GUT MICROBIOMES AND ITS EFFECT ON COGNITIVE HEALTH

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ABSTRACT

The human gut microbiomes play important role in brain physiology and pathophysiology. The microbiome of gut linked to the brain through vagus nerve and help in the cognitive development and health. In adults gut microbiomes may affect the nervous system by causing stress, anxiety, depression and cognition increasing clinical and proclinical reports show that gut microbiomes may cause the neurological disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and stroke. Further study help to show us an evidence that how per and probiotic balance the brain functions in healthy and diseased individual. The parental diet also contributes in causing changes in infant microbiome that is high or low fat ratios can effect adversely on neonatal cognitive health later in life. The need of taking a constant supply of nutrients of a fetus from the mother changes with the gut microbiome of mother. Western diet plays a very major role in gut microbiome in changing the behavioral characteristics for cognitive health. The type of nutrition is a major factor that is related to cognitive impairments or causing obesity and its effects on human physical and mental health. The following review article sheds light on interrelation of gut micro biomes with the host's immunity, while explaining the correlation of intestinal permeability and obesity. Furthermore, the production of enzymes induced by micro biota and their effects associated with systemic inflammation. Secondly, cognitive dysfunctions and importance of leptin concentrations and white adipose tissues in that regard is also explained. Thirdly, the blood brain barrier – BBB and its communicatory network with gut micro biomes is discussed. Finally, a psychiatric perspective of microbiota and brain relation is given while further focusing on the same communication network.

Key words; Gut microbiomes, vagus nerve, Gut brain axis, metabolic signaling, laptine resistance

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INTRODUCTION

The bio directional link between gut microbiome and the nervous system is critical to brain function. The gut is one of the largest organs in the body, performing numerous physiological processes such as nutrition metabolism, absorption, and maintaining the physical barrier of epithelial tissue in the gut (Breit *et al*., 2018; Collins *et al*., 2012). The microbiota-gut-brain-axis change the behavior of person and dysregulation of this axis cause neurological disorders such as Parkinson's disease, Alzheimer's disease, strokes, multiple sclerosis and brain injury (Cryan *et al*., 2020).

Gut microbiome play a key role in the life of neonates. As the mother is the main factor for the supply of nutrition or diet in infants and neonates, so the gut microbiome of mother greatly affects the gut microbiome of infant and cause changes accordingly . The changes may lead to cognitive health of infants and neonates that impairs the cognitive behavioral characteristics in human infants that cause impairment in hippocampus structure leads to mental disorders and changes in other brain functions (Davidson *et al*., 2018) . This type of nutrition is usually avoided because obesity generally affects the cognitive health by changes the brain functions and its impacts are mostly adverse and leads to mental disorders (Cryan *et al*., 2020).

As we all know gut microbiota is actually the biggest symbiotic interaction with the host body. It plays keep roles in the balancing of homeostasis in the intestines . Human Body, including all the mucosal environments, the gut and the skin serves as a host to a huge number of microorganisms, which is collectively known as microbiome. All of this research has demonstrated that the gut microbiome is more than a spectator; it actively interacts with and influences various functions within the host, including metabolism, nutritional responses, circadian rhythmicity, and, most critically, the immune system (Ding *et al*., 2010).

As we all know, obesity is considered the mother of all diseases, and gut microbiota has been shown to be one of the promoters of obesity and related diseases. As the gut microbiota is regarded as the metabolic entity of the body, it regulates nutritional efficiency, energy balance, and homeostasis, as well as body weight. As a result, any alteration in the normal functioning of the gut microbiota, such as an increase in normal intestinal permeability, results in chronic inflammation, which promotes obesity and other metabolic dysfunctions such as fatty liver disease (Formy-Germano *et al*., 2019).

MATERIAL AND METHODS

Genetic microbiome profiling

In certain experiment DNA extraction and 16s rRNA was taken from the females candidates having age between 40 to 89 as an observation study.

Cognitive measures

We have four different clinical valid measures of cognitive functions such as verbal fluency test, Deary lie Wald reaction time test (DLRT), mini mental state examination (MMSE) and Cambridge. Neuropsychological test automated battery-paired-associated learning test (CANTAB.PAL).

Associate analysis

In liner mixed effects models R lme4 package is used. Microbiomes traits were different on the base of dependent and independent factors. Such as sample collection methods, gender, family and relatedness. It also depends upon the diet and medicine such as antibiotics used by the person.(Jackson *et al*., 2018)

Elements of Gut microbiome

The GMB contain commercial and pathogenic bacteria, viruses, fungi, and protozoa and also contain their genetic material, secreted proteins and metabolic end products. It helps to develop the functions of body (Gao *et al*., 2020) . The main phyla are Firmicutes, bactericides, actinobacteria and proteobacteria. 90 percent of gut microbiomes are in firmicutes and bacteroidetes. All these microbes which are present in different phyla release different metabolites, harmonies and neurotransmitters with different subscription to variable cognitive function. When compositions of GMB are imbalance it termed as dysbiosis . It is very difficult to eradicate. Dysbiosis causes so many diseases such as irritable bowel syndrome, diabetes, and CNS disorders.(Øyri *et al*., 2015).

Multiplications of cognitive disease due to GMB

The Gut-Brain axis is act like a two face communication system so it can manage the signals between gut and brain such as; neural, endocrine, immunological and metabolic signaling. The gut microbiomes and its metabolites involve the gut brain axis through following pathways and change the cognitive functions (Hantsoo *et al*., 2019). Firstly hypothalamic-pituitary-adrenal (HPA) is affected by the GMB dysbiosis in which it play major role to manage stress response and cognitive function. In human GMB dysbiosis cause depression and anxiety which is associated with HPA dysfunction. When HPA activity is increase it may affect the memory and learning activities of human (Hasan Mohajeri, 2018).

On another way GMB and metabolites interact with blood brain barrier and enhance the permeability and transportation rate by activating the inflammatory response. Inflammatory markers such as interleukin (IL)-6, monocyte chemo attractant protein (MCP)-1 and other cytokines are releasing from endothelial cells and immune cells through GMB metabolites(Jasarevic *et al*., 2004).

Vagal-nerves link the GMB with CNS and autonomic nervous system (ANS). Vagal nerve is stimulated by the product of GMB such as short chain fatty acids (SCFA). CNS impulse move along the ANS pathway and release neurotransmitter choose gastrointestinal epithelia, mucus layers and mucosa by regulating the permeability, motility and secretion (Krabbe *et al*., 2004).

CNS functions are modified by the variety of neurotransmitter and hormones that are released and consumed by the microorganisms of the GMB. Such as human body serotonin is synthesis in gastrointestinal tract, production of serotonin is affected by the gut microbiota and their metabolites which decrease the neurotransmitter and increased the symptoms (Maffeis and Morandi, 2017).

Prefrontal cortex, an area important for complex cognitive tasks such as planning and decision-making can modify by the activity of GMB in myelination, myelin plasticity, and microRNA. In predevelopment stage level of myelination is lower in germ free mice compared to pathogen free mice in the brain development stage. In all these pathways GMB help to enhance the functions of brain including cognition. (Gao *et al*., 2020)

Modulation of mammalian behavior by Gut microbiota

Depression, anxiety and stress

Depression is a worldwide life threatening psychiatric disorder which is caused by the stress. In depression patients level of HPA is disturb so due to this level of corticotrophins releasing factors and cortisol become so high and also proinflammatory cytokines are also found in patient blood plasma. Study proves that gut microbiome directly affect the brain (Mouries *et al*.,2019) . Anxiety and depression is also due to the change of gut microbiome which affect the functions of brain. Sudo et al. study the effect of HPA axis due to microbiome. Their original study based on the stressed germ free mice. They introduce a bacterial strain, Bifidobacterium infantis to remove the side effects of HPA. L rhamnosus has ability to suppress the antidepressants activities in vagotomized mice by reducing the brain function. On other side there are several studies in which gut microbiomes help to reduce depression and anxiety. Probiotic yogurt or multispecies capsule for 6 weeks can reduce the symptoms of depression and anxiety (Myles *et al.*, 2014).

Analysis of fecal sample shows that the microbiome of normal healthy patient is different from the effected. Composition of faeccalibacterium organism may alter from depressed to healthy one. Also number of gram positive and gram negative bacteria in anxiety patient is different. In depressant people number of these bacteria may increase such as; Roseburia, Phascolarctobacterium, Megamonas, Clostridium, Lachnospiraceae incertae sedis, Blautia, Oscillibacter, Parasutterella, Parabacteroides, and Alistipes, whereas are reduced such as; Ruminococcus, Dialister, Prevotella, Faecalibacterium, and Bacteroides (Ochoa-Reparaz *et al*., 2011)..

Cognition

The chance of giving cognitive support to humans may be greater in the age when nutrients are required at high level such as gestation, infancy and older age (Fig 1). .

Study also shows that microbiome may affect the neurodevelopment. Short chain fatty acids are produced by Gut microbiomes and have a main function in brain development and brain activities (Richards *et al*., 2016). Butyrate is important short chain fatty acids which involves in the epigenetic modulation of brain function. Butyrate shows positive effects in Alzheimer's disease through enhancing the memory performance. Butyrate also helps to recover neurodegenerative disorders, including Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and ataxia (Rromano-Keeler *et al*., 2014).

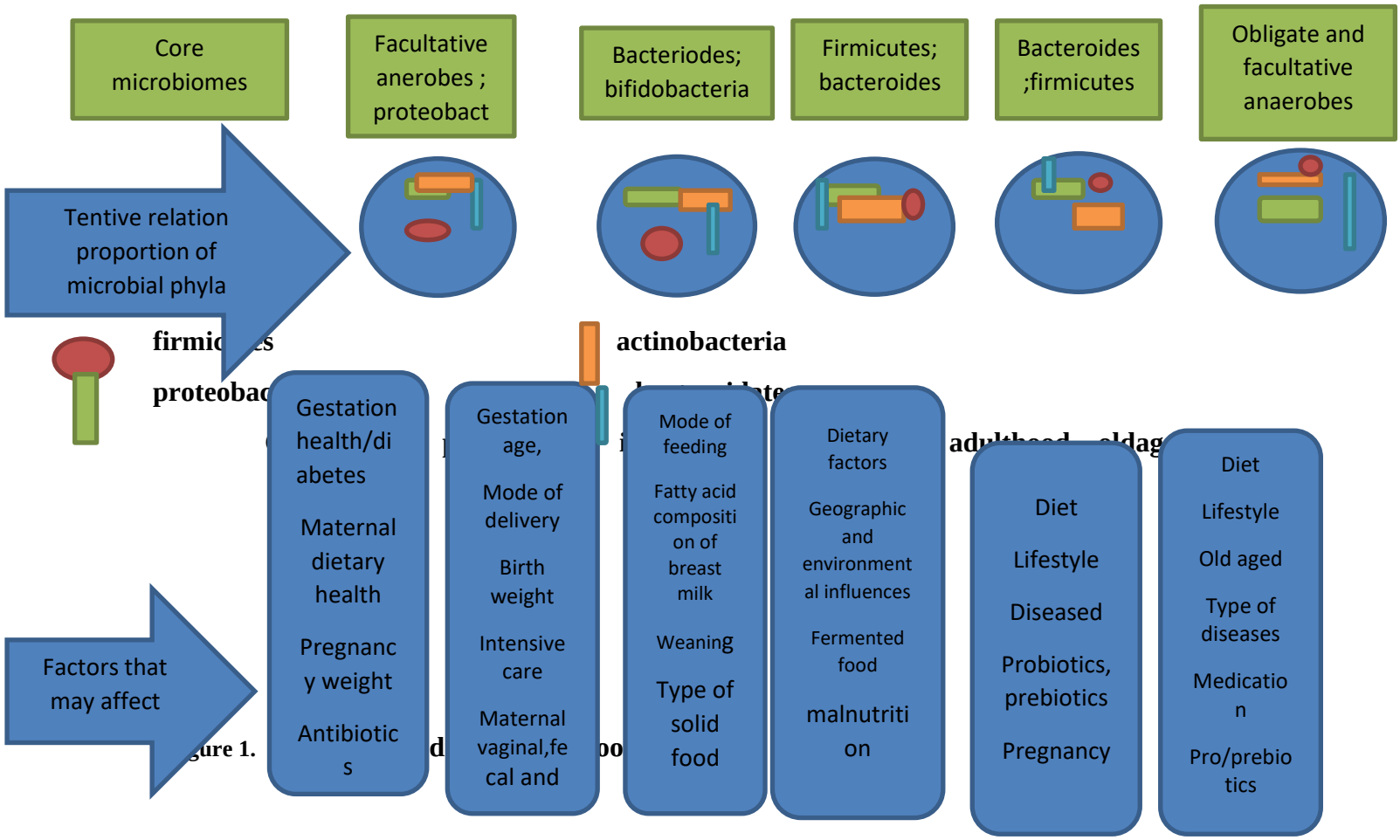

Figure 1: Age-related changes in human gut microbial ecosystem

Mechanistic evidence of microbial influence on neuronal signaling

As we know that gut and brain communicate with each other through vagus nerve.The incoming information from the gut via the vagus nerve to the brain is treated in the nucleus tractus

solitaries, which has large projections that include the parabrachial nucleus, which further projects to the prefrontal cortex as well as the amygdala.Study shows that expressions of receptors subunit NMDArec28 are effected by the N-methyl-D-aspartate (NMDA) in amygdala. Tryptophan and serotonin are required during the life span. Tryptophan help in the regulation of serotonin when level of tryptophan is alter due to the consumption of western diet. So in this case the microbiome and neurotransmitter affect the behavior. In mice, study give tremendous result that when mice is treated with antibiotics level of tryptophan in blood and BDNF level in hippocampus is also being disturb (Tappy and Le., 2010) .

Gut microbiomes – Brain interaction in cognitive

Organisms expose to microorganisms early in development to throughout the life. During the development of embryo, it expose to the microorganisms in utero to the birth process where it receive a lot of microbiota which remain retain in GI tract throughout their life cycle. The first microorganisms which are exposed to the human after their caesarian are Bifidobacterium, Lactobacillus, Enterobacteriaceae, and Staphylococcus while due to vaginal birth dominant flora are Veillonella and Lachnospiraceae.(Hasan- Mohajeri *et al*., 2018)

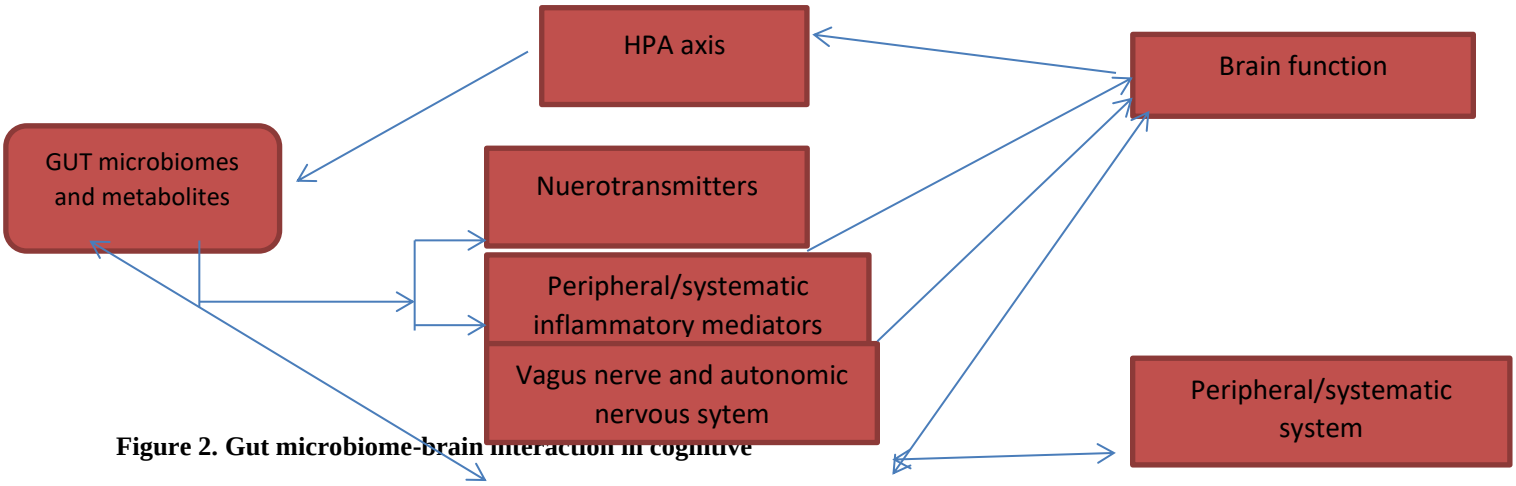

Figure 2. Gut microbiome-brain interaction in cognitive

Gut Brain axis/ second brain

The beneficial bacterial in gut not only provide nutrients to the body but also give them vitamins, energy, and other metabolites. Some good bacteria of GI make a protective biofilms. In recent study it has been proved that bacteria that live in GI may affect the function of brain (Fig 2). The gut brain axis is communication of gut microbiomes with the brain and play an important role in

maintaining the brain health or bad microbiota influence the human behavior and may affect the pathophysiology of mental illness (Tito *et al*., 2012) . System such as central nervous system, the sympathetic and parasympathetic branches of autonomic nervous system, enteric nervous system, immune system and endocrine system ensure the functions of microbiota-gut-brain axis are linked (Tremlett *et al*., 2012).

In other side irritable bowel syndrome (IBS) and inflammatory bowel disease are two human illnesses which is caused by the faulty gut brain communication. IBS is caused by the gastroenteritis due to the use of antibiotics (Winek *et al*., 2016). Because of bowl disease it may cause comorbid psychiatric conditions. Germ free mice also show brain abnormalities as compare to normally animals. Level of calcium binding protein calbindin in the enteric neurons in germ free mice or normal mice is same but their expressions in both are different. Immune system is also disturbed with absence of gut microbiomes. As we study germ free mice lack all the gut bacteria so they show abnormalities in the immune system. Probiotic treatments help to recover the neural functions in B and T cell. (Breit *et al*., 2018)

Microbiota and neurodevelopment

Microbiota-gut-brain axis plays an important role in the mental health. Microbiomes in the gut send signals directly and indirectly to the brain by releasing vitamins, neurotransmitters and neuroactive microbial metabolites such as fatty acids through vagus nerve via nueroimmune and neuroendocrine pathways. Study shows that the animals which are missing the gut microbiota show abnormal brain function because microbiomes active the inflammatory reaction in the brain by regulating the activation of microglial cells and affecting myelination. (Cryan *et al*., 2020)

Role of psychobiome bacteria in gut; probiotics and prebiotic's

Cognitive performance of human and animal model is improved by prebiotics and probiotics. Diet plays a major role for the improvement of GI tract. Consuming a diet which count high, amount of sugar and fats can change the abundance of Bifidobacterium and bacteroides, firmicutes. In recent studies proved that taking acute and chronic prebiotic supplements improved the cognitive performance in humans (Yatsunenko *et al*.,2012).

By taking probiotic supplements which improved the cognitive performance in mouse. But they are not for depression. Probiotic supplements attenuate HPA axis and in hippocampus

neurogenesis it decrease the stress and protect the mice. In healthy adults single and mixed probiotic supplements may affect positively.(Cryan *et al*., 2020).

Microbial and neurological disorders

Microbiota-Gut-brain axis plays a major role in the mental health. Some of causes harmful effects on the brain function in human. Because of these illness patients may face many disease as mentioned in the following section

Multiple sclerosis

Microbiota causes so many neurological disorders which are based on immune system. Children's who are affected with the multiple sclerosis, have large scale differences in alpha and beta delivery of gut microbiota as compared to the healthy children without autoimmune disease up to age 18 years. In this disease, interleukin producing CD4 T cells are affected by the immunomodulatory effects of gut microbiota (Richards *et al*., 2016).

Parkinson's disease

According to seminal research, Parkinson's disease occurs due to aggregation of alpha synuclein protein in brain and also in mucosal and submucosal nerve fibers and ganglia of Parkinson's patient. Alpha synuclein is move from gut to brain through vagus nerve (Oyri *et al*., 2015) . Old rat has more amount of amyloid like produced by the bacteria so increase alpha synuclein in their blood as compare to Young.

Alzheimer's disease

Neuroinflammation and neurodegeneration seen in the patients of Alzheimer's disease. According to the studies, Escherichia coli and shigella bacterial taxa is increase in the fecal sample of Alzheimer's disease patient (Jakson *et al*., 2018).

Stroke and brain injury

Systematic and peripheral risk factors can increase the pathophysiological response to the stroke and brain injury such as neuroinflammation. Stroke occurs due the hypertension which may lead to the heart problems. Clostridium butyricum is a bacterial strain which cause neuroprotective in an animal model of cerebral ischemia reperfusion injury(Winek *et al*., 2016).

Epilepsy, amyotrophic lateral sclerosis and Huntington disease

Researchers and clinicians are focused to recover the microbiota in gut for these diseases. Because if microbiomes of gut is regulated then physiology and behavior of these diseases become normal. According to the studies ketogenic diet is used for the treatment of epilepsy. Because it regulated the gut microbiota. Amyotrophic lateral sclerosis is caused by the lower abundance of butyrate producing bacteria. Huntington disease is occurring due to genetic disorders.Intrinsic factors (e.g., changes to protein homoeostasis, mitochondrial dysfunction, and uncontrolled corticostriatal input) and extrinsic environmental factors (eg, ethnicity, geographic region, tea consumption, and alcohol and tobacco use) can medium development of Huntington's disease.(Tremlett *et al*., 2017).

Effect of Gut microbiomes on maternal and neonatal health

In the early life of neonatal microbiomes, there are different microbial species in neonatal gut that progressively stimulates and promotes gut maturation. A gut microbiome that is fully developed in neonatal stimulates the other health aspects and acts as a driver for stimulation these health factors. In neonates, the gut microbiome shows higher adaptability and plasticity than exhibited by the adults. It usually stimulates the long term health aspects in neonates and helps them to grow developed properly.(Rromano-Keeler *et al*., 2014)Many important studies are emerging that describe the importance of gut microbiome during the early life as it supports the immune system of neonates. It also helps in host metabolism and colonization resistance to many other infectious agents. This relationship between the gut microbiome and immune system is a type of symbiotic relationship as it gives susceptibility to many other diseases later in life by providing strength to immune system in neonates (Tito *et al*., 2012). In certain neonates, the gut microbiome is sometimes altered with metabolism uncovered the links as it increased susceptibility to the development of food allergy, asthma and autism.Many commensal bacterial species that are known as microbiomes effect on infant health and human diseases. Neonatal gut microbiomes are usually colonized with maternal and environmental flora and grow and get mature toward a stable composition over 2–3 years (Yatsunenko *et al*., 2012).

Parental microbiome

Parental dietary intake changes the microbiome of offspring like the fat intake of parental microbiome dietary fatty acids also effects immunity, partially through modulation of responses to microbes**.** High fat intake in parental dietary fat consumption during gestation and lactation stimulates and strengthen offspring immunity. There was a study that was conducted on mouse models using previous observations in search for the influence of high fat intake in their dietary and their effect on the offspring immunity (Tappy and Le, 2010). They compare pups of mice fed either a Western diet fatty acid profile or a standard low-fat diet. They hypothesized that diet of parents are much effective on immunity of offspring certainly. So, Pups from western diet breeders were not diabetic or obese but still had bad results in models of infection, autoimmunity, and allergic sensitization. They showed colonic inflammatory responses with the increased amount of circulating bacterial LPS and muted systemic LPS responsiveness. These harmful impacts of the WD were associated with the changes of the offspring gut microbiome (Myles *et al*., 2014)**.**

Effect of maternal gut

A continuous supply of nutrients and substances to the fetus is important for the fetal development and maturation during pregnancy. The need of getting a supply of nutrients and substances of a fetus from the mother changes with the gut microbiome of mother. There are many important metabolites of maternal gut that are originated from certain microbial species across the placental barrier and contribute to the formation of the blood-brain barrier and innate immune development in fetus. The nutritional status of mother also influences the placental function give alterations to the structure and metabolic potential of the maternal bacterial microbiome.(Jašarević et al., 2017)

Effects on vaginal microbiomes during pregnancy

During childbirth, the bacterial communities that are present in the maternal vagina also play a effective role in offspring postnatal growth and development. The bacterial communities in maternal vagina, provide the primary inoculum that take place in colony form in the neonate gut at birth, the composition of these pioneer communities contributes disproportionally to long-term health outcomes. The transmission of bacterial colonies that colonize the vagina has been proposed to make a disordered interaction of neonate-microbe that is necessary for immune education, metabolism, and neurodevelopment (Tremlett *et al.*, 2017)**.**

Effect on postnatal brain development

Gut microbiome plays a very bidirectional communicator role in between gastrointestinal tract and nervous system as it grows and develops throughout the lifespan of offspring (Fig 3). The development of gut microbiome in early life may lead to brain development procedures and it also effects the brain development processes afterwards in life like may cause brain disorders and other neuro-degenerative diseases in an individual (Winek *et al*., 2016).

The evolutionary trajectory of infant microbiome is related to process and growth of infant brain development. There are various factors that influence microbial gut community of individuals as it is a dynamic ecosystem for an infant. These factors include:Hospital environment, Use of medication, Delivery mode, Feeding, Life experiences, Gender, Gestational age and Postnatal ageThe gastrointestinal tract microbiota plays a significant role in the brain axis that include central nervous system, endocrine nervous system, autonomic nervous system evolving sympathetic and parasympathetic nervous system, and also hypothalamus-adrenal pituitary axis. (Hantsoo *et al*., 2019).

This signaling of whole network enables top-down communication from the brain to the neurons and secretory hormones of GI tract. In the bottom-down communication, signals influence from gut to affect the parts of brain like hypothalamus and amygdala that control stress and emotional activities of body (Rromano-Keeker *et al*., 2014) . So, these signaling networks can influence the alterations in brain like hypothalamus and amygdala that control stress and emotional activities of body. So, these signaling networks can influence the alterations in brain functions via GI tract.

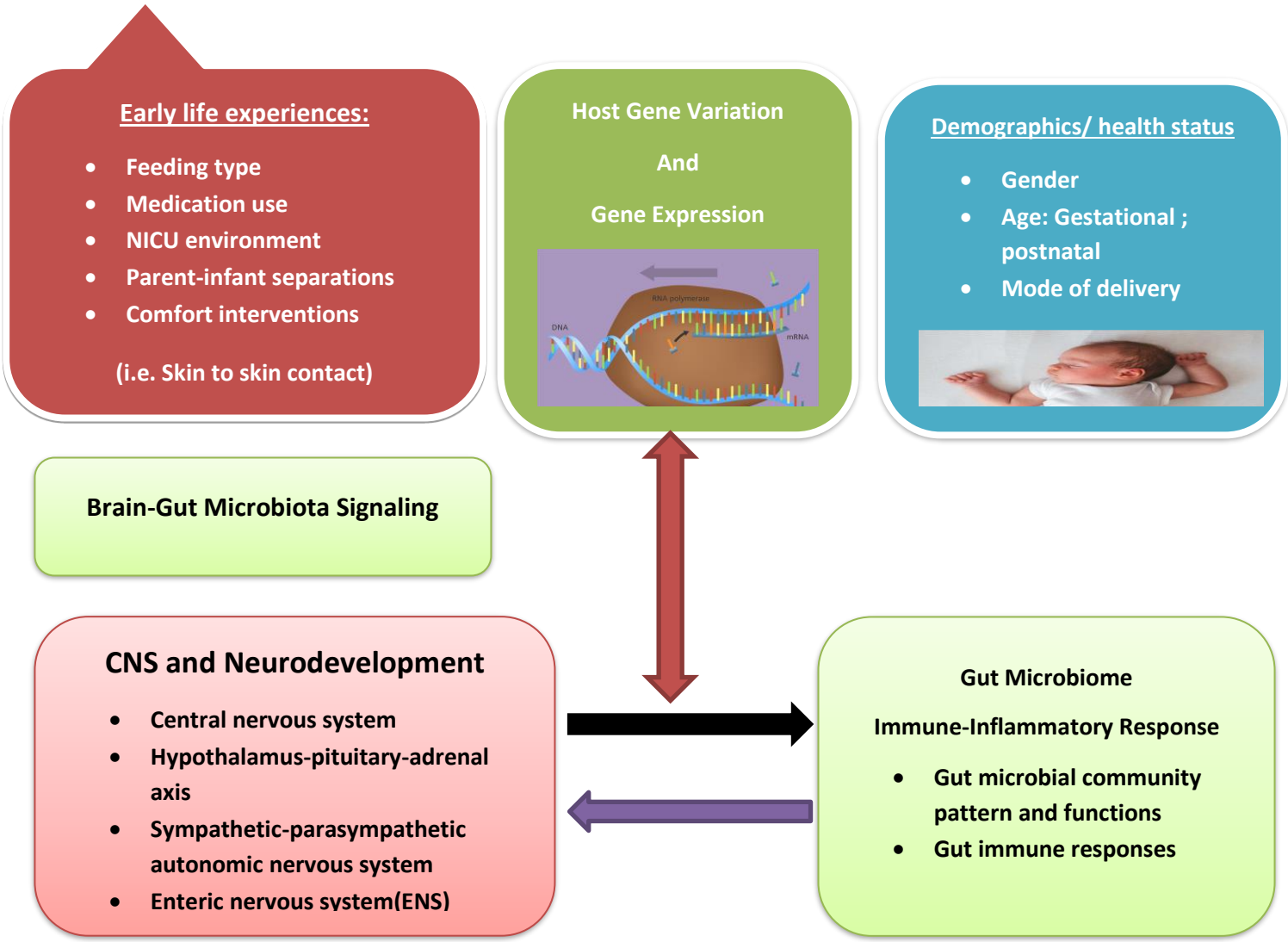

Figure3. showing the effect of gut microbiome on neonatal cognitive health

Gut microbiomes modification for improved cognitive; Diet

Diets that are high in fat and sucrose are mostly known as western diet. They play a significant role in influencing behavior and gut microbiome modifications. The diet that induces modifications in gut microbiome causes alterations in anxiety, cognitive flexibility and brain learning skills. Studies have shown that the diet that is high in sucrose can cause impaired spatial memory that is a loss in the brain functions and flexibility of cognitive health also get affected.

So, diet plays a very major role in gut microbiome in changing the behavioral characteristics for cognitive health. Obesity is the usually associated with cognitive impairments that reduces quality of life and quality of health system (Collins *et al*., 2012). These impairments are important for response inhibition, episodic memory and spatial cognition related to brain. The hippocampus part of brain changes the food seeking behavior in humans that some people show a driving behavior in eating food quickly and take more meals per day than the actual requirement that later on leads toward obesity and other health issues (Ding *et al*., 2010). This change in function of hippocampus works well in obesity and may impair adaptive decision making around eating and food. These impairments lead to cause changes in weight loss and cause the more weight gain in humans. The results of obesity in middle aged people usually compares with cognitive performances, cognitive decline risk and dementia problem in humans (Cryan *et al*.,2020). It can reduce volume of brain and changes the connectivity of white matter and volume of grey matter also reduces due to it. These changes in the brain structure usually impair with cognitive health and behavioral characteristics and it depends on function of hippocampus and temporal lobe. The other research related to these diet related problems may lead towards improvement in cognition and thus also helps in quality of life for humans.(Davidson *et al*., 2018)**.**

Role of nutrition in obesity related to cognitive impairment_

The type of nutrition or diet is a major factor that is related to cognitive impairments or causing obesity and its effects on human health. The western diet is usually being discussed_ the diet that contain high amount of saturated fats along with added sugars that cause negative effects on cognitive health functions like alteration of hippocampus functions (Hasan Mohajeri *et al*., 2018). The factors included in this diet are the influence of gut microbiome towards brain by using the axis between them that is gut-brain axis by changing the proportion of commensal bacteria in GI tract. So, the negative effect of consuming this diet impairs the neurocognitive functions that link the gut microbiome with dietary and metabolic impairment of hippocampus and associated mnemonic lacking.The gut barrier is a specialized semi-permeable and mucosal barrier strengthened by tight function proteins. This barrier allow nutrient and water entry and also prevents the entry of other harmful substances but western diet consumption allow the entry of these harmful substances as well. It causes changes in the function of brain parts that strongly

impacts the neurocognitive functions and alteration in these functions causes impairment in cognition.The western diet consumption impairs the permeability of gut microbiome that allows the harmful chemical substances to enter into the microbiome and usually develops the metabolic disorders and also causes the neurocognitive impairment (Maffeis and Morandi, 2017).

The Gut Micro biomes and Immune System

As the mammals gut region contains microorganism's community which is biologically called as microbiota such as viruses, fungi, bacteria and parasites. Microbial genome consists of 3 x 10^6genes in their genetic sequences which in comparison to human genome is 15folds compact.The symbiotic relationship of the host and the microbe is mutually beneficial. The host in actual provides the microorganisms with basic nutrients and shelter and in return the Gut micro biota help in promoting the growth of metabolic system and maturation of intestinal immune system by providing useful nutrients such as vitamins and fatty acids. Microbial colonization actually occurs by the development of immune system. Fast and immediate colonization of gut micro biota in the GIT tracts on new burns actually help in providing immunity by developing gut immune system.(Hantsoo *et al*., 2019).

As we know that immune system in actual is regulated by immune organs, immune cells, soluble cytokines and cell receptors. The intestines mucosal immune system is actually dependent on 3 main parts are like payer s Patches, Lamina propriety and the epithelial

As mucus layer of epithelial is considered as the first line of defense. The mucus layer and AMPs actually acts as mucosal barriers which help in restricting the symbiotic bacteria. Epithelial cells are considered as the 2nd line of defense in the intestinal mucosal immune system by either direct defensing or by sending chemical signals in the form of cytokines or chemokine's.The balancing of the intestinal immune system and gut micro biome plays a crucial role in maintaining the host homeostasis and defense.The dynamic interaction of the gut micro biome and environmental factors actually shape up the mucosal and systemic immunity. Diet and exogenous substrates are considered the most crucial parts of regulation of intestinal or gut micro biome.(Richards *et al*., 2016).

Gut microbiome Dysbiosis

The main aim of intestinal micro biota and mucosal immunity is to maintain intestinal homeostasis. As if the balance or homeostasis is disrupted it will lead to many major consequences such as IBD.

IBD

It is abbreviated as Inflammatory Bowel disease. It is actually result as the imbalance of homeostasis .It is heterogeneous disease which is influenced by a lot of factors such as genetics, environmental and microbial. This all results in the inflammation or destruction of intestines and an abnormal immune response. Crohn's disease and Ulcerative colitis are the major IBDs.Intestinal disposes lead to an abnormal immune system which in result cause inflammation or serious effects on the gastrointestinal tract. Although studies have shown that the Rapid formation of Next Generation sequencing technology which actually helped in identifying the causative specie for intestinal disposes.Gut micrbiota actually produced many immunogenicity substances such as Bacteriodes fragilis. As it play a crucial and very positive regulatory role in the human system. Intestinal microbiota modification acts as powerful preventive and therapeutic tool against inflammations.(Rromano-Keeler *et al*., 2014).

Intestinal permeability, immune system and systemic inflammation

Recent researchers have predicted that diet has strong influence over the intestinal micro biota and this ultimately affects the intestinal permeability and also cause inflammation. The dietary fluctuation like high fructose and hi fat diets on the gut micro biome.

High fat diets, As the high fat diets cause reasonable changes on the gut micro biome as it also effects on intestinal permeability , inflammation and other obesity related complications. As this high fat diet influenced the gut micro biota permeability and normal functioning which results in the metabolic endotoxin which is crucial for the production of metabolic syndrome. High fat diets have result in increment in the body weight and also cause ideal tumor necrosis factor as well. High fat diets have also caused alteration in gut epithelial integrity microbiota which cause systemic inflammation which in further results in obesity. Diet induced changes in microbiota causes the development of metabolic endotexmia, insulin resistance and metabolic syndromes. (Ding *et al*., 2010).

High Fructose diets

High fructose diets cause hepatic and extra hepatic insulin resistance, obesity and insulin resistance and hypertension. Fructose is actually now a major part of the modern diet now. As fructose is considered the major culprit in promoting obesity.(Tappy and Le, 2010)

Systemic Inflammation

Interactions of micro biota, diet, gut permeability causing endotexmia and inflammation. Both high fat and high fructose diets because hepatic steattosis. Hepatic inflammation can cause predispose of other organs such as lung, kidney and brain. Intestinal permeability allows gut derived toxins cross the intestinal barrier and activates the Kupffer cells which are primed to produce inflammatory cytokines which cause liver inflammation or injury and systemic inflammation. There are gut derived products which actually gut derived toxins crosses the gut barrier which are not only endotoxins but LPS.

Cognitive dysfunction

There is this possibility of alteration in brain physiology and behavior by changes in gut microbiota. As in old studies cognition is always linked with brain and central nervous system organs. So now non-nervous system factors also influences in the cognitive dysfunctions such neurodegenerative diseases, cerebrovascular diseases by gut resident bacteria of GIT tract. Changes of blood brain barriers ,brain vascular physiology and brain structure are among the critical reasons for the brain dysfunctions. The habitat of microbiota do have some influence too as the bi-directional brain-gut signaling through humeral ,neural and immunological pathogenic pathways.The CNS changes the gut microenvironment by maintaining gut motility and secretion and mucosal immunity by the help of neuronal glial epithelial pathways. Bacteria react to the changes caused by the extrinsic and intrinsic factors by the formation of neurotransmitters or neuromodulators in the intestine to effect host CNS.(Collins *et al*., 2012)

White adipose tissues and Leptin concentrations

Imbalance accumulation of white adipose tissues in overweight and obese patients generally occurs as a result of increase the circulation levels of adipokines. Adipose dysfunction and adipokine deregulations are considered to be the culprits in promotion of obesity and other obesity related disorders. So any increase in the adipose tissues leads to obesity which in turn effects the CNS which in turn altered the brain metabolism , brain atrophy , neuron inflammation and neuronal dysfunction , mood and behavioral changes and cognitive declines.It is now cleared that adipose tissues do effect the cognitive dysfunctions (Krabbe *et al*., 2004).The adipokines do

effect the brain morphologies.Adipose tissues form adipokines type leptin and TNF-a actually are involved as they can cross the blood brain barriers and directly act on brain while other act on brains epithelial cells.so in result they cause many pathological changes in the brain functions such as inflammations , blood brain barrier integrity is also compromised (Myles *et al*., 2014).

Leptin Concentrations

It is majority produced by Adipose tissues specifically by subcutaneous tissues in humans and by white adipose tissues in rodents. Circulation of leptin influenced by multi factors such as metabolism , body fat weightage , sexual dimorphism and circadian rhythms. Leptin actually cross the blood brain barrier by getting bind to the leptin receptors or getting interacted with them .

Leptin Resistance

Response to leptin also decreases with obesity, aging and neurodegenerative disease in a process called as Leptin resistance. Leptin resistance effects a lot of processes such as food intake , insulin sensitivity ,inflammation and cognition. Leptin resistance actually promotes the production of leptin by adipocytes and hyperleptinemia. Triglycerides also cause hindrance in blood brain barrier leptin transport which in result causes central leptin deficiency. (Forny-Germano *et al*., 2019).

Discussions and Results

Peripheral inflammation signaling in humans

To interpret the changes in the CNS the way of communicating must be among CNS and periphery. As fever and neuroendocrine pathologies have depicted that periphery communicate to CNS through by neural or humeral pathways.Peripheral inflammatory mediators have impacted on brain function and they also play crucial roles which cause inflammation and other symptoms like other cognitive disorders. As the systemic infusion of inter leukins and tumor necrosis factors alpha also promotion suppression food intake , poor memory ,social exploration. It also cause cognitive dysfunction in peripheral lipopolysaccharides and endotoxins which promote the stimulation of proinflammatory cytokines (Jackson *et al*., 2018) . This interferes among many neuromolecular processes like hippocampal neurogenesis, synaptic plasticity and synaptic scaling as it cause dendritic atrophy which ultimately effects memory and thought.

Aging has also been related with proinflammatory cytokine expression in the periphery (Krabbe *et al*., 2004).

Central Inflammation signaling

Many epidemiological researches are giving importance to the role of inflammation in the modeling or affecting the cognitive function. The gut receives regulatory signals from the CNS. This bidirectional interaction has some serious effects. The gut-CNS signaling occurs through the central regulation satiety. Diet patterns as they are controlled by CNS food intake which ultimately affect the nutrient availability to the gut. Satiation signaling peptides are the key modulators which help in CNS-Gut control. These signals are usually raised from the GI tract and sometimes from the brain too.CNS can effect gut micro biome by both pathways neural and endocrine pathways either by direct and indirect ways.CNS disorders are either considered as immune mediated and non immune mediated. Immune mediated disease are actually triggered by autoimmune disorders such as multiple sclerosis and Non immune mediated disorders are stress , depression , anxiety and autism.(Ochoa-Repáraz *et al*., 2011).

Blood Brain Barrier

Gut micro biota is considered as one of the pivotal member for the blood brain integrity. As BBB is actually a semipermeable barrier which is made up of specialized epithelial cells in the microvasculature.It also differentiate the CNS from Peripheral blood.Microorganism induced blood brain barrier dysfunction cause many psychological disorder such as stress, anxiety, depression and autism spectrum disorders. And many critical neurological disorders such as Parkinson’s disease, Alzheimer’s disease and Schizophrenia.Possible way by which micro biota may have affected the cognitive. Health are Either BBB modulation by the gut influenced neurotransmitters and bacterial metabolites. May metabolic diseases such as Diabetes in which the blood brain barrierPermeability is increased. This all lead to Alzheimer’s disease amyloid b peptidedeposition.Microbiota disposes also caused disruption in theProtective function of blood brain barrier such as its permeability, behavioral changes and tightjunction changes (Mouries *et al*., 2019).

Gut Micro biome and Psychiatrist perspective

Imbalances of gut micro biome have serious effects on brain and it cause serious psychiatric illness.The role of micro biota in regulating mood cognitions, stress, anxiety and social behaviors. The role of micro biome in causing psychiatric disorders by causing alteration in theDiversity of the Disorders in treatment of autism, schizophrenia and attention deficit autismsome mood disorders such as bipolar , stress and anxiety disorders.Microbes in gut are suspected to alteration by treatments or medication used to treat

Psychiatric Disorders so they get to play important roles in maintaining the gut metabolism

either by naturally or orally administered medication.The beneficial

Strategy of micro biotas to be used as treatment technique is as we know micro biotas are

Readily diverse and dynamic so micro biota are manipulated by number of factor such as food, diet exercise and stress reduction.(Breit *et al*., 2018).

A quote from Hippocrates, "Let food be thy medicine and medicine be thy food,"

So personalized medication are being used according to the nature of gut micro biome as a

Base for The treatment of psychiatric disorders and future adjunct therapies.

CONCLUSION

Reviewed that gut microbiomes (GMB) linked with brain through vagus nerve and by producing neurotransmitters such as GABA, acetylcholine and serotonin. It not only help to modify human physiology such as CNS functions and cognition but also experimental animals show that GMB dysbiosis causes negative effects on cognitive functions, can be treated by the prebiotic, probiotics and dietary modifications. Further researches are required to identify of pathology of microbiomes and individual changes to the microbiomes pattern. Many external and internal factors also affect the microbiota and it can be modified by diet and other intervention. Clinical studies proved that gut microbiomes may affect the nervous system and causes neurological disorders. Neonatal gut microbiomes are usually colonized with maternal and environmental flora and grow and get mature toward a stable composition over 2–3 years. The gastrointestinal tract microbiota plays a significant role in the brain axis that includes central nervous system. The diet that contain high amount of saturated fats along with added sugars that cause negative effects on cognitive health functions like alteration of hippocampus functions. Gut micro biota is crucial for the Intestinal homeostasis and for the brain health. The Gut micro biota have great

impact on the immune System of The human as any alteration to the gut microtome will lead to serious ailments such As obesity, diabetes and many other neurodegenerative ailments. However there are still some Modifications required in the study and analysis of experimental design, subjects, and Models. Analytical approaches and quality control protocols in the study of gut micro biome in Relation to cognition. As the relation of host with symbiotic microorganism is considered as Clear Association rather than a casual interaction. So diet, lifestyle approach genetic and Environmental factors have serious influenced over the modifications of demographics of gut microbiome in relation to cognitive health.

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