SUBSTANCES OF ABUSE

AND THE FETAL NERVOUS SYSTEM

by

Maddison Elizabeth Benoit

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Thesis Supervisor:

Rachel Davenport

Second Reader:

Andrea Aspbury

ABSTRACT

The human nervous system is a specialized organ system composed of two distinct components: the central and peripheral nervous systems. The central nervous system contains the brain and the spinal cord, which perform various functions, including receiving, processing, and responding to sensory information. The fetal nervous system development begins at nine weeks gestation and continues after the fetus is born. A teratogen is a substance that causes congenital disorders within a developing fetus. A critical period is the length of time an organ system is most at risk for teratogenic consequences; the central nervous system has the most extended fetal critical period, ranging from nine weeks gestation until the fetus's birth. Common abuse substances that act as teratogens include stimulants such as caffeine, nicotine, prescription medications, and illegal drugs, as well as depressants including alcohol, marijuana, and opioids. These substances have varying teratogenic effects depending on the type and amount used and the fetus's exposure duration.

DEDICATION

This thesis is dedicated to my parents, Tom, and Elizabeth Benoit. With their endless love and support, I was able to make it to where I am today. I love you both and thank you for everything.

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I also want to thank my siblings, parents, and grandparents for always rooting for me and being my biggest supporters. I honestly could not have made it to where I am today without their love and support throughout my entire life and college career. I would also like to thank my close friends for being understanding during this process, and I especially would like to thank my partner Tre for supporting me and always believing that I could do whatever I set my mind to. I love you all, and I can never thank you enough for what you all have done for me!

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LIST OF ABBREVIATIONS

Abbreviations

ADHD: Attention-Deficit Hyperactivity Disorder
ARBD: Alcohol-Related Birth Defects
ARND: Alcohol-Related Neurodevelopment Disorder
ANS: Autonomic Nervous System
CB1: Cannabinoid Receptor
CNS: Central Nervous System
FAS: Fetal Alcohol Syndrome
FASD: Fetal Alcohol Syndrome Disorder
FDA: Food and Drug Administration
GABA: Gamma-Aminobutyric Acid
MOP: μ Opioid Receptor
nAChRs: Nicotinic Acetylcholine Receptors
NOWS: Neonatal Opioid Withdrawal Syndrome
OUD: Opioid Use Disorder
PNS: Peripheral Nervous System
PTSD: Post-Traumatic Stress Disorder
SIDS: Sudden Infant Death Syndrome
RVLM: Rostral Ventral Lateral Medulla
THC: Δ9-Tetrahydrocannabinol

I. INTRODUCTION

The human nervous system consists of the central and peripheral nervous systems that work with one another to execute specific tasks through the transmission of information between the brain, spinal cord, and various nerves throughout the body. The peripheral nervous system (PNS) splits into two distinct pathways, the autonomic and somatic nervous systems, to regulate involuntary and voluntary functions of the body. The autonomic nervous system further divides into the sympathetic, enteric, and parasympathetic nervous systems to control the operations of visceral organs and involuntary physiological processes. The central nervous system (CNS) consists of the brain and spinal cord that receive and process information from the PNS and transmit information back to the PNS coordinate movement or form a response. The brain is an organ composed of three main divisions: the cerebrum, cerebellum, and brainstem (Goldstein et al., 2023). The brainstem connects the brain to the spinal cord to send and receive information from the PNS through a network of branched nerves. Development of the CNS is a highly regulated process, including the proliferation, migration, and organization of neurons and glial cells. Neurons and glial cells are types of cells found in the brain. Neurons specialize in sending and receiving messages for whole-body control and cognition, while glial cells act as support, scaffolding, and protection of neurons (Leibovitz, Lerman-Sagie, & Haddad, 2022).

The fetal period of CNS development in humans begins at nine weeks gestation and continues until birth. Fetal CNS development is organized into early, midterm, and early or late preterm development. Due to the delicate nature of the fetal CNS, the network is susceptible to foreign substances known as teratogens. A critical period is the period during development with the highest susceptibility to teratogenic impacts and congenital effects. The CNS has the most prolonged critical period, lasting from three weeks gestation to birth. Substances of abuse, including stimulants and depressants, may act as teratogens during CNS development and have

varying impacts depending on the type of substance and length of exposure. Common stimulants used during pregnancy include caffeine, nicotine, prescription medication, and illegal drugs, while common depressants include alcohol, marijuana, and opioids (Li, 2021).

II. OVERVIEW OF THE HUMAN NERVOUS SYSTEM

Divisions of the Nervous System

The peripheral and central nervous system each have unique properties and importance for maintaining homeostasis and whole-body control. The CNS has two main components: the brain and the spinal cord (Silbereis et al., 2016). In contrast, the PNS is a series of nerves branching from the spinal column and extending throughout the body. The PNS gathers information from the environment through receptors and transmits these signals to the CNS, allowing the body to process and respond to stimuli (Maldonado & Alsayouri, 2023). The CNS transmits signals to the PNS as well, eliciting responses such as muscle contraction and glandular secretion. The PNS also consists of ganglions branching off the spinal column. Ganglions are collections of neuronal cells that create the peripheral nerves, allowing for information collection through the senses, such as hearing, smell, and taste (Murtazina & Adameyko, 2023). The PNS is comprised of the autonomic and somatic nervous systems.

The autonomic nervous system (ANS) controls the body's involuntary functions, including heart rate, blood pressure, respiration, digestion, and sexual arousal. The ANS comprises three distinct systems: the sympathetic, parasympathetic, and enteric nervous systems. The sympathetic nervous system allows the body to have a "fight or flight" response via vasodilation of blood vessels and an increase in heart rate that induce an individual's response to a stressful situation. The somatic nervous system (SNS) regulates other functions, including inhalation, the immune organ function of the spleen and lymph nodes, and the up- or down-

regulation of inflammation. The somatic nervous system regulates the body's voluntary movements utilizing skeletal muscle. The somatic nervous system divides into two main types of nerves: afferent and efferent. Afferent nerves transmit signals about body information from the PNS to the CNS, while efferent nerves transmit information from the CNS to the PNS to cause muscle contraction (Akinrodoye & Lui, 2022).

The PNS is also responsible for "rest and digest" processes. The main anatomical component of the PNS is the vagus nerve, which helps regulate processes, involved in lowering heart rate and blood pressure and restarting digestion by increasing salivation. The vagus nerve is also vital for detecting foreign substances within the body and promoting healing in areas of inflammation or damage in many of the body's major organs.

The enteric nervous system (ENS) controls the contraction and relaxation of the muscles within the gastrointestinal system, and secretion and absorption within the digestive tract. (Waxenbaum, Reddy, & Varacallo, 2022).

Central Nervous System

The CNS consists of the brain and the spinal cord and is the largest and most complex part of the human nervous system. The CNS is the most intricate and complex part of the human body and is an essential part of an individual's ability to receive, process, and respond to sensory information sent by the PNS. The CNS regulates more complex functions as well, such as sleep, learning, memory, and cognition (Thau, Reddy, & Singh, 2022).

Neural Tissue and Signaling

Most of the tissue within the brain comprises either neurons or various types of glial cells, such as oligodendrocytes, microglia, and astrocytes. Neurons are specialized cells that transmit electrical and chemical signals throughout the body (Ludwig, Reddy, & Varacallo,

2022). During chemical signaling, the terminal of one neuron releases neurotransmitters across a synaptic cleft to bind to receptors on another neuron, leading to a resulting electrical signal. Chemical signals are either excitatory or inhibitory depending on the nature of the neurotransmitter and the electrical change it causes (Bigbee, 2023). The axon, located at the end of a neuron, regulates the transition of electrical signals sent throughout the neuron to chemical signals between cells by releasing neurotransmitters, neuromodulators, or neurohormones (Ludwig, Reddy, & Varacallo, 2022). The axon is wrapped with myelin sheaths, produced by oligodendrocyte cells, which expose regularly spaced nodes of Ranvier. Myelin sheaths wrap around the axon as insulation to increase the conduction velocity of action potentials along the axon. An action potential is an electrical signal caused by the rapid reversal of the electrical gradient on either side of the neuron membrane by opening and closing potassium channels and sodium channels at different rates and times within the cell membrane. The nodes of Ranvier are areas without myelin sheath insulation and serve as locations for action potentials to occur allowing them to move from one node to the next down the axon. The axon is attached to the cell body, also known as the soma, of the neuron, which holds the nucleus and other cellular organelles. Surrounding the soma are dendrites that are responsible for receiving synaptic inputs or afferent signals and regulating electrical signaling. Dendrites are projections of the cell membrane that increase surface area leading to increased opportunity for other neurons to form connections (Bigbee, 2023).

Several neurotransmitters are located throughout the CNS to allow chemical transmission between neurons. Acetylcholine, dopamine, serotonin, norepinephrine, glycine, glutamate, gamma-aminobutyric acid (GABA), and adenosine are examples of neurotransmitters important for CNS function. Neurotransmitters produce varying effects depending on their

location and how they are released within various regions of the brain. For example, acetylcholine regulates the development of the CNS, primarily in motor neurons, as well as the functions of memory, learning, attention, arousal, and involuntary muscle movement. Dopamine is a neurotransmitter vital for learning, motor control, reward, executive functioning, and emotions. Serotonin manages heart rate, respiration, arousal from sleep, and mood. Norepinephrine regulates stress, sleep, focus, and inflammation. Glycine and GABA are inhibitory neurotransmitters that inhibit the transmission of signals between neurons by decreasing the probability of an action potential. In contrast, glutamate is an excitatory neurotransmitter that increases the probability of an electrical signal. Adenosine modulates the release of neurotransmitters, synaptic plasticity, and neuroprotection during low blood flow, hypoxic, or oxidative stress events (Sheffler, Reddy, & Pillarisetty, 2023).

Anatomy of the Brain

The brain is divided into a left and right hemisphere with a network of nerves connecting both hemispheres together, called the corpus callosum. The corpus callosum allows for the transfer of information between each hemisphere (Goldstein et al., 2023). Both efferent and afferent information crosses between each hemisphere via the brain stem and in some cases the spinal cord. This means that the left side of the brain controls and receives information from the right side of the body, and the right side of the brain controls and receives information from the left side of the body. The principal divisions of the developed brain are the cerebrum, cerebellum, and brainstem. There are hundreds of unique regions of the brain, however, this manuscript will only cover a selection of larger structures.

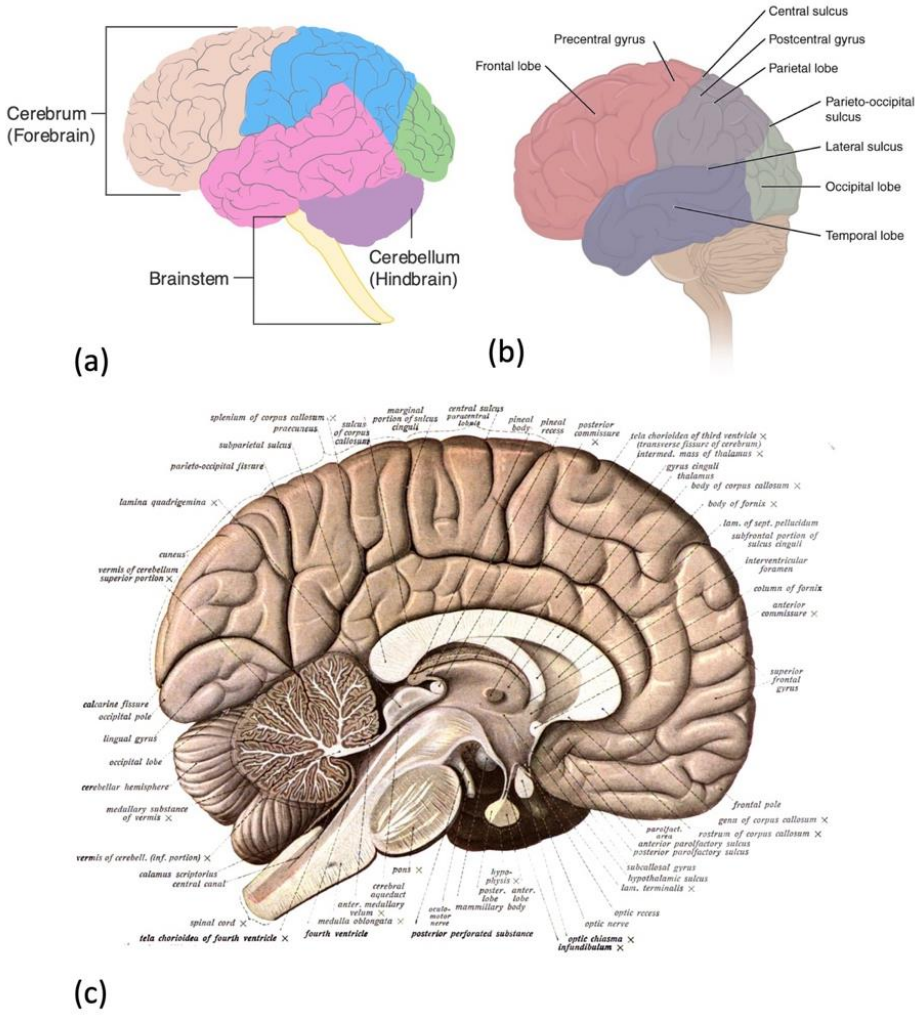

Figure 1: (a) Main areas of the brain by Cancer Research UK, under Creative Commons license [https://commons.m.wikimedia.org/wiki/File:Diagram_showing_some_of_the_main_areas_of_the_brain_CRUK_188.svg]; (b) Main lobes, sulci, and gyri of the cerebral cortex by OpenStax, under Creative Commons license [https://commons.m.wikimedia.org/wiki/File:1306_Lobes_of_Cerebral_CortexN.jpg]; (c) Labeled sagittal cross-section of the brain by Dr. Johannes Sobotta, under public domain [https://commons.wikimedia.org/wiki/File:Sobo_1909_624.png].

Cerebrum

The cerebrum is the largest part of the brain and comprises an outer layer called the cerebral cortex and an inner layer of white matter. The cerebral cortex contains six layers of grey matter. The deeper layer of the grey matter includes a region that receives sensory input, creates output pathways through the cortex, and mediates communication between regions of the cortex (Miyashita, 2022). White matter contains myelinated axons, allowing it to receive and transmit information to and from the brain and send information quickly to other areas within the brain (Bui & Das, 2022). The cerebrum forms sulci and gyri. Gyri are the folds or bumps within the brain separated by the grooves called sulci. Both increase the brain's surface area to enhance cognitive function. The gyri serve as functional centers that form a network to link distant gyri to close sulci. In contrast, sulci communicate with closely connected regions of the cerebral cortex (Lin et al., 2021). Four lobes comprise the cerebral cortex, which is the top portion of the cerebrum, including the frontal, temporal, parietal, and occipital lobes (Jawabri & Sharma, 2023). The frontal lobe, situated at the anterior part of the cerebrum, is the largest lobe with regulatory functions encompassing movement, language, memory, attention, affect, mood, personality, self-awareness, and ethical or moral reasoning. Key segments include the primary motor cortex, overseeing voluntary body movement, and the prefrontal cortex, governing complex cognitive behaviors such as decision-making, reasoning, personality, and social conduct (Maldonado & Alsayouri, 2023). Located bilaterally in the brain, the temporal lobe houses regions crucial for language perception, both spoken and written, auditory processing, and communication. Additionally, structures like the amygdala and hippocampus within this lobe play vital roles in memory functions (Bui & Das, 2022). Positioned dorsally, behind the frontal lobe, the parietal lobe encompasses the primary sensory cortex, responsible for receiving and

processing sensory information related to temperature, touch, pain, pressure, vibration, and thalamic signals. The lower part of the parietal lobe contains the secondary somatosensory cortex, essential for interpreting thalamic signals to support functions such as learning, language, spatial recognition, sensorimotor planning, and object discrimination based on shape, size, or weight (Jawabri & Sharma, 2023). The occipital lobe, the smallest within the cerebral cortex, is situated at the posterior aspect of the cerebrum and houses the visual cortex. This region processes and interprets visual information received from the retinas through the thalamus. Subsequently, the data is transmitted to other brain areas for further analysis, contributing to the determination, recognition, and comparison of visual input (Jawabri & Sharma, 2023).

Deep within the cerebrum underneath the lobes are subcortical structures including the thalamus, pituitary and pineal glands, basal ganglia, and limbic system. The thalamus controls the relay of information from the senses of vision, hearing, taste, and touch, and plays a key role in the processes of sleep, consciousness, learning, and memory. The pituitary gland contains both the posterior and anterior pituitary glands. The anterior pituitary gland releases several hormones regulating bodily functions such as growth, puberty, ovulation, and stress, while the posterior pituitary gland releases hormones important for bodily functions such as birth of a fetus and constriction of smooth muscle. The pituitary gland and hypothalamus communicate to regulate the release of hormones through the bloodstream to various areas in the body (El Sayed, Fahmy, & Schwartz, 2023). The pineal gland regulates the release of melatonin based on the amount of light in the environment, affecting sleep-wake cycles (Arendt & Aulinas, 2022). Basal ganglia, located within the white matter of the cerebral cortex, are responsible for the regulation of muscle movement (Thau, Reddy, & Singh, 2022).

The piriform and cingulate cortexes, hippocampus, septal nuclei, amygdala, nucleus accumbens, hypothalamus, and anterior portion of the thalamus communicate together to regulate emotions, behavior, memory, and olfaction. These structures form the limbic system. The piriform cortex processes and interprets olfactory information from the nasal cavities (Thau, Reddy, & Singh, 2022). The cingulate cortex hooks around the corpus callosum and is involved in the functions of emotion, learning, and memory (Rolls, 2019). The hippocampus regulates memory and learning and is essential for spatial navigation, regulation of the hypothalamus, and emotional behavior (Anand & Dhikav, 2012). Septal nuclei control the abilities of learning, memory, pleasure, reward, movement, and cognition (Kamalkhani & Zarei, 2022). The primary function controlled by the amygdala is emotional processing including emotions of fear, anxiety, and depression (Thau, Reddy, & Singh, 2022). The nucleus accumbens regulates addiction and reward mechanisms in the brain and serves as an interface between the motor and limbic systems (Salgado & Kaplitt, 2015). Regulation of heart rate, blood pressure, appetite, thirst, temperature, regulation of smooth muscle movement to control digestion and blood flow, and the release of hormones are functions of the hypothalamus. The hypothalamus connects the endocrine system and CNS to regulate the release of hormones to maintain homeostasis. It can translate emotions into a physical response by evoking feelings of fear, anger, pleasure, or excitement (Ackerman, 1992). The thalamus regulates sleep and consciousness and serves as a relay system for sensory information to be transmitted and interpreted by other areas of the brain based on the type of sensory information (Thau, Reddy, & Singh, 2022).

Cerebellum

The cerebellum is located at the posterior portion of the cerebrum along the base of the skull and regulates posture, balance, and coordination of movement. The cerebellum is a relay

system for signals from the motor cortex to the spinal cord to execute specific muscle movements. The cerebellum may refine the instructions sent from the brain and relay them to the spinal cord to adjust and compare them with signals from various muscles or joints throughout the body to maintain balance. Information on the right and left sides of the cerebellum does not cross over like the cerebrum, meaning the left side controls the left side of the body, and the right side controls the right side. However, information coming from the cerebrum crosses before entering the cerebellum, such that the left cerebrum projects to the right cerebellum and on to the right side of the body (Ackerman, 1992).

Brainstem

The brainstem starts at the base of the cerebellum and connects the brain to the spinal cord. The brainstem contains the midbrain, pons, medulla oblongata, and various tracts essential for sending information about sensory and motor functions to the spinal cord. Spanning throughout the brain stem and branching forward is the reticular formation, which regulates the level of consciousness through the reticular activation system. Through sensory axons, visual, auditory, and sensory impulses activate reticular activation system neurons and send the information to the thalamus and other areas of the cerebrum. The stimulation of these neurons causes the cerebrum to be continuously activated, giving an individual the feeling of alertness while repetitive weak stimuli are filtered out (Thau, Reddy, & Singh, 2022).

The midbrain is located at the top of the brain stem, close to structures such as the thalamus and hypothalamus. The midbrain maintains the constriction and dilation of the pupil, and controls motor and sensory pathways through ascending and descending pathways to the spinal cord. Ascending pathways send sensory information; descending pathways send signals to the spinal cord to become motor movement and reflexes dispersed throughout the PNS

(Caminero & Cascella, 2022). The midbrain controls the functions of sleep and consciousness through connection to the reticular formation. It also modulates pain, control of emotional responses regarding fear and anxiety, cardiovascular control, and vocalization (Sciacca et al., 2019).

The pons conducts signals from the brain to the cerebellum and midbrain and divides into two sections: the ventral and dorsal tegmentum (Sciacca et al., 2019). This network of nerves, extending from the brain to the spinal cord, plays a pivotal role in refining voluntary movement and conveying motor and sensory information, encompassing vision and hearing. Additionally, the pons is instrumental in maintaining respiratory functions (Keser et al., 2015).. The dorsal tegmentum contains various types of cranial nerves and white matter integral to the auditory pathway used in the localization of sound. The ventral portion of the pons regulates reward processing, learning, memory, and stress modulation (Sciacca et al., 2019).

The medulla oblongata is the link between the brain stem and the spinal column and serves as a control center for unifying the cardiovascular and respiratory systems. Within the medulla oblongata is the rostral ventral lateral medulla (RVLM), which uses excitatory neurons to carry information to pre-sympathetic neurons in the spinal cord to regulate baseline arterial pressure in the circulatory system. The RVLM contains a ventral respiratory column to regulate respiratory patterns and rhythm. The ventral respiratory column enables connection to fibers in the RVLM to maintain the profusion of oxygen to tissues throughout the body. The medulla oblongata contains a variety of nuclei and tracts important to ascending sensory fibers and descending motor fibers that flow to the spinal column to execute several functions (Iordanova & Reddivari, 2022).

Ventricular System

The ventricular system within the brain delivers cerebral spinal fluid through a network of fluid-filled cavities to support and cushion the brain within the skull (Shenoy & Lui, 2022). Movement of cerebral spinal fluid via the ventricles provides a source of nutrients, protection, and waste removal from the brain. Cerebral spinal fluid also helps maintain a homeostatic environment within the brain (Sakka, Coll, & Chazal, 2011). Four ventricles make up the system, including two lateral ventricles within the right and left hemispheres of the cerebrum, a third ventricle in the deeper region of the cerebrum, and a fourth ventricle along the brainstem (Shenoy & Lui, 2022). The ventricular system of the brain flows to the spinal cord to exchange cerebral spinal fluid. Cerebral spinal fluid within the spinal cord helps provide buoyancy for both the spinal cord and brain to reduce the weight of the brain from approximately fifteen hundred grams to fifty grams (Sakka, Coll, & Chazal, 2011).

Anatomy of the Spinal Cord

The spinal cord is the portion of the CNS that connects to the PNS. Cerebral spinal fluid surrounds the spinal cord, providing nutrients and protection, and discards waste material from the CNS (Telano & Baker, 2022). The spinal cord contains white matter, which consists of myelinated sensory and motor neurons, and grey matter, which consists of unmyelinated sensory and motor neurons. The spinal cord creates an "H" shape, forming projections, called horns, at different segments of the spinal cords grey matter. The anterior horn contains motor nerves, the posterior horn contains sensory nerves primarily for pain and temperature, and the lateral horn consists of autonomic nerves. The white matter of the spinal cord organizes into tracts ascending towards the brain or descending from the CNS to the PNS. One of the ascending tracts is the dorsal column, which is responsible for pressure sensation, touch discrimination, vibration

sensation, and the ability to sense motion, action, and location (Harrow-Mortelliti, Reddy, & Sheleishvili, 2023).

Other ascending tracts include the lateral spinothalamic tract, responsible for pain and temperature; the anterior spinothalamic tract, accountable for carrying crude touch and pressure information; and the dorsal and ventral spinocerebellar tracts, which transmit unconscious details about the body's sense of movement, location, and action. The descending tracts include the lateral and anterior corticospinal, vestibulospinal, rubrospinal, and reticulospinal tracts. The lateral corticospinal tract regulates conscious control of skeletal muscle, while the anterior corticospinal tract controls movement of the muscles of the body. The vestibulospinal tract relays information from the inner ear to control head position and modifies muscle tone to regulate posture and balance. The rubrospinal tract helps regulate the movement of the flexor and extensor muscles. The reticulospinal tract maintains, provides nutrients to, and influences the corticospinal tract (Harrow-Mortelliti, Reddy, & Sheleishvili, 2023).

III. DEVELOPMENT OF THE FETAL CENTRAL NERVOUS SYSTEM

Gestation time in humans is approximately forty weeks from conception. The stages of pregnancy are divided into three trimesters. The first trimester spans from conception to thirteen weeks, the second trimester is from fourteen to twenty-six weeks, and the third trimester is from twenty-seven to forty weeks. Babies born before thirty-seven weeks gestation are considered preterm, while those born between thirty-eight and forty weeks are full-term, and those born after forty weeks are post-term (Fayed et al., 2022). Gestation begins with the embryonic stage when a fertilized egg implants within the uterus and develops into an embryo. This period lasts from fertilization to eight weeks gestation. The embryonic stage is followed by the fetal stage, which begins around nine weeks gestation and lasts until the birth of fetus. The fetal stage is

characterized by organogenesis. The focus of this manuscript is on the fetal development stages, which are divided based on development into early, midterm, preterm, and late preterm stages.

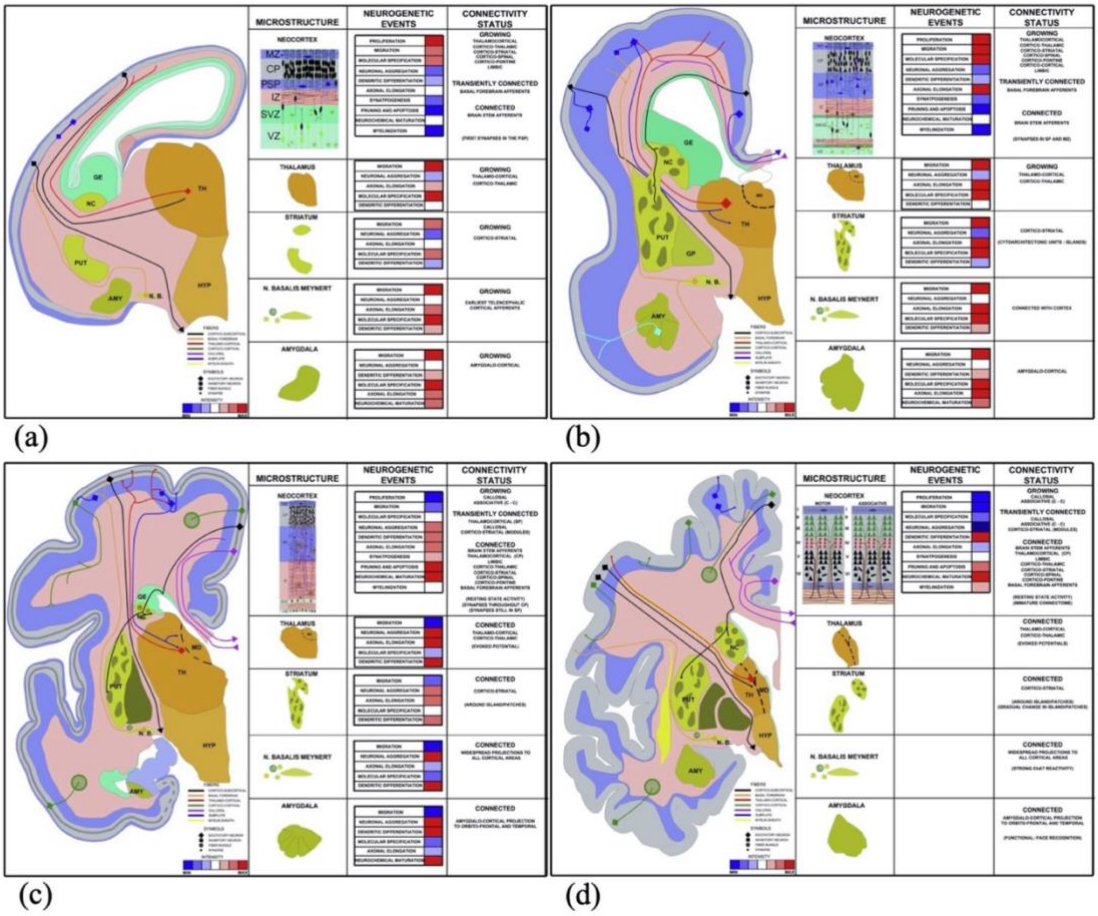

Figure 2: Differences in anatomy, microstructure, neurogenetic events, and connectivity status of the fetal brain based on the developmental stages: (a) Early, (b) Midterm, (c)Preterm, and (d) Neonatal. Abbreviations: VZ- ventricular zone, SVZ-subventricular zone, ISVZ- inner subventricular zone, OSVZ- outer subventricular, PSP-pre-subplate, SP-subplate zone, CP-cortical plate, MZ- marginal, AMY- amygdala, GE- ganglionic eminence, GP- globus pallidus, HYP- hypothalamus, MD- mediodorsal thalamus, N.B.- nucleus basalis of Meynert, NC- nucleus caudate, PUT- putamen, TH- thalamus. Reprinted from NeuroImage, 188, I. Kostović, G. Sedmak,M. Judaš, Neural histology and neurogenesis of the human fetal and infant brain, 743-773, Copyright (2019), with permission from Elsevier.

Early Fetal CNS Development

The fetal human CNS development period begins at nine weeks gestation and continues until the fetus's birth. The brain begins as a smooth (lissencephalic) structure that later develops the sulci and gyri characteristic of a mature adult brain. At nine weeks until twenty-two weeks gestation, the fissure that divides the cerebral left and right hemispheres develops. The primary sulci and gyri form around the same time the lobes begin to differentiate and create folds within the brain. At fourteen weeks gestation, several sulci begin to form, including the cingulate, Sylvian, parieto-occipital, and calcarine sulci (Stiles & Jernigan, 2010).

Typical neurons do not divide to make new neurons, so during the production of neurons in the early fetal stage every neuron produced has one neural progenitor cell, a specific type of cell that allows for the division of neurons. Fetal brain development occurs asymmetrically, meaning that more neurons are produced in one hemisphere versus the other, causing minor structural differences between the hemispheres. The neural progenitors continue to divide, and the number of neural progenitors increases until the completion of neurogenesis within the brain. The mature neurons migrate to form the layers of grey matter called the neocortex, a set of layers in the cerebral cortex (Stiles & Jernigan, 2010). The layers of the neocortex include the ventricular, sub-ventricular, intermediate, and marginal zones, the pre-subplate, and the cortical plate (Kostović, Sedmak, & Judaš, 2019). During neurogenesis, the division of neurons begins within the ventricular and sub-ventricular zones located at the core of the fetal brain, and the division creates the germinal matrix, where most of the neurons and other brain cells are produced (Leibovitz, Lerman-Sagie, & Haddad, 2022). The intermediate zone consists of the fetal white matter composed of afferent axons from the basal ganglia and thalamus and efferent axons from the cortical and pre-subplate regions of the neocortex. The marginal zone contains

dendritic fibers of developing neurons and Cajal-Retzius cells, which regulate the migration of neurons within the neocortex. The cortical plate consists of compact layers of post-migratory neurons arranged to begin the development of the cerebral cortex. The pre-subplate contains the extracellular matrix, a support network during migration (Kostović, Sedmak, & Judaš, 2019). The neuron progenitors continue to divide within the proliferation zone, and the number of neuron progenitors increases until the completion of neurogenesis within the brain (Stiles & Jernigan, 2010).

During the early fetal period, radial glial cells produce neurons and extend their processes to create a scaffold for the neurons to migrate to the outer layers of the cerebral cortex and produce neurons. The migration pattern creates the gyri and sulci formations and directs the growth of the brain. The brain develops from the inner core in radial and tangential patterns. The radial migration of neurons occurs in a spiral using glial cells that extend from the ventricular system to the outer layer of the cortex. During tangential migration, neurons come from the basal ganglia and use axons from already developed neurons as their guide to relocate to the cerebral cortex. Most neuron migration occurs between twelve and twenty weeks of gestation. The neurons that develop first compose the inner layers, while those that develop last compose the outer layer of the cerebral cortex. The pial membrane surrounds the brain to prevent neuron migration outside the brain (Leibovitz, Lerman-Sagie, & Haddad, 2022).

Mid-term Fetal Development:

The mid-term fetal development period ranges from fifteen to twenty-three weeks gestation. Dendritic development during the mid-fetal period increases in the subplate, marginal zone, and cortical plate. The cortical plate sits immediately below the marginal zone and is a compact layer made up of younger post-migratory neurons. The subplate, a layer below the

layers of the cortex containing differentiated post-migratory neurons, begins development during the mid-fetal period (Kostović, Sedmak, & Judaš, 2019). This region allows communication across the cortex through axon-guided molecules that bring axons ascending from the thalamus and descending within the cerebral cortex. The subplate enables the transmission of signals between various regions of the cerebral cortex across both hemispheres to further enhance the formation of the six-layered cortex. The growth of axons and dendrites allows the creation of inter-neuronal synapses (Leibovitz, Lerman-Sagie, & Haddad, 2022).

The parietal, frontal, and temporal lobes begin to differentiate from one another, and the amygdala and thalamus become organized structures while the hippocampus starts to form. Neurotransmitter specification begins in the mid-fetal period and is essential for neurons and synapses. Neurotransmitter specification is the regulation of gene expression within neurons to determine which neurotransmitter they will release and which ones they will respond to. The thalamocortical, corticothalamic, corticostriatal, corticospinal, corticopontine, and corpus callosum pathways develop rapidly during the mid-fetal period. The thalamocortical pathway transmits information from receptors throughout the body, including the retina, cochlea, muscle, or skin, and sends the data to sensorimotor regions of the neocortex via the thalamus. The corticothalamic pathway sends information from the cortex to the thalamus, the corticospinal sends information from the cortex to the spinal cord, and the corticostriatal sends data from the cortex to the striatum within the basal ganglia. The corticopontine pathway connects the right and left hemispheres of the cerebrum with the cerebellum and passes through the pons (Leibovitz, Lerman-Sagie, & Haddad, 2022 and Kostović, Sedmak, & Judaš, 2019).

Early and Late Preterm Fetal development:

The early preterm fetal period from twenty-four to twenty-eight weeks gestation marks the maturation of primary sulci and gyri (Kostović, Sedmak, & Judaš, 2019). At twenty-four weeks gestation, the central and superior temporal sulci form, with the superior frontal, pre-central, inferior frontal, post-central, and intraparietal sulci forming at twenty-five weeks gestation (Stiles & Jernigan, 2010). The early preterm period marks a gradual decrease in proliferation within the ventricular zone. Afferent fibers from the thalamus and nearby structures migrate to the four cerebral cortex lobes at approximately twenty-four weeks gestation (Kostović, Sedmak, & Judaš, 2019).

Late preterm development begins at approximately twenty-nine weeks gestation. After the production of neurons, a process called cortical organization begins. During this process, the six layers of the cerebral cortex mature, and the neurons within each layer begin to grow axons and dendrites (Leibovitz, Lerman-Sagie, & Haddad, 2022). Dendritic differentiation of various types of neurons occurs during the late preterm fetal period to create the lobes of the cerebral cortex. Growth of afferent axons and synaptic activity between these neurons and brain stem nuclei begins as the cerebral cortex matures. At twenty-nine to thirty-four weeks gestation, the proliferation of neurons decreases; however, the expansion of glial cells continues, and radial glial cells become astrocytes (Kostović, Sedmak, & Judaš, 2019). Astrocytes and oligodendrocytes start to differentiate in the third trimester, approximately twenty-nine to forty weeks gestation (Leibovitz, Lerman-Sagie, & Haddad, 2022).

During the late preterm period, synaptic pathways such as the thalamocortical and corticothalamic develop rapidly and display activity like a mature adult brain (Kostović, Sedmak, & Judaš, 2019). At approximately thirty-eight weeks gestation, the subplate disappears,

becoming the white matter of the cortex (Leibovitz, Lerman-Sagie, & Haddad, 2022). The synaptic activity of somatosensory, visual, and auditory pathways occurs within the late preterm stage of fetal development. The presence of behavioral states or consciousness, event-related cortical responses to external stimuli, resting state activity during sleep, and inter-hemispheric synchronization during the late preterm period indicate that the fetus is progressing to the next developmental stage, the neonatal stage (Kostović, Sedmak, & Judaš, 2019).

Neonatal Stage

The neonatal stage begins at the fetus's birth and spans for approximately one month, often called the newborn stage of development. During this phase, the limbic system matures, and the infant engages in social interactions and complex responses to sensory stimulation. The newborn brain begins to resemble a mature adult brain in terms of cortical sulci and gyri; however, the infant's brain is only a quarter of the size of a mature adult brain. The production and migration of neurons ends, while the production and migration of astrocytes and oligodendrocytes continues. Myelination of axons occurs, creating a more compact layer of white matter. A rapid increase in synaptogenesis occurs all over the neonatal cortex, with the most significant growth within the prefrontal cortex region (Kostović, Sedmak, & Judaš, 2019).

Teratogens and Critical Periods

The delicate processes of the developing CNS make the network susceptible to foreign substances. When a pregnant individual uses a substance of abuse, the effects extend to the developing fetus, impacting fetal development. A teratogen is a substance that may produce congenital disorders or defects within the fetus and includes substances such as caffeine, alcohol, nicotine, and some illegal drugs. The effects of different teratogens range from mild to severe depending on the type and amount of substance used. During fetal development, bodily systems

have timelines of increased susceptibility to teratogens called critical periods. The critical period for the CNS is the longest of any system and ranges from conception to the fetus's birth. At around three weeks gestation until twenty weeks gestation, the main areas for impaired development are the structural components of the CNS. At twenty weeks gestation until birth, functional as well as structural components are susceptible to developmental impairments caused by teratogen exposure (Li, 2021). The typical critical period for substances of abuse is during the first trimester, however various substances have critical periods that extend beyond the first trimester depending on their potency.

IV. STIMULANT EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Caffeine, nicotine, prescription medications, and illegal drugs such as cocaine and methamphetamine are common substances of use and abuse with varying effects on an individual's body, particularly the central nervous system. Any change to the brain's biochemistry may impact its function and structure. The abuse of drugs is the excessive, maladaptive, or addictive use of drugs for non-medical purposes despite social, psychological, and physical problems that may arise from such use (Britannica, 2023). A stimulant increases the activity of physiological responses within the CNS (Fiani et al., 2021). Stimulants are often easily accessed and have mood-altering properties that entice the user to use or abuse them frequently.

Prescription and Illegal Drugs:

Stimulants include prescription medication such as dextroamphetamine (brand name Adderall) and non-prescription controlled substances such as cocaine and methamphetamine. Dextroamphetamine, cocaine, and methamphetamine directly inhibit dopamine, serotonin, and norepinephrine reuptake by binding to neurotransmitter reuptake channels (Stahl, 1998).

Blocking or inhibiting of the reuptake channels results in more of the neurotransmitter staying in the synapse for a longer period, causing a heightened signal for a longer time. The mechanism of action for each type of stimulant is slightly different in terms of binding affinity to reuptake channels, the overall strength of the physiological impact, and which systems are affected. The influx of dopamine from stimulant use produces a euphoric response that increases energy and cognition (Delphin-Rittmon, 2021). However, dextroamphetamine, cocaine and methamphetamine can induce capillary damage in the brain and other adverse effects such as increased anxiety, paranoia, hallucinations, and psychosis.

Dextroamphetamine, when used to treat attention-deficit hyperactivity disorder (ADHD), helps alleviate ADHD symptoms and does not generally cause concerning side effects However, medication abuse can lead to psychosis, depression, negative affect, insomnia, and anxiety. Other stimulant medications to treat ADHD, such as Ritalin and Vyvanse, have similar actions and consequences but are outside the scope of this thesis. Abuse of methamphetamine leads to reduced availability of transporters for dopamine and serotonin, atrophy of grey matter due to cell death, axon and axon terminal destruction, reduced nerve fibers, oxidative stress, and inflammation of the parietal lobe and the basal ganglia. The effects of daily abuse of methamphetamine include impairment of dopamine and serotonin pathways, psychosis, impaired cognition, attention, psychomotor activity, memory, and decision-making. The effects of chronic cocaine use include physiological and psychological problems such as depression, irritability, insomnia, dopamine receptor impairment, and impairment of specific cognitive abilities, including poor memory, attention, response inhibition, cognitive flexibility, and psychomotor performance (Delphin-Rittmon, 2021).

In the United States, the rate of stimulant abuse by pregnant individuals has increased over the last decade (Ross et al., 2015). Stimulant abuse by a pregnant individual during the fetal stage of development may harm the fetus's body systems, especially the CNS. While there is varying information about the severity of the impacts of stimulant abuse on the fetal nervous system, stimulants pose a significant risk to the developing fetal nervous system. The critical period for cocaine and methamphetamine abuse occurs during all trimesters of pregnancy, while the critical period for dextroamphetamine is currently unknown. Children prenatally exposed to prescription stimulants such as dextroamphetamine, when used to treat ADHD of the mother, are generally not impacted by the medication. However, the abuse of prescription stimulants may harm the fetus, depending on the dosage and time interval of the abuse. In a study conducted on children prenatally continuously exposed to amphetamines such as dextroamphetamine, researchers found some of the children had higher rates of ADHD, aggression, and deficits in memory, attention, and motivation (Ross et al., 2015). Another study on children exposed to methamphetamine and cocaine prenatally found that children had reduced head circumference, increased risk of cerebral hemorrhage due to vasoconstriction, and impaired memory. The study found that these children also performed worse on visual recognition tests. The impairment was not to the visual cortex but rather to the processes and pathways within the cerebral cortex associated with memory. Limitations of the study revealed that these effects may only create a developmental delay versus permanent damage; further research is necessary to determine if the impacts were permanent (Plessinger, 1998).

Methamphetamine abuse by pregnant individuals produces neurotoxic effects on fetal development as well. Infants exposed to methamphetamine during gestation had impairments of microglia, oxidative stress, toxicity due to over-excitation, and neuron inflammation. At the age

of five, these children had increased instances of anxiety, depression, and decreased motor coordination. An analysis of structural changes via neuroimaging found that infants exposed to methamphetamine prenatally had reduced hippocampus volume and alterations in white matter myelination, maturation, and structure (Li et al., 2021).

Abuse of cocaine by pregnant individuals may lead to structural changes within the fetal CNS, leading to future behavioral changes. Research on infants exposed to cocaine during the fetal development period found decreased volume of the prefrontal and frontal cortex and alterations within the dopamine receptor network (Grewen et al., 2023). Other studies also found that children exposed to cocaine during gestation had an increased risk of impaired behavior regulation, attention, and abstract reasoning (Smid, Metz, & Gordon, 2019).

Caffeine

Caffeine is a central nervous system stimulant. Caffeine is found in many consumable items, including energy drinks, coffee, soft drinks, tea, and chocolate. Caffeine is easy to access; one can purchase caffeinated products in many places, such as grocery stores, restaurants, and online. Studies show that approximately eighty percent of the population in the United States uses caffeine daily (Fiani et al., 2021). The effects of caffeine vary depending on the individual and the amount ingested. Caffeine binds to adenosine receptors throughout neural tissue, decreasing the ability of adenosine to regulate sleep, increasing arousal, and enhancing cognition, memory, and learning. Caffeine is an antagonist, a chemical that binds to a receptor to inhibit the receptor from producing a response. Adenosine signaling within the CNS is vital for neurotransmitter release, synaptic plasticity, and neuroprotection in ischemic, hypoxic, and oxidative stress events. Adenosine controls the release of specific neurotransmitters such as norepinephrine, dopamine, acetylcholine, serotonin, glutamate, and GABA (Sheth et al., 2014).

The change in the concentration of these neurotransmitters alters an individual's mood, memory, alertness, and cognitive function (Fiani et al., 2021).

Caffeine also increases dopamine release, causing the individual to feel increased pleasure and energy. Serotonin and norepinephrine transmission are also altered with caffeine, impacting mood, arousal, stress, and sleep. The increased release of serotonin and norepinephrine from caffeine use enables an individual to remain alert during fatigue (Fiani et al., 2021, Sheffler, Reddy, & Pillarisetty, 2023). The Food and Drug Administration (FDA) recommends a maximum of four hundred milligrams of caffeine daily in a healthy adult (Mitchell et al., 2014). When ingested amounts exceed the recommended dose, an individual may experience increased anxiety and tremors. Caffeine withdrawal is common and occurs after an individual has consumed caffeine for at least three consecutive days and then abruptly stops caffeine consumption (Watson, 2003). Caffeine withdrawal leads to headache, fatigue, difficulty concentrating, and dysphoric mood, including feelings of anger, guilt, or failure (Meredith et al., 2013).

Caffeine use during pregnancy may increase the risk of impairments to CNS development during the fetal stage. The recommended limit for caffeine exposure is two hundred milligrams daily, or around two cups of coffee for pregnant individuals during any trimester. After two hundred milligrams, the risk of harmful consequences increases for CNS fetal development, with the effects creating lifelong developmental impacts (Watson, 2003). The exact duration of the critical period for caffeine exposure is still uncertain. Various studies indicate the critical period is during the first trimester, but more research is needed to confirm this hypothesis. The increased estrogen activity in pregnancy causes inhibition of the breakdown of caffeine, leading to increased exposure through the placenta. However, other studies on

caffeine use disagree on the severity of impacts; some studies suggest there is little to no evidence of developmental impacts, while others suggest caffeine abuse creates lasting effects on cognitive functioning. A study conducted in Japan on children exposed to high doses of caffeine during fetal development found that infants six months to twelve months of age exposed to greater than three hundred milligrams of caffeine per day had a reduced risk of developmental impairments rather than increased risk of developmental impairments. However, in the same children at twelve months, a negative impact on gross motor skills was observed (Nishihara et al., 2022). These results may be due to the ability of caregivers to appropriately assess their children, indicating some children may have had impacts at six months, but their caregivers didn't notice this.

Other research on children prenatally exposed to caffeine found that the same children at ages nine to eleven had an increased chance of developing problems with externalizing behaviors such as aggression or impulsivity. Males exposed to higher levels of caffeine in utero had a greater risk of externalizing problems in general, while females were more likely to have issues related explicitly to rule following (Zhang, Manza, & Volkow, 2022). A study on children exposed to more than two hundred milligrams of caffeine per day in utero had a twofold increased risk for impaired development and lower IQ at age five and a half compared to children exposed to less than one hundred milligrams per day. Exposure to higher levels of caffeine during mid to late-term fetal development may also create impairments in the hypothalamic-pituitary-adrenal axis due to increased concentration of glucocorticoids (Qian et al., 2020). Glucocorticoids provide anti-inflammatory support to the development of fetal organ systems during pregnancy, but an increased concentration may cause impaired immune system

function (Solano & Arck, 2020). The damage to the hypothalamic-pituitary-adrenal axis may compromise neuroendocrine metabolism within neuronal tissue (Qian et al., 2020).

Nicotine:

Nicotine is a stimulant attained through cigars, cigarettes, electronic cigarettes, chewing tobacco, and products utilized to quit smoking. Nicotine interacts with nicotinic acetylcholine receptors (nAChRs) throughout neuronal tissues, specifically within the thalamus, hippocampus, cerebral cortex, basal ganglia, and cerebellum (Swan & Lessov-Schlaggar, 2007). The activation of nAChRs by nicotine causes an indirect increase of neurotransmitters, including acetylcholine, dopamine, GABA, glutamate, serotonin, and norepinephrine (Benowitz, 2009). The increase of these neurotransmitters leads to a short period of enhanced cognitive functions, including attention, working memory, and executive functioning (Swan & Lessov-Schlaggar, 2007). The increase in dopamine and serotonin levels leads to a change in mood, making the individual experience pleasure and reward from nicotine exposure.

Nicotine abuse increases the number of nAChRs within the brain, creating a desensitization to nicotine based on the upregulation of receptors. The overproduction of nAChRs throughout the brain increases tolerance, making nicotine less effective unless taken at a higher dosage. The tolerance to nicotine can lead to withdrawal symptoms when nicotine use is ceased, including depression, anxiety, and stress (Benowitz, 2009). While acute use of nicotine can have beneficial impacts on cognitive function, chronic abuse can lead to harmful effects on the brain. Smoking nicotine causes oxidative stress, increased inflammation, and atherosclerosis. Atherosclerosis is a hardening of blood vessels that interrupts blood flow, causing alterations in the blood-brain barrier, cerebral blood flow, and brain metabolism, which increases the risk of heart attack and stroke (Swan & Lessov-Schlaggar, 2007). Other effects of chronic nicotine use

include increased rates of cancer, specifically lung cancer, gum disease, gastrointestinal tract issues, and pulmonary hypertension.

Exposure to nicotine during fetal CNS development increases the risk of structural changes and psychological problems. Nicotine exposure in fetuses often occurs due to maternal smoking or exposure to second-hand smoke. Nicotinic acetylcholine receptors are essential in fetal CNS development due to their role in the modulation of neurotransmitter release, protection of neuronal migration and proliferation, and synaptic development (Dwyer, Mcquown, & Leslie, 2009). The timeline and level of nicotine exposure during fetal development determines the severity and extent of CNS damage (Blood-Siegfried & Rende, 2010). The critical period for nicotine exposure occurs during the first trimester of pregnancy (Thakur et al., 2011). Dwyer, Mcquown, and Leslie (2009) reported a reduction in overall brain volume, white and grey matter, and gyri formation in children exposed to nicotine during fetal development. Additionally, Castro, Lotfipour, and Leslie (2023) identified nicotine exposure during fetal growth as a significant factor in sudden infant death syndrome (SIDS). The risk of SIDS is associated with an increased concentration of altered neurons within the pons, given its primary role in controlling sleep and respiration. Further research on the impact of parental smoking during pregnancy on brain structure revealed alterations in hippocampal formation. These changes in the hippocampus may contribute to auditory-cognitive deficits in males and auditory and visual deficits in females (Blood-Siegfried and Rende 2010).

Decreased levels of norepinephrine and epinephrine are typical in infants with nicotine exposure, leading to depression of the automatic nervous system functions regulating cardiovascular and respiratory activity (Blood-Siegfried & Rende, 2010). Other studies have correlated the increased risk of ADHD in children with prenatal exposure to nicotine due to the

alteration of dopamine receptors during the fetal stage of development (Castro, Lotfipour, & Leslie, 2023). Alteration of dopamine receptors within the fetal brain led to an increased risk of addiction during adolescence and adulthood due to the altered function of the reward system (Smith, Dwoskin, & Pauly, 2010).

V. DEPRESSANT EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Depressants are substances that inhibit the brain's activity and impact cognitive function. Commonly abused depressants are alcohol, marijuana, and opioids. The abuse of depressants can lead to lifelong consequences depending on the frequency and dosage of the substance. Depressants harm the already developed CNS but pose an even greater risk to the developing fetal CNS.

Alcohol:

The use of alcohol impacts the anatomical structure and physiological processes of the CNS. Alcohol is a CNS depressant that slows down areas of the brain and impairs cognitive function. Anatomical changes within the brain due to alcohol include reduced grey and white matter, increased ventricular swelling, and the widening of sulci. Reduction in grey matter primarily occurs within the prefrontal and cingulate cortexes and the striatum, a region on the basal ganglia involved in executive functioning. The reduced white matter within the corpus callosum is due to the disruption of myelination and axonal integrity, which impairs the sending of action potentials. The deterioration of grey matter causes impairments in executive functioning, such as working memory, self-regulation, emotional control, reward processing, and movement (Nutt et al., 2021). The hippocampus and amygdala become damaged after abuse of alcohol over a lengthy period, leading to memory loss. The anatomical impacts of alcohol abuse may be reversed through abstinence and intensive addiction treatment if necessary; however, if

the abuse continues for longer than a few months, the damage becomes permanent. (Oscar-Berman et al., 1997).

Ethanol, the chemical name for alcohol, interacts with assorted receptors within the brain, including those for GABA and serotonin. GABA is an inhibitor; ethanol increases the release of GABA, thereby inhibiting synaptic pathways. The inhibition of synaptic pathways impairs cognitive function, leading to symptoms such as memory deficits, unbalanced gait, and behavioral changes (Nutt et al., 2021). Chronic abuse of alcohol may lead to down-regulation of GABA receptors, causing over-excitation within the brain and leading to seizures during withdrawal (Oscar-Berman et al., 1997). Alcohol consumption causes a temporary increase in serotonin levels, increasing sociability, and produces an altered state of consciousness (Nutt et al., 2021).

Alcohol abuse by a pregnant individual poses a serious risk to the development of the fetal CNS. The critical period for fetal alcohol exposure is during the first and second trimesters (Thakur et al., 2011). Chronic alcohol abuse during pregnancy may lead to fetal alcohol spectrum disorder (FASD). FASD includes many types of conditions related to alcohol exposure, including fetal alcohol syndrome (FAS), partial FAS, alcohol-related neurodevelopment disorder (ARND), and alcohol-related birth defects (ARBD). The severity and type of damage to the CNS determine which category a child with prenatal exposure falls under. A FAS diagnosis requires the presence of facial abnormalities associated with the disorder, growth deficiency in either height, weight, or head circumference, brain structure abnormalities, and neurobehavioral impairment. Partial FAS is diagnosed when there is not a confirmed case of prenatal alcohol exposure, but the child exhibits all symptoms of FAS. The diagnosis of ARND requires a confirmed case of maternal alcohol abuse and neurobehavioral impairments. ARBD-diagnosed

children have confirmed prenatal alcohol exposure, and one or more physical abnormalities related to the disorder such as heart, kidney, bone, or hearing impairments. FASD is an umbrella term for all the observed impacts of prenatal alcohol exposure, as most children do not fall under one specific diagnosis (Mattson, Bernes, & Doyle, 2019).

Structural and behavioral changes have been observed in studies on infants and children with repeated prenatal alcohol exposure during the first and second trimesters. However, the impacts are variable between each case; some fetuses repeatedly exposed may not suffer any consequences, while some exposed only once or twice develop severe consequences, however the mechanism behind these differences is currently unknown. Disruptions to the hippocampus, basal ganglia, cerebellum, and corpus callosum development are common among infants with prenatal alcohol exposure. Other areas of impaired development include the abnormal migration of neurons or glial cells, enlargement of the ventricles, and changes in the vasculature of the hippocampus and cerebrum (Gibbard, Wass, & Clarke, 2003). Autopsies performed on the brains of infants, children, and adults with prenatal alcohol exposure found apoptosis (induced cell death) of neurons, damage to radial glia and astrocytes, and inappropriate activation of microglia. However, the most common brain abnormality was microcephaly, an abnormally small brain (Jarmasz et al., 2017). Prenatal alcohol exposure may increase rates of behavioral problems, including reduced academic performance, deficits in motor skills, and impairments in attention, memory, executive function, learning, and language. Impairments of attention, memory, executive functioning, learning, and language occur due to the abnormality of brain development within the hippocampus and limbic system. In children diagnosed with FASD, the most common behavioral problems include anxiety, ADHD, depression, post-traumatic stress disorder (PTSD),

oppositional defiant disorder, conduct disorders, and language disorders (Nunez, Roussotte, & Sowell, 2011).

Marijuana:

Cannabis, commonly known as marijuana, is a psychoactive compound containing Δ9-tetrahydrocannabinol (THC). THC interacts with cannabinoid (CB1) receptors in brain regions responsible for executive functioning, motor control, and memory, including the cerebral cortex, hippocampus, and cerebellum (Iverson, 2003). The cannabinoids found within marijuana interact with the endocannabinoid network of the CNS, which plays a role in maintaining homeostasis, neuroplasticity, and regulation of neurotransmitter release. THC interacts with CB1 receptors within various regions as an agonist, a ligand that initiates neurotransmission when it attaches to the receptor (Burggren et.al, 2019). Acute effects of marijuana use in some individuals include increased appetite, decreased stress, risk-taking behaviors, and mood changes, specifically those associated with pleasure and reward. Marijuana abuse occurs when individuals regularly seek the acute effects that alter their mood and behavior through the excess dopamine release. Daily use of marijuana over more than a few months may impair memory, executive function, and processing speed (Burggren et.al, 2019).

The interaction with the CB1 receptors within the cerebral cortex and hippocampus alters memory, stress response, behavior motivation, reward, and self-control. Inconsistencies among studies on frequent cannabis use occur regarding changes within brain structure. Burggren et.al, (2019) reported on changes within the temporal lobe, specifically the hippocampus and amygdala, the neocortex, and the cerebellum, and also found abnormalities within grey matter density and atrophy of these regions. However, variations of this study produced conflicting results, indicating no evidence to suggest abnormal changes to brain structure. The differences

between each study included the amount and length of time of cannabis use by subjects and whether the alterations within brain structure were negative, positive, or had no impact on function. Another area of concern is whether THC has a direct impact on structural differences, or if differences between each individual's brain development caused an increased likelihood of THC use.

Use of marijuana during pregnancy poses a significant threat to the developing fetal nervous system. The critical period of cannabis exposure during pregnancy remains unknown due to lack of consistent research. Prenatal abuse of marijuana impacts the endocannabinoid system of the fetal brain; this system promotes synaptic plasticity, neuronal migration, and differentiation. THC crosses the placental barrier easily, allowing the chemical to engage with the fetal endocannabinoid system, increasing the risk of brain abnormalities. THC causes irregular endocannabinoid signaling within the hippocampus and cortical layer of the fetal brain, specifically affecting neuronal and glial differentiation. A study found that the hippocampus and cortical layers had disruptions within their synaptic connectivity due to the degradation of proteins that aid in synaptic connections that promote normal cognitive function. Results from the same study suggested that decreased production of various neurotransmitters within the hippocampus created a higher risk for deficits in learning and memory. In male children specifically, prenatal marijuana exposure has been linked with a reduction of dopamine receptors within the amygdala, causing changes in the regulation of emotional behavior (Nashed, Hardy, & Laviolette, 2021).

Prenatal exposure to marijuana may also increase the risk of psychological impairments. However, research on the impacts is limited. A study on children between the ages of nine and eleven exposed to marijuana *in utero* found increased vulnerability to symptoms of psychosis. A

similar study found that children of the same age had increased internalizing behaviors such as anxiety or depression and externalizing problems, including rule-breaking and aggressive behaviors (Nashed, Hardy, & Laviolette, 2021). One study found a slight increase in the rate of autism among children prenatally exposed to marijuana (Nashed, Hardy, & Laviolette, 2021); however, the study was based on caregivers' reports and may not be accurate, indicating more research is needed to suggest a correlation.

Sleep disturbances also occur in those exposed to marijuana during the fetal stage of development. Research indicates that the endocannabinoid system may regulate sleep, but exposure *in utero* increases the risk of sleep disturbances. A study found that infants exposed to marijuana had increased motility, arousal, and sleep disruptions. The same children had similar problems at age three, along with increased rates of inefficient sleep, more extended periods of arousal after sleep, and increased risk of waking up at night (Nashed, Hardy, & Laviolette, 2021). However, the sample size of this study was relatively small, making more research necessary to determine if there is correlation between sleep disturbances and *in utero* marijuana exposure.

Opioids:

Opioids are drugs produced naturally or synthetically and prescribed for pain management. Opioids include prescription painkillers such as morphine, fentanyl, and OxyContin and illegal drugs such as heroin (Herlinger & Lingford-Hughes, 2022). Opioids interact with the CNS through opioid receptor proteins found on nerve cells in the brain and spinal cord. Opioids act as central nervous system depressants, inhibiting the transmission of signals from painful stimuli (Viganò, Rubino, & Parolaro, 2005). Side effects of opioid use include drowsiness, mental confusion, and respiratory depression. Opioids interact with the

brain's reward center to produce a euphoric response; the desire for the euphoric response leads to the daily abuse of opioids. Long-term abuse of opioids leads to opioid use disorder (OUD), a chronic condition characterized by brain damage (Herlinger & Lingford-Hughes, 2022).

Individuals with OUD have an increased risk for white and grey brain-matter abnormalities. A neuro-imaging study on opioid-dependent individuals revealed atrophy in the frontal and temporal gyri within the cerebral grey matter (Wollman et al., 2017). A previous study found a reduction in the brain's white matter regions, specifically those that connect the limbic system to the prefrontal cortex. Problems with cognition, network dysfunction of dopaminergic reward systems, impulsivity, and emotional processing occur in individuals with OUD. Negative emotional processing occurs due to changes within the hypothalamic-pituitary system responsible for hormone production to control levels of anxiety and depression. Stimulation of μ opioid (MOP) receptors within the medulla causes respiratory depression, leading to brain hypoxia, increased glucose levels, and rapid increase in internal temperature, resulting in the death of neuronal cells. The risk for dementia increases after the abuse of opioids due to microglial activation that produces an inflammatory response and increased neurofibrillary tangles. Opioid abuse may influence psychiatric disorders such as anxiety, depression, post-traumatic stress disorder, and schizophrenia. MOP receptor agonists such as methadone and buprenorphine help recovering OUD patients with withdrawal symptoms. Naloxone is an opioid receptor antagonist and is used in cases of opioid overdose to reverse respiratory depression and prevent brain hypoxia (Herlinger & Lingford-Hughes, 2022).

Opioid abuse during pregnancy threatens the developing fetal central nervous system. The recent epidemic of opioid abuse in the United States has led to more research on the impacts of opioids and medications such as methadone on the fetal CNS. Current research suggests the

critical period of opioid exposure *in utero* occurs during the first trimester, however more research is necessary to confirm this. The rate of maternal opioid use has increased four times since 2013, with infants diagnosed with neonatal opioid withdrawal syndrome (NOWS) increasing five times since 2000 (Stover & Davis, 2015). NOWS is a common consequence of maternal opioid abuse that impacts the fetal nervous system. A NOWS diagnosis occurs in approximately ninety-four percent of infants prenatally exposed during the critical period to *opioids.* Infants with NOWS have hyperirritability of the CNS and disturbances within the autonomic nervous system (Tobon, Habecker, & Forray, 2019).

Anatomical differences are observed in infants diagnosed with NOWS. Infants exposed to opioids often have significantly smaller brain volume, cerebral volume, and basal ganglia (Tobon, Habecker, & Forray, 2019). A study done on children prenatally exposed to opioids found that they had reduced volumes of the basal ganglia, thalamus, hippocampal regions, and cerebral white matter even in adolescence, suggesting the impacts of prenatal opioid exposure have long-term implications (Caritis & Panigrahy, 2019). Behavioral and cognitive changes occur frequently in children exposed to opioids and those diagnosed with NOWS. Research on children exposed to opioids *in utero* had increased rates of learning and memory problems, educational delays, and lower scores in cognitive performance compared to unexposed children (Conradt et al., 2019). Increased rates of ADHD and autism spectrum disorder are also observed in children exposed to opioids during fetal CNS development (Vishnubhotla et al., 2022). Methadone is the preferred treatment of maternal addiction throughout pregnancy; however, the effects of methadone are like, though less severe than, the impacts of opioids on the fetal CNS. Research into naloxone to reverse the effects of opioid

overdose in a pregnant individual found naloxone has no relation to the diagnosis of NOWS and no harmful impacts on the fetus (Tobon, Habecker, & Forray, 2019).

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