimulation (d) mechanical stimulation (e) chemical stimulation (f) Optogenetic stimulation. (Peng et al., 2021)

**8.1 Electrical stimulation:** Electrical stimulation means changing the action potential of neurons by changing the intracellular potential. (Luan et al., 2014) The intracellular potential can be changed by either localized depolarization or hyperpolarization of the cell membrane. To change the action potential two electrodes are placed across a neuron which will supply the current to the neuron and cause a change in the potential gradient across the neurons. How fast or slow one particular neuron will polarize or depolarize will depend upon the activation time constant of the voltage-gated ion channel. (Luan et al., 2014) The electrical potential gradient for stimulation can be generated by using (a) a voltage stimulator **or** (b) a current stimulator (c) charges stimulator. In the voltage control electrical stimulation, the voltage is supplied between two electrodes. It is one of the simplest methods of stimulation. It is mainly used for deep brain stimulation (Hardesty & Sackeim, 2007), and muscular stimulation. (Wong et al., 2004) In current controlled electrical stimulation the current is applied between the two electrodes. The current supplied can control the imbalance in the charge present across the neurons and the charge delivered to the electrodes. (Luan et al., 2014) **It is used to know the physiology of the CNS of the human brain.** In charge control stimulation, the charge delivered by the electrode is **controlled by controlling** the voltage supplied to the electrodes. (Ghovanloo, 2006) (Rosellini et al., 2011)

**8.2 Magnetic Stimulation:** In this method of neuromodulation the potential gradients across the neurons are changed by applying the magnetic field around the neurons. Generally, this method is applied by the transdermal means e.g. transcranial magnetic stimulation. It is mainly used for **stroke treatment and depression treatment.**

**8.3 Chemical stimulation:** This method of neurostimulation includes the use of some chemicals such as changing the fluid around the nerve cells, controlling over release of neurotransmitters and changing the ionic gradient. (Luan et al., 2014) The chemical method of stimulation is greatly successful and gives a longer-term effect across the large cross-sectional area. The changes in the ionic concentration across the neurons can cause the action potential of the cell to change and subsequently change the nerve function. This method is widely accepted among neuroscientists.

**8.4 Optogenetic stimulation:** Optogenetics is a new technique of Neuromodulation. It is applied by using some of the "Opsins" which the light-sensitive protein is found in our eye. These Opsins are mainly applied across the cell membrane of neurons. The



Opsins can change the effect and rate of the intracellular electrical and biochemical processes in cells by modulating their signaling cascades. The opsins can have different temporal, chemical and spectral properties.

**8.5 Mechanical stimulation:** It is the new emerging technology of Neuromodulation. This technique is not much understood today but has a high potential for modulation. This method is non-invasive and has higher spatial resolution. It is mainly used for retinal prostheses.

## 9. Neurostimulation

In this method of system engineering the nuts function or are stimulated using some devices. These devices can stimulate continuously or at some point of time. Neurostimulation can be invasive or noninvasive. If the nerves are stimulated by implanting some of the electrical devices into the brain then it is called an invasive means of neurostimulation e.g. VNS, DBS, RNS, and CPCS (Starnes et al., 2019). If the nerves are stimulated but not by the permanent installation of any electrical devices then it is considered to be the noninvasive means of neurostimulation e.g. TMS, tDCS. (Starnes et al., 2019) The method of Neurostimulation includes (1) Deep brain stimulation (2) Vagus nerve stimulation (3) Spinal cord stimulation (4) Sacral nerve stimulation.

**9.1 Deep Brain Stimulation:** This method of Neurostimulation can stimulate to a higher extent within the brain. It involves the stimulation of sensory thalamic nuclei which includes ventral posteromedial and ventral posterolateral nucleus; and periaqueductal - periventricular gray regions. The mechanism for deep brain stimulation is not much understood but some literature reveals the general mechanism for deep brain stimulation, which includes the implantation of a neurostimulator by surgical means and the implantation of two electrodes around the neurons. The initial deep brain stimulation treatment shows 50 - 80% of the positive response. (Starnes et al., 2019) Some of the side effects or adverse events associated with deep brain stimulation include intracranial hemorrhage (Bergey et al., 2015), seizures, pulmonary embolism and pneumonia *etc.* (Martinez-Ramirez et al., 2015)

**9.2 Vagus Nerve Stimulation:** The Vagus nerve is considered to be the main nerve of our parasympathetic nervous system. It is the longest nerve of our nervous system. It originates from the medulla and extends to the heart, lower respiratory tract and gastrointestinal tract. It carries Motor sensory and parasympathetic information from one part of the brain to the other part. The mechanism of VNS includes the implantation of the VNS device in the chest under the clavicle (Ginn et al., 2019; Starnes et al., 2019) and the two wires are placed on the left and right vagus nerves of the neck. (Bakhtiarzadeh et al., 2023) The device will give the electrical impulse continuously which will be received by the *vehicle* nerve and carried to the brain. The non-invasive devices for neuro-stimulations are getting more attention as they are easily available have low cost are easily implantable and do not have any serious side effects such as pain at the site of infection wound *etc.* VNS has some common side effects which

include cough, voice alteration and paresthesia. (González et al., 2019) The VNS is mainly famous for the treatment of pain which includes the release of inhibitory neurotransmitters such as GABA, norepinephrine and serotonin (Yuan & Silberstein, 2017) which can reduce the level of glutamate in the trigeminal nucleus and inhibit the stimulation of nociceptors then block the perception of pain. (Yuan & Silberstein, 2017)

**9.3 Spinal Cord Stimulation:** This is one of the most common methods of neuron stimulation which is also called deep column stimulation. The mechanism of spinal cord stimulation includes the implantation of electrodes across the area that covers the epidural space. (Ginn et al., 2019) The epidural space dura mater covers the spinal nerve and Dural sac; and the periosteum and ligament within the Vertebral canal and the intervertebral foramen which will send the electric current to the dorsal column of the spinal cord. The amyloid beta fibres modulate the dorsal column of the brain. The spinal cord stimulation can also involve the stimulation of the spinal cord by balancing the oxygen supply (Linderoth & Foreman, 1999), in cases when the blood flow is restricted or reduced in some part of the body because of which the oxygen supply may also get affected called ischemia. (Linderoth & Foreman, 1999) The spinal cord is highly stimulated then the calcitonin-related peptide will be released (Croom et al., 1997), which may cause the blood flow will increase in the blood vessels due to the widening of blood vessels. (Croom et al., 1997) Some of the side effects of spinal cord stimulation include infection, allergic reaction, and pain at the implantation site, implantable pulse generator, Epidural Fibrosis, epidural Hematoma, Dural puncture and neurological injury. (Kumar et al., 2006)

**9.4 Sacral Nerve Stimulation:** Sacred nerves are those that provide the motor and sensory nerves for the urinary bladder and muscles for the urinary tract, posterior thigh and other lower extremities. The mechanism of the SNS includes the implantation of an SNS device sub dermally just above the buttocks while the electrodes are placed in the sacral foramen. (Ginn et al., 2019) The electric current produced by the electrodes will stimulate the pelvic nerves. (Ginn et al., 2019) Some of the side effects have been observed among the individuals who use the SNS device such as pain at the site of implantation infection, transient electric shock and the Bowel function which includes absorption of neutrons and fluid from the food. (Ginn et al., 2019)

### 9.5 Application:

1. DBS is widely used in the treatment of Parkinson's disease. It is supported by the fact that the DBS lead to an improvement in the tremors score which shows the stability of Parkinson's disease. The tremors score has reduced from 3.3 to 0.8 within the 27 months which shows the high success rate of DBS in the treatment of Parkinson's disease (Blomstedt et al., 2007).
2. DBS in the cerebellum improves the ability of the cerebellum to form new neural connections which strongly helps in recovery from stroke (Ginn et al., 2019).

3. **VNS in modulating the release** of neurotransmitters such as serotonin, norepinephrine and dopamine; and brain structure which will regulate our mood and subsequently depression.
4. VNS is used for the treatment of inflammatory diseases such as rheumatoid arthritis. The **coal** energy inflammatory pathway stimulated by the electric impulse produced during VNS can reduce the initiation associated with rheumatoid arthritis. Alternatively, it will reduce the release of pro-inflammatory cytokines and also it will stimulate the release of immune-affected cells which will travel to the joints and reduce the pain. (Ginn et al., 2019)
5. On VNSs stimulation the adrenergic neurons of the spleen get activated which will release the norepinephrine to the **beta2** adrenergic receptor. The activated **beta to add energy** receptors releases the choline acetyltransferase enzyme. **The Ach Release on choline style transparent** will interact with **alpha 7** nicotinic acetylcholine receptor which inhibits the release of pro-inflammatory cytokines, JAK/STAT/NFk  $\beta$  signaling pathway. It will reduce the pain caused by Rheumatoid arthritis.
6. VNS stimulates the release of inhibitory neurotransmitters. The inhibitory neurotransmitter reduces glutamate levels in the trigeminal nucleus which will lead to the reduction in the intensity of pain in the cerebral cortex. (Ginn et al., 2019)
7. VNS treatment stimulates the release of insulin and glucagon from the pancreas which will help in the treatment of type 2 diabetes.
8. VNS is also used for stroke recovery, heart failure and tinnitus.
9. SCS helps in replacing the painful sensation with a pleasant sensation.
10. SCS follow the gate theory which reveals that an increase in the electrical stimulation of the brain causes the gate in the dorsal Horn **will get close** as a **result the pain signals between the brain and spinal cord stop**. (Ginn et al., 2019) (Melzack & Wall, 1965)

## 10. Neuro devices

Neurological devices can be utilized to diagnose prevent and treat a variety of neurological disorders and conditions including but not limited to Alzheimer's, Parkinson's major depressive disorders, epilepsy spinal cord injury and traumatic brain injury. These devices offer a variety of services including neuro Diagnostic stimulation and more. (Keene et al., 2000) In the concept of Neuro devices what is rapidly increasing is the wearable Technology. Sensors Incorporated in the latest microprocessors help in the long-term tracking of bio-signals. The sensors and body-worn devices are used to track various body functions such as working ability body temperature oxygen saturation, heart rate and many others. Also, there are electroencephalography devices which are wearable and available along with the neuro-modulation devices. (Alahi et al., 2021)

### 10.1 Electrocardiography

Electrocorticography (ECoG) is a technology related to the field of neurophysiology in which electrodes are used to record the electrical impulses of the brain during surgery. Electrocorticography produces the same brain potentials as scalp Electroencephalography does, however, the dispersion and reduction of the scalp and skull potentials are not present in the Electrocorticography. (*Microelectrode Array* / *Axion Biosystems*, n.d.) Electrocorticography electrodes are well suited for the recording of large neural Pathways and overcome the limitations of rigid electrodes. Also, electrocorticography electrodes facilitate the two-way connection of the brain tool to the external electronic devices. (McKee et al., 2011)

## 10.2 Microelectrode Arrays (MEAs)

Microelectrode Arrays (MEAs) or a network of densely packed microscopic electrodes located at the base of each well of a multi-well membrane-electrode (MEA) plate. Electrophilic cells including cardiomyocytes and neurons can be grown over the electrodes forming a continuous network and the functioning or electrical activity of this network can be monitored. (Ferguson et al., 2019) These microelectrode Arrays (MEAs) have some chemical as well as physical effects on the brain cells and tissues that are to some extent related to the materials fabricated in the MEAs.

With new designs of microelectrode arrays coming, it is very important or advisable to choose materials that are mechanically compatible with the brain. The brain. Additionally, the amount of strain placed on the brain can be increased and the FBR (Foreign Body Response) can be exacerbated when microelectrode arrays are tethered to the Skull. (Xu et al., 2021) Along with this, the electrode thickness and surface topography majorly affect the strain caused by the microelectrode arrays and the resultant destruction of brain tissues and cells. (*Intro to Brain Computer Interface*, n.d.) The kinematic analysis of a microelectrode array optimizes the design parameters of a particular microelectrode array including the tip fillet and wedge angle, the electrode thickness, the stiffness and the surface friction coefficient. Microelectrode array with its 20 ml filtrate, radius  $45^\circ$  wedge angle,  $40\ \mu\text{m}$  thickness, 200 GPa (gigapascal) Young's modulus and 0.1 frictional Coefficient demonstrated optimal performance. Advanced and Systematic design and development of microelectrode array is vital for reducing damage caused by the strain and the resultant FBR (foreign body reaction). There are two types of microelectrodes which are invasive (in Vivo) and non-invasive (in vitro). In vivo microelectrode typically refers to the hard metal microwares (silicon-based micro needles) that penetrate the tissues and are planted in the organ to measure electrophysiology on the other hand in non-invasive microelectrode array, Semiconductor chip technology is majorly used. The microelectrode array chips employ's conductive electrodes or other susceptible Semiconductor devices to monitor and evaluate a wide range of analytes including tissue commerce cellular and biomolecular samples. (Saha et al., 2021)

## 10.3 Applications of Neuro-devices

Neuro devices such as microelectrodes play a vital role in the determination of electrodermal activities by the insertion of microscopic electrodes beneath the skin, which eventually provide non-invasive longitudinal recordings. Majorly this neuro device

measures skin conducting response (SCR) skin conductance level and signals of electoral activity. Where electro-dermal activity measures the electrical properties of the skin. (Sharma et al., 2011)

Furthermore, electro dermal activity also determines or records these seizure events such as Generalized tonic-clonic scissors (GTCS), when used along with an electroencephalogram. Electro dermal activity potential increases its activity during Postictal Generalized Electroencephalogram Suppression (PGES) and when electro dermal activity responds during this event, it is easy to observe the patterns involved in the same. (Benabid et al., 2019)

Neuro devices such as Microelectrode Arrays and Electrocardiography (ECG) have been of great use in the condition of Amyotrophic Lateral Sclerosis (ALS) and Tetraplegia. (Vansteensel et al., 2016) Many brain-computer interfaces systems utilize electrocardiography to record, amplify and translate brain signals into computer instructions for external devices which further can be used to restore communication between motor neurons. (*Microelectrode Array | Axion Biosystems*, n.d.) (*EEG Test (Electroencephalogram): Purpose, Procedure, & Results*, n.d.) Microelectrode helps in the detection of spontaneous activity of Hematopoietic induced pluripotent Stem Cells (HIPSC) - derived neuronal cells after differentiation and maturation. It is also used in neurotoxicology studies and drug cleaning. Microelectrode array shows potential in neural development and neural characterization, as well as electrical stimulation. This electrical stimulation also detects cardiomyocyte pacing which further helps in the detection of abnormality in cardiac functioning.

## **11. Brain - machine interfaces**

Brain- Machine Interfaces (BCI) are the systems that make it easier for the human brain to communicate with a bunch of different machines. Brain- Machine Interfaces operate in three different stages firstly it collects the brain signals, then it interprets the signals collected and lastly it gives the output of instruction to a connected device based on the received brain signals, specifically used in the central nervous system. (Shih et al., 2012)

Brain- Machine Interface after a broad range of adaptability either by increasing or decreasing human peripheral working capacity and other potential applications in a wide range of domains such as rehabilitation, cognitive processing, Robotics, video gaming and neuroscience. (Sullivan et al., 2007) Brain signals of any type can be used to control a brain- machine interface system. The most widely studied are electromagnetic signals which are primarily produced by altering the polarity of the post-synaptic membrane of neurons through stimulation of voltage-regulated and ion-regulated channels. The use of non-invasive brain- machine interfaces based on electroencephalograms which is the most common research method due to its low risk and ease of conducting studies and recruiting participants. Brain- machine interface therapy may offer an additional layer of assistance to conventional neurorehabilitation methods and may reduce expenses by eliminating the requirement for a full-time rehabilitation therapist. (Hoffmann & Micera, 2011)

### **11.1 Electroencephalography**



Electroencephalography sensors are electronic devices designed to detect electrical signals from the brain, which are typically generated by large groups of neurons in the vicinity of the brain surface. The signals are measured over a long period and the sensor can detect the small variations in the electrical current between the skin and the sensor electrodes amplify the current and apply any necessary filtering such as Bandpass filtering. (Zrenner et al., 2016)

Electroencephalography devices necessitate in reliable electrical connection between individual electrodes and the scalp of the wearer. Some electroencephalography devices also measure physiological as well as psychological data, in which psychological data measures heart rate and muscle activity. Also, there are many other devices such as electromyography which specifically measures or records muscle activity, Electroencephalography which measures human eye movement and ECG measures cardiac activity and many others. The electrical activity measured by EEG normally vary from  $-100$  to  $+100$   $\mu\text{V}$  (Read & Innis, 2017) . The electrical activity measured in the brain by Electroencephalography is derived from the combined postsynaptic potentials (PSP) of the brain cortical neurons. These postsynaptic cells, alter the ionic flux through the cell membrane.

## **11.2 Application of brain- machine interfaces**

Brain- machine interface-based devices such as electroencephalograms. Electroencephalogram has a great role in the detection of seizures by specifically measuring the electrical signals of the brain by using electrodes attached to the scalp. Electroencephalograms potentially detect seizures in brain damage or tumors epilepsy stroke and encephalitis (brain inflammation) (Rosenblatt & Gotman, 1999)

Electroencephalogram is also used in the assessment of drug profiles. It collect the data through frequency bands before and after the drug application and interprets the changes through statistical test. (Cook et al., 1998) The Electroencephalogram also records or measures signals related to ECG (heart rate), Respiration and intracranial pressure. (Goldman et al., 2002) Electroencephalogram uses the frequency bands which detect the power of electrical activity. With the higher frequency determines low electrical power and vice versa. in the electrical activities Gamma activities of ( $>35\text{Hz}$ ) have less power than beta activities with 14 to 30 Hz which further have less power than Alpha activity with 18 to 30 Hz which further has less power than theta with 4 to 7 Hz and further Delta with less than  $< 4$  Hz. The delta frequency band depict altered consciousness, sleep and drowsiness, whereas on the other hand Alpha frequency band or activity is associated with inhibitory and attention control in the brain. (Schalk et al., 2004) (Kasim et al., 2017)

The electroencephalogram is connected with many other fields and exerts various applications accordingly. The electroencephalogram has the potential to help individuals with motor activity impairments as it can control the prosthetic hand or arm. (Beyrouthy et al., 2017; Guger et al., 2017; Jacoby et al., 2015). These signals used in the electroencephalogram help provide information regarding brain- wave activities. Which further helps in the diagnosis of several cognitive impairments and diseases related the brain.

## **12. Neuroprostheses**

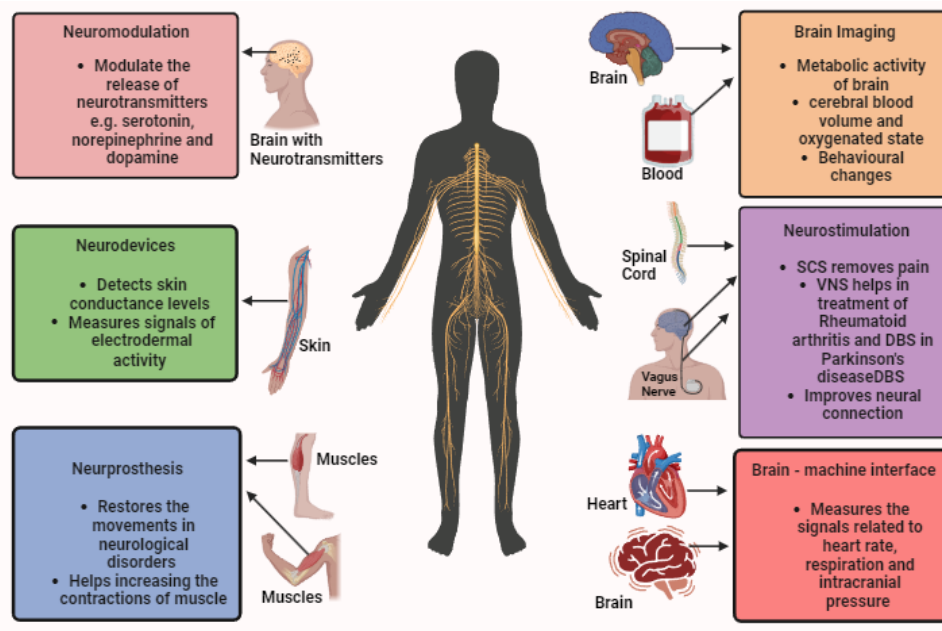
Neural prostheses are devices that enable electrical stimulation of peripheral Nervous system, spinal nervous system and central nervous system myogenic regions and nerve structures to improve replace or restore nerve function in a person with motor or sensory neuromuscular impairment. (Schwartz et al., 2006) Neuroprostheses is a combination of Neuro technology and neuroscience which further combines neural interfaces. (Leuthardt et al., 2006) The Neuroprosthetic devices plays a vital role in the diagnosis of the patients with medical conditions (or interacting with the external environment) due to an injury, stroke or illness. These Neuroprosthetic devices can effectively substitute the biological mode of signal transmission that eventually benefits the patients. (Donoghue et al., 2007; Grill & Kirsch, 2000; Lebedev & Nicolelis, 2006; Sakas et al., 2007) Neuroprosthetic devices are of great importance in the diseased condition where the severity is below average level and some abnormal symptoms are there as it enhances the overall condition to the normal state.

### **12.1 Applications of Neuroprostheses**

Neuroprostheses has a great potential for the patients with Tetraplegia or arm Monoplegia. In this disease condition, the implementation of Neuroprosthetic movements in the minor shoulder transmits into the basic fundamental activities in the contralateral arm and hand. Also, it has been beneficial as the connector electrodes in the prosthetic devices have great potential in the interface of the human nervous system which eventually helps treatment of certain disorders. (Zong et al., 2012) Also, Neuroprosthetic devices can help patients work independently in their daily activities. This also decreases the economic burden on the patients as now they don't have to depend on any kind of assistance. All this can be done by neuromuscular stimulation through or with the help of neuro-prosthetic devices. Neuroprostheses devices can potentially restores the movements in many neurological disorders such as cerebral palsy. Also, neural processes can potentially use in the treatment of certain neurological disorders in which the muscles and moto neurons are functional.

In the conditions of stroke or Spinal Cord Injury (SCI), which after the use and implementation of neural prosthetic devices, enhances the neurological state of being of patient. Neuroprostheses is used to restore functions of certain muscles by enhancing the contractions in them which eventually helps in the optimal functioning of muscles. It helps stimulating the effective muscle fibres in the targeted muscles to restore the function & movement. (Cheusova et al., 2006)

Applications of various methods of neural system engineering has been mentioned in fig. 4



**Fig.4. Applications of Neural System Engineering.**

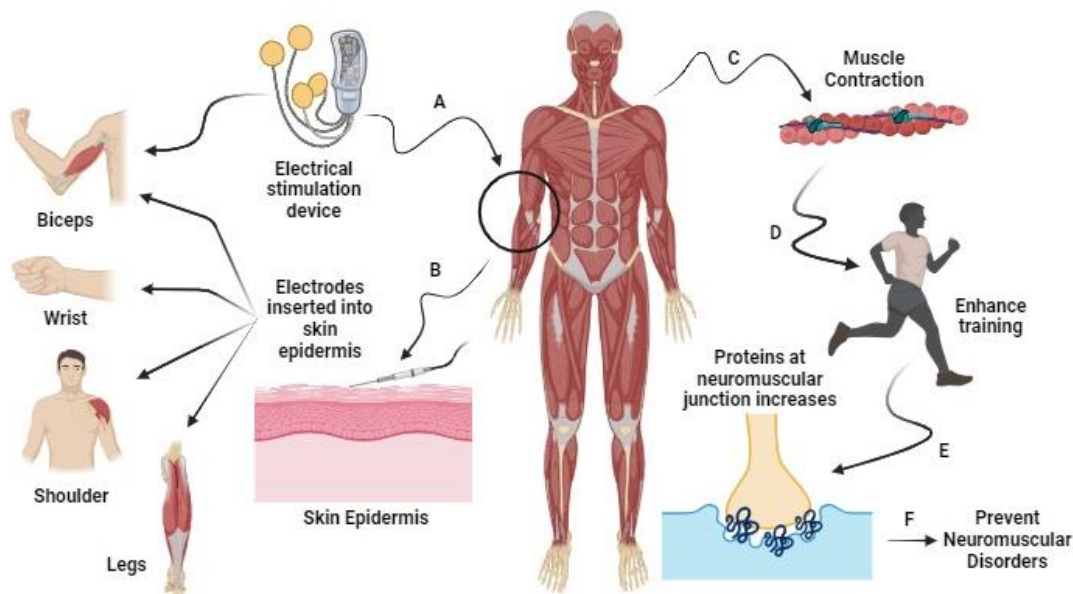
### 13.1 Conclusion

The clustering of acetylcholine receptors at the neuromuscular junction is one of the most important events for the development of the neuromuscular junction with the communication between the muscles and nerves. The acetylcholine clusters also affect the physiology of many neuromuscular disorders such as myasthenia gravis, Neuromyotonia (Isaac's syndrome), Lambert Eaton myasthenic syndrome and many others. Not alone acetylcholine receptor clusters but LRP4 protein, MuSK protein and Agrin combined to form a complex at the motor end plate. (Zhu et al., 2008) In the signaling pathway at the neuromuscular junction, Agrin binds to the LRP4 protein and activates the kinase domain of MuSK to self-phosphorylate MuSK, which is also phosphorylated casein kinase 2 (CK2). (Bredahl et al., 2016) This MuSK then enter into the cell membrane which then promotes or induce acetylcholine receptor clustering. (Morton et al., 2019)

Exercise training also helps in the enhancement of expression of Neurotrophic factors, specifically in the skeletal muscles. Exercise training alone can enhance the expression of particularly Brain-derived neurotrophic factor (BDNF). Exercise training can help improve muscle force production and prevent the condition of muscle atrophy. (Boucein, 2012; Dickinson et al., 2017; Lopes & Baudisch, 2017)

Electrical muscle stimulation variables also hold the potential of enhancing muscle strength which benefits during exercise training. These electrical muscle stimulation devices use signal generators and skin electrodes to send electrical pulses to the user's muscles. These pulses further induce involuntary muscle contractions enabling the device to engage the user's limbs. In one of the prototypes of electrical muscle stimulation, the electrodes are attached to half the side of the body which further activates the wrist, shoulder, biceps, triceps and legs. Electrical muscle stimulation

helps stimulate the parts of the body which are difficult to reach by normal methods. (Poh et al., 2012) The application of electrical muscle stimulation helps in the enhancement of exercise training strength which eventually increases the levels of different proteins present in the neuromuscular Junction. This enhancement of proteins further facilitates acetylcholine receptor clustering which helps in the communication of Muscle cells and Nerve cells. This communication between Nerve cells and the Muscle cells prevents certain neuromuscular disorders such as Myasthenia gravis and many others. Role of Neuromodulation in Muscles and Neuromuscular Disorders has been shown in fig.5.



**Fig.5. Role of Neuromodulation in Muscles and Neuromuscular Disorders**

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### Conflict of Interest

The authors and co-authors have declared no conflict of interest.

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