5-2024

Biofeedback using virtual reality, conscious interoception, and breathing exercises modulates blood pressure and heart rate variability in people with and without cervical spinal cord injuries.

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BIOFEEDBACK USING VIRTUAL REALITY, CONSCIOUS INTEROCEPTION, AND BREATHING EXERCISES MODULATES BLOOD PRESSURE AND HEART RATE VARIABILITY IN PEOPLE WITH AND WITHOUT CERVICAL SPINAL CORD INJURIES

By

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B.A., University of Kentucky,1992
M.S., University of Louisville, 2020

A Dissertation
Submitted to the
University of Louisville Graduate School
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy
in Interdisciplinary Studies: Specialization in Translational Neuroscience

Interdisciplinary Studies
University of Louisville

Louisville, Kentucky

May 2024

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A Dissertation Approved on

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DEDICATION

I would like to dedicate this dissertation and all the hard work it took to make it happen to my grandmother, Clyde Butler, who in the 1930s really wanted to go to high school but had no way to get there, and to the many women in many parts of the world almost 100 years later who are still denied the opportunity of education.

ACKNOWLEDGEMENTS

I want to thank my mentor, Dr. Daniela Terson de Paleville for her guidance, time, and patience, as well as the other members of my committee: Dr. David Magnuson, Dr. Camilo Castillo, Dr. Douglas Lorenz, Dr. Irving Joshua, and Dr. George Pantalos for their willingness to discuss my ideas with an open mind, Dr. Thomas Chelimsky from Virginia Commonwealth University's Autonomic Center, Dr. Jack Ginsberg, a veritable encyclopedia of heart rate variability, the research assistants on this project: Kaden Kozlowski, Addie Wanner, Jae Fish, Tryphena Sithu and Jocrisse Uwimana for always having my back, our amazing research participants, Laura Spaulding for teaching me that "[yoga] asana is only the tip of the iceberg" and "the breath gets the brain's attention first," my meditation teacher Dean Sluyter: your intuitive intelligence embodies what Einstein said: "If you can't explain it simply, you don't understand it well enough," Camie Michelle Arington, for seeing me since I was a little girl, and especially my family Mauricio and Isvara Torres, Trudy, Carl, and Adam Colvin, my "cheerleaders."

ABSTRACT

BIOFEEDBACK USING VIRTUAL REALITY, CONSCIOUS INTEROCEPTION, AND BREATHING EXERCISES MODULATES BLOOD PRESSURE AND HEART RATE VARIABILITY IN PEOPLE WITH AND WITHOUT CERVICAL SPINAL CORD INJURIES

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April 16, 2024

There is an immediate need for fast-acting blood pressure (BP) modification without the side effects of pharmaceutical interventions for people with spinal cord injuries (SCI), especially injuries above thoracic level six.[1,2] These cervical injuries usually cause detrimental sympathetic nervous system alterations. People with cervical SCI often present with symptoms of autonomic dysfunction similar to astronauts in microgravity, hence the mutual research interests of both space and SCI physiologists. In space, there is less gravity to pull blood away from the brain, so the sympathetic nervous system is not required to be as active to increase BP and restore cerebral perfusion. This alteration in the demand for sympathetic modulation of BP, in addition to other factors, changes the nervous systems of astronauts, both in space and upon return to Earth.[3,4] Researchers from the National Aeronautics and Space Administration (NASA) found a biofeedback protocol, autogenic feedback training exercise (AFTE) to be successful in attenuating orthostatic hypotension in space crews.[5] In previous investigations, people with SCI were found to be better able to self-generate BP modifications than non-injured (NI) people, possibly due to

the creation of a novel neural feedback loop.[6] Inspired by AFTE, our protocol added breathing exercises, mental and virtual reality (VR) imagery, and interoceptive attention. First, we investigated whether VR or mental imagery created the most change in BP and heart rate variability (HRV), alternating three-minute stimulating and relaxing training cycles in 17 NI participants and 14 participants with SCI. Second, we trained 13 people with SCI and seven NI control participants using our autonomic biofeedback protocol for self-modulation of BP, for one hour per session with eight or nine training sessions over one month. Participants' feedback goal was to increase during stimulation cycles and then decrease during relaxation cycles their mean arterial pressure (MAP) by at least five millimeters of Mercury (mmHg). We measured hemodynamic response to head-up tilt testing, the Valsalva maneuver, and paced deep breathing before and after the series of training sessions. We administered selected surveys from the Tulsky Quality of Life for SCI[7] inventory and the Body Perception Questionnaire[8] to assess any changes in quality of life and interoception. Mean increases and decreases in MAP for all participants were significantly greater than five mmHg during cycles. Yet, this mean was no different in pre/post autonomic testing or five-minute rest periods before and after training, which suggests the training could be most useful when acute BP changes are desired, such as in a hypertensive or hypotensive state. Significant improvements in both time and frequency domain HRV measurements correlated with increased BP variability in five-minute rest periods before and after each training in all

participants, which suggests acutely increased volitional BP variability may also be cardioprotective, a novel finding.

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CHAPTER I

INTRODUCTION

Human Nervous System Overview

Humans interact physically and emotionally with their environment through their nervous systems. The human nervous system is divided into the central nervous system (CNS) and the peripheral nervous system. The CNS is composed of the brain and spinal cord and is protected by the skull, vertebral column, and the blood-brain barrier.[9] The peripheral nervous system receives information from internal and external environmental stimuli and then sends this information to the CNS. The CNS interprets the significance of the signal and then sends chemical or electrical signals to direct body function.

The fundamental units of the nervous system are nerve cells, otherwise known as neurons. Neurons are "electrically excitable cells that transmit signals throughout the body."[9] Neurons transmit impulses to other neurons or cells by releasing neurotransmitters into a synaptic cleft, which is the space between neurons. The neurotransmitters either excite or inhibit the electrical signal.[5] A typical neuron is comprised of a soma, axon, and dendrites.

The soma is the body of the neuron. It contains organelles with different functions such as creating proteins from genetic information and maintaining the structure and energy of the neuron. An axon is an extension of the soma covered

in a myelin sheath which enhances electrical transmission of efferent signals. Efferent signals take information from the soma and send it outward to body tissue, organ, or structure.[10] Incoming information is received by dendrites. Dendrites branch out from the soma to receive these afferent signals. A group of axons in the CNS is known as a tract while a group of axons in the peripheral nervous system is a nerve.[11] A plexus is a network of nerves near or in the target organ."[11]

A ganglion is a group of nerve cells in the peripheral nervous system. Ganglia can be broadly divided into the sensory ganglia of the somatic nervous system, and the autonomic ganglia of the autonomic nervous system. Each soma in a ganglion is covered by satellite cells, and each ganglion is covered by dense connective tissue. Satellite cells supply nutrients and have a protective and structural function for the ganglion. Satellite cells also have receptors and their additional neurochemical roles are still being discovered.[12]

Satellite cells are an example of glial cells. Neurons maintain their signaling ability through the support of glial cells.[11] Glia consist of satellite cells, astrocytes, oligodendrocytes, Schwann cells, and microglia.[13] Astrocytes are located only in the CNS and maintain the chemical environment for neuron signaling, form the blood-brain barrier, and some have stem cell-like qualities.[11] Oligodendrocytes, also only located in the CNS, are responsible for creating myelin. Myelin is an insulating material wrapping around axons that speeds the transmission of electrical signals.[13] Cells in the peripheral nervous system that lay down myelin are known as Schwann cells.[13] Microglia are similar to

macrophages in that they remove cellular debris and secrete signaling molecules such as cytokines.

Neurons most commonly communicate with each other via neurotransmitters.[11] Neurotransmitters carry information across the synapse and enable the transfer of electrical information through chemical signaling. Some examples of neurotransmitters are acetylcholine (ACH), norepinephrine, dopamine, serotonin, glutamate, gamma-aminobutyric acid (GABA), and glycine. Neurons can also release neurohormones into the bloodstream. Some neurons secrete neuromodulators in addition to neurotransmitters. These do not cause excitatory or inhibitory electrical potentials as neurotransmitters do; instead, they modulate the action of the synapse. Examples of neuromodulators are adenosine triphosphate (ATP), nitric oxide, and endocannabinoids.[14] Some neurotransmitters, such as norepinephrine (NE), also are released as hormones in other parts of the body.[13] This description serves as an overview to illustrate just a few of the complex interactions affecting neurotransmitter-receptor interaction. This interaction can also be affected by signaling from other neurons, hormones, or glia.[13]

The peripheral nervous system signals the visceral or autonomic motor system to create movement in smooth muscle and glands. It also signals the motor nerves of the somatic motor system to create movement of skeletal muscles.[15] To allow the sensory experiences of sight, sound, touch, temperature, pain, odor, and taste, our peripheral sensory ganglia and nerves send afferent (sensory) signals to the brain and spinal cord which then in response send

efferent (motor) signals. The peripheral nervous system is composed of 12 pairs of cranial nerves, receptors, and 31 pairs of spinal nerves.

The cranial nerves provide motor and sensory innervation mainly to the head and neck.[13] Afferent cranial nerves include the olfactory (cranial nerve one), responsible for the sense of smell, the optic (cranial nerve two) for vision, and the vestibulocochlear (cranial nerve eight) for hearing and balance. Efferent cranial nerves include the oculomotor (cranial nerve three) and trochlear (cranial nerve four) for eye movement, accessory (cranial nerve 11) for shoulder and head-turning, and the hypoglossal (cranial nerve 12) for tongue movement. Mixed afferent and efferent cranial nerves include the trigeminal (cranial nerve five) for facial sensation, facial (cranial nerve seven) for facial expression, glossopharyngeal (cranial nerve 11) for oral sensation and taste, and the vagus nerve (cranial nerve ten). Instead of innervating the head, the vagus nerve provides sensory and parasympathetic innervation to the neck and most of the organs in the chest and abdomen. Vagal tone is how responsive the vagus nerve is to needed cardiovascular changes and is measured by HRV.[16] HRV is correlated with the capacity to regulate stress responses and can be influenced by breathing.[17]

Receptors are cells or groups of cells that receive stimuli.[10] They are each specialized to respond to one type of stimulus. There are seven different types of receptors, differentiated by their specialty. Proprioceptors receive and process information about body position. Nociceptors respond to pain. Photoreceptors respond to light. Mechanoreceptors sense touch and pressure and respond to

movement, such as the stretch receptors in the lungs, or baroreceptors detecting BP in the carotid body and aorta. Chemoreceptors respond to chemical changes, such as different concentrations of oxygen or carbon dioxide in the blood. Thermoreceptors respond to temperature.[18] The spinal nerves and cranial nerves work together to create both conscious responses of movement and unconscious responses of autonomic processes and reflexes. The entire nervous system, as with all body systems, adapts and changes as needed to maintain homeostasis,[14] a stable equilibrium between interdependent physiological processes.[19] The intermediary between the brain and the peripheral nervous system is the spinal cord.

Spinal Cord Anatomy

Millions of neurons with complex connections comprise the delicate and sensitive spinal cord. The spinal cord extends from the lower part of the brainstem, surrounded by the first cervical vertebra (C1), and ends at the first lumbar vertebra (L1). References to vertebral bones are distinguished by “C” for cervical, “T” for thoracic, “L” for lumbar, and “S” for sacral, with corresponding numbers. The spinal cord is protected by (proximal to distal) the pia mater, arachnoid mater, dura mater, and vertebral bones.[20] The cauda equina is composed of long rootlets that extend from L1 to the coccyx.

There are 31 pairs of spinal nerves (eight cervical, twelve thoracic, five lumbar, five sacral, and one coccygeal). Spinal nerves emerge from the spinal cord in between the correspondingly named bones. Cervical spinal nerve segments innervate muscles of the upper body, such as the neck, arms, and

hands. The first seven cervical nerves exit above the same numbered cervical vertebrae, but the eighth cervical nerve exits between the seventh cervical and the first thoracic vertebrae. Thoracic spinal nerve segments mainly innervate muscles of the torso. Lumbar spinal nerve segments innervate the lower body, such as muscles of the lower back, legs, and feet. Sacral and coccygeal nerves also innervate muscles of the legs and feet as well as the genitalia.

Spinal nerves carry somatosensory information and motor instructions out of the spinal cord. They leave the spinal cord and form a plexus of interconnected nerve roots and then branch to form nerve fibers.[15] Afferent sensory fibers enter the spinal cord gray matter through the dorsal root, and their cell bodies are in the dorsal root ganglia. Efferent descending motor fibers' cell bodies are in the ventral horn, and they exit from the ventral root. The dorsal and ventral roots meet, and afferent and efferent fibers are then enclosed together in a spinal nerve. The spinal nerve spans the area between the spinal cord and a particular body region.

The body surface can be mapped with dermatomes (areas of the skin supplied by a single spinal nerve root), and myotomes (groups of muscles supplied by a single spinal nerve root). Spinal nerves also carry autonomic fibers that supply internal organs. Sometimes pain from an organ creates pain in the same dermatome supplied by the same spinal nerve. An example of this referred pain is when a myocardial infarction may be felt in the arm.

The American Spinal Injury Association International Standards for Neurological Classification of SCI (ISNSCI) Impairment Scale (AIS) is used to

grade the level and severity of a person's motor and sensory neurological impairment following SCI. The ISNSCI is a standardized examination consisting of a myotomal-based motor examination, a dermatomal-based sensory examination, and an anorectal examination. The motor evaluation assesses the strength and function of specific muscles on both sides of the body through resistance and gravity. It identifies the lowest spinal segment with intact function. The sensory examination evaluates differing sensations (light touch with a cotton ball, then a pinprick) in specific dermatomes to determine the lowest spinal segment with intact sensation. The rectal exam tests sensation and the ability to squeeze the muscles in this area. If there is no muscle movement or sensation in this area, which is supplied by nerves from the sacral area of the spinal cord, the injury would be classified as "complete." Based on the findings of these examinations, an injury severity or grade and level are assigned. [21]

Reflexes are "automatic responses to detectable change."[14] Some of these changes happen due to a typical reflex arc. Reflexes can be classified in several ways: spinal reflexes are integrated by the spinal cord, such as the withdrawal reflex, one example of which is quickly withdrawing one's hand from a hot stove. Cranial reflexes are integrated by the brain stem or hypothalamus, such as pupils adjusting to light changes. Innate reflexes are unlearned responses, such as the aforementioned withdrawal and pupillary response. Conditioned reflexes are learned responses, such as salivating when food is detected. Somatic reflexes are between motor neurons and skeletal muscle - as in the withdrawal reflex. Autonomic reflexes are transported via the autonomic

nervous system to smooth muscle, cardiac muscle, or glands.[14] Hormones and/or metabolites may also be involved in the “decision” of the unconscious response. The brain can also override a reflex such as voluntarily preventing micturition if the time is not convenient, or as when a diver, with practice, overrides a head straightening reflex to flip into a dive.[14] This is an example of how “simple reflexes” can be quite complex.

The cross-sectional anatomy of the spinal cord is composed of gray and white matter.[1,2] The gray matter (an accumulation of neuronal cell bodies)[11] is shaped like a butterfly and a different neuronal cell type is in each “horn” of the butterfly shape. Afferent neurons synapse onto interneurons in the dorsal horns. Interneurons are the intermediary neurons between afferent and efferent neurons.[14] The cell bodies of somatic efferent neurons are in the ventral horns. The cell bodies of autonomic efferent neurons are in the lateral horns. In addition to the cell bodies, like in the brain, there are also dendrites and supportive glial cells in the gray matter. Spinal cord gray matter is highly vascularized, in contrast to the low density of capillaries in the white matter.[13]

The white matter is composed of axon tracts and commissures, so named because of the color of the lipids in the myelin. It is separated into tracts of interneuron axons extending the length of the cord. Each tract transmits a certain type of information. Some are ascending tracts (cord to brain for sensory input), and some are descending tracts (brain to cord for motor output), generally named for their origin and termination. They travel ipsilaterally (same anatomical side) or contralaterally (opposite anatomical side), depending on the tract,

crossing at different levels of the CNS. This distinction helps to locate lesions or pathology according to which symptoms are present.[1,2]

Ascending tracts in the spinal cord carry sensory information in afferent pathways from the body to the brain. There are three types of ascending tracts: the dorsal column medial lemniscus (DCML), spinothalamic, and spinocerebellar.[13] The DCML pathway transports information about vibration, proprioception, and fine touch. The dorsal columns are divided into two regions: fasciculus gracilis for information from below T6-T8; and fasciculus cuneatus for information from above T6-T8, but below the head.[13] The cranial nerves transport information about the head. The spinothalamic tract has two components, often referred to collectively as the anterolateral system. The anterior spinothalamic tract carries information about crude touch and pressure, and the lateral spinothalamic tract carries information about pain and temperature.[13] The spinocerebellar tracts transmit proprioceptive signals from the body to the brain. This information comes from the rate of muscle stretch from Golgi tendon organs and muscle spindle complexes. There are four different tracts, depending on whether the information comes from Golgi tendon organs, muscle spindle complexes, or from upper or lower limbs.[11,14]

Descending tracts carry motor information in efferent nerves from upper motor neurons of cortical structures. These tracts transmit this information to lower motor neurons, to move muscles. In each tract, there are two types of neurons. Upper motor neurons, brain and brainstem to the ventral horn of the spinal cord, and lower motor neurons, from the ventral horn of the spinal cord to

the peripheral muscles. Some motor tracts are under conscious control, and some are the site of unconscious reflexes. Motor tracts can be grouped functionally into pyramidal and extrapyramidal tracts.

Pyramidal tracts are the site of conscious control of muscles from the cerebral cortex of the brain to the muscles of the body and face. Pyramidal tracts pass through the pyramids (located on the brain stem) and are either corticospinal (cortex to spine) or corticobulbar (cortex to head and neck). Most corticospinal tracts decussate, or cross, in the anterior medulla. These crossed fibers form the lateral corticospinal tract, while uncrossed fibers enter the anterior corticospinal tract. In the anterior corticospinal tract, the axons decussate at the level of the spinal cord in which they innervate. Both tracts then synapse with lower motor neurons on the same side. In contrast to the majority decussation of the corticospinal tracts, only 50% of the corticobulbar tracts decussate. Extrapyramidal tracts are the sites of unconscious control of muscles from the brainstem to postural muscles to control balance and locomotion. They do not pass through the pyramids. There are four extrapyramidal tracts: reticulospinal, vestibulospinal, rubrospinal, and tectospinal.

The medial reticulospinal tract contributes to voluntary movements in response to stimulation of the reticular activating system which is in the brain stem. The lateral reticulospinal tract contributes to the inhibition of voluntary movements and reduces muscle tone. Two vestibulospinal tracts control anti-gravity muscles via lower motor neurons. Both the medial and lateral vestibulospinal tract control ipsilateral postural and tone adjustments in response

to vestibular signals from the inner ear and cerebellum.[13] The rubrospinal tracts supply upper limb and trunk flexors.[13] Disinhibition of the rubrospinal tract leads to upper limb flexion. Inhibition of the rubrospinal tract leads to upper limb extension.[13] The tectospinal tract is involved in reflexive responses to visual and auditory stimuli.[11,14]

Interneurons are neither motor nor sensory, but relay information between the two, either through excitatory or inhibitory neurotransmitters. The efficacy of this translation is crucial. Most are in the gray column of the gray matter and are structurally complex and numerous with a wide variety of functions. Interneurons in the spinal cord can be broadly divided into local and propriospinal. Local interneurons make short connections at the same vertebral level; propriospinal interneurons make long connections, different from the level of the cell body.[13] Interneurons are classified as either excitatory or inhibitory. The two most common neurotransmitters released from interneurons are GABA, the primary inhibitory neurotransmitter, and glutamate, the primary excitatory neurotransmitter. As of 2020, there have been 23 different types of interneurons identified in the spinal cord.[22]

Autonomic Nervous System

The human autonomic nervous system (ANS) innervates cardiac muscle, smooth muscle, adipose tissue, and most exocrine glands. Exocrine glands have a duct that secretes onto an epithelial surface; these include sweat, tears, bile, and lymph. The ANS also innervates endocrine glands. Endocrine glands are ductless glands that secrete right into the blood, for example the pituitary gland,

adrenal gland, and pancreas. Every autonomic nerve pathway from the CNS to an organ is a two-neuron chain: preganglionic and postganglionic. There are three subdivisions of the ANS, the sympathetic (SNS), parasympathetic (PNS), and enteric nervous system.

The SNS is commonly known as the “fight or flight,”[23] part of the ANS, and is engaged (when needs are beyond tonic) during emergency or stressful situations. The PNS is commonly known as the “rest and digest” nervous system. Both systems can excite and inhibit. In other words, even though the SNS is known as “fight or flight,” inhibition by the SNS can accompany or replace excitement by the PNS, as well as vice versa.[11] The enteric nervous system governs the function of the gastrointestinal tract. It can function independently of the brain and spinal cord. It has many autonomous functions but communicates with the CNS via the PNS and SNS.[2] Most organs are innervated by both SNS and PNS fibers, generally exerting opposite effects. A tonic level of activity, or tone, is usually occurring in both parts of the ANS. The balance shifts to meet specific demands.

Some notable exceptions to dual innervation are most blood vessels and sweat glands. Most arterioles and veins are innervated, but only by the SNS. Arteries and capillaries are not innervated. The only blood vessels that are dually innervated are in the penis and clitoris. Sweat glands are only innervated by the SNS.[11,14] Salivary glands are innervated by both the SNS and PNS, but they are not antagonistic. Both stimulate the secretion of saliva, but the composition and volume of the saliva are different: when the PNS is in charge, there is more

saliva to aid digestion. When the SNS is in charge, there is more amylase enzyme in the saliva — so that starch is broken down more quickly into sugars for emergency use. The blood vessels supplying the salivary glands are innervated by the SNS, causing vasoconstriction when needed. Salivary gland function is an example of a seemingly simple process of the ANS that is very intricate and subtle.

Sympathetic preganglionic fibers originate in the thoracolumbar portion of the spinal cord, are very short, and use the neurotransmitter ACH. Most sympathetic postganglionic fibers are long and use the neurotransmitter NE, ending on the effector organs, and are known as adrenergic fibers.[11,14] Parasympathetic preganglionic fibers originate in the brainstem and sacral areas of the CNS. These fibers are long and terminate in postganglionic fibers in or near the effector organs. Preganglionic and postganglionic fibers of the PNS both use ACH as a neurotransmitter and are therefore called cholinergic. 11,14 There are a few exceptions to this general description. The sympathetic postganglionic fibers supply sweat glands and the periosteum in bones secretes ACH.[24] Some non-adrenergic and non-cholinergic autonomic fibers release other neurotransmitters such as nitric oxide and ATP to some blood vessel smooth muscle. Some autonomic fibers release co-transmitters along with ACH and NE, such as dopamine, ATP, endogenous opioids, and others.[11,14]

Afferent visceral information is usually unconscious, for example, baroreceptors monitoring BP or chemoreceptors monitoring carbon dioxide or potassium levels. However, the CNS does regulate autonomic output both

directly and indirectly. It begins with visceral afferents to the CNS, and sometimes an alternate route: CNS, visceral afferents, CNS again. For example, urination, defecation, and erection are integrated at the spinal cord level, but all these reflexes begin conscious control at higher cortical levels.

The adrenal medulla is the outer portion of the adrenal gland and is a unique endocrine part of the SNS. The CNS stimulates preganglionic fibers to allow the adrenal medulla to secrete 20% NE and 80`% epinephrine hormones into the blood. NE and epinephrine are, along with dopamine and cortisol, the "catecholamines."[11,14] Catecholamines can serve as hormones, neurotransmitters, or both.[10]

Each ANS neurotransmitter can go to several receptor types on the receiving tissue. Both ACH and NE stimulate activity in some tissues and inhibit activity in others. This is why ANS body responses (and pharmaceutical effects) depend on the receptors on and in the tissue, not only the neurotransmitter. There are two cholinergic receptors: nicotinic and muscarinic. Nicotinic receptors are found on all postganglionic autonomic cells and respond to ACH released from both SNS and PNS preganglionic fibers. Muscarinic receptors bind with ACH released from parasympathetic postganglionic fibers.[11,14]

Adrenergic receptors are alpha 1 (most sympathetic tissue, usually excitatory), alpha 2 (digestive organs, usually inhibitory), beta 1 (heart, only excitatory), or beta 2 (arterioles and bronchioles, usually inhibitory). Both alpha receptors have more of an affinity for NE than epinephrine. B1 receptors have

approximately equal affinities for both, and B2 binds only with epinephrine.[11,14] Alpha-adrenergic receptors are an important part of the regulation of BP.

Hemodynamics

Hemodynamics are the forces or mechanisms involved in the circulation of blood, including BP and heart rate (HR).[10] Hemodynamic homeostasis is primarily maintained by the following actions of the ANS: when BP veers from its set point, baroreflex stretch receptors in the carotid, aorta, heart, and lungs signal neurons in the brain stem which then modulate the firing of the sympathetic preganglionic neurons located alongside the spinal cord between T1 to L2 vertebral segments. The sympathetic preganglionic neurons then send projections either to peripheral sympathetic ganglia that control the diameter of blood vessels (and consequently total peripheral resistance) or to the adrenal medulla to secrete catecholamines directly into the bloodstream. Endocrine signaling of the adrenal medulla can also begin in many areas of the cerebral cortex, traveling directly from the pituitary gland to the bloodstream,[13] bypassing (or augmenting) sympathetic preganglionic neurons via the hypothalamic-pituitary axis. The blood-brain barrier is much more permeable in the hypothalamus and the area lining the third and fourth ventricles of the brain.[13] The medulla in the brainstem is most directly responsible for autonomic output, but its response originates in the hypothalamus, which can also receive input from myriad other connections in the brain.

The baroreflex signals to the brain stem also signal the vagus nerve, which, as its etymology indicates, “wanders” through the body affecting the heart,

but also the digestive tract and the abdominal viscera. The vagus nerve can serve as a “brake” allowing any needed sympathetic efferent activity to progress uninhibited. Visceral afferent signals all go to the nucleus solitarius in the brainstem,[25] and many of the sympathetic signals then go on to the sympathetic preganglionic neurons, but they also go to other areas of the brain, for example, the locus coeruleus which produces NE as a neurotransmitter signaling the amygdala, the thalamus and the hypothalamic pituitary adrenal axis, eventually increasing or decreasing plasma cortisol.[26]

Blood pressure is also adjusted by the renin-angiotensin aldosterone system (RAAS). RAAS contributes to BP regulation by changing plasma sodium concentration and extracellular fluid volume and has a role in regulating vascular tone. It is dependent on hormonal changes which induce genes to produce vasoactive proteins, beginning with renin release in the kidneys, and ending with aldosterone. [27]

A reduction in BP causes the kidneys to release renin into the bloodstream where it converts angiotensinogen into angiotensin I, then an enzyme in the lungs, angiotensin-converting enzyme I produces angiotensin II which can act directly on blood vessels to constrict and increase BP. Angiotensin II then stimulates the release of aldosterone which causes the kidneys to retain salt and water, which increases the amount of fluid in the body. Angiotensin II also acts on the hypothalamus to increase thirst (to further increase fluids in the body), and produce vasopressin, which increases blood vessel constriction to raise BP.[28]

This classical RAAS pathway can also cause inflammation, an increase in cell stress, and insulin resistance.[29] Conversely, angiotensin I, II, and aldosterone are eventually broken down and can become part of an alternate RAAS pathway that acts to lower BP, inflammation, and insulin resistance. These pathways work to balance systemic effects.[29]

RAAS is considered slower acting than the baroreflex response to BP change, yet still plays a role in acute BP adjustments. [30]Circulating renin increases in minutes after a sharp drop in BP.[31] Sitting upright has been found to double plasma renin within 15 minutes.[32] In an investigation of the role of RAAS after a initiating a social stress test, investigators found the highest renin levels 1 minute after the test and the highest renin levels 10 minutes after the stress test.[33]

BP modification routes beyond the baroreflex are important to study in a population with altered SNS response such as people with SCI. Could people with SCI, due to homeostatic necessity, develop an alternate autonomic feedback route (or routes) with more cognitive and endocrine influence on BP than the NI “normal” route?

Mind/Body Relationship

The question of how the mind affects the body and vice versa has been debated for millennia,[34] the details of which are beyond the scope of this dissertation. Whether the philosophical viewpoint is Eastern or Western, the debate comes down to either dualism or monism. Dualism maintains a separation between mind and body; a Western example is the viewpoint of Rene

Descartes,[35] known for his quote, “I think therefore I am.” Descartes considered the capacity for thought in no way connected to the body. An Eastern example of dualism is the early yoga of Samkhya and Patanjali.[36] This is the yoga of rejecting the body and all its attachments to obtain enlightenment.[36] Monism’s Western and Eastern parallels would be the philosophies of both William James 30 and Tantra,[36] which contend that mind and body are of the same essence. Tantra sees everything as coming from a unified awareness, including all bodily functions, and would see the goal of transcending the body as pointless. Most modern philosophers of mind contend that mental processes will eventually be explained in physical terms as science continues to evolve, but philosophical nuances and questions to this view abound.[37]

A classic early twentieth-century theory based on monism, proposed by William James and Carl Lang maintains that an experience of an emotion occurs AFTER a peripheral physiological response instead of the other way around. How the emotion is experienced depends on the interpretation of the physiological state.[38] Porges,[39] Thayer [40] and others later built on this theory, emphasizing the importance of interoception, or noticing inner body sensation as it happens. Paraphrasing Porges’ theory which elaborates on this concept: the better the HRV, the better the interoception and positive adaptations of the body, both cardiovascular and psychological.[39]

Toward the end of the twentieth century, Thayer and Lane proposed the neurovisceral integration model,[40] which suggests that neural networks in autonomic and cognitive self-regulation are also involved in the control of cardiac

autonomic activity.[40] Recent updates to this model suggest both “top-down” and “bottom-up” modulation of both physiological and psychological processes can be integrated according to the needs of a person. In our study, we incorporated interoception and HRV measurement, and SCI-specific quality-of-life surveys.

Spinal Cord Injury

SCI is a devastating condition resulting in sensory, motor, and autonomic impairments which increase morbidity and hasten mortality. It changes myriad facets of life: physical, financial, social and psychological. Treatment can be prohibitively expensive and ongoing for the rest of the person’s life. According to the National Spinal Cord Injury Statistical Center (NSCISC), there are approximately 17,900 new cases each year and 296,000 people living with SCI in the United States.[41,42] The estimated worldwide prevalence of people living with SCI is 20.6 million.[43] The average age of injury has increased from 29 years during the 1970s to 43 since 2015. Seventy-eight percent of new cases are male, and 24% of injuries are to non-Hispanic black people, higher than the proportion of non-Hispanic black people in the United States, which is 13%. Motor vehicle accidents are the leading cause of injury, followed in order by falls, violence (most often gunshot wounds), sports, medical/surgical, and other causes.[44] Acute care hospital stays have declined from 24 days in the 1970s to 11 days presently. Rehabilitation lengths of stay have also declined from 98 days in the 1970s to 30 days. Incomplete tetraplegia (paralysis of the arms and legs) is the most frequent neurological category. The frequency of incomplete and complete paraplegia (paralysis of the lower half of the body) is about the same.[44]

Average yearly healthcare costs adjusted for the year 2022 are $429,348 for an injury or loss of motor function at any level, to $1,315,554 for high tetraplegia in the first year. Each subsequent year average costs are $52,150 to $228,450, respectively.[45] The average remaining years of life for persons with SCI have not improved since the 1980s and remain significantly below the life expectancies of people without SCI.[45]

Since each tract of the spinal cord carries specific information, damage can interfere with some functions, while others remain intact. The location and extent of sensory and motor deficits, along with imaging, can determine the level and extent of the injury.[11] Increasing focus on the secondary complications of dysautonomia in people with SCI has made The International Standards to Document Autonomic Function following SCI (ISAFSCI) recommended adjunct measurements to the ASIA Impairment Scale.[46] The Autonomic Standards Assessment Form is used to "track the association between changes in ANS function correspondent with changes in the neurological level of injury and completeness of injury as classified by the ASIA Impairment Scale."[46]

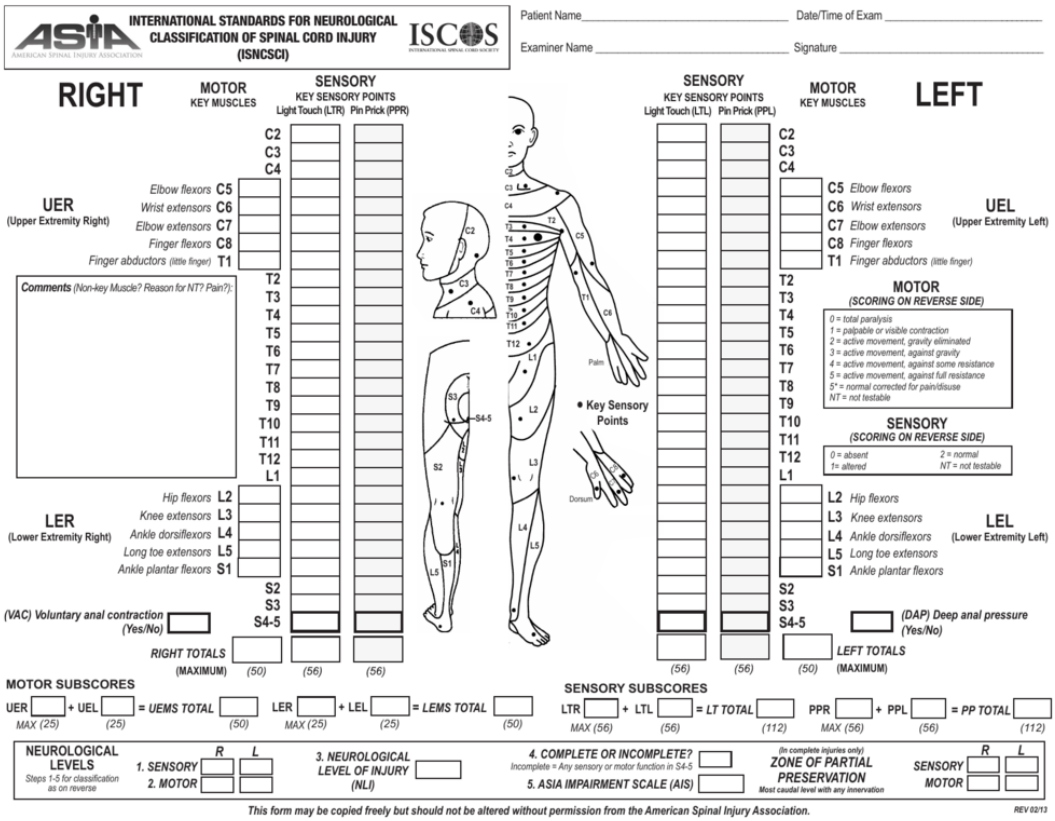
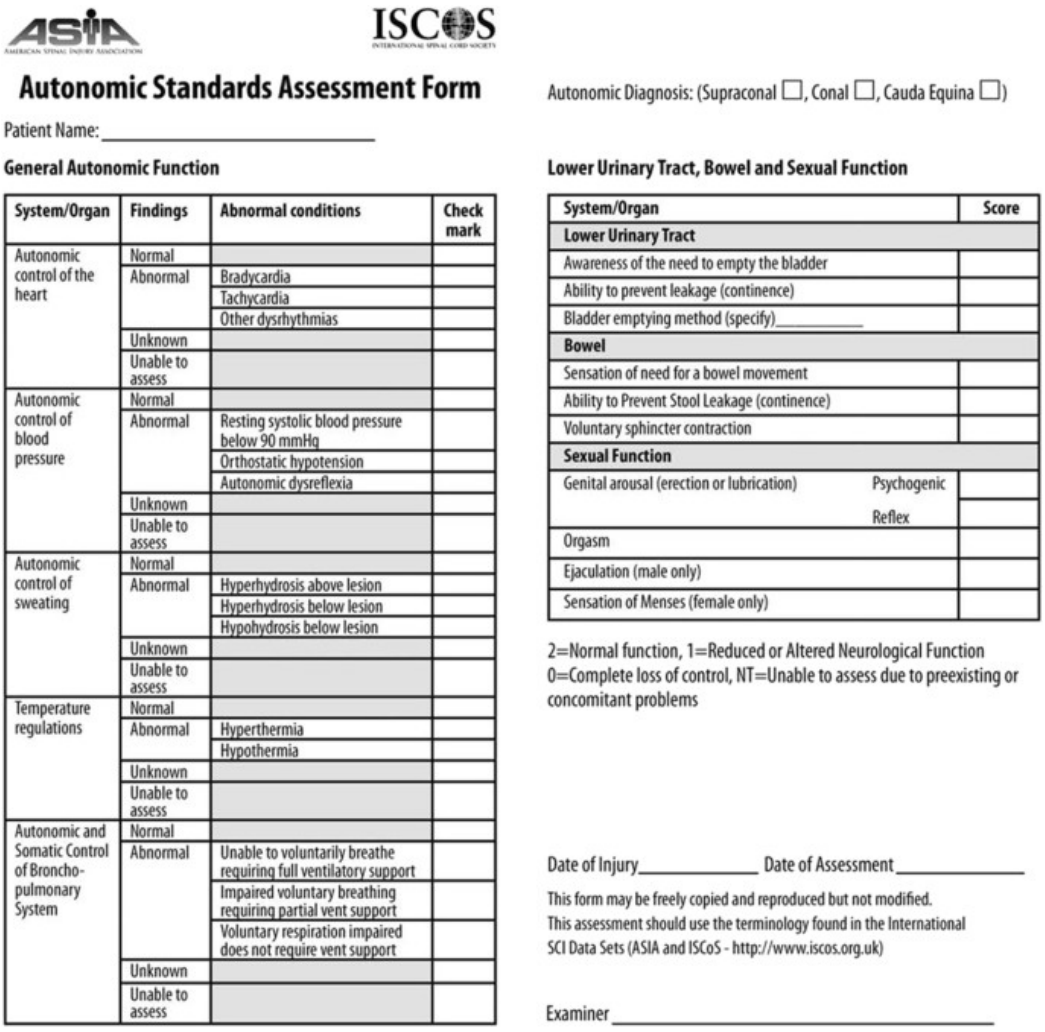


Figure 1: The ASIA Impairment Scale grades the level and severity of a person's motor and sensory neurological impairment following SCI.



Autonomic Standards Assessment Form

Autonomic Diagnosis: (Supraconal ☐, Conal ☐, Cauda Equina ☐)

Patient Name: _____

General Autonomic Function

System/Organ	Findings	Abnormal conditions	Check mark
Autonomic control of the heart	Normal		
	Abnormal	Bradycardia	
		Tachycardia	
		Other dysrhythmias	
	Unknown		
	Unable to assess		
Autonomic control of blood pressure	Normal		
	Abnormal	Resting systolic blood pressure below 90 mmHg	
		Orthostatic hypotension	
		Autonomic dysreflexia	
	Unknown		
	Unable to assess		
Autonomic control of sweating	Normal		
	Abnormal	Hyperhydrosis above lesion	
		Hyperhydrosis below lesion	
		Hypohydrosis below lesion	
	Unknown		
	Unable to assess		
Temperature regulations	Normal		
	Abnormal	Hyperthermia	
		Hypothermia	
	Unknown		
	Unable to assess		
Autonomic and Somatic Control of Broncho-pulmonary System	Normal		
	Abnormal	Unable to voluntarily breathe requiring full ventilatory support	
		Impaired voluntary breathing requiring partial vent support	
		Voluntary respiration impaired does not require vent support	
	Unknown		
	Unable to assess		

Lower Urinary Tract, Bowel and Sexual Function

System/Organ		Score
Lower Urinary Tract		
Awareness of the need to empty the bladder		
Ability to prevent leakage (continence)		
Bladder emptying method (specify)_____		
Bowel		
Sensation of need for a bowel movement		
Ability to Prevent Stool Leakage (continence)		
Voluntary sphincter contraction		
Sexual Function		
Genital arousal (erection or lubrication)	Psychogenic	
	Reflex	
Orgasm		
Ejaculation (male only)		
Sensation of Menses (female only)		

2=Normal function, 1=Reduced or Altered Neurological Function
0=Complete loss of control, NT=Unable to assess due to preexisting or concomitant problems

Date of Injury_____ Date of Assessment_____

This assessment should use the terminology found in the International SCI Data Sets (ASIA and ISCoS - http://www.iscos.org.uk)

Examiner _____

Figure 2: The Autonomic Standards Assessment Form tracks changes in autonomic function after SCI.

Pressure ulcers, autonomic dysreflexia, and pneumonia/atelectasis are the most common long-term secondary medical complications after SCI.[47] 2015 data indicates 30% of people with SCI are re-hospitalized one or more times following injury, with stays an average of 18 days. Diseases of the genitourinary system are the leading cause of re-hospitalization, followed by diseases of the

skin. Respiratory, digestive, circulatory, and musculoskeletal diseases are also common causes of hospitalization.[44]

Historic causes of death according to NSCISC are pneumonia and septicemia. In the last two decades, cardiovascular and cerebrovascular diseases have increased as a leading cause of death in SCI.[48,49] This is due to people with SCI having more risk factors for cardiovascular disease as well as advances in acute care for septicemia and pneumonia. These risk factors are physical inactivity, dyslipidemia, chronic inflammation, abnormal glycemic control, and BP irregularities.[48]

Individuals with cervical or upper thoracic SCI often suffer debilitating secondary complications resulting from abnormal ANS activity. [50-53] Studies in humans [54] and animals [55,50] demonstrate that lesions on the cervical or upper thoracic segments of the spinal cord (i.e., T6 and above) result in damage to sympathetic preganglionic neurons, causing sole reliance on sympathetic activity below the level of the injury and autonomic dysfunction in multiple systems. Dysautonomia in SCI can cause multiple symptoms including autonomic dysreflexia,[51] orthostatic and arterial hypotension, cardiac dysrhythmias,[56] bradycardia,[57] difficulties with psychogenic sexual arousal,[58] attenuated cardiovascular response to exercise, incontinence,[59] chronic pain,[60] gastrointestinal disorders, and others. Recovery of normal autonomic cardiovascular function is most frequently ranked to be a higher priority than regaining motor function among people with SCI.[61]

After cervical or upper thoracic SCI, the above hemodynamic pathways are interrupted, reducing sympathetic tone below the injury and leaving the sympathetic preganglionic neurons exclusively controlled by spinal reflexes, which eventually become hyperresponsive.[59] Parasympathetic outflow remains unopposed through the intact vagus nerve.[59] This loss of central control of sympathetic preganglionic neurons results in both arterial and orthostatic hypotension via abolished compensatory vasoconstriction, especially in large vascular beds, like skeletal muscle and splanchnic region vessels, with concomitant reduced venous blood return.[62]

Orthostatic hypotension is defined as a decrease in systolic BP of 20 mmHg or more, or in diastolic BP of 10 mmHg or more,[63] when sitting up from a lying down position. This can compromise blood flow to the brain and cause syncope, nausea, deficits in cognitive performance, fatigue, and an increased susceptibility to pressure ulcers due to reduced tissue perfusion.[64] In able-bodied individuals, changing from supine to upright causes only slight changes in HR and BP,[65] yet in people with SCI, particularly those with higher injuries, BP usually decreases and HR increases. [66] This hemodynamic response in people with SCI is due to the interruption of descending sympathetic vasomotor tracts. [67] This changes both excitatory and inhibitory sympathetic control, reduces sympathetic tone below the injury, changes the morphology of the sympathetic neurons, alters plasticity in spinal circuits, and creates hyperresponsive alpha adrenoreceptors. [54,68]

Hypotension is only one side of the unique hemodynamic dichotomy of people with SCI. The hyperexcitable state of spinal reflexes prevents baroreflex modulation of sympathetic preganglionic neurons, leading to the dangerous hypertension of autonomic dysreflexia, which occurs regularly in people with tetraplegia, accounting for 91% of motor complete cases (AIS A-B) and 27% of cases with motor incomplete SCI (AIS C-D).[69] Autonomic dysreflexia continues unabated until an aggravating stimulus (e.g. bladder distension or pressure sore) is rectified.[59] Autonomic dysreflexia often occurs multiple times a day with headaches and sweating symptoms, yet sometimes is asymptomatic.[70,71]

In addition to maladaptive plasticity and hyperresponsive reflexes, peripheral changes contribute to impaired hemodynamics after SCI. Lower BP, lower catecholamines,[72] and enhanced sensitivity of adrenergic receptors in peripheral vasculature impair myogenic activity in arterioles.[73] In addition to hemodynamic detriments directly caused by sympathetic changes, other causes are hyponatremia and low plasma volume, cardiovascular deconditioning, and motor deficit leading to loss of skeletal muscle pumping activity.[62] Non-pharmaceutical options with varying degrees of efficacy for hypotension include exercise,[74] electrical stimulation,[75] abdominal compression,[76] increasing fluid intake,[77] and altering sleeping positions.[78] There is an immediate need for effective non-invasive and non-pharmaceutical interventions to ease these myriad dysautonomic consequences in people with SCI.[1,2]

Biofeedback

If someone takes their temperature or steps on a scale, they have engaged in biofeedback. As a therapy, however, biofeedback enables an individual to learn how to change physiological activity to improve health and performance. Brain waves, heart function, breathing, muscle activity, and skin temperature measurements “feed-back” information to the user. The presentation of this information along with changes in thinking, emotions, and behavior—supports desired physiological changes. Ideally, these changes can continue without the ongoing use of an instrument.[79] Therapeutic biofeedback is based on operant conditioning, in which a desired behavior is followed by a reward, thus reinforcing the behavior.[10]

According to metanalyses by Tan et al,[80] biofeedback in healthcare settings is efficacious for female urinary incontinence,[81] anxiety,[82] attention deficit hyperactivity disorder,[83] chronic pain,[84] adult constipation,[85] hypertension,[86] motion sickness,[87] Raynaud’s disease,[88] and temporomandibular disorder.[89] It has been found “probably efficacious” for alcoholism/substance abuse,[90] arthritis,[91] diabetes,[92] fecal incontinence,[93] pediatric headaches,[94] insomnia,[95] traumatic brain injury,[96] male urinary incontinence,[97] and vulvar vestibulitis.[98]

Biofeedback research pioneer Neal Miller along with colleague John Dollard in the book *Social Learning and Imitation* [99] determined four fundamentals to successful “visceral learning” or learning by the ANS:

1. Drive: the person must want something
2. Cue: a person must notice something
3. Response: a person must do something
4. Reward: a person must get something they want

We have used all these parameters in our protocol design. Our participants *want* to succeed at moving their BP, they *notice* their interoceptive body sensation, they *do* something by using specific techniques, and they *get rewarded* with feedback.

Spinal Cord Injury and Blood Pressure Biofeedback

The literature on the effectiveness of biofeedback for BP improvement after SCI is scarce. [6,100,101] In a case study by Bernard Brucker in 1977, the participant successfully raised and lowered their BP and sustained the learned change, with an impressive mean increase of 48 mmHg in both systolic and diastolic BP.[100] Interestingly, this participant used imagery (sexual or horse racing) at first in his training, but then let go of the images and just focused on raising BP.[100] Ince conducted a study in two subjects with cervical SCI suffering postural hypotension, showing that biofeedback resulted in an increase in BP from hypotensive to normotensive rates, also with a sustained change.[101]

After the above case studies, Brucker designed a larger BP biofeedback study for their doctoral dissertation entitled “Learned Voluntary Control of Systolic BP by Spinal Cord Injury Patients.” Ten participants ranged from C3 to T11 injury levels. Two suffered from orthostatic hypotension. Training consisted of 25 one-hour sessions. Nine of the ten participants learned to make reliable and large

voluntary increases in BP and the two hypotensive participants were able to sustainably modify their BP to "completely overcome their postural hypotension."[6] The effects of postural hypotension would return if the participants chose or were instructed not to control their BP. As previously discussed, hypertension modification through biofeedback has been found efficacious in NI participants, yet the changes were moderate.[80] Brucker's results indicate that not only can people with SCI learn to control their BP, but they also learn voluntary changes of larger magnitude than NI individuals. Brucker postulates, "One possible explanation for this could be the lack of normal homeostatic control…it is this lowered efficiency in regulation which may permit a large voluntary manipulation of an autonomic response to occur."[6] Interestingly, the only study found in a person without SCI in which large voluntary changes were learned was by a person who had suffered a stroke with brain stem damage.[102] This damage may have affected the participant's BP regulation in ways similar to a cervical SCI.

In both Brucker studies, the author chose not to use breath modification, thinking it would mean a lack of "visceral learning," since breathing changes can, on their own, modify BP.[103-105] By using breathing exercises in our proposed study, we may be confounding mechanisms, but also increasing the variance in intervals between relaxation and stimulation, which, like the concept of high-intensity interval training in exercise physiology, is more effective due to these oscillations.[106] In addition to the BP raising and lowering capabilities of breathing, there may also be effects from intermittent hypoxia, shown to have many advantages in SCI.[107] We must also keep in mind normal BP variability, and how

a dysfunction in baroreflex sensitivity can increase it.[108] As complex as this subject tends to get, we must not forget that it is possible that a very simple tool like breathing could create a big difference in physiological parameters. In alignment with our goal of keeping the protocol simple and easy to learn, we chose to add VR.

Virtual Reality

Immersive VR uses a head-mounted device and full immersion into the 360-degree virtual world. In neurorehabilitation settings, VR has been shown to increase engagement and decrease treatment resistance.[109] In our protocol, participants watched a set of three-minute videos, some relaxing (e.g., beach scenes, campfires), and some stimulating (e.g., sharks, horse races). The videos were consistent for all participants.

The VR headset poses a non-significant risk of eye strain, headache, pallor, sweating, dryness of mouth, fullness of stomach, disorientation, vertigo, ataxia (not applicable in people with SCI), nausea, and vomiting.[110] The risk of these VR-induced adverse symptoms and effects with our state-of-the-art commercial equipment with advanced visuals is very low. In a meta-analysis of VR studies and side effects, in the new generation of commercial VR head-mounted displays there were “zero incidents of adverse symptomology and dropouts.”[111] VR is effective for white-coat hypertension.[112] No studies could be located for the attenuation of hypotension with VR, which indicates a research gap.

How VR works has a lot to do with how vision works. We see illusions all the time in daily life and piece them together and perceive them as real, moved from point to point by visual saccades, especially salient when visual and motor frames of reference are congruent.[113] We investigated the difference between mental imagery and VR imagery in cardiovascular and hemodynamic response to determine the most effective choice to use in the remainder of the study. We hypothesized that VR imagery would be more effective at creating beneficial responses. This is because creating mental imagery requires concentrated focus and is more difficult to generate than visual perception (which includes VR).[114] VR may make this focus easier.[115]

VR has been used in SCI rehabilitation to reduce pain[116,117] and improve motor function.[118] Eye tracking or voice activation can be used to control the VR experience, which would be especially beneficial for many people with SCI who have limited hand and arm function. It could increase independence if incorporated into future technology. Autonomic biofeedback with VR could offer a practical, fun, and safe tool that could improve and maintain healthier hemodynamic variables, minimize patient dependence on pharmacological interventions, and be incorporated into other neurorehabilitative therapies.

Hypotheses and Specific Aims

Overall Aim: To investigate the effects of autonomic biofeedback training on BP, HR, and quality of life in individuals with SCI.

Specific Aim 1: To compare BP and HR response between mental imagery and VR imagery in 14 participants with SCI and 17 NI individuals.

Hypothesis 1.1: All participants will show higher MAP and HR during VR autonomic biofeedback training sessions compared to mental imagery training sessions during stimulation cycles and lower MAP and HR during relaxation cycles.

Specific Aim 2: To investigate the effects of autonomic biofeedback training on BP and HR responses among individuals with cervical SCI.

Hypothesis 2.1: Individuals with cervical SCI will show more normotensive systolic and diastolic BP in the head-up tilt test after eight sessions of autonomic biofeedback.

Hypothesis 2.2: All participants will show higher HRV and baroreflex sensitivity during and after eight sessions of autonomic biofeedback.

Hypothesis 2.3: Individuals with cervical SCI will show more variability in MAP than NI individuals during autonomic biofeedback training.

Outcome Measurements: MAP, HR, and interbeat interval were all measured with Caretaker 4 (Charlottesville, Virginia, USA) continuous BP monitor. The interbeat interval was converted to HRV frequency and time domain analyses with Kubios HRV software (Varsitie 22, 70150 Kuopio, FINLAND).

Specific Aim 3: To investigate the effects of autonomic biofeedback on self-reported bowel and bladder management, anxiety, depression, interoception, pain, pressure ulcers, resilience, trauma, and autonomic reactivity in individuals with cervical SCI.

Hypothesis 3.1: Individuals with cervical SCI will show improved scores on the Tulsky Quality of Life for SCI combined with the Body Perception Questionnaire.

CHAPTER II

RESEARCH DESIGN AND METHODS

Protocol Design

Our autonomic biofeedback study was inspired by NASA's Autogenic Feedback Training Exercise (AFTE). AFTE is a combination of autogenic training,[119] which uses cognitive imagery to control physiologic responses [119] (e.g. "feel your hands getting warm and heavy") and biofeedback.[120] NASA astronaut training using this combination has shown greater efficacy and decreased learning time to control physical responses than using the modalities separately.[121] People exposed to microgravity and people with SCI suffer similar secondary complications,[122] including atrophy and fiber-type change in muscle,[123,124] bone demineralization,[125,126] cardiovascular,[127,128] renal,[129,130] immune,[131,132] sensory-motor changes[133,134] and orthostatic intolerance.[3,66] Up to 67% of astronauts experience nausea, vomiting, loss of appetite, sleepiness, and lethargy of space motion sickness during the first three days of space flight, shortly after weightlessness occurs.[4] The cause is multifactorial, involving components of fluid shifts from weightlessness, the sensory conflict between optical and vestibular input, and enteric nervous system changes.[4] The ANS plays a significant role in the pathophysiology of this variant of motion sickness.[4] Cowings et al*.,* in a 2000 study of AFTE with 33 NI men, reported fewer symptoms of nausea and orthostatic hypotension[135] in addition to improved

HRV[135] compared to their counterparts receiving the anti-nausea drug promethazine.[121]

Our study was inspired by the pioneering work of Cowings' et al successful use of AFTE to attenuate orthostatic hypotension.[5] In our autonomic biofeedback protocol, we kept the oscillatory nature of the training cycles learned from a study of AFTE adapted for gastric motility disorders: relax then stimulate, back and forth.[136] We kept the autogenic aspects, using cognitive imagery to imagine cold hands when trying to raise BP and imagining warm hands when trying to lower it. Then we added specific breathing techniques and VR, hypothesizing that the BP raising and lowering effects would increase. Participants received biofeedback via a verbal acknowledgment of BP changes.

When designing the protocol for this autonomic biofeedback study, we looked at other factors that could change BP besides sympathetic-mediated vasoconstriction, which is limited in many people with SCI. With the shallow, fast-breathing technique *Kapalabhati*,[105] there is less activation of pulmonary stretch receptors, so likely less vagal influence, plus it varies intrathoracic pressure with the respiratory pump to increase BP.[105] We chose a vibratory and extended exhale breath in the relaxation cycles to increase vagal stimulation, known as *Brahmari*.[17,137] *Kapalabhati* and *Brahmari* are examples of yoga *pranayama*, which means "breath control."[36]

We also used imagery (VR and/or mental) — both stimulating and relaxing, hypothesizing that cognitive changes: inducing, and then mitigating stressful thoughts, would both increase and decrease BP. These oscillations

between stimulation and relaxation could “train” the baroreflex and perhaps create more normotensive autonomic responses to BP changes. This training also takes advantage of the unique nervous systems of people with SCI: since their tactile and proprioceptive inputs are reduced, they may rely more on visual cues for learning.[138]

In addition to visual cues, we focused our interoception cues on the face. Carotid baroreceptor signals travel through the glossopharyngeal nerve to reach the nucleus solitarius.[13] As previously discussed, many of the sympathetic baroreceptor signals then go on to the sympathetic preganglionic neurons, but they also go to other brain areas including the locus coeruleus which produces NE as a neurotransmitter signaling the amygdala, the thalamus and the hypothalamic pituitary adrenal axis, eventually increasing or decreasing plasma cortisol. The glossopharyngeal nerve provides motor, parasympathetic, and sensory information to the mouth and throat, as well as transporting baroreceptor signals from the carotid. These shared pathways are one of the reasons our interoception cues in the relaxation cycles are all focused on the face. The other reason we focus our interoception cues on the face is that the somatosensory area of the brain reorganizes following SCI. In animal studies, we have learned that since much of the body loses afferent stimulation post-injury, the face and head are represented more in the somatosensory cortex because the sensory and motor areas of the face and head, even in high injuries, remain active.[139] Perhaps having more somatosensory representation of the glossopharyngeal innervated face and head will increase downstream cognitive influences on BP.

The creation of a novel feedback loop through operant conditioning and biofeedback, altered baroreflex sensitivity, peripheral vascular hypersensitivity to catecholamines, somatosensory brain reorganization [140] and multiple avenues off the nucleus solitarius are all examples of why a focus on direct cortex to plasma catecholaminergic endocrine influence and the vagal “brake” may be of value. Using images, emotion, interoception and breathing capitalizes on this possible alternate route.

Ethical Approval for Human Studies

This study was formally approved by the University of Louisville Institutional Review Board (IRB: #20.0168) in compliance with all the institutional and federal regulations concerning the ethical use of human volunteers for research studies.

Facilities/Resources

The Novak Lab in the Health and Sport Sciences Department, Student Activities Center, Belknap Campus, University of Louisville, and a private exam room on the sixth floor of Frazier Rehabilitation Institute were the performance sites of this research project.

Participants

Individuals with chronic cervical SCI and NI individuals participated in this study. (One participant with a thoracic injury participated in the Aim 1 comparison of VR and mental imagery, all other participants with SCI sustained cervical injuries). NI subjects were included to evaluate normal baseline variables and to serve as a control group. All participants in the Aim 2 full training protocol were

involved in this study for approximately six weeks, including eight or nine training sessions, twice per week, a pre-training testing session, and a post-training testing session.

Recruitment Procedures

Individuals with SCI were referred by Dr. Camilo Castillo, Director of SCI Medicine and Fellowship Program, UofL Health Frazier Rehab Institute. Additionally, flyers for recruiting participants were placed in various locations at both the Belknap and the Health Science Center campuses at the University of Louisville. Once potential participants were identified, they were invited individually for an informational session. All participants were fully informed of the purposes, risks, and potential benefits of participation in the study during the informational session with one or more members of the research team. The participants signed an informed consent approved by the University of Louisville Institutional Review Board before entering the study.

Inclusion/Exclusion Criteria

Non-Injured Participants

- Must not be taking any BP medication.
- Must be in stable medical condition without known cardiopulmonary disease.
- Must be a non-smoker.
- Must be at least 18 years of age.

Participants with Spinal Cord Injury

- Must have a cervical or thoracic SCI.
- Must be in stable medical condition without cardiopulmonary disease.
- Must be a non-smoker.
- Must be at least 18 years of age.

  *** Participants with SCI taking BP-modifying drugs were approved for participation by the supervising physician on a case-by-case basis. Out of the 14 participants with SCI, none were taking drugs to increase BP, and three discontinued hypertensive medication on training days with approval from the supervising physician.

Equipment/Instruments Overview

This facility was equipped with the Caretaker 4 (Charlottesville, VA, USA) which recorded continuous BP, HR, and interbeat interval via a pneumoplethysmographic finger cuff connected to a wrist-worn small monitor with an accompanying Samsung tablet. Also included in the lab were a VR immersive headset Meta Quest 2 (Meta Platforms, Menlo Park, California, USA), a Bailey Electric Tilt Table (Lodi, OH, USA), and a Hoyer Presence Heavy Duty Lift (Joerns Healthcare, Charlotte, NC, USA). HRV parameters derived from the interbeat interval were analyzed on Kubios HRV software (Varsitie 22, 70150 Kuopio, FINLAND).

In 2021 for our preliminary data collection and case study, detailed in Chapter III, we used an electrogastrogram connected to a four-channel recording

device: Sandhill/Diversatek (Milwaukee, Wisconsin, USA) to measure gastric electrical activity and a Meda-Sonics photoplethysmograph model PPG-13 (Mountain View, California, USA) to measure microvascular blood volume. After the case study, we did not use this equipment further, as it was not necessary to answer our Specific Aims.

Immersive Virtual Reality

The immersive VR headset was Meta Quest 2 (Meta Platforms, Menlo Park, California, USA). The headset was placed on each participant before beginning the training session and left on until the end of the training session. Stimulation and relaxation scenarios began and ended according to the cycle of training. A member of the research team controlled the timing of the scenarios via a synchronous laptop computer. The headset was thoroughly sanitized with alcohol wipes in between participants.

Continuous Blood Pressure Monitor

The Caretaker Continuous BP Monitor model 4 (Charlottesville, Virginia, USA) included a pneumoplethysmograph with a velcro strap on the second phalange of the left hand and connective tubing leading to the hemodynamic measurement unit, which rests on the wrist also with a Velcro strap, on the left hand. After determining BP from a manual BP sphygmomanometer and cuff, the hemodynamic measurement equipment was calibrated while synced to an accompanying Samsung tablet. The participant's number and the number of the training session were entered into the tablet. All training events were recorded on the hemodynamic measurement equipment by pressing and holding the "HR"

box on the tablet, then entering Roman numerals that correspond to marked events. After the training session, a report was created with hemodynamic measurements including systolic BP, diastolic BP, MAP, HR, respiration rate and oxygen saturation level. Descriptive statistics of each measurement and an event log of the manually marked events during training were also included in the report. A detailed log accompanied every report, this included the interbeat interval. This data was automatically synced to the cloud storage service of the University of Louisville, Cardbox, every fifteen minutes. All data (including scanned training logs) were also saved on Ms. Torres' desktop computer as well as a securely locked flash drive.

Tilt Table

Participants were assisted by two trained personnel to transfer to the Bailey Electric Tilt Table (Lodi, OH, USA) using either the Hoyer lift (Joerns Healthcare, Charlotte, NC, USA) or a sliding board, depending on injury level and the participant's preferred transfer method. Wide Velcro straps connected to the tilt table secured the participant in three places: the chest, hips, and just above the knees with feet placed securely on the standing board at the end of the tilt table. The tilt table was only used for pre/post-testing and measurements were taken either supine or at a 45-degree tilt.

Quality-of-Life and Interoception Surveys

The Tulsky Quality-of-Life for SCI are individual instruments in short form, validated in the SCI population.[7] We included questions about bowel and bladder management, anxiety, depression, pain, pressure ulcers, resilience, and trauma.

The Tulsky instruments were followed by the Body Perception Questionnaire short-form survey, validated in the NI population, to measure interoception and autonomic reactivity. The combined instruments were entered into a Qualtrics online format so that participants, many of whom have limited hand function, were able to “swipe” their answers. These surveys were administered before and after the full training protocol.

Pre/Post Testing Overview

Autonomic nervous system evaluations were performed before and after the eight or nine training sessions. These included baseline hemodynamic measurements, the Valsalva maneuver, head-up tilt testing, and paced deep breathing.

Participants remained on the tilt table for the entirety of pre/post testing: either supine or at a 45-degree tilt during tilt testing. The Caretaker 4 continuous BP monitor was in use at all times during the testing. All pre/post-testing procedures were explained to the participant before beginning testing.

Baseline Assessments

For baseline measurements, the participant rested quietly on the tilt table, breathing normally for five minutes. Hemodynamic variables including HR and BP were recorded with the continuous BP monitor.

Valsalva Maneuver

Cardiovagal baroreflex function was measured with the Valsalva maneuver. The Valsalva maneuver was performed using an analog respiratory

force pressure gauge with a one-way valve setup. It consisted of a T-shaped piece with 22-millimeter ends to which one-way valves were attached. Valsalva was measured during maximal expiratory effort starting from near total lung capacity. The pressure meter incorporated a 1.5-millimeter diameter leak to prevent glottic closure and to reduce buccal muscle contribution during measurements. The assessment required that a forceful expiratory effort be maintained for 15 seconds, reaching 40 mmHg (or as close as possible) on the pressure gauge. After a one-minute rest, the Valsalva maneuver was repeated.

Tilt-Test

For pre-testing, the tilt table was mechanically raised 45 degrees[141] for three minutes. The participant remained quiet and breathed normally for this passive tilt test. After the passive tilt test, the tilt table was lowered flat and the participant became supine. Then, five-minute ending resting measurements were taken while the participant remained still and quiet on the tilt table. For post-testing, the passive tilt test was done exactly as in pre-testing.

Paced Deep Breathing

HRV measurements were analyzed by entering the interbeat interval from the Caretaker telemetry device into Kubios HRV software during the five-minute rest periods before and after autonomic testing. We also measured HRV through paced deep breathing during pre/post. Guided by the researcher, participants inspired for five seconds and expired for five seconds, for one minute. This is known as coherent breathing, which optimizes HRV.[142] The researcher used a stopwatch to count, and guide participants' inspiration and expiration with the

researcher's hand and arm, going up for five seconds, then down for five seconds. The researcher said "inhale" and "exhale" while her arm moved. The participant knew to synchronize their breath to the researcher's hand and arm movement, due to procedural explanations to the participant upon arriving at the lab for pre/post testing.

Modified Autogenic Feedback Training Overview

For the full training protocol, each participant received eight or nine individual sessions of autonomic biofeedback and two pre/post sessions within six weeks (scheduled twice a week). Each session lasted approximately 60 minutes. The relaxation/stimulation imagery was viewed through the state-of-the-art advanced commercial VR head-mounted display Meta Quest 2. Participants began training with mental imagery and the remaining sessions were with VR imagery. For the VR sessions, participants viewed four different stimulation scenarios and four different relaxation scenarios. HR, BP (including systolic BP, diastolic BP, MAP), and interbeat interval were measured and recorded with the Caretaker 4 (Charlottesville, VA, USA).

The SCI participants remained seated in their wheelchairs during training. NI participants were seated in a chair with their feet on the ground and knees flexed at 90 degrees. After achieving a five-minute quiet baseline, HR and BP were recorded, followed by eight three-minute cycles alternating between relaxation and stimulation. For the relaxation cycles, the participant completed breathing and imagery exercises to help facilitate relaxation. The relaxing exercises included slow deep breathing with a full expiration (inspiring to a count

of 4 and expiring to a count of at least 6 making the “mmm” sound, known as *Brahmari*). This continued for 30 seconds, and then the participants were guided to focus their attention on interoceptive (inner) body sensation and then relaxing VR imagery. Next, they were guided to use stimulating imagery and *Kapalabhati* breathing during arousal trials. With this breath, the participant inspired and expired ten quick, shallow breaths through the nose with a regular breath in between, three times, then focused on stimulating imagery as well as interoceptive body sensation. After the eight cycles, the second rest period of five minutes was recorded. Participants were guided step by step throughout the training session by the researcher.

The participants were given BP goals for relaxation and stimulation: five MAP points below and five above the number recorded at the beginning of the cycle, respectively. Verbal acknowledgment of success in attaining these goals served as auditory biofeedback, allowing the participants to close their eyes and concentrate on the imagery and interoception of the body.

Two researchers recorded data during training. One researcher labeled event markers on the hemodynamic recording equipment, and the other researcher kept handwritten records of real time events. The beginning and end times of each cycle were recorded in milliseconds on the hemodynamic recording equipment. The marked events were then visible on a report of each session created by the system’s software. The training data file was then labeled by the researcher with the beginning and end times of the cycles from the information in

the report and included HR, systolic BP, diastolic BP, MAP, and interbeat interval.

During training, a second researcher observed the wrist monitor of the hemodynamic recording equipment for MAP changes and recorded them on a written record for each training session. The wrist monitor showed HR, MAP, Systolic BP, and Diastolic BP approximately every second. Mean arterial pressure was chosen as the "goal" for two reasons: first, it shows a combination of systolic and diastolic pressures with the formula (MAP = Diastolic BP + 1/3 (Systolic BP-Diastolic BP), and also because in order to verbally let the participant know if they met their goals, only one number could be accurately monitored at a time.

The hemodynamic recording equipment sampled at a default rate of 500 hertz. The number of vital signs reported in the training data file depended on the HR of the participant. For example, if the participant's HR was 60 beats per minute, the hemodynamic recording equipment recorded in the data file vital signs every second, similar to what was observed on the wrist monitor. If the HR was faster than 60 beats per minute, more recordings per second were recorded. This is why each training cycle data file was labeled with the beginning and end times, then means, maxima and minima calculated from that. Each three-minute cycle had approximately 180-360 data points. The handwritten recordings were used to confirm the highest MAP in stimulation cycles, and the lowest MAP in relaxation cycles. This data was then used to confirm how many cycles were "successful" (increase or decrease of at least 5 mmHg) in stimulation and

relaxation cycles respectively, as well as calculations of means during rest periods and training.

Pre-Training Informational Session (all verbal cues are in italics)

Explanation: *"The relaxation cycles are designed to lower your BP and the stimulation cycles are designed to increase your BP. We will continuously monitor you for safety and stop the training if your BP gets into unsafe numbers"* (systolic BP over 180 or under 80). *"We also have a physician on call at all times during every training session."* Participants with SCI were required by the supervising physician to bring a prophylactic prescription for topical nitroglycerin to each training session and pre/post-testing. All research staff were knowledgeable about autonomic dysreflexia and orthostatic intolerance.

Explanation: *"All feelings are allowed and perfect just as they are."*

Reason for Explanation: During self-generated mental stimulating sessions participants might recall an intense memory, perhaps even a trauma. While we never want to retraumatize, allowing all mental imagery takes judgment out of the picture. The social cognitive theory of self-regulation [143] on which cognitive processing therapy is based, [144] helps the limbic system engage, but not overwhelm. [145] Accepting all feelings without shame or judgment allows recognition of interoceptive physiological sensation (either relaxing or stimulating) as it begins, to potentially avoid anxiety or anger and consequent detrimental choices in life. [39] Also, sometimes the stimulating imagery may be sexual, and we want to reduce the possibility of a participant feeling shame. Allowing all feelings could encourage a participant to look at a memory more objectively, disengage it

from limbic associations, and see it as a thing that happened to them, not as something that defines them.[143] This could be very important for people with SCI, since even “non-traumatic” SCI may not be medically defined as “trauma”, but the total life change that ensues is inherently traumatic. Physiologically we are going “back and forth,” theorizing that the response of the baroreflex and arterioles is adapting for cardiovascular improvements, but also, we are going “back and forth” psychologically, which could have emotion regulation benefits.[146,145] In other words, the next time aggravating imagery comes up in “real life,” the participant could know how it feels physically, and could quickly acknowledge it, then intentionally move on to more relaxing physiological parameters to “respond” rather than “react.” This bidirectional cognitive oscillation is known as “working with opposites” in some yoga traditions.[147]

Explanation: “*You know how when you think of biting into a lemon your mouth waters? Or do you get embarrassed and you blush? These are examples of your thoughts affecting your physical body. That is exactly what we are doing in this study, except instead of those examples, you will try to move your BP with your thoughts, or what you see on a VR screen, and with your breathing.”*

Reason for Explanation: Participants must believe they can do this and have simple examples to explain the concept.

Explanation: *“Allow” your hands to be warm like it is their natural state and “make” your hands cold by picturing them in ice water, or whatever cold image works for you.”*

Reason for Explanation: Autogenic training (which inspired our protocol) describes passive concentration as “allowing” warmth vs active concentration as “making” hands cold.[148,119]

Explanation: *“During the body sensing cues, for example, I will guide you to move your attention to the space between the eyes, then the scalp, jaw, space between the lips, and the shoulders. You don’t have to change or do anything, just be curious about and notice the area.” “After you have been in your imagery for a while, I will say ‘Notice how your body feels.’ You can still be in your imagery, just take a brief pause to notice — it could be your whole body or just a part. You may feel a contraction in the stimulating part and a melting opening in the relaxing part, whatever and wherever you feel, your way is the right way.”*

Reason for Explanation: This is modeled on Richard Miller’s iRest post-traumatic stress therapy protocol [149] noticing body sensation as a way to focus the mind and move away from the ruminating default mode brain network (all the thoughts evolutionarily developed to protect us, which are mostly “worries”).[150]

Explanation: “*When I say, ‘Use your senses to experience it’, I don’t mean all at the same time, maybe just notice, what you see, then smell, then touch, then hear. You don’t have to do each sense every cycle but do be sure to include senses other than what you see. Your way is the right way.”*

Reason for Explanation: “Using your senses” could be confusing or stressful to understand. Also, this kind of mental focus can be very challenging at first. It is important to make the participants feel confident that their way is the right way.

Explanation: (for individuals with SCI): *"When I say, "make your hands cold" or "allow your hands to be warm" you may have little or no sensation there, just use your imagination. Same with pulling the belly in on the fast breathing, that may not work so well for you. Again, imagine it. Even if you just imagine it, the muscle fires."* [151]

Reason for Explanation: It is important to respect the possibility of atypical sensations in individuals with SCI.

Table 1 below details the timing of the training cycles.

3-minute relaxation cycle	3-minute stimulation cycle
00:00-00:30 relaxation breathing: *"Inhale for 4 and 'mmm' out for at least 6, long exhale"*	00:00-00:30 stimulation breathing: *"Now the mosquito out of the nose breath" "soft belly 1 and"* (breathe together) *"relax. inhale. exhale, inhale, and"* (3 sets of 10)
00:30-01:00 interoception: *"Notice the distance between your eyes, space between the lips, scalp, jaw, shoulders."*	00:30-01:00: interoception: *"Notice how your body feels."*
01:00-02:30 relaxing imagery: *"Now go to your relaxing imagery. Use your senses to experience it."*	01:00-02:30 stimulating imagery: *"Now go to your stimulating imagery. Use your senses to experience it."*
02:30-3:00 autogenics: *"Allow your hands to be warm and heavy."*	02:30-03:00 autogenics: *"Make your hands cold."*
3:00 verbal feedback: *"You met your BP goal"* or *"You did not meet your BP goal, but you are doing the training perfectly."*	3:00 verbal feedback: *"You met your BP goal"* or *"You did not meet your BP goal, but you are doing the training perfectly."*

Table 1: Stimulation and relaxation training cycle details (verbal instructions in italics)

Breathing Exercise Details

Type of Breath: *Brahmari* (in for 4, out for 6 with "mmm" sound)

Number of Breaths at a Time: 3

Duration: approx. 30 seconds

Frequency: four times, once at the beginning of each relaxation cycle

Effects of Breath on Nervous System: decreases BP [103,104]

Verbal Explanation to Participant: *"We will call this breath the "mmm" breath. This breath is to lower your BP. Inhale through your nose gently for 4 counts into your belly, do not take a giant breath, just almost effortless: like a bun rising in an oven. Gently cap off the breath, don't push down. Exhale a semi-loud and low "mmmm" (It will take approximately 6 counts for a full yet not forceful exhale but take all the time you need to exhale).*

Demonstrate it. Practice it together.

Type of Breath: *Kapalabhati* (fast, "bellows" breath)

Number of Breaths at a Time: ten, three times

Duration: thirty seconds

Frequency: five times, once at the beginning of each stimulation cycle

Effects of Breath on the Nervous System: increases BP [105]

Verbal Explanation to Participant: *"This is a breath to increase BP. We will do three rounds of breathing, and I will do it with you. First, take a quick, gentle one-count soft belly inhale. Keeping your hand on your belly can help but it is optional. Another word for this breath is "bellows" breath, so it's not a deep inhale and a slow, choppy exhale. You do inhale during the fast ten belly breaths but focus on the exhale and the inhale will happen by itself. I will say, "Soft belly one," then breathe the ten breaths with you. Then "relax, inhale, exhale, inhale, and" (these are not full breaths, just quick ones - having a slower breath in between the ten fast ones is to increase safety) we do three sets of the ten breaths. We call this one the "mosquito out of the nose" breath because that makes it easier to understand."* Demonstrate it. Practice it together.

Heart Rate Variability Measurements

How to get a PDF report from Kubios standard software:

1. Download secondary vitals in the hemodynamic measurement unit's log (this has the interbeat interval column in it) in CSV UTF file format.

2. Open each column separately in Kubios standard software as a custom ASCII file.

3. Check "none" in the time index column.

4. Import and save the data in cloud storage and encrypted computers.

We measured HRV during five-minute baselines and paced deep breathing. SDNN is the standard deviation of normal-to-normal beats and represents the time between heartbeats. Frequency spectra represent the amplitude of the

heartbeats. The three different frequency measurements we used represent mechanisms of HRV changes. We used the natural log version of the frequency measurements because it approximates the normal distribution of data due to our low sample size. High frequency HRV (HF), represents vagal contributions to HRV.[152] Low frequency (LF) measurements represent baroreflex sensitivity,[153] and very low-frequency measurements (VLF) represent changes made via the renin-angiotensin-aldosterone (RAAS) system.[154-156]

Statistical Analysis

All measured outcomes: systolic BP, diastolic BP, MAP, HR, and HRV measured in the standard deviation of normal-to-normal beats (SDNN), HRV measured in (HF), (LF), and (VLF) were summarized with means and standard deviations, minima, and maxima. Summary statistics were calculated by the study group (cervical SCI and NI). Outcome data were also summarized graphically with boxplots for univariate data and scatterplots for bivariate data. All hypothesis tests were conducted at the 0.05 level, and all analyses were conducted using the open-source R software environment (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, v 4.3.2).

CHAPTER III

CASE REPORT:[1] AUTOGENIC BIOFEEDBACK TRAINING IMPROVES AUTONOMIC RESPONSES IN A PARTICIPANT WITH CERVICAL MOTOR COMPLETE SPINAL CORD INJURY[157]

Introduction

The autonomic nervous system innervates smooth, cardiac, and skeletal muscle, secretory glands, and metabolic and immune cells to regulate homeostasis in essential physiological activities such as digestion, respiration, cardiovascular function, and some endocrine functions. [13] Neurons in the brain stem modulate the firing of the sympathetic preganglionic neurons located alongside the spinal cord between T1 to L2 vertebral segments. [13,67] The sympathetic preganglionic neurons then send projections either to peripheral sympathetic ganglia that control the diameter of blood vessels or to the adrenal medulla to secrete catecholamines directly into the bloodstream.[13] These two actions are the primary modulators of blood vessel diameter and total peripheral resistance, regulating hemodynamic homeostasis. [13,158] In addition to the central and peripheral nervous systems, the enteric nervous system regulates digestive function.[159] The intrinsic nerve plexuses, the submucosal plexus, and the myenteric plexus are the two major nerve fiber networks that innervate the digestive tract, and together they are termed the enteric nervous system.

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Individuals with cervical or upper thoracic SCI often suffer debilitating secondary complications resulting from aberrant autonomic nervous system activity,[50-53] and have disruptions in enteric nervous system activity.[52] Studies in humans[54] and animals[54,55] demonstrate that lesions on the cervical or upper thoracic segments of the spinal cord (i.e., T6 and above) result in damage to sympathetic preganglionic neurons, causing sole reliance on sympathetic activity below the level of the injury, causing autonomic dysfunction in multiple systems. Dysautonomia in SCI can cause multiple symptoms, including autonomic dysreflexia,[51] orthostatic and arterial hypotension,[56] cardiac dysrhythmias, bradycardia,[57] difficulties with psychogenic sexual arousal,[58] attenuated cardiovascular response to exercise, incontinence,[59] and chronic pain.[60] Additionally, gastrointestinal[160] and cardiopulmonary disorders[161-163] are among the most prevalent sequelae after SCI. It has been documented that SCI interrupts descending pathways to the lumbosacral neurons that control colonic motility, defecation[164-167], and upper gastrointestinal dysmotility.[168] Recovery of normal autonomic cardiovascular function is most frequently ranked to be a higher priority than regaining motor function among people with SCI.[61]

After cervical or upper thoracic SCI, the above pathways are interrupted, reducing sympathetic tone below the injury and leaving the sympathetic preganglionic neurons exclusively controlled by spinal reflexes, which eventually become hyperresponsive.[59] Parasympathetic outflow remains unopposed through the intact vagus nerve.[59] This loss of central control of sympathetic preganglionic neurons results in both arterial and orthostatic hypotension via

abolished compensatory vasoconstriction, especially in large vascular beds, like skeletal muscle and splanchnic region vessels, with concomitant reduced venous blood return.[62] Orthostatic hypotension is defined as a decrease in systolic blood pressure of 20 millimeters of mercury or more or diastolic blood pressure of 10 millimeters of mercury or more[63] when sitting up from a lying down position, which can compromise blood flow to the brain and cause syncope, nausea, deficits in cognitive performance, fatigue, and increased susceptibility to pressure ulcers due to reduced tissue perfusion.[64] In able-bodied individuals, changing from supine to upright causes only slight changes in heart rate and blood pressure.[66] In people with SCI, particularly with higher injuries, blood pressure usually decreases and heart rate increases.[66]

This opposite response is due to the interruption of descending sympathetic vasomotor tracts.[67] This changes both excitatory and inhibitory sympathetic control, reduces sympathetic tone below the injury, changes the morphology of the sympathetic neurons, alters plasticity in spinal circuits, and creates hyper-responsive alpha adrenoreceptors.[54,68]

Hypotension is only one side of the unique hemodynamic dichotomy of people with SCI. The hyperexcitable state of spinal reflexes prevents baroreflex modulation of sympathetic preganglionic neurons, leading to the dangerous hypertension of autonomic dysreflexia, which occurs regularly in people with tetraplegia, accounting for ninety-one percent (91%) of motor complete cases AIS A-B and among twenty-seven percent (27%) of cases with SCI motor incomplete SCI AIS C-D.[69] Autonomic dysreflexia continues unabated until an

aggravating stimulus (e.g. bladder distension or pressure sore) is removed.[59] Autonomic dysreflexia often occurs multiple times a day with headaches and sweating symptoms, yet sometimes without symptoms.[70]

In addition to maladaptive plasticity and hyperresponsive reflexes, peripheral changes impair hemodynamics after SCI. Lower blood pressure, lower catecholamines,[169] and enhanced sensitivity of adrenergic receptors in peripheral vasculature impair myogenic activity in arterioles.[73] In addition to hemodynamic detriments directly caused by sympathetic changes, other causes are hyponatremia and low plasma volume, cardiovascular deconditioning, and motor deficit leading to loss of skeletal muscle pumping activity.[62] There is a need for effective non-invasive and non-pharmaceutical interventions to ease these myriad dysautonomic consequences in people with SCI.[170]

Autogenic Feedback Training Exercise (AFTE) combines autogenic therapy, which uses cognitive imagery to control physiologic responses[119], and biofeedback which provides visual and/or auditory feedback of responses to stress (e.g. HR).[120] This combination has shown greater efficacy and decreased learning time to control physical responses than using the modalities separately.[121] Space motion sickness has been an identified ailment beginning with the early Apollo space flights through the Space Shuttle program.[4] Up to sixty-seven percent (67%) of astronauts experience nausea, vomiting, loss of appetite, sleepiness, and lethargy of space motion sickness during the first three days of space flight, shortly after weightlessness occurs.[4] The cause is multifactorial, involving components of fluid shifts from weightlessness, a sensory

conflict between optical and vestibular input, and enteric nervous system changes.[4] The autonomic nervous system plays a significant role in the pathophysiology of this variant of motion sickness.[4] The primary feature is an activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system, as well as changes in the myoelectric and mechanical activity of the stomach.[171,172]

Cowings et al. in a 2000 study of AFTE with 33 NI men, reported fewer symptoms of nausea and orthostatic hypotension and improved HRV [173] compared to their counterparts receiving promethazine treatment.[121] AFTE has also been used successfully to modulate autonomic and enteric responses in patients with gastrointestinal motility disorders.[136,174] We present a proof of concept study to determine if AFTE could be an effective and non-invasive alternative to improve autonomic responses in people with SCI.

Materials and Methods

Participants

A convenience sample of two participants was used in this proof-of-concept study. The participant with SCI was a 34-year-old female, two years post-injury, chronic cervical sensory and motor complete (C5/6, ASIA A) height 165 cm, and body weight 77 kg. Clinical characteristics included spastic paralysis, impaired sweating below the injury, depression, and lower extremity edema. She had a colostomy and a Mitrofanoff's procedure. Her daily medications included Midodrine five milligrams for hypotension, Gabapentin 300 mg for neuralgia, and Trazodone and Escitalopram 50 and 20 mg, respectively

for depression. The NI participant was a normotensive 52-year-old male, with a height of 163 cm, and a body weight of 81 kg.

Equipment

HR and BP were recorded using a Dinamap monitor model 8100; (Critikon, Inc. Tampa, Florida, USA). Microvascular blood volume was monitored in the middle finger of the left hand using an infrared light-emitting diode probe connected to a Meda-Sonics photoplethysmograph model PPG-13 (Mountain View, California, USA). Gastric electrical activity was monitored via an electrogastrogram which measures gastric myoelectrical activity via three electrodes attached to the skin along the gastric border.[175] Transmitted electrical impulses were then detected and recorded using a four-channel recording device Sandhill/Diversatek (Milwaukee, Wisconsin, USA). Changes in BP, HR, gastric electrical activity, respiratory rate, and microvascular blood volume were measured during training.

Modified Autogenic Feedback Training

The SCI participant remained seated in her wheelchair during training. The NI participant remained seated in a comfortable chair with his feet on the ground and knees flexed at 90 degrees. After achieving a stable five-minute baseline, HR and BP were recorded, followed by thirty minutes divided into five cycles alternating both relaxation and stimulation. For the relaxation cycles, the participant was instructed to complete breathing and imagery exercises to help facilitate relaxation. The relaxing exercises included slow deep breathing with a full exhale (inhaling to a count of four and exhaling to a count of six), continuing

for 30 seconds, and then focusing attention on interoceptive body sensation and relaxing imagery. Then they were instructed to use stimulating imagery and *kapalabhati* breathing during arousal trials. *Kapalabhati* breathing is a yoga breathing technique that involves fast, shallow abdominal respiratory movements and has been shown to modulate cardiovascular responses in NI individuals.[105] With this breath, the participant exhaled and inhaled ten quick, shallow breaths through the nose with a regular breath in between, three times, focused on aggravating imagery as well as an interoceptive body sensation. Each cycle consisted of a three-minute interval of relaxation followed by three minutes of stimulation. After the five cycles, the second baseline of five minutes was recorded.

The participants were given HR goals for relaxation and stimulation: Five beats per minute below and five above baselines recorded at the beginning of the session, respectively. Verbal acknowledgment of success in attaining these goals served as auditory biofeedback to allow the participants to close their eyes and concentrate on the body's imagery and interoception. Blood pressure feedback was also given but without specific numeric goals.

Statistical Methods

All measured outcomes: systolic BP, diastolic BP, MAP, and HR were summarized with means and standard deviations, minima, maxima, and percentage of change. Summary statistics were calculated by the study group (one participant with cervical SCI and one NI participant). Outcome data were also summarized graphically with boxplots for univariate and bivariate data.

Results

Microvascular Blood Volume

Figure 3 shows that the participant with SCI's microvascular blood volume in the finger decreased a mean of 23% across eight cycles while Fig. 4 shows the NI participant's decreased a mean of 54% from the beginning to the end of the stimulation cycles in each of eight trainings.

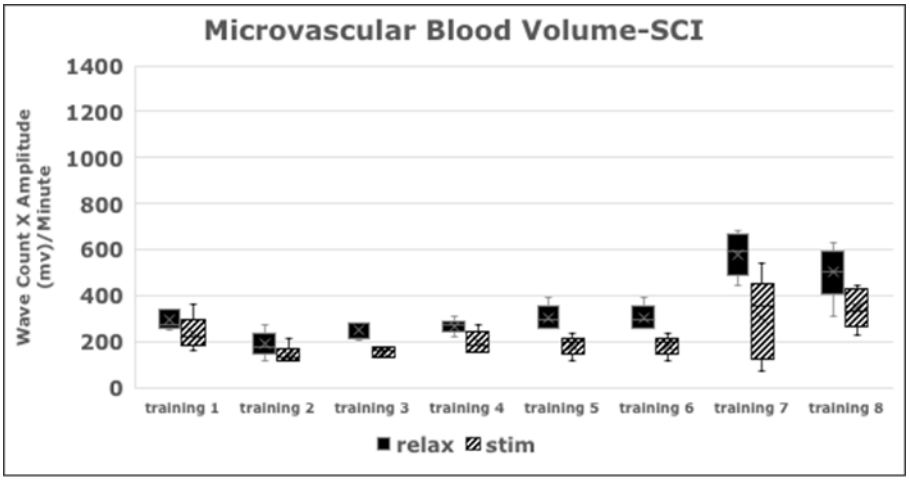

Figure 3: Case study participant with SCI's microvascular blood volume in the finger, measured with photoplethysmography, decreased by a mean of 23% from relaxation cycles to stimulation cycles. The box represents the interquartile range, the lines extending up and down away from the box end in maxima and minima respectively. The line in the center of the box is the median, and the "x" denotes the mean.

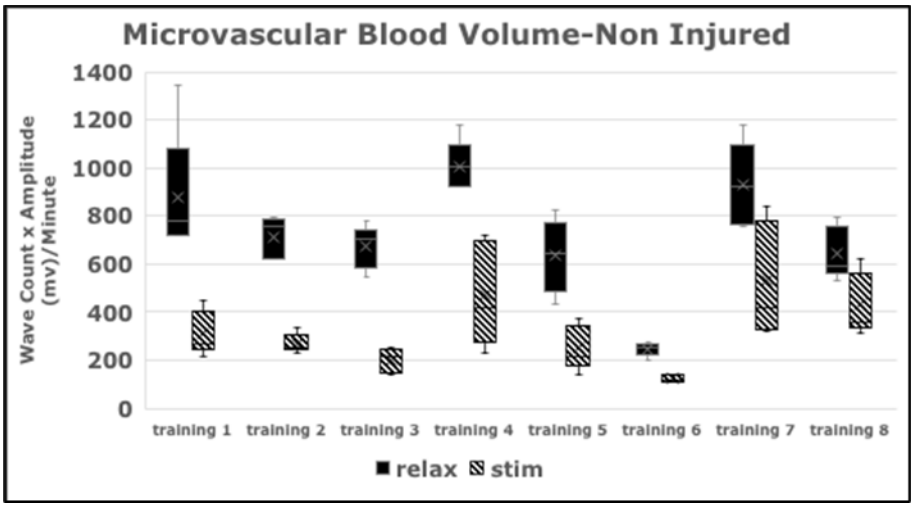

Figure 4: NI participant's microvascular blood volume in the finger, measured with photoplethysmography, decreased by a mean of 54% from relaxation cycles to stimulation cycles.

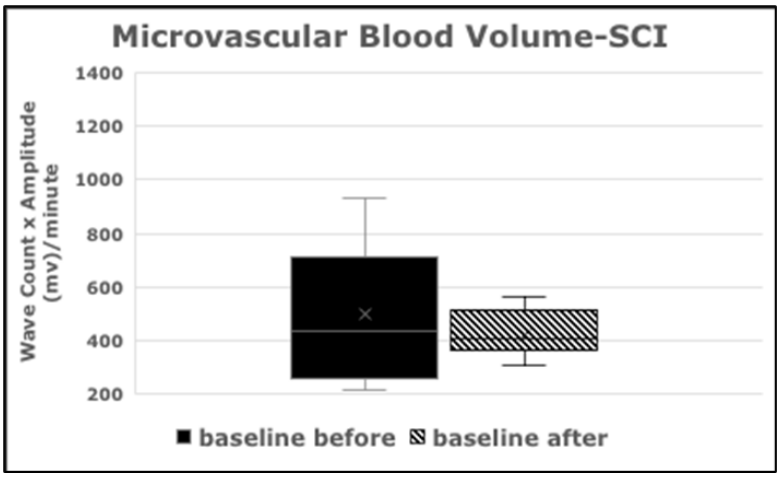

Figure 5: Participant with SCI's microvascular blood volume in the finger decreased and decreased variability in the five-minute rest periods before and after each of the eight trainings.

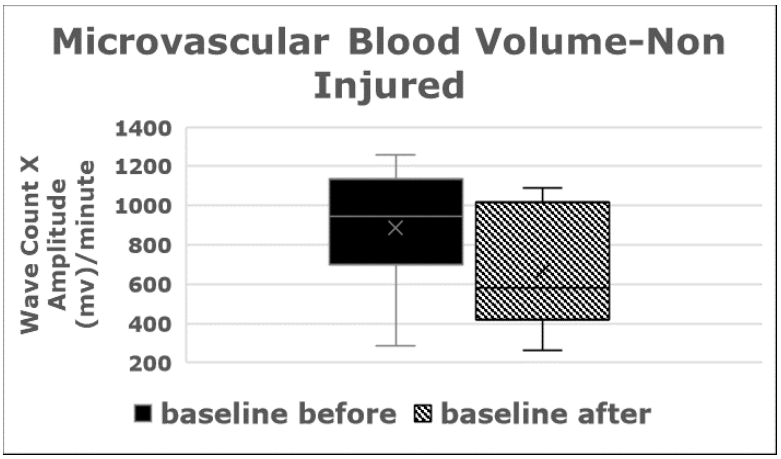

Figure 6: NI participant's microvascular blood volume in the finger decreased in the five-minute rest periods before and after each of the eight trainings.

Gastric Electrical Activity

Changes in gastric electrical activity were found in the participant with SCI but not in the NI participant.

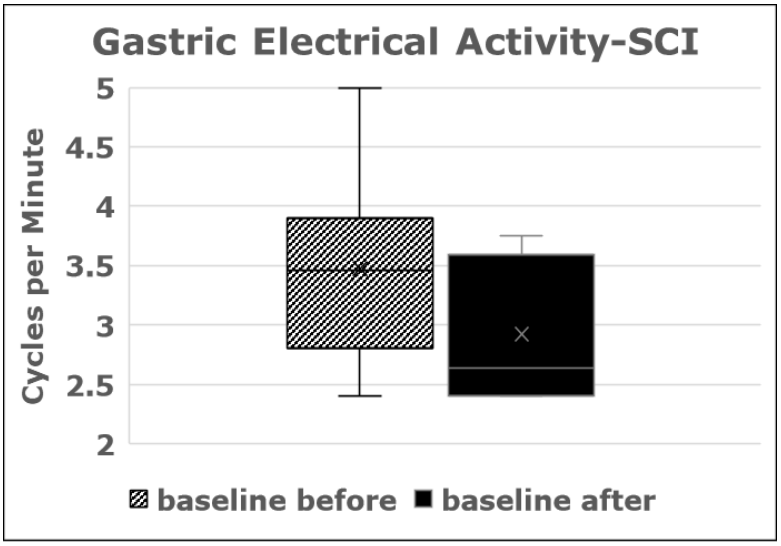

Figure 7: In the five-minute rest periods before and after each training, the participant with SCI's gastric electrical activity, measured via electrogastrogram, decreased and decreased variability, becoming progressively closer to the normal range of three cycles per minute.

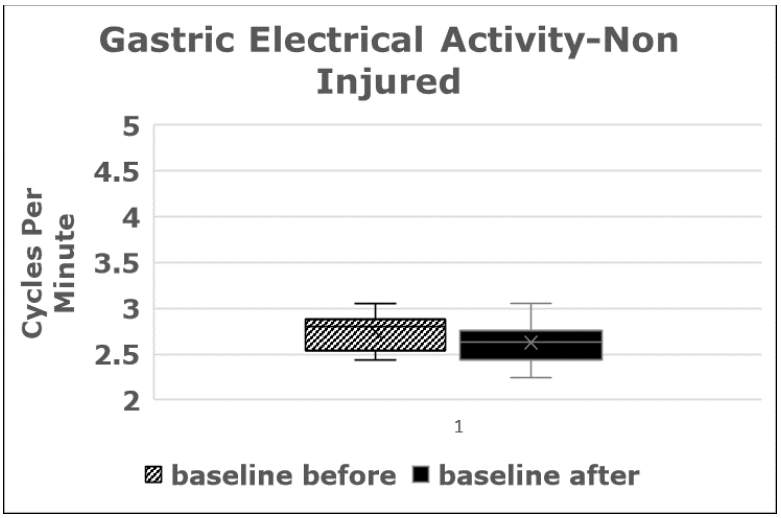

Figure 8: In the five-minute rest periods before and after each training, the NI participant showed no change in gastric electrical activity, measured via electrogastrogram.

Heart Rate

Figure 9 shows that the participant with SCI's baseline HR decreased, and the NI participant's HR also decreased (Figure 10).

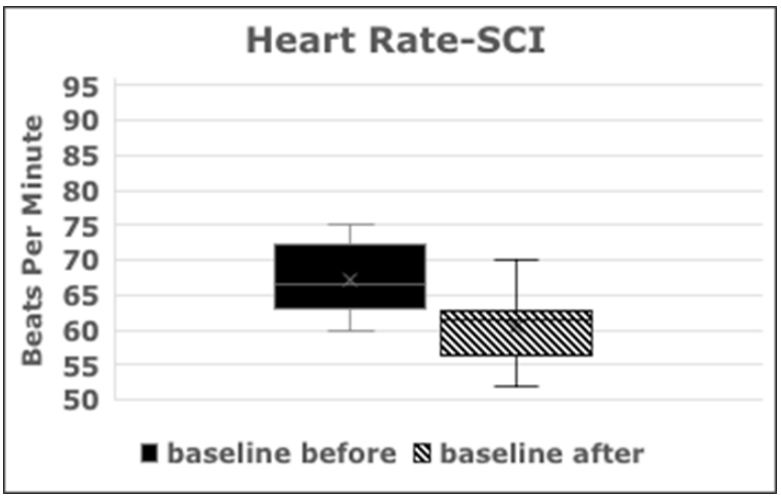

Figure 9: The participant with SCI's baseline HR decreased in the five-minute rest periods before and after each of the eight trainings.

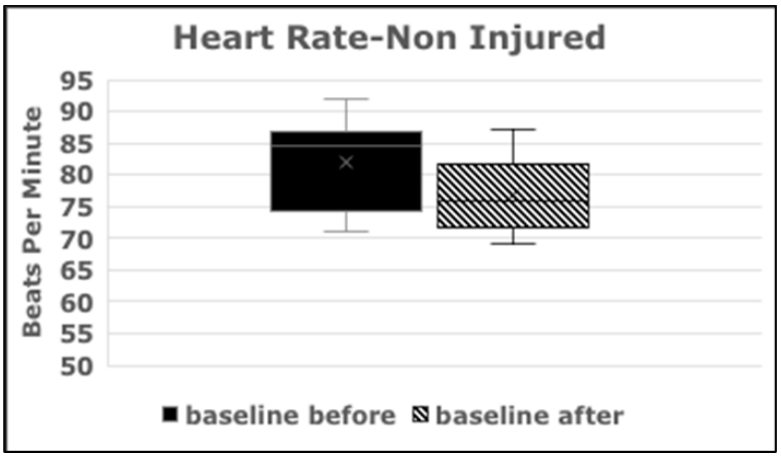

Figure 10: The NI participant's baseline HR decreased in the five-minute rest periods before and after each of the eight trainings.

Mean Arterial Pressure

In Fig. 11, the participant with SCI's MAP increased and decreased variability while the NI participant showed no change (Figure 12).

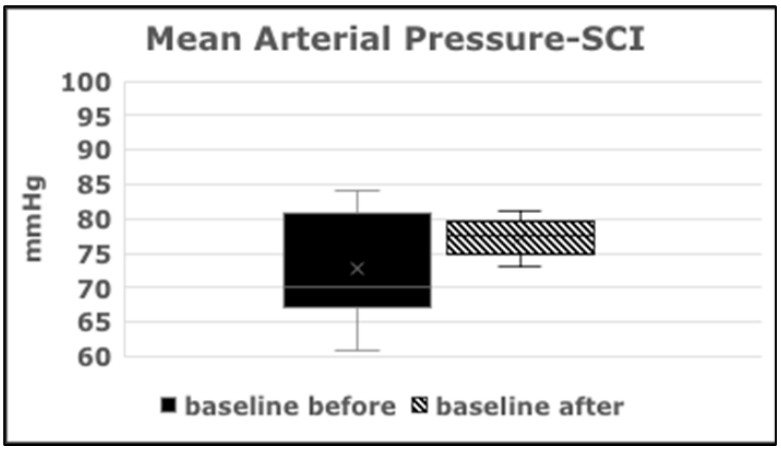

Figure 11: The participant with SCI's baseline MAP increased and decreased variability in the five-minute rest periods before and after each of the eight trainings.

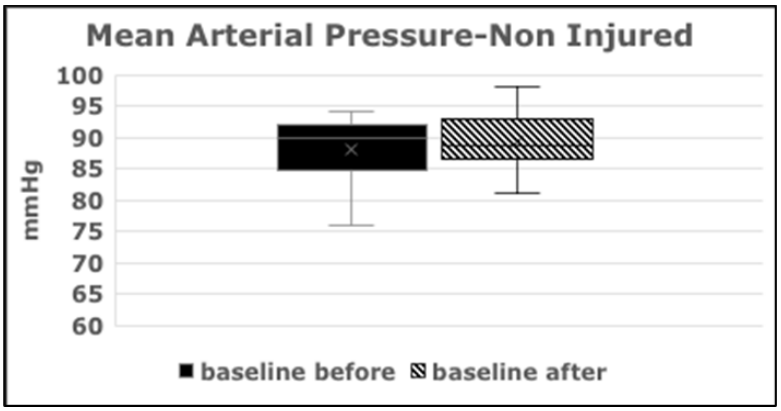

Figure 12: The NI participant's MAP showed no change in the five-minute rest periods before and after each of the eight trainings.

Discussion

The literature on BP, biofeedback, and SCI is scarce.[100,101] In one case study from 1977 the participant successfully raised and lowered his BP and sustained the learned change.[100] Ince conducted a study on two participants with SCI suffering postural hypotension, showing that biofeedback increased BP from hypotensive to normotensive rates, also with a sustained change.[101] The possibility of a practical, safe tool that could improve and maintain healthier hemodynamic variables could minimize patient dependence on pharmacological interventions and decrease adverse physiological events.

When designing this protocol, we looked at other factors that could change blood pressure besides sympathetic-mediated vasoconstriction, such as breathing. With our fast-breathing technique *kaphalabhati,*[105] there is less activation of pulmonary stretch receptors, so less vagal influence, plus it varies intrathoracic pressure with the respiratory pump to increase blood pressure[105]

through baroreflex modulation. We chose an extended exhale breath in the relaxation cycles to increase vagal stimulation.

We also used both stimulating and relaxing imagery, hypothesizing that cognitive changes, inducing and then mitigating stressful thoughts, would increase and decrease BP. These oscillations between stimulation and relaxation could “train” the baroreflex and create more normotensive autonomic responses to BP changes. This training also takes advantage of the unique nervous systems of people with SCI: since their tactile and proprioceptive inputs are reduced, they may rely more on visual cues for learning.[138]

One of the possible mechanisms that could explain the volitionally increased and decreased BP of the SCI participant is improved baroreflex sensitivity, possibly through mitigated arterial stiffness.[176] The microvascular blood volume changes indicate a possible sympathetic role since photoplethysmograph amplitude directly relates to vascular distensibility.[177] Although there are many other intrinsic vasoactive substances to consider, it is unlikely the response would be due to increased epinephrine or norepinephrine, as previously shown.[169] Other possible mechanisms are a large and rapid release of vasopressin creating a pressor effect, spinal reflex or peripheral alpha adrenoreceptor hyper-responsiveness, or cortisol fluctuations due to the stressful imagery. Another possibility is increased excitatory or inhibitory vagal response through breath modification or conscious interoception controlled by cognitive connections to the vagus nerve.[73]

This case study represents the first indication that training participants with SCI using the modified AFTE intervention has the potential to improve quality-of-life with easy-to-achieve effects either in the clinic or at home through autonomic response adaptation. A key limitation of this proof-of-concept study is the small sample size of only two participants that is not matched in age and sex between the participant with SCI and the NI individual. Future studies should be conducted in larger sample sizes for SCI and NI participants matching sex, age, and body size, feedback specified to BP changes, continuous BP and HR monitoring, quality-of-life surveys, and autonomic assessments such as head-up tilt, HRV, Valsalva maneuver, and cold pressor test.

CHAPTER IV

COMPARING VIRTUAL REALITY TO MENTAL IMAGERY FOR BLOOD PRESSURE AND HEART RATE VARIABILITY IMPROVEMENT IN PEOPLE WITH AND WITHOUT SPINAL CORD INJURY

Introduction

Immersive VR uses a head-mounted device and full immersion into the 360-degree virtual world. It has been found effective for managing hypertension,[112,178] but, to our knowledge, no literature exists on the use of immersive 360-degree videos or VR for the effect of BP and HR changes after SCI. Mental imagery is a representation of sensory information in the mind without a direct external stimulus.[179] Mental imagery is more challenging for the brain to generate than all forms of retinal perception, including VR.[114] We hypothesized that biofeedback using immersive 360-degree VR videos with headsets would effectively modulate BP. Thirty-one participants, including 14 individuals with SCI and 17 NI, participated in this study. Participants were asked to watch eight short, immersive 360-degree videos, alternating between stimulating and relaxing to raise then lower MAP by at least 5 mmHg respectively.

Biofeedback has been used to modulate both BP and HRV.[180-182] Immersive VR has been successfully used for BP modulation.[112,178] To our knowledge, there has been no clear evidence that biofeedback combined with VR is more effective than traditional biofeedback, though survey data indicated that it increased treatment motivation and attentional focus.[183] Several VR stress

studies have included autonomic measurements. [178,184,185] One study compared the effects of immersive VR experiences in two scenes of elevator rides, one in a typical indoor elevator ride and the other in an elevator located outside the building. Participants watching the scene with the elevator on the outside of the building increased HR, galvanic skin response, and decreased HRV, indicating an increased stress response. However, no significant change in BP was found. [184] Different BP results were found in another study using calm nature scenes. This study compared four scenarios: VR with and without audio, audio only, or the participants just sitting quietly, given no direction. BP was significantly lowered in only the audiovisual VR scenario.[178]

Park et al. compared two mental stressors in veterans with post-traumatic stress disorder (PTSD) and a control group without PTSD. The two stressors consisted of watching VR imagery of military combat and performing mental arithmetic. The veterans with PTSD had significantly more muscle sympathetic nerve activity during both stressors than controls. They also had significantly higher increases in HR during VR, and diastolic BP during mental arithmetic than controls.[185] However, neither group showed a significant difference in sympathetic response to the cold pressor test. The cold pressor test is more a physical stressor than a mental stressor. In the cold pressor test, baroreflexes do not regulate sympathetic activation,[186] suggesting that mental stress affects baroreflex sympathetic augmentation more than non-mental stress.

There are important differences between visual perception (with or without VR) and mental imagery. Mental imagery is “the creation of a perceptual

representation in the absence of retinal input.*"* [187] Modern imaging techniques have uncovered many overlapping brain regions in the functioning of both. They both produce the experience of "seeing," though mental imagery is usually described as less detailed and requiring more effort.[188] We know there are separate mechanisms between the two, from people with the condition of aphantasia who are unable to create mental imagery, yet their retinal vision works perfectly. Conversely, there are people with very vivid mental imagery, for example, someone with an eidetic, photo-like memory, and others who are burdened by lifelike hallucinations, such as some people with PTSD or schizophrenia. People with schizophrenia have an overabundance of visual brain connections — too many to gauge which perceptions are more "real."[189]

Visual perception begins with the simple (such as a shadow that could be a snake) to complex (such as quickly knowing that the shadow is only a rope). This continuum has evolved to keep us safe, and we focus on and become conscious of whatever is most salient to us personally. This difference in salience is why there is no set "reality," only different perceptions. Actual brain processing of retinal perception and mental imagery mirrors this simple to complex continuum: modern imaging studies have shown that the beginning of visual perception is mostly concentrated on the superficial cortical layers of the brain area V1 and is more excitatory to surrounding synapses. Mental imagery, in contrast, begins in executive brain areas, has additional connections in the deeper layers of the visual cortex, and is more modulatory. Mental imagery is more "top down" and visual perception is more "bottom up."[114] Because of this,

mental imagery for most people poses greater challenges and increases engagement of complex and executive brain areas.[114]

Some forms of meditation use mental imagery.[149] Meditation has been shown to lower BP via the relaxation response.[190,191] Eliciting the relaxation response (and meditation) is as simple as sitting quietly and still with closed eyes, allowing thoughts to come and go.[192,193] Transcriptome studies of the relaxation response have found it elicits positive changes in metabolism, insulin, and inflammation, in addition to BP changes as effective as pharmaceutical interventions.[190] The likely mechanism for these BP changes is increased nitric oxide, a vasodilator.[194] Nitric oxide vasodilates via postganglionic sympathetic neurons and antagonism of noradrenergic signaling.[195-198] When people are not meditating or focusing their attention, they use the default mode network of the brain.[199] Mindfulness is focusing on one's present-moment feelings, mind, and/or body, and is usually measured via qualitative studies.[200] It can also be measured with functional magnetic resonance imaging which during mediation and mindful states shows decreased functioning in the default mode network. [199]

SCI significantly affects BP, and previous studies have shown that mental imagery is beneficial for BP modulation in this population. [6,101] However, mental imagery can be difficult to maintain and requires more executive brain function than retinal perception, which includes VR. Because people with SCI are highly likely to be diagnosed with PTSD due to their injury,[201] self-generated mental imagery has the potential to retraumatize. For these reasons, and because there

is a research gap, we wanted to compare VR to mental imagery for hemodynamic modification.

Materials and Methods

Participants

Seventeen women and 14 men (N=31) age (38±14) participated in this study. Fourteen participants had a sustained chronic SCI (more than 12 months since injury) and 17 were NI. Participants with SCI were classified using the American Spinal Injury Association Impairment Scale (AIS) as follows: eight were cervical motor complete (AIS A-B), five were cervical motor incomplete (AIS C-D), and one was thoracic motor complete. The participants with SCI were between the ages of 24 and 67 (44±14). NI participants were between the ages of 21 and 65 (32±14). All participants were in stable medical condition without cardiopulmonary disease and were non-smokers. Table 2 shows the participants' demographics and clinical characteristics.

Participant	Sex	Age	Injury Level	AIS	Years Since Injury	Height (cm)	Weight (kg)
1	F	22	non-injured	N/A	N/A	170	63
2	F	22	non-injured	N/A	N/A	170	64
3	F	21	non-injured	N/A	N/A	158	50
4	F	48	non-injured	N/A	N/A	170	75
5	F	33	non-injured	N/A	N/A	180	82
6	F	40	non-injured	N/A	N/A	158	80
7	F	65	non-injured	N/A	N/A	165	86
8	F	22	non-injured	N/A	N/A	165	68
9	F	27	non-injured	N/A	N/A	188	102
10	M	22	non-injured	N/A	N/A	181	90
11	M	47	non-injured	N/A	N/A	163	82
12	M	53	non-injured	N/A	N/A	183	98
13	M	25	non-injured	N/A	N/A	178	65
14	M	28	non-injured	N/A	N/A	185	91
15	M	22	non-injured	N/A	N/A	178	80
16	M	23	non-injured	N/A	N/A	173	72
17	M	24	non-injured	N/A	N/A	173	70
18	M	34	C3	A	3	180	109
19	M	53	C3	C	6	185	84
20	F	32	C4	A	5	170	84
21	M	28	C4	B	3	180	118
22	M	67	C4	C	52	173	66
23	F	62	C4	C	3	170	75
24	F	36	C4	C	19	160	70
25	F	60	C4	D	1	163	99
26	M	42	C5	B	4	178	61
27	F	34	C5	A	3	165	81
28	M	24	C5	A	2	188	104
29	F	50	C6	A	34	174	46
30	F	35	C6	B	3	150	95
31	F	55	T7	A	16	158	53
Mean±SD		37±15			11±15	172±10	79±17

Table 2: Clinical characteristics of participants (N=31) in VR/mental comparison of Modified Autogenic Feedback Training

Equipment

BP, HR, and interbeat interval were measured and recorded with Caretaker Continuous BP Monitor 4 (Charlottesville, VA, USA). The interbeat interval was then filtered at a medium threshold to eliminate any data with excessive ectopic beats using Kubios HRV software (Varsitie 22, 70150 Kuopio, FINLAND). The

VR head-mounted device was Meta Quest 2 (Meta Platforms, Menlo Park, California, USA).

Modified Autogenic Feedback Training

The lab space was accessible for people in wheelchairs, with two researchers per participant at a time in attendance. The door was closed, the room quieted, and the lights dimmed. After the study details were explained and written consent obtained, participants attended two sessions on separate days within one week. They were randomly assigned to their first session as either VR or mental. Sessions began with a five-minute quiet baseline, then eight three-minute cycles alternating between relaxation and stimulation. NI participants were seated in a non-reclining chair with their feet on the ground, and knees flexed at 90 degrees. Participants with SCI were seated upright in their wheelchairs. BP was measured with a manual sphygmomanometer and cuff to calibrate the telemetric BP measurement device, which continuously monitored BP and HR.

For the relaxation cycles, participants completed breathing exercises and imagery to help facilitate relaxation and tried to decrease their BP. For the stimulation cycles, participants completed breathing and imagery exercises with the intent to increase their BP. After the eight cycles, a five-minute rest period was recorded. Participants were guided step-by-step throughout the training session by the researcher. For the mental training session, participants were asked to picture in their minds a safe, comforting image during relaxation cycles, or an exciting or frustrating image during stimulation cycles. For the VR sessions,

the headset was put on before the beginning of the first training cycle and left on for the remainder of the training session. The three-minute, 360-degree videos were relaxing (e.g., beach scenes, campfires) and then stimulating (e.g., sharks, horse races).[202] The video playlist was consistent for all participants.

The participants were given BP goals for relaxation and stimulation: five MAP points in mmHg below and five above the number recorded at the beginning of the cycle, respectively. Verbal acknowledgment of success in attaining these goals served as auditory biofeedback, allowing the participants to close their eyes, except when watching VR, to concentrate on their intention to modify BP. Since BP naturally varies with spontaneous respiration[203], and participants' goals were to move their BP, we measured the difference in variation during training as compared to the five-minute rest periods before and after training. We also measured whether BP variability correlated with HRV.

A researcher gave verbal instructions to the participant and recorded MAP at the beginning of the cycle, the MAP goal, whether the goal was achieved, when, and the highest or lowest MAP in the cycle. A second researcher marked events on the telemetric physiological recording unit. The VR images were cast onto a laptop and advanced using the Meta Quest 2's right-hand control apparatus, just behind the participant. A physician specializing in SCI medicine and rehabilitation research was on site or in the same building during all the sessions. The training was discontinued if systolic BP was over 180 or under 80 mmHg.

Statistical Methods

All measured outcomes: systolic BP, diastolic BP, MAP, HR, HRV (SDNN, HF, LF, VLF) were summarized with means and standard deviations, minima, and maxima. Summary statistics were calculated by the study group (cervical SCI and NI). Outcome data were also summarized graphically with boxplots for univariate data and scatterplots for bivariate data. All hypothesis tests were conducted at the 0.05 level, and all analyses were conducted using the open-source R software environment (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, v 4.3.2).

Results

Figure 13 illustrates an example VR training session for a participant with C6A SCI. Figure 14 illustrates the same participant's mental training. The blue and red areas are the alternating relaxation and stimulation cycles, respectively. The gray areas are the five-minute rest periods before and after training. In these graphical representations of systolic and diastolic BP, acute changes which occurred during or just after the breathing portion of the training can be seen in both the relaxation cycles and the stimulation cycles, yet the times in between the acute changes appear to have less extreme variation in mmHg than in the rest periods before and after training. These graphical representations are from only one participant. When the data from all participants was included, MAP variability increased significantly from the rest period before training to during training, details of which are forthcoming in the next sections. In Figures 13 and

14, the times between acute changes during training notably appear “smoother”, with less variability.

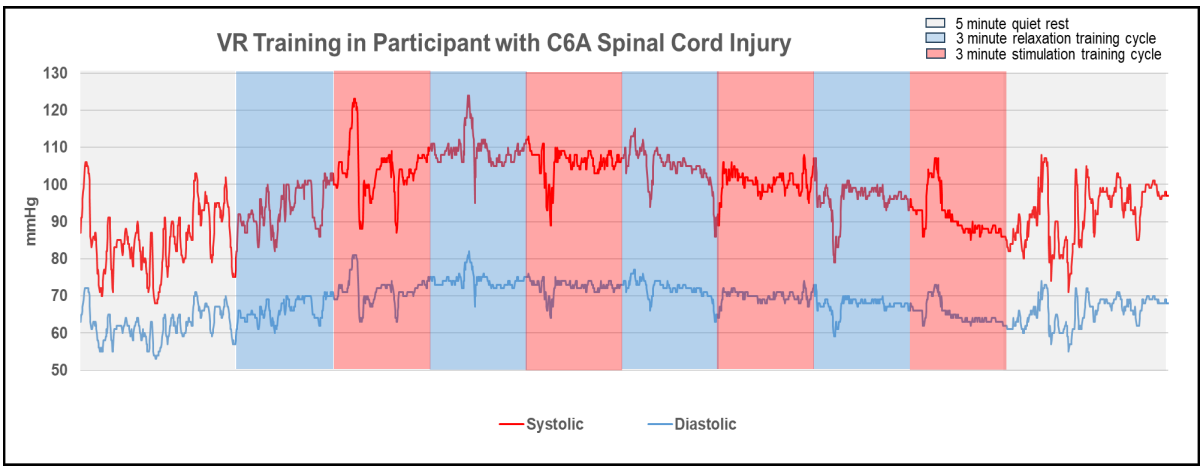

Figure 13: BP changes in VR imagery training in participant with C6A SCI. The blue and red areas are the alternating relaxation and stimulation cycles, respectively. The gray areas are the five-minute rest periods before and after training.

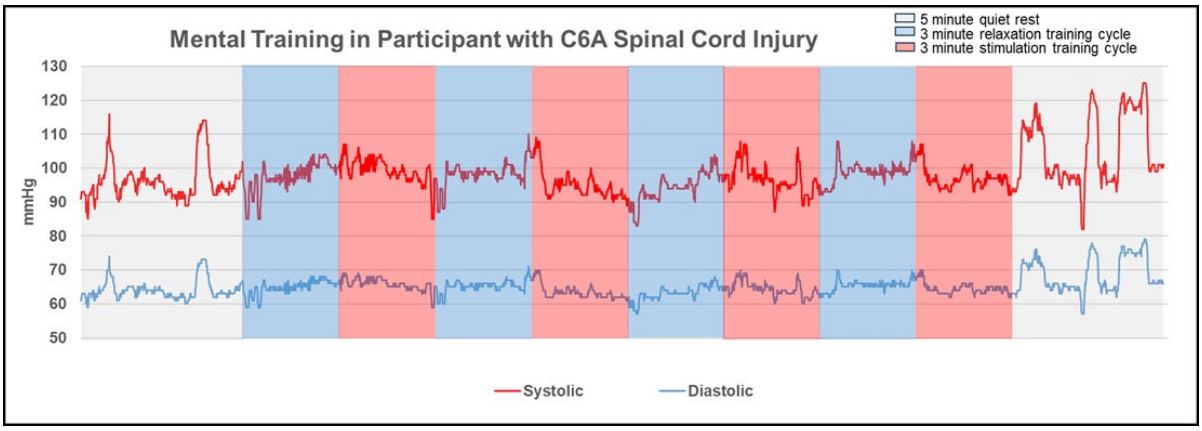

Figure 14: BP changes in mental imagery training in participant with C6A SCI. The blue and red areas are the alternating relaxation and stimulation cycles, respectively. The gray areas are the five-minute rest periods before and after training.

Mean Arterial Pressure Changes During Training

We then compared participants with SCI and NI participants' mean maximum increase (in stimulation cycles) or decrease (in relaxation cycles) of MAP in both VR and mental training. Testing with repeated measures ANOVA, participants with SCI showed significantly more decrease in MAP during relaxation cycles than NI participants ($p = 0.0421$). There was no significant difference in increase for participants with SCI for stimulation cycles, although it was very close ($p = 0.0695$) as shown in Figure 15. This figure compares participants with SCI and NI participants' mean maximum increase (in stimulation cycles) or decrease (in relaxation cycles) of MAP in both VR and mental training.

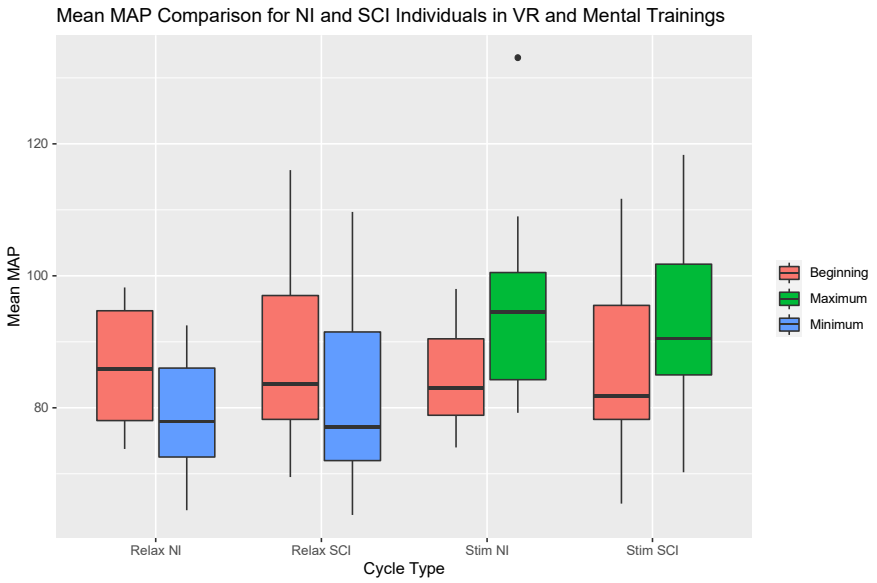

Figure 15: Mean maximum increase and decrease of MAP. Participants with SCI showed significantly more decrease in MAP during relaxation cycles than NI participants ($p = 0.0421$) during the first two trainings: one training using VR and one using mental imagery. In this box and whisker plot, the box itself is the interquartile range. The lines extending up and down away from the box end in maxima and minima respectively. The line in the center of the box is the median.

Differences in overall mean MAP and HR were not significant between VR and mental cycles; however, the differences in MAP variability and HRV were significant.

Mean Arterial Pressure Variability Before, During, and After Training

Coefficients of variation (CV) in MAP were compared between the training segments and the five-minute rest periods before and after the training segments (Figure 16). One-way repeated measures ANOVA of overall data showed a significant difference in MAP variation in the five-minute rest periods before and after training ($p = 1.85e-6$). To evaluate this further, pairwise t-tests compared "Before" and "During," as well as "During" and "After" for each visualization type. For the mental cycles, there was a significant increase in MAP variability from "Before" to "During" ($p = 1.466e-4$) but not from "During" to "After" ($p = 0.5729$). For the VR group, there was a significant increase in MAP variability between "Before" and "During" ($p = 5.837e-5$) and also between "During" and "After" ($p = 0.0417$). Figure 16 shows a comparison of MAP variability in the five-minute rest periods before and after training, broken down by visualization type. These findings indicate volitional BP modification beyond normal variations of spontaneous breathing. All outliers were included in data analysis.

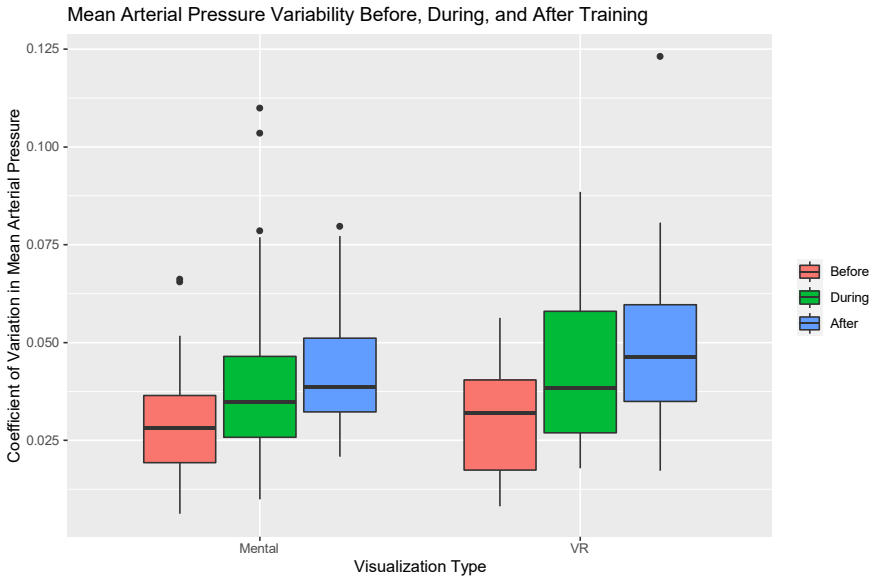

Figure 16: Significant differences in MAP variability in both VR and mental trainings indicate volitional BP modification beyond normal variations of spontaneous breathing. All changes were significant except for “during” to “after” in the mental cycles. The dots in the upper part of the graph denote outliers.

Heart Rate Variability Before and After Training

HRV measured in the standard deviation of normal-to-normal beats (SDNN) showed a significant increase ($p = 9.29e\text{-}4$) from the five-minute rest period before to the five-minute rest period after training in both VR and mental sessions, as shown in Figure 17.

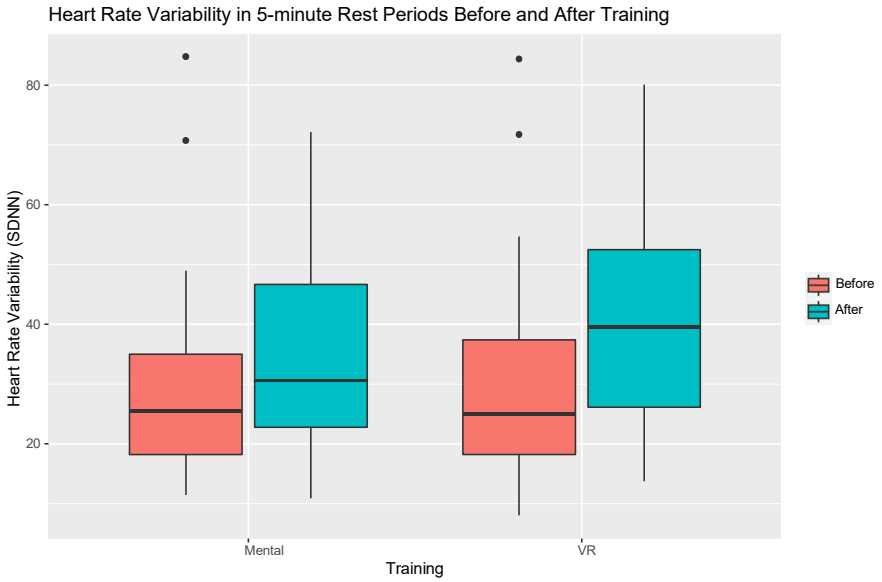

Figure 17: HRV measured in the standard deviation of normal-to-normal beats showed a significant increase (p = 9.29e-4) from the five-minute rest periods before to the five-minute rest period after training in both VR and mental sessions.

Heart Rate Variability and Blood Pressure Variability Correlation

Because of the increase in both HRV and BP variability, we conducted further correlation analyses between them. In the VR sessions, increased variation in MAP from the five-minute rest period before training to the five-minute rest period after training showed a significant correlation (0.6031138) (p = 0.006265) with the increase in HRV during those same periods. The statistical test used was Pearson's product-moment correlation test. Mental sessions did not show this correlation (0.2971452) (p = 0.2033). We also tested for the correlation between MAP variability and HRV with mental and VR data aggregated using the cluster-weighted Pearson's product-moment correlation test, which also showed a significant correlation between increased MAP

variability and increased HRV. The cluster-weighted correlation was 0.4767479 ($p = 0.001116$), as shown in Figure 18.

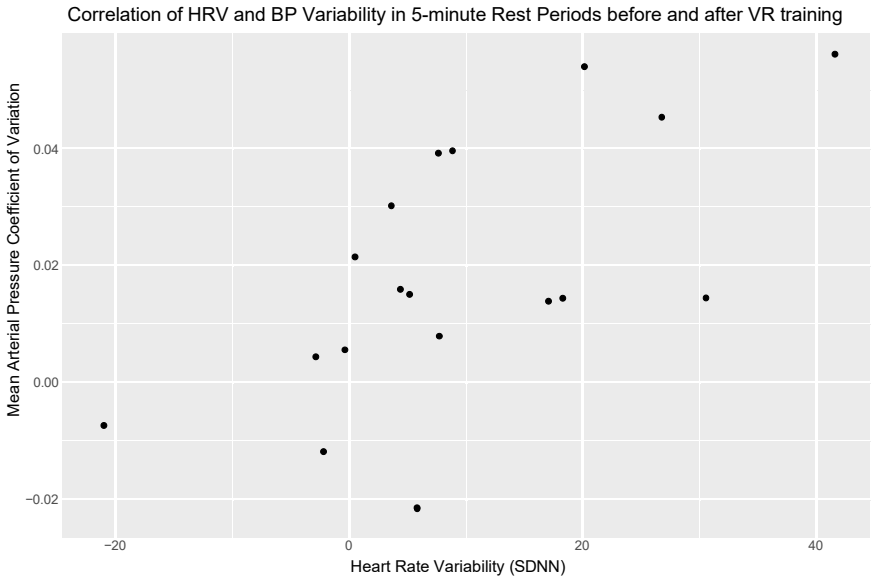

Figure 18: BP variability and HRV showed a significant correlation only in the VR session.

Discussion

To our knowledge, this is the first study looking into the effects of VR on BP and HRV after SCI. During normal breathing at rest, BP naturally decreases during inhalation and increases during exhalation. Participants' BP variability significantly increased beyond normal breathing levels during training compared to the five-minute rest periods before and after training. In VR sessions, not only did the variability in BP increase significantly during training, but it increased even further in the five-minute rest period after training.

Increased HRV is cardioprotective in a healthy person without cardiovascular arrhythmias.[204] Reduced HRV is correlated with all-cause

mortality and is a strong indicator of future health problems.[205,206] HRV reflects the ability to adaptively respond to physiological or psychological stress.[39,40] HRV showed significant improvement in our study. To indicate whether the increase in BP variability seen in this training may also be cardioprotective, we did a correlation analysis between HRV and the coefficient of variation of MAP. The positive correlation we found may indicate that acute increasing and decreasing BP volitionally has different cardiovascular consequences than the detrimental BP highs and lows throughout the day for many people with SCI since higher HRV is a positive cardiovascular outcome.

Participants with SCI brought their MAP down significantly more in relaxation cycles than NI people. This could be because of adapted vagal dominance, since sympathetic influences on the baroreflex are often "offline" in people with cervical SCI. Or it could indicate more cognitive influence on volitional BP modification. This invites further study. With our focus on both increasing and decreasing BP, physiologically, we went "back and forth," theorizing that the response of the baroreflex and arterioles would adapt for cardiovascular improvements, but also, we went "back and forth" psychologically, between relaxation and stimulation, which could have emotion regulation benefits.[145,146]

To our knowledge, no studies have been conducted on the attenuation of hypotension with VR, which indicates a research gap. There is also a research gap comparing the effects of mental and VR imagery. Visual perception is especially salient when visual and motor frames of reference are congruent

[207,208]; however, according to recent functional magnetic resonance imaging evidence, VR interventions integrate body-based cues to create a spatial "map" in the brain just as effectively without using motor movements.[209] This could be especially relevant for people with limited mobility. Further, we believe that including eye tracking or voice activation could enhance the experience for SCI participants with limited hand and arm function. This could increase independence if incorporated into future technology and neurorehabilitative therapies. In conclusion, autonomic biofeedback using mental and/or VR imagery could be an effective adjunct tool for fast-acting, non-pharmaceutical BP modification and HRV improvement for people with and without SCI.

Acknowledgments: The authors are grateful to the research participants, and to Dr. Shannon Putman, Kaden Kozlowski, Addie Wanner, and Jae Fish for their support during data collection.

Funding: The material is based upon work supported by NASA Kentucky under award number 80NSSC20M0047. This work was also supported by The Owsley Brown Frazier Endowed Chair in Physical Medicine and Rehabilitation.

CHAPTER V

VIRTUAL REALITY BIOFEEDBACK MODULATES BLOOD PRESSURE AND HEART RATE VARIABILITY IN PEOPLE WITH CERVICAL SPINAL CORD INJURIES

Introduction

VR has been found effective for managing hypertension,[112,178] but to our knowledge, no literature exists on the use of VR biofeedback for the effect of BP and HR changes after SCI. We hypothesized that biofeedback using immersive 360-degree VR videos with VR headsets, conscious interoception, and breathing exercises would effectively modulate BP and HRV. Twenty participants, including 13 individuals with cervical motor complete SCI and seven NI individuals, participated in this study. Participants received verbal feedback on whether or not they reached their goals of increasing and decreasing their MAP by at least five mmHg. In addition to eight biofeedback training sessions, we conducted pre/post autonomic testing including head-up tilt, the Valsalva maneuver, and paced deep breathing.

Materials and Methods

Participants

Twelve women and eight men (N=20) aged (39±14) participated in this study. Thirteen participants had a sustained chronic cervical SCI (more than 12 months since injury) and seven were NI. Participants with SCI were classified using the American Spinal Injury Association Impairment Scale (AIS) as follows:

eight were cervical motor complete (AIS A-B) and five were cervical motor incomplete (AIS C-D). The participants with SCI were between the ages of 24 and 67 (43±14). NI participants were between the ages of 21 and 65 (31±10). All participants were in stable medical condition without known cardiopulmonary disease and were non-smokers. Table 3 shows the participants' demographics and clinical characteristics.

Participant	SCI or NI	Sex	Age	Injury Level	AIS	Years Since Injury	Height (cm)	Weight (Kg)
1	SCI	M	34	C3	A	3	180.3	108.9
2	SCI	M	53	C3	C	6	185.4	83.9
3	SCI	F	32	C4	A	5	170.2	83.9
4	SCI	M	28	C4	B	3	180.3	117.9
5	SCI	M	67	C4	C	52	172.7	65.8
6	SCI	F	62	C4	C	3	170.2	74.8
7	SCI	F	36	C4	C	19	160	70.3
8	SCI	F	60	C4	D	1	162.6	99.3
9	SCI	M	42	C5	B	4	177.8	61.2
10	SCI	F	34	C5/6	A	3	165.1	80.7
11	SCI	M	24	C5/7	A	2	188	104.3
12	SCI	F	50	C6/7	A	34	174	46.3
13	SCI	F	35	C6/7	B	3	149.9	95.3
Mean±SD			**43±14**			**11±16**	**172±11**	**84±21**
14	NI	F	22	N/A	N/A	N/A	170.2	63.5
15	NI	F	21	N/A	N/A	N/A	157.5	50.3
16	NI	F	48	N/A	N/A	N/A	170.2	74.8
17	NI	F	33	N/A	N/A	N/A	180.3	81.6
18	NI	F	40	N/A	N/A	N/A	157.5	79.8
19	NI	M	25	N/A	N/A	N/A	177.8	64.9
20	NI	M	28	N/A	N/A	N/A	185.4	90.7
Mean±SD			**31±10**				**171±11**	**72±14**

Table 3: Clinical characteristics of participants in eight sessions of modified autogenic feedback training (N=20).

Equipment

BP, HR, and interbeat interval were measured and recorded with Caretaker Continuous Blood Pressure Monitor 4 (Charlottesville, VA, USA). The interbeat

interval was then filtered at a medium threshold to eliminate any data with excessive ectopic beats using Kubios HRV software (Varsitie 22, 70150 Kuopio, FINLAND). The VR head-mounted device was Meta Quest 2 (Meta Platforms, Menlo Park, California, USA).

Modified Autogenic Feedback Training

The lab space was accessible for people in wheelchairs, with two researchers per participant at a time in attendance. The door was closed, the room quieted, and the lights dimmed. After details were explained and written consent obtained, individual participants completed pre-autonomic testing consisting of a 45-degree head-up tilt, the Valsalva maneuver, and HR measured during paced deep breathing. They then were randomly assigned to begin the training protocol using either mental or VR imagery. Only one session used mental imagery, and the others used VR. Eight participants completed nine training sessions, and 12 participants completed eight sessions. Sessions were approximately twice a week for one month. After the training sessions were complete, post-testing was conducted, with the same outcome measures as pre-testing.

Sessions began with a five-minute quiet baseline, then eight three-minute cycles alternating between relaxation and stimulation. NI participants were seated in a non-reclining chair with their feet on the ground, and knees flexed at 90 degrees. Participants with SCI were seated upright in their wheelchairs. BP was measured with a manual sphygmomanometer and cuff to calibrate the telemetric BP measurement device, which continuously monitored BP and HR.

During the relaxation cycles, participants completed breathing exercises, interoception, and imagery to help facilitate relaxation and decrease BP. For the stimulation cycles, participants completed breathing exercises, interoception, and imagery with the intent to increase their BP. After the eight cycles, a five-minute rest period was recorded. Participants were guided step-by-step throughout the training session by the researcher. For the mental training session, participants were asked to picture in their minds a safe, comforting image during relaxation cycles, or an exciting or frustrating image during stimulation cycles. For the VR sessions, the headset was put on before the beginning of the first training cycle and left on for the remainder of the training session. The three-minute, 360-degree videos were relaxing (e.g., beach scenes, campfires) and then stimulating (e.g., sharks, horse races).[202] The video playlist was consistent for all participants.

The participants were given BP goals for relaxation and stimulation: five MAP points in mmHg below and five above the number recorded at the beginning of the cycle, respectively. Verbal acknowledgment of success in attaining these goals served as auditory biofeedback, allowing the participants to close their eyes, except when watching VR, to concentrate on their intention to modify BP. Since BP naturally varies with spontaneous respiration,[203] and participants' goals were to move their BP, we measured the difference in variation during training as compared to the five-minute rest periods before and after training. We also measured whether BP variability correlated with HRV.

A researcher gave verbal instructions to the participant and recorded the MAP at the beginning of the cycle, the MAP goal, whether and when the goal was achieved, and the highest or lowest MAP in the cycle. A second researcher marked events on the telemetric physiological recording unit. The VR images were cast onto a laptop and advanced using the VR right-hand control apparatus just behind the participant. A physician specializing in SCI medicine and rehabilitation research was on site or in the same building during all the sessions. The training was discontinued if systolic BP was over 180 or under 80 mmHg.

Statistical Methods

All measured outcomes: systolic BP, diastolic BP, MAP, HR, HRV (SDNN, HF, LF, VLF) were summarized with means and standard deviations, minima, and maxima. Summary statistics were calculated by the study group (cervical SCI and NI). Outcome data were also summarized graphically with boxplots for univariate data and scatterplots for bivariate data. All hypothesis tests were conducted at the 0.05 level, and all analyses were conducted using the open-source R software environment (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, v 4.3.2).

Results

Heart Rate Variability in Eight Sessions of Autonomic Biofeedback Training

We compared HRV during the five-minute rest periods before and after each autonomic biofeedback training session. HRV cannot be accurately measured during the active part of the training session because the breathing exercises would invalidate the results. All HRV parameters increased

significantly. We analyzed one time-domain HRV measurement, the standard deviation of normal-to-normal beats (SDNN), and three frequency domain HRV measurements: high frequency (HF), low frequency (LF), and very low frequency (VLF). The SDNN changes represent the differences in time between heartbeats, whereas the frequency measurements represent the amplitude of the heartbeats. In Figures 19 and 20, repeated measures ANOVA showed significant SDNN changes in participants with SCI ($p = 4.52e-4$) and NI participants ($p = 1.23e-5$) respectively.

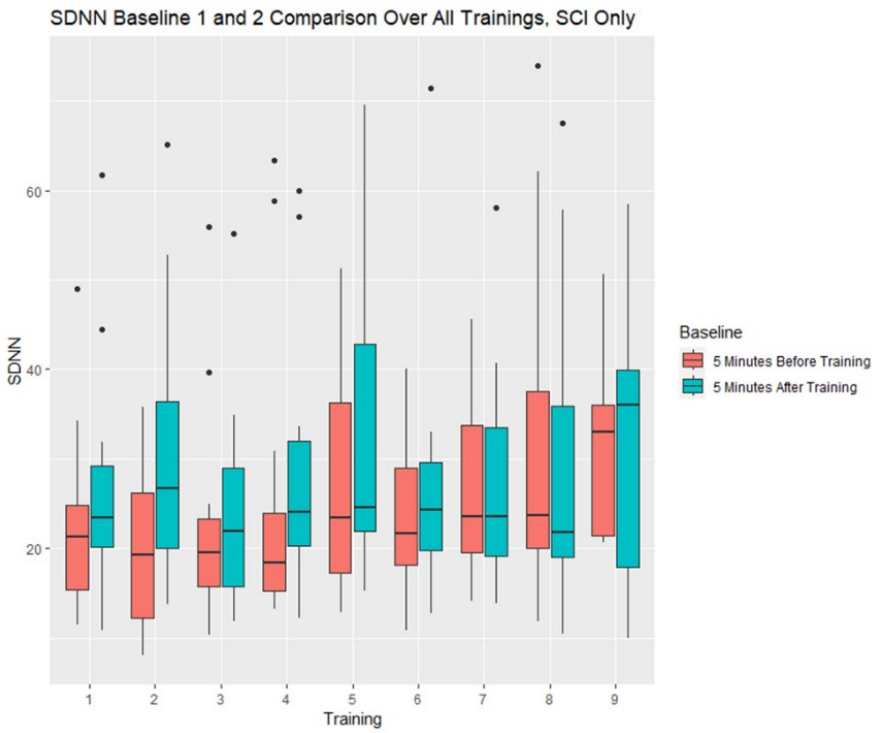

Figure 19: HRV during the five-minute rest periods before and after each training increased significantly for participants with SCI. In this box and whisker plot, the box is the interquartile range. The lines extending up and down away from the box end in maxima and minima respectively. The line in the center of the box is the median. The dots on the upper part of the graph denote outliers.

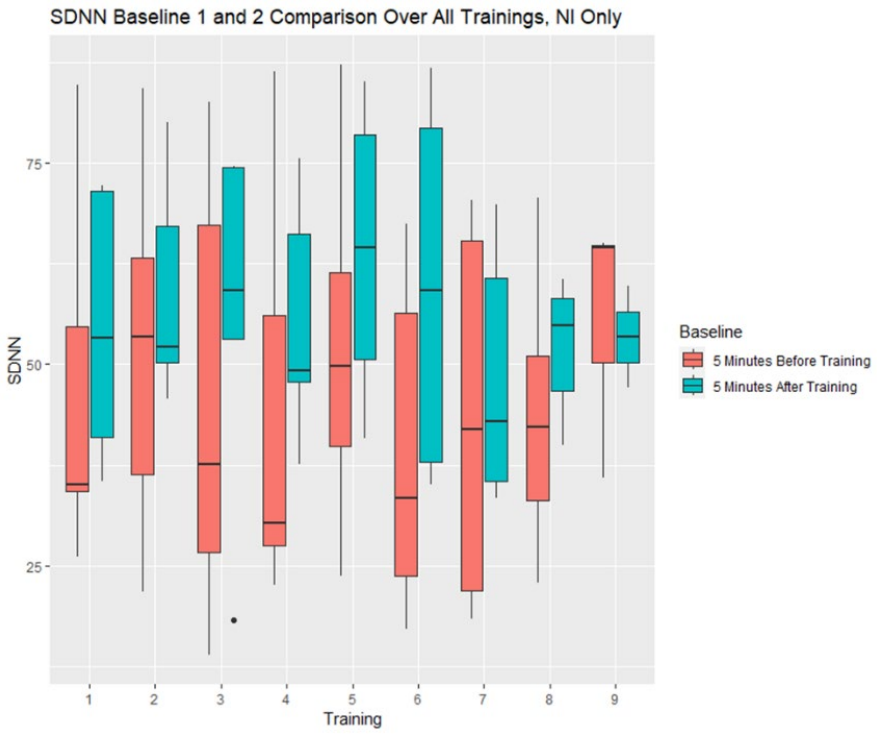

Figure 20: HRV measured in the five-minute rest periods before and after each training increased significantly for NI participants.

The three different frequency domain measurements represent mechanisms of HRV changes. We used the natural log version of the frequency measurements because it approximates the normal distribution of the data since our sample size was low. HF HRV represents vagal contributions to HRV.[152] LF measurements represent baroreflex modulations,[153] and VLF measurements represent changes made via the renin-angiotensin-aldosterone system (RAAS).[154] Changes in RAAS may be less cardioprotective than other mechanistic changes in HRV because these changes indicate that the kidneys are more active in changing BP instead of direct baroreflex mechanisms.

Table 4 shows which HRV parameters had the most and least significant increases using repeated measures ANOVA of the means of each parameter in each training's five-minute rest period before and after. From this chart, we see that VLF HRV had the most significant changes for all participants. Very low frequency heart rate variability's mechanism of change is RAAS.[154] The next most significant changes were in baroreflex[153] (LF HRV) then vagal[152] (HF HRV) changes in NI participants, and vagal[152](HF HRV) then baroreflex[153] (LF HRV) changes in participants with SCI.

	HRV measurement	P value
most significant increase	VLF SCI	0.000000506
	VLF NI	0.00000115
	SDNN NI	0.0000123
	LF NI	0.0000346
	HF NI	0.00012
	SDNN SCI	0.000452
	HF SCI	0.013
least significant increase	LF SCI	0.015

Table 4: All frequency and time domain HRV measurements in the five-minute rest periods before and after each training increased significantly in all participants. Different frequency measurements are affected by different mechanisms: high frequency HRV (HF) represents vagal contributions to HRV.[152] Low frequency (LF) measurements represent baroreflex modulations,[153] and very low frequency (VLF) measurements represent changes made via the renin-angiotensin-aldosterone system.[154]

Heart Rate Variability in Pre/Post-Autonomic Testing

In contrast to the above significant HRV changes in the rest periods just before and after each training, we did not find significant changes in HRV in pre/post testing. Five-minute supine baseline hemodynamic measurements were recorded just before autonomic testing consisting of head-up tilt, the Valsalva maneuver, and paced deep breathing. Using a paired Wilcoxon test appropriate for time-domain measurements, we did not find a significant difference between the means of SDNN pre/post ($p = 0.766$). The other three frequency domain HRV measurements also did not show a significant change in pre/post-testing. Here we used paired t-tests: $p = 0.8103$ (HF), $p = 0.7701$ (LF), $p = 0.5136$ (VLF).

The above HRV measurements were analyzed by entering the interbeat interval from the hemodynamic measurement unit into Kubios HRV software. We also measured HRV through paced deep breathing during pre/post. Guided by the researcher, participants inspired for five seconds and expired for five seconds, for one minute. This is known as coherent breathing, which optimizes HRV.[142] When compared to normative values, 77% of participants with cervical SCI showed impaired HRV measured through paced deep breathing.[210] Details of participants' paced deep breathing results are included in the cardiovagal results in Table 7.

Blood Pressure in Eight Sessions of Autonomic Biofeedback Training

MAP did not show significant changes when measuring the five-minute baselines before and after each training for participants with SCI ($p=.218$) nor NI

participants (p=.343). However, *variabilities* in HR showed significant changes. Variabilities in BP also changed significantly during the rest periods.

During spontaneous breathing, BP naturally decreases with inspiration and increases with expiration. We wanted to see if the variation in MAP changed during training, to indicate whether volitional changes were taking place. The coefficient of variation (CV) is the standard deviation divided by the mean. In Figure 21 below, we compare the CV in the five-minute rest period before training, during training, and then the five-minute rest period after training. Both participants with cervical SCI (p=5.39e-14), and NI participants (p=4.41e-07), significantly increased MAP variation from the first rest period to the second. NI participants significantly increased MAP variation from “before” to “during” (p=3.53e-06), but not “during” to “after” (p=0.721). Participants with SCI increased both “before” to “during” (p=8.97e-15) and then decreased “during” to “after” (p=1.81e-08), yet this decrease in the five-minute rest period after training was still significantly higher than the rest period before training.

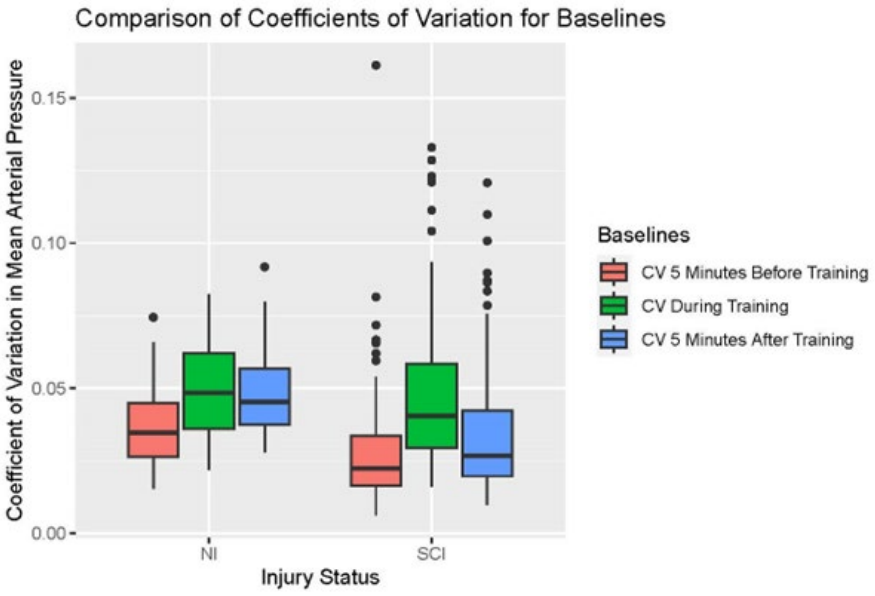

Figure 21: All participants' MAP variability increased significantly from the five-minute rest period before training, to during training, indicating volitional BP modification. NI participants' MAP variability remained elevated in the five-minute rest period after training.

In addition to measuring BP changes in the five-minute rest periods before and after training, we measured whether participants were able to meet their feedback goals during the training cycles. Participants' goals during training were to increase then decrease their MAP by five mmHg in stimulation and relaxation cycles respectively. In all cycles, the difference between the beginning cycle MAP mean and maximum means in stimulation cycles or minimum means in relaxation cycles was found to be significantly greater than five ($p=2.2e-16$). Mean MAP changes in successful cycles were similar in both cohorts: the mean MAP increase in successful stimulation cycles for participants with SCI was 10.03 and for NI participants 10.92. The mean MAP decrease in successful

relaxation cycles for participants with SCI was 9.5 and for NI participants 10.03 as shown in Figure 22.

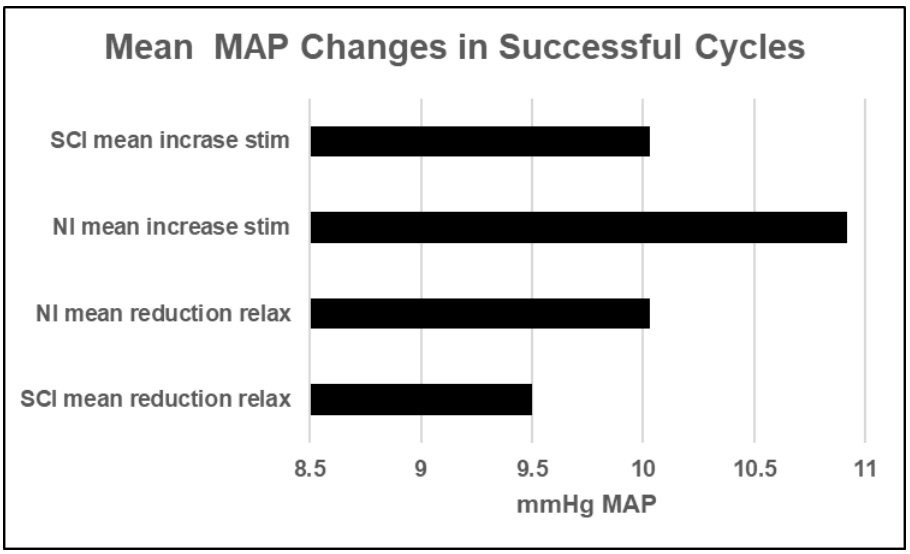

Figure 22: Mean MAP changes in successful cycles (when change was at least 5mmHg) during training were similar for all participants ranging from 9.5-10.92 mmHg.

NI participants had successful cycles more often than participants with SCI. Percentages of successful cycles were similar between relaxation and stimulation in both cohorts. Participants with SCI had successful relaxation cycles 62% of the time and successful stimulation cycles 60% of the time. NI participants had successful relaxation cycles 80% of the time and successful stimulation cycles 78% of the time (Figure 23). Figure 24 illustrates during what part of the training cycle participants most often met their goals of at least five mmHg increase during stimulation cycles or decrease during relaxation cycles.

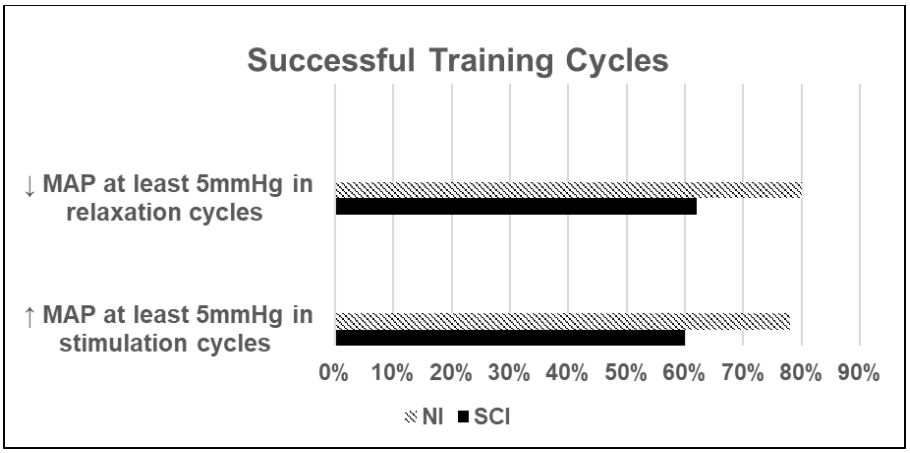

Figure 23: NI Participants had successful cycles more often than participants with SCI: Participants with SCI had successful relaxation cycles 62% of the time and successful stimulation cycles 60% of the time. NI participants had successful relaxation cycles 80% of the time and successful stimulation cycles 78% of the time.

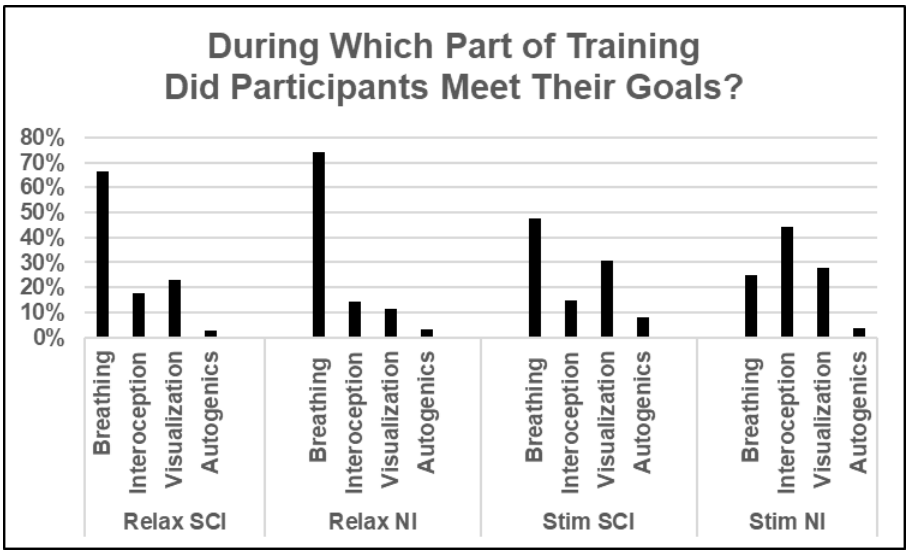

Figure 24: Participants most frequently met their goals during the breathing exercise portion of the training, except for NI stimulation cycles which were most successful just after the breathing, during interoception.

We then separated the data between the cycle types in all the cycles and tested the difference between the beginning MAP mean and minimum or maximum MAP in the cycle using repeated measures ANOVA (Figure 25). Participants with SCI and NI participants were similarly successful in their raising and lowering of MAP, with no significant difference attributed to the injured status: relaxation cycles (p=0.4250), or in the stimulation cycles (p=0.196) as seen in Figure 25.

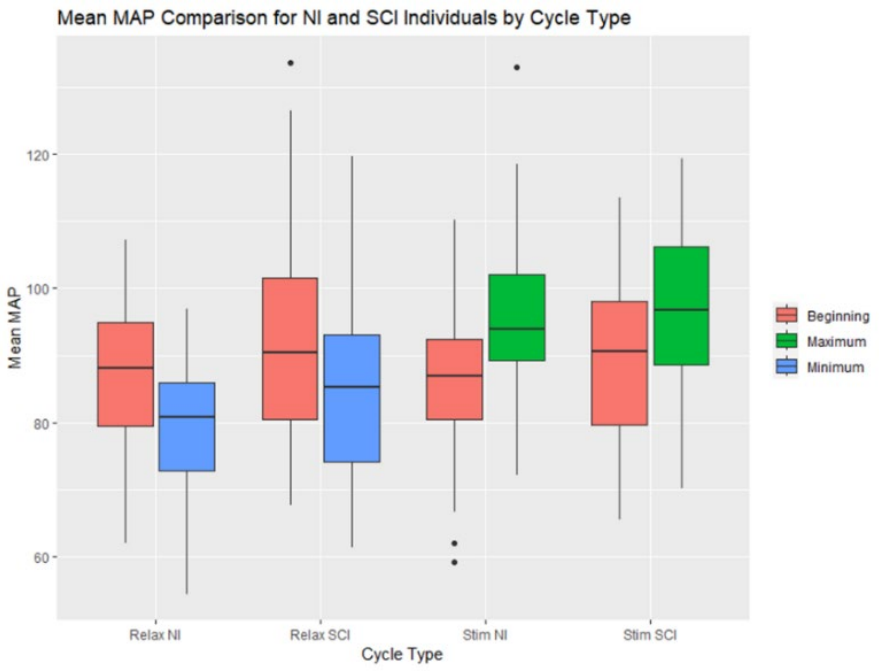

Figure 25: Mean MAP comparison by cycle type. When all cycles were taken into consideration, whether they were successful (changing at least 5mmHg) or not, participants with SCI and NI participants were similarly successful in their raising and lowering of MAP, with no significant difference attributed to the injured status.

Blood Pressure in Pre/Post-Autonomic Testing

Figure 26 below shows comparisons for the mean systolic and diastolic BP 30 seconds before tilt and the minimum BP during tilt. The tilt test can show whether a participant experiences orthostatic hypotension, which is a 20 mmHg decrease in systolic BP or a 10 mmHg decrease in diastolic BP. All participants with SCI except one showed orthostatic hypotension in either pre, post, or both, as did three of the seven NI participants. In this graph, we can see that BP did not change significantly from pre to post. To elucidate whether post values became closer to normotensive than pre values, we compared the means of pre- and post-systolic (SBP) and diastolic (DBP) and did not find a significant difference: SBP ($p=0.285$), DBP ($p=0.4137$). Values were considered normotensive if they were in a range of 90/60-120/80.

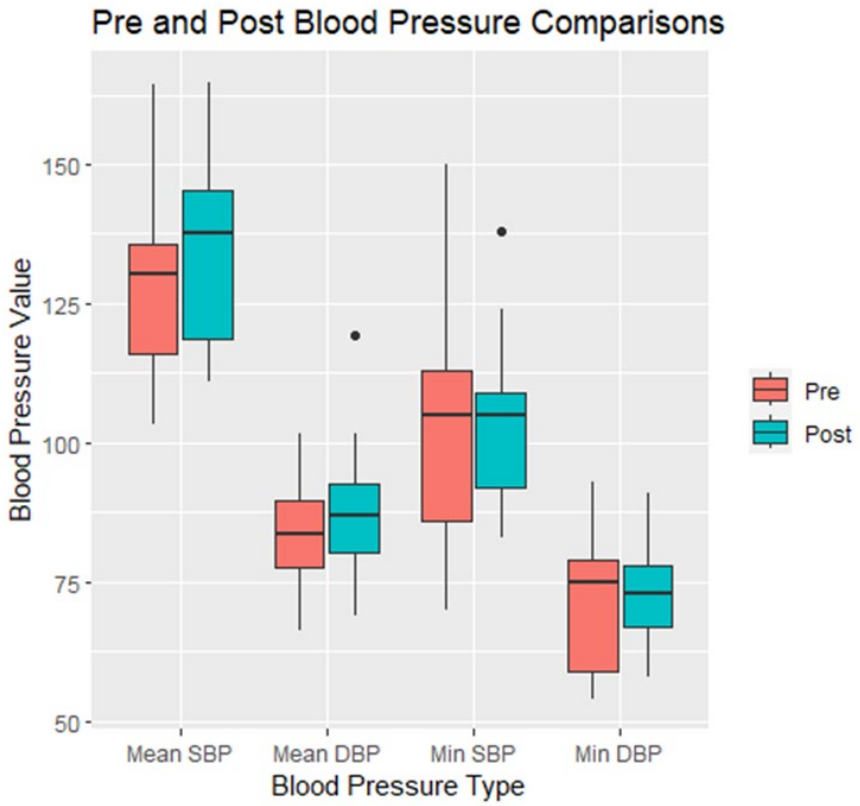

Figure 26: All participants' BP during the tilt test did not change significantly from pre to post.

We then looked at proportions: how many were in the normotensive range pre-and post-test. For systolic BP, we had five in the normotensive range for both, five for post-test but not pre-test, three for pre-test but not post-test, and zero for neither. The normal test for this type of analysis is McNemar's test, but due to the small sample size, we used an alternative to this called the exact binomial test. With this, we did not find a significant difference (p=0.7266). It is also worth noting that McNemar's test does give about the same result (p=0.7237). For diastolic BP, we had five in the normotensive range for both, five for post-test but not pre-test, one for pre-test but not post-test, and two for

neither. Using the exact binomial test to evaluate this, there is not a significant difference (p=0.2188). Finally, we aggregated them. For this, we had four in the normotensive range for both, three for post-test but not pre-test, zero for pre-test but not post-test, and six for neither. Using the exact binomial test to evaluate this, we did not find a significant difference (p=0.25).

To elucidate whether there was a smaller range of systolic and diastolic BP reduction during tilt, we first calculated the amount the systolic BP dropped in the pre-and post-testing, and then compared these using a one-sided paired t-test to see if the pre-test drop was greater than the post-test drop. The test did not show a significant difference (p=0.7417). We did the same for diastolic BP, and the results were similar (p=0.7344). Next, we again compared the proportions of those that showed hypotension in the pre-test vs those that showed hypotension in the post-test. For systolic BP, diastolic BP, and an aggregate of both, the results were the same: we had six show it in both, four in the post-test but not the pre-test, two in the pre-test but not the post-test, and one in neither. Using the exact binomial test, we did not find a significant difference (p=0.6875).

In Table 5 below we show all participants' cardiovagal responses measured in HR during paced deep breathing and the Valsalva ratio, along with successful relaxation cycles and mean MAP decreases. According to age and sex-specific normative values of the Valsalva ratio,[210] only three out of 13 participants with SCI showed normal cardiovagal response both pre and post. Similarly, three out of 13 participants with SCI showed a normal cardiovagal

response in HR during paced deep breathing. Only one participant with SCI showed a normal cardiovagal response in both outcome measurements. Despite the majority of participants with SCI showing vagal abnormalities, they were successful in relaxation cycles in a range of 31-90% of the time.

Cardiovagal Response and MAP Decreases							Successful	Mean
Participant	Injury Level	AIS	HRDB Pre	HRDB Post	VR pre	VR post	Relaxation Cycles	MAP Decrease
1	C3	A	12 ± 3.8	11 ± 2.8	1.29	1.68	46%	8.7
2	C3	C	8 ± 2.2	6 ± 1.7	1.25	1.22	47%	10.9
3	C4	A	9 ± 2.3	7 ± 2	1.17	1.1	81%	10
4	C4	B	10 ± 2.9	12 ± 3.8	1.64	1.2	64%	8.1
5	C4	C	18 ± 5.6	30 ± 8.8	1.3	1.18	72%	8
6	C4	C	9 ± 2.8	8 ± 1.6	1.36	2.13	75%	8
7	C4	C	11 ± 2.9	13 ± 4	1.31	1.26	31%	6.4
8	C4	D	4 ± 1.5	5 ± 1.6	1.39	1.4	44%	8
9	C5	B	10 ± 2.7	13 ± 3.5	1.5	1.58	46%	8.2
10	C5	A	5 ± 1.1	5 ± 1.1	2.24	2.03	53%	7.5
11	C5	A	6 ± 1.9	6 ± 1.8	1.29	1.21	53%	12.5
12	C6	A	4 ± 1.3	7 ± 1.8	1.22	1.29	90%	10.9
13	C6	B	9 ± 2.3	7 ± 2.1	1.29	1.34	72%	15.8
Mean ± SD			**9 ± 3**	**10 ± 3**	**1.4 ± .28**	**1.43 ± .33**	**62% ± .17**	**9.46 ± 1.8**
14	NI	NA	15 ± 3.8	14 ± 3.2	1.59	2.35	50%	7.6
15	NI	NA	22 ± 3.1	11 ± 3.1	1.35	1.4	94%	11.3
16	NI	NA	6 ± 1.5	7 ± 2	1.09	1.06	84%	14.22
17	NI	NA	14 ± 3.8	10 ± 3	1.5	1.26	81%	10.12
18	NI	NA	16 ± 4.3	8 ± 2.6	1.1	1.1	69%	8.95
19	NI	NA	14 ± 4.5	16 ± 4.8	2.1	2.4	94%	9.9
20	NI	NA	5 ± 1.3	11 ± 3.5	1.71	2.01	86%	8.1
Mean ± SD			**13 ± 3**	**11 ± 3**	**1.49 ± .36**	**1.65 ± .58**	**80% ± .16**	**10 ± 2.2**

Table 5: Cardiovagal response pre/post and MAP increase during training: the yellow highlights mark less than normative response.[210] HRDB=heart rate measured during deep paced breathing, VR=Valsalva Ratio, MAP=mean arterial pressure, AIS=injury rating according to ASIA impairment scale.

Table 6 below shows adrenergic response pre/post and MAP increases during training. All but one participant with SCI showed orthostatic hypotension during head-up tilt in pre-/or post-testing. Despite most participants showing

adrenergic deficiencies as measured by head-up tilt, participants with SCI had successful stimulation cycles in a range of 30-88% of the time.

Sympathetic Adrenergic Response and MAP Increases						
Participant	**Injury Level**	**AIS**	**OH pre**	**OH post**	**Successful Stimulation Cycles**	**Mean MAP Increase**
1	C3	A	+	+	69%	12.4
2	C3	C	+	+	53%	7.7
3	C4	A	+	+	64%	11.2
4	C4	B	+	+	47%	8.3
5	C4	C	+		77%	14.1
6	C4	C			55%	9.9
7	C4	C	+	+	51%	10.9
8	C4	D	+	+	64%	9.3
9	C5	B		+	30%	6.2
10	C5	A	+	+	44%	8.5
11	C5	A		+	59%	8.6
12	C6	A	+	+	88%	8.8
13	C6	B	+	+	80%	14.5
Mean ± SD					**60% ± .16**	**10.3 ± 2.5**
14	NI	NA	+	+	94%	11.7
15	NI	NA			97%	10.1
16	NI	NA			64%	9.2
17	NI	NA			89%	8.8
18	NI	NA	+	+	84%	17.5
19	NI	NA			50%	11.2
20	NI	NA	+	+	66%	8
Mean ± SD					**78% ± .18**	**10.9 ± 3.2**

Table 6: Adrenergic response pre/post and MAP increases during training: the plus signs indicate orthostatic hypotension (OH), AIS=injury rating according to ASIA impairment scale.

Heart Rate Variability and Blood Pressure Variability Correlation

Because of the changes in MAP variability before, during and after training, we wanted to see if MAP variability correlated with HRV, and it did. Figure 27 is a scatterplot mapping the changes in SDNN (HRV) against the changes in the coefficient of variation in MAP, for SCI participants: Pearson's product-moment correlation test gives a value of 0.228, which is significant (p=0.0197). For NI participants, the correlation test gave a value of 0.319, which is also significant (p=0.0201) (Figure 28).

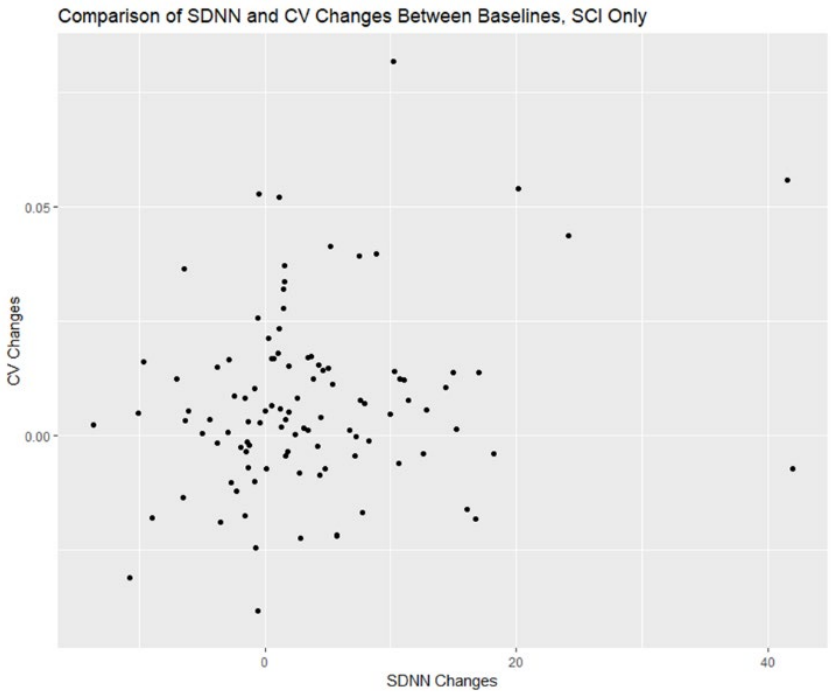

Figure 27: There was a significant correlation (p=0.0197) between HRV and MAP variability in participants with SCI during the five-minute rest periods before and after each of the eight trainings.

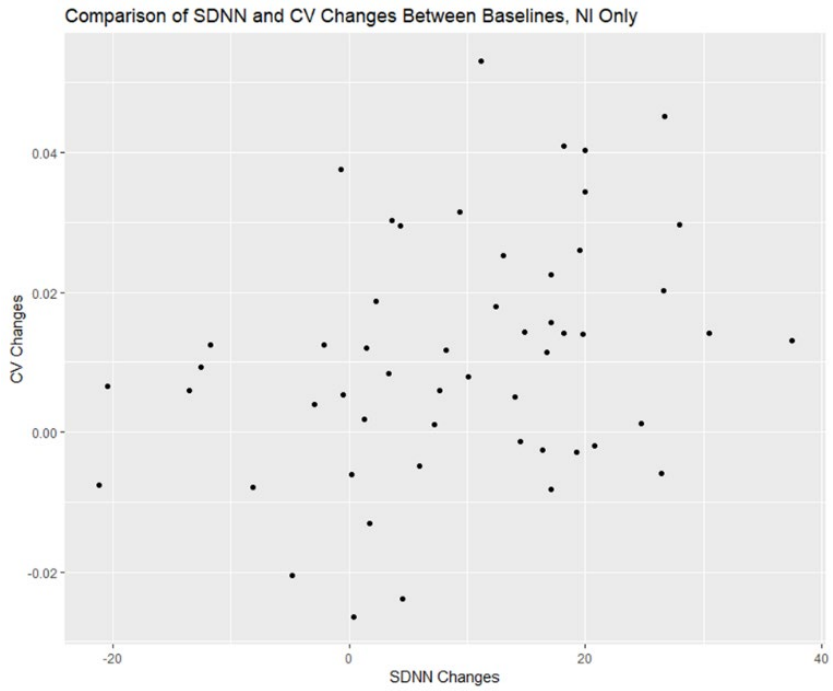

Figure 28: There was a significant correlation (p=0.0201) between HRV and MAP variability in NI participants during the five-minute rest periods before and after each of the eight trainings.

Discussion

To our knowledge, this is the first study of the effects of VR biofeedback on BP and HRV in individuals with SCI. In humans during spontaneous breathing at rest, BP decreases during inspiration and increases during expiration. In our study, all the participants' BP significantly increased beyond spontaneous breathing levels during training compared to the five-minute rest periods before and after training, which indicates volitional modulation. In contrast to the significant HRV and BP variability changes in the rest periods just before and after each training, we did not find significant changes in HRV nor BP in pre/post

testing. This indicates that training may be most useful for the acute modulation of BP. NI participants' MAP variation increased during training and remained at increased levels in the rest period after training, whereas participants with SCI's MAP variability increased during training but came back down again in the rest period after training. This interesting contrast invites further study.

Refuting our hypotheses, NI participants had successful training cycles more often than participants with SCI. Participants most frequently met their goals during the breathing portion of training, except for NI stimulation cycles, in which participants were most often successful during interoception, which occurred just after the breathing. In normal healthy BP modulation, increasing BP takes longer than decreasing BP since vagal effects occur faster than the sympathetic influence on the sinoatrial node of the heart. NI results concur with this, with the success rates occurring most often during interoception. Since participants with SCI were more successful during the actual breathing instead of just after, this could indicate an alternate route to BP modification and increase the likelihood of breathwork being a useful adjunct tool for BP modulation in this population.

Another indication participants with SCI may have relied more on an alternate BP modification route, in addition to or instead of the normal baroreflex route, are the results of autonomic testing. Only one participant with SCI showed a normal cardiovagal response in both the Valsalva ratio and HR measured through paced deep breathing. Despite the majority of participants with SCI showing vagal abnormalities, they were successful in relaxation cycles in a range

of 31-90%. The majority of participants with SCI also showed adrenergic deficiencies as measured by head-up tilt, yet participants had successful stimulation cycles in a range of 30-88% percent of the time. The participant with SCI who was most successful at 88% of stimulation cycles, showed orthostatic hypotension both pre and post and had an AIS rating of A (motor complete). This participant's success in raising their MAP is an example of how ratings of complete injuries may not always be *autonomically* complete.

High HRV is considered cardioprotective in people without cardiovascular arrhythmias.[204] Low HRV correlates with all-cause mortality and is a strong indicator of future health problems.[205,206] HRV reflects the ability to adaptively respond to stress.[39,40] HRV showed significant improvement in our study. To indicate whether the increase in BP variability seen in this training may also be cardioprotective, we did a correlation analysis between HRV and the coefficient of variation of MAP. The positive correlation we found may indicate that acute volitional BP modulation has different cardiovascular consequences than the detrimental BP highs and lows throughout the day for many people with SCI since higher HRV is a positive cardiovascular outcome.

No studies to our knowledge have been conducted on the attenuation of hypotension with VR biofeedback, which indicates a research gap. Autonomic biofeedback using mental and/or VR imagery could be an effective adjunct tool for fast-acting, non-pharmaceutical BP modification and HRV improvement for people with and without SCI.

CHAPTER VI

QUALITY OF LIFE AND INTEROCEPTION SURVEYS

Introduction

During the proof-of-concept pilot study of our training protocol[157] in 2021, a participant with cervical motor complete SCI reported to the researchers after her fifth training that she felt the urge to urinate for the first time since her injury. She said, “It was not an AD [autonomic dysreflexia] feeling, just a need to urinate*”.* This reported change in interoception (the sensing of internal body sensation) could have been a training effect, so we decided to include surveys about interoception and quality-of-life pre and post in our larger study. With our focus on both increasing and decreasing BP, physiologically, we went "back and forth," theorizing that the response of the baroreflex and arterioles would adapt for cardiovascular improvements, but also, we went "back and forth" psychologically, between relaxation and stimulation, which could have emotion regulation benefits.[145,146,211]

For people with SCI, like everyone else, there is no one way that they feel or do not feel on the inside, regardless of their motor or sensory “completeness” of injury rating. Much of the visceral interoceptive signals are brought to the brain by afferent vagal and cranial nerve fibers. Since these pathways are not directly affected by SCI, these sensations should remain unchanged, as was found in a study of 66 people with cervical SCI, most reported no change in nausea,

hunger, or the feeling of visceral dread after their injury.[212] Visceral vagal and cranial nerve interoceptive routes are not likely to change due to SCI. Still, interpretation of other signals such as nociception, temperature sensation, and the need for micturition and defecation, is likely to change since these signals travel via sympathetic afferent nerves in the dorsal column of the spinal cord.[212]

Interoceptors are molecular sensors in peripheral neurons that transduce signals that the brain interprets. Some examples of interoceptors are chemoreceptors, mechanoreceptors, and nociceptors. In addition to the route of peripheral interoceptors to the CNS, other areas also receive interoceptive input such as vascular, endocrine, and immune areas.[213] Interoceptive signals are first processed in brain areas such as the nucleus of the solitary tract, parabrachial nucleus, and thalamus,[214] then higher brain regions such as the hypothalamus, insula, anterior cingulate cortex, and somatosensory cortex.[215] The insula is activated when individuals consciously direct attention to their interoceptive sensations.[216] Some conditions that alter interoception are chronic pain, anxiety,[217] depression, PTSD,[218] and obesity,[219] all of which are also often comorbidities in people with SCI.[220] The effects of modulating interoceptive networks remain largely unknown.[204] To measure both interoception and quality-of-life, we combined instruments from the Tulsky SCI Quality of Life[7] surveys with the Body Perception Questionnaire.[8]

The Body Perception Questionnaire to Measure Interoception

Body awareness (interoception) and autonomic reactivity were surveyed with the Body Perception Questionnaire Shortform.[8] This instrument was not SCI-

specific, as it was validated in the general population. The T-scores are based on a combined sample of American participants recruited online (n = 2048). Participant age ranged from 18 to 95 years (Mean = 46.34, SD = 17.19). Fifty-one percent (51%) were female. The Body Perception Questionnaire[8] measures interoception and autonomic reactivity and is based on Stephen Porges' Polyvagal Theory.[39] One of the tenets of the theory is that people who have been through psychological trauma have less interoceptive awareness and more autonomic reactivity due to adaptations in their autonomic responses to danger.[221] Though medical procedures are not considered a cause of PTSD in the Diagnostic and Statistical Manual of Mental Disorders,[222] people with SCI are highly likely to be diagnosed with PTSD whether from the trauma of the situation in which the injury occurred, or the adaptation to life after the injury.[201,223]

Polyvagal theory describes how our physiological state is involved with our psychological state during and after trauma. Porges postulates that there is a hierarchy of responses to danger, depending on our nervous system's adaptation to trauma. According to the theory, there are two distinct vagal circuits, both approximately 80% afferent and 20% efferent: [224] the ventral vagal complex and the dorsal vagal complex. Both pathways begin in the medulla. The ventral vagal complex leads to the supradiaphragmatic effectors: the heart, lungs, face, throat, and head. These fibers are evolutionarily newer, myelinated, and cause the classic and physiologically beneficial "rest and digest" response. When humans feel safe, this part of the vagus nerve dominates.[39] Efferent pathways of the dorsal vagal complex lead to the subdiaphragmatic effectors such as the

stomach, liver, pancreas, and kidneys. They are unmyelinated, and cause less beneficial (but sometimes necessary for survival) “freeze” response: bradycardia, sometimes syncope, and potentially death.[39]

It is well established that chronic activation of the sympathetic nervous system causes many detrimental physiological and psychological effects. The sympathetic nervous system evolved because mammals needed more oxygen to respond to stressors as they transferred from ocean-dwelling to land-dwelling.[225] According to Porges, if the sympathetic nervous system engages for a person to run from a situation and they cannot — for whatever reason (for example being “pinned” into a car in an accident, or physically restrained as a rape victim, or any injury that immobilizes us, such as a SCI) the older unmyelinated part of the vagus nerve (the dorsal vagal complex) takes over with a consequential “freeze” response: bradycardia, possible syncope, even possible death. Chronic activation of the dorsal vagal complex, like an overreactive sympathetic response, also can cause detrimental effects.[39] When the dorsal vagal complex is activated due to trauma we cannot physically get away from, the nervous system does not shift easily back to homeostasis.[221] Seen from the perspective of the Polyvagal Theory, the inherent physical and psychological trauma of SCI, especially the immobilization and altered sympathetic autonomic response, make the answers to the Body Perception Questionnaire survey fascinating. The only other study that could be found that used this survey in the SCI population was a study of 45 people with paraplegia. In this study, people with incomplete injuries

had greater interoceptive awareness than those with complete injuries as measured by the Body Perception Questionnaire.[226]

Tulsky Quality of Life Surveys for People with Spinal Cord Injuries

The Tulsky SCI-QOL is a series of quality-of-life surveys validated in the SCI population.[7] Scores use a standardized T-metric, with a mean of 50 and a standard deviation of 10. Higher scores represent a greater amount of the construct being measured. For example, for resilience, a T-score of 60 would represent an individual functioning at one standard deviation better than the mean of the SCI population. For Bowel Management Difficulties, a T-score of 60 would indicate an individual performing one standard deviation worse than the mean of the SCI population. Qualitative input to validate the survey was obtained through interviews, focus groups, and cognitive debriefing of individuals with SCI and clinicians. Item pools were tested in a multi-site sample (n = 877) and calibrated using item response theory. Initial reliability and validity testing was performed in a sample of individuals with traumatic SCI (n = 245).[227]

Methods of Administering the Surveys

We combined the Tulsky SCI QOL surveys for bowel difficulties, bladder difficulties, anxiety, depression, pain, pressure ulcers, trauma, and resilience, with the Body Perception Questionnaire into an online Qualtrics survey distributed through the University of Louisville to the participants. We used a sliding bar answer format, in hopes that this would make answering easier for participants with limited hand mobility.

Pre-surveys were administered within four days of beginning training and post-surveys within four days of training completion. Pre- and post-surveys were identical except for two questions at the end of the post-survey: “Do you feel better?” and “Is there anything else you would like us to know?” With a small sample size such as ours (N=13) we knew significance would be difficult to determine, but the possibility of a clinical effect could be elucidated through these two qualitative questions.

Raw scores were transformed into T-Scores with validated scoring tables with open-source availability for all the surveys. Increased scores in bowel and bladder difficulties, anxiety, depression, pain, pressure ulcers, trauma, and autonomic reactivity would show worse functioning while increased scores in resilience, and interoception would show better functioning.

Results

Figure 29 shows the pre- and post-Tulsky Quality of Life T-scores; no significant difference was found between pre and post.

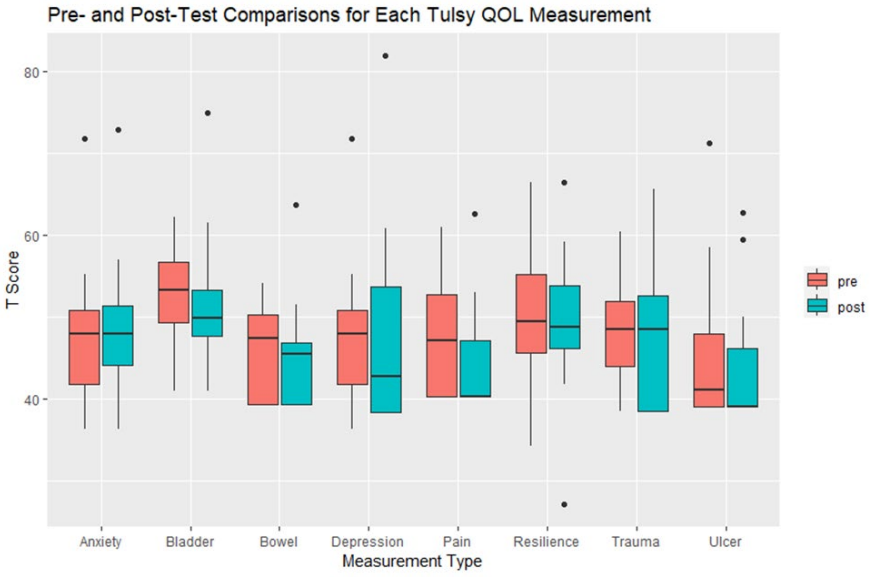

Figure 29: Tulsky Quality-of-Life for people with SCI scores showed no significant change from pre to post. Outcome measurements included bowel and bladder difficulties, anxiety, depression, pain, pressure ulcers, and trauma. In this box and whisker plot, the box represents the interquartile range. The lines extending up and down away from the box end in maxima and minima respectively. The line in the center of the box is the median. The dots above and below the boxes denote outliers.

Figure 30 shows the pre and post-test T Scores for the Body Perception Questionnaire.[8] No significant differences were found in pre or post.

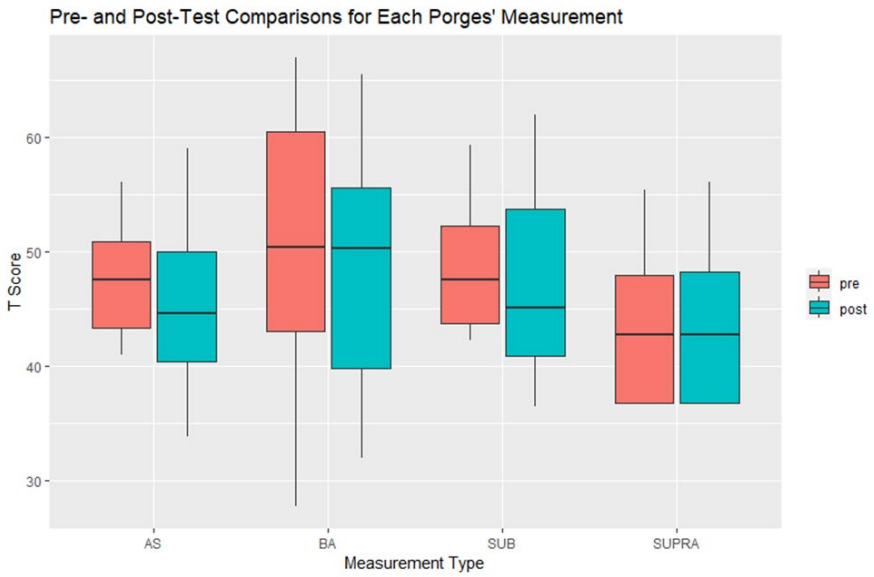

Figure 30: The Body Perception Questionnaire showed no significant change from pre to post. Body Awareness T-Scores: Supradiaphragmatic Reactivity (SUPRA), Subdiaphragmatic Activity (SUB), Body Awareness/Interoception.

Table 7 shows the (adjusted) p-values produced from a paired t-test, comparing the pre-and post-test results for each measurement's "T" column. The p-values are adjusted according to the Benjamini-Hochberg procedure to correct for multiple testing by decreasing the false positive rate. Please note that if every p-value is non-significant, this procedure may set each p-value to a common non-significant value, as seen with the Tulsky measurements.

Measurement	Adjusted P-values
Tulsky	
Bladder	0.879
Bowel	0.879
Ulcer	0.879
Anxiety	0.879
Depression	0.879
Pain	0.879
Trauma	0.879
Resilience	0.879
Porges	
Body Awareness (Interoception)	0.6
Supra-Diaphragmatic Reactivity	0.454
Sub-Diaphragmatic Reactivity	0.092
Autonomic Sensitivity	0.101

Table 7: Pre and post-values from the combined surveys of selected Tulsky QOL for SCI[227] surveys and the Body Awareness Questionnaire.[8] Neither showed significant change.

At the end of the post-survey, we asked participants two questions:

1. Is there anything else you would like to tell us?

2. Do you feel better?

Three participants responded to the first question:

1. “I enjoyed learning the breathing techniques and have incorporated them into my daily routine.”

2. “I have been using the technique for lowering my BP, almost every day either to calm down from a PTSD episode or to help me relax my entire body for sleep. It was amazing to learn how much can change with just breathing differently.”

3. “The breathing exercises have been useful in my normal life, especially the lowering BP side. It helps with calming racing thoughts and focus when I'm thinking about too many things at once. I suspect the breathing has been the most effective, but I also have "emotional blunting" due to medications, etc. so I rarely feel anything particularly strongly. I was impressed by how effective the breathing techniques were for that reason.”

Out of the 12 responses to "Do you feel better?" ten participants responded yes and two responded no.

Discussion

We did not find a significant quantitative difference in responses in the quality-of-life surveys or the interoception and autonomic reactivity surveys from pre to post. The written answers to the qualitative questions indicate the protocol may improve quality of life in areas such as improving sleep, reducing BP and PTSD, calming “racing thoughts”, improving focus, and “feeling better” in general. Respondents’ mean interoception percentile (49^{th}) indicates that people with cervical SCI may have the same levels of interoception as approximately half the population of NI people, despite their impaired sympathetic response.

CHAPTER VII

CONCLUSIONS

Biofeedback is efficacious in modifying BP in both NI and people with SCI as shown in previous studies.[5,6,100,101,180,181] In these previous studies of participants with SCI, the main research question was whether the autonomic nervous system adapted solely via cognitive focus, without skeletal muscle or respiratory influences on BP.[6,100,101] People with cervical SCI were included as participants in these studies not to create a tool for them to use, but because their paralysis eliminated the contribution of skeletal muscle to BP changes.

Our research group focused more on the development of a tool for BP modulation. Our concept is akin to high-intensity interval training in which brief periods of intense exercise rotate with relaxation or low-intensity exercise.[106] High-intensity interval training is more effective for positive cardiovascular adaptations than both continuous moderate exercise and continuous intense exercise by themselves.[106] Our 30 minutes of oscillating stimulation then relaxation training showed the most change in MAP acutely: most often during or just after the 30 second breathing portion. *Brahmari* was the breathing to lower BP, and *kapalabhati* was the breathing to increase BP.

Future directions include isolating the breathing to compare its efficacy with this protocol. Because BP increases with the stimulating breathing,

kapalabhati, it is important to point out that the participants only did three rounds of ten quick breaths for approximately 30 seconds in every three-minute cycle, with a normal breath in between the ten. We designed it this way to keep the breathing safe and to avoid over-stimulation. Though this breath could be useful during hypotensive episodes, it also has the potential to be abused, in for example, the dangerous athletic practice of intentionally inducing autonomic dysreflexia, known as "boosting" to improve athletic performance.[228] This is a possibility only if the breath were to be used for too long or used without quiet breathing in between the fast cycles. The acute, short-term increases found in our study make inducing autonomic dysreflexia unlikely, but further studies of the breathing methods would be warranted.

We found our protocol to be effective in modifying BP acutely during training and increasing HRV when comparing rest periods before and after training, but no significant change in HRV or BP was found in pre-post measurements. Despite most participants with SCI showing both cardiovagal and adrenergic abnormalities in pre-post testing, they had a success rate in relaxation cycles a range of 31-90%, and successful stimulation cycles a range of 30-88% percent of the time. The participant with SCI who was most successful at 88% of stimulation cycles, showed orthostatic hypotension both pre and post and had an AIS rating of A (motor complete). This participant's success in raising their MAP is an example of how ratings of complete injuries may not always be *autonomically* complete, or *discomplete*.[229] For modifying BP, the protocol may be most useful when acute changes are needed. Some of the examples of times

in which this protocol could be useful for people with SCI are during a bout of orthostatic intolerance, autonomic dysreflexia, transferring, exercise, sex, a bowel program, or even when trying to increase concentration on an activity due to hypotension's detrimental cognitive effects.

Our findings of increased HRV across spectra when comparing the five-minute rest periods before and after training invites future exercise research. People with cervical SCI have difficulty increasing HR during exercise, which limits beneficial cardiovascular adaptations.[230] This breathing could be added to an exercise protocol to determine possible HR improvement. Supporting this idea, studies of acute sympathetic stimulation through sperm removal in men with cervical SCI have shown improvement in left ventricular function. Our study could possibly be considered acute sympathetic stimulation during the *kapalabhati* stimulating breathing, though more direct sympathetic measurements would be warranted to confirm this. Most likely, the stimulating breathing BP increases were due to increased actions of the respiratory pump. Irrespective of the mechanistic origin, MAP variability increased during training, which could provide an adaptive cardiovascular challenge.

Some of our hypotheses were refuted. NI participants had more successful cycles and more changes in mmHg of MAP in these successful cycles than participants with SCI. However, when looking at total cycles, whether or not the cycles changed at least 5mmHg, there was no difference attributed to injured status. This similar overall data from both cohorts suggests an alternate BP

modification route for the participants with cervical SCI since their normal route of sympathetic vasoconstriction is compromised.

Virtual Reality and mental imagery had similar effectiveness on MAP changes. Since mental imagery is more difficult to produce than visual perception such as VR,[114,188] and mental imagery has the potential to be retraumatizing, VR could be a useful tool for BP modification. Also, in the virtual world, visual and motor frames of reference have been shown to create learning and spatial maps in the brain just as effectively as non-virtual visual perception.[209] For people with limited hand mobility, the technology of VR continues to advance with eye tracking and haptic improvements which could make rehabilitation both more fun and more effective for this population.

The surveys did not show quantitative changes in interoception or quality of life outcomes, yet the qualitative responses indicated the protocol could be useful for improving sleep, lowering BP, attenuating PTSD, calming “racing thoughts,” improving focus, and “feeling better” in general.

Several interesting findings in our study led to more questions we investigated in addition to our original proposal’s specific aims. HRV and BP variability showed significant changes during the rest periods before and after training; this led to our seeing if they correlated. The positive correlation we found could mean that acute volitional changes in BP (which occurred during the training) may be more cardioprotective than the many daily ups and downs of BP during the day for many people with SCI.

Specific HRV frequency analyses of the five- minute rest periods before and after training indicated an increase in all mechanisms of HRV change, especially RAAS (VLF), which could be less cardioprotective than if the changes were mostly in vagal (HF) or baroreflex (LF) changes. Evidence from the general population correlates increased RAAS with detrimental inflammation, vascular restructuring and vascular fibrosis, [231,232] although there also exists an alternate RAAS route that is beneficial and decreases inflammation.[29] In previous studies, people with cervical SCI have shown higher renin levels during orthostatic challenge than noninjured people which supports the possibility of increased RAAS being the mechanism for increased VLF HRV in our study.[169,233,234]

The HRV analyses compared the five-minute rest period before training to the five-minute rest period after training. The training itself was approximately 30 minutes. Thirty minutes is sufficient for RAAS to be a possible mechanism for these HRV changes.[30-33] These changes in HRV frequency may indicate mechanisms, but it would be important in future research to combine other knowledge with this, as many changes could have taken place due to the variety of molecular, mechanical, hormonal, and psychological influences on hemodynamic changes. It is also important to remember that all HRV spectra showed significant increases in both participants with SCI and NI participants: VLF, indicating possible RAAS influences, yet also increased vagal (HF) and baroreflex (LF) contributions.

Higher HRV is correlated with higher interoception.[39] Since our data showed HRV increases from the five minutes before training to the five minutes

after training, this creates an interesting perspective from which to frame new research questions. In SCI research, there is much focus on sensory and motor function, less on autonomic, and even less on interoception. But something as seemingly innocuous as feeling when you have to urinate, while not so important to the NI population, could be life-changing for someone with a SCI.

Our protocol of biofeedback using virtual reality, conscious interoception, and breathing exercises showed the most change in acute MAP during or just after the breathing potion of training, and HRV across spectra before and after the 30-minute training, possibly most influenced by RAAS, though this warrants further research including measurements of plasma renin levels. Heart rate variability measurements for people with altered autonomic nervous systems, such as people with cervical SCI, may show differing mechanisms, adaptations, and prognostic implications than NI people. This must be kept in mind for future studies. Autonomic biofeedback using VR, conscious interoception, and specific breathing exercises could be a useful tool for BP adjustments and HRV improvement for people with and without SCI.

REFERENCES

1. Kitzman P, Cecil D, Kolpek J. The risks of polypharmacy following spinal cord injury. *The journal of spinal cord medicine*. 2017 Mar 2017;40(2)doi:10.1179/2045772314Y.0000000235
2. Mestre H, Alkon T, Salazar S, Ibarra A. Spinal cord injury sequelae alter drug pharmacokinetics: an overview. *Spinal cord*. 2011 Sep 2011;49(9)doi:10.1038/sc.2011.58
3. Buckey J, Lane L, Levine B, et al. Orthostatic intolerance after spaceflight. *Journal of applied physiology (Bethesda, Md : 1985)*. 1996 Jul 1996;81(1)doi:10.1152/jappl.1996.81.1.7
4. Lackner JR, Dizio P. Space motion sickness. *Exp Brain Res*. Nov 2006;175(3):377-99. doi:10.1007/s00221-006-0697-y
5. Cowings PS. *Autogenic-feedback training : a potential treatment for post-flight orthostatic intolerance in aerospace crews*. NASA technical memorandum ; 108785. National Aeronautics and Space Administration, Ames Research Center ; [National Technical Information Service, distributor]; 1994.
6. Brucker B. *Learned Voluntary Control of Systolic BLood Pressure by Spinal Cord Injury Patients*. New York University; 1977.
7. Tulsky DS, Kisala PA, Victorson D, et al. Overview of the Spinal Cord Injury--Quality of Life (SCI-QOL) measurement system. *The journal of spinal cord medicine*. 2015;38(3):257-69. doi:10.1179/2045772315Y.0000000023
8. Cabrera A, Kolacz J, Pailhez G, Bulbena-Cabre A, Bulbena A, Porges SW. Assessing body awareness and autonomic reactivity: Factor structure and psychometric properties of the Body Perception Questionnaire-Short Form (BPQ-SF). *Int J Methods Psychiatr Res*. Jun 2018;27(2):e1596. doi:10.1002/mpr.1596
9. Ludwig Parker EP. Neuroanatomy, Central Nervous System (CNS). 2021;
10. Medical Dictionary by Merriam-Webster. 2022.
11. Purves D. *Neuroscience*. Sixth edition. ed. Oxford University Press; 2018.
12. Hanani M, Spray DC. Emerging importance of satellite glia in nervous system function and dysfunction. ReviewPaper. *Nature Reviews Neuroscience*. 2020-07-22 2020;21(9):485-498. doi:doi:10.1038/s41583-020-0333-z
13. Felten DL, O'Banion MK, Maida MS, Netter FH. *Netter's atlas of neuroscience*. Fourth edition. ed. Elsevier; 2022.
14. Sherwood L. *Human physiology : from cells to systems*. Ninth edition ed. Cengage Learning; 2016.
15. Catala Martin M. Gross anatomy and development of the peripheral nervous system. *Handbook of clinical neurology*. 2013;115:29-41.
16. Laborde S, Mosley, E et al. | Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research – Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Frontiers in Psychology*. 2017;8doi:doi:10.3389/fpsyg.2017.00213
17. Gerritsen RJS, Band GPH. Breath of Life: The Respiratory Vagal Stimulation Model of Contemplative Activity. *Frontiers in human neuroscience*. 2018;12:397. doi:10.3389/fnhum.2018.00397
18. Beran Roy R. Paraesthesia and peripheral neuropathy. *Australian family physician*. 44(3):92-5.
19. Oxford Languages and Google - English | Oxford Languages. 2022;
20. Khan Yusuf SY. Neuroanatomy, Spinal Cord. 2021;

21. Roberts TT, Leonard GR, Cepela DJ. Classifications In Brief: American Spinal Injury Association (ASIA) Impairment Scale. BriefCommunication. *Clinical Orthopaedics and Related Research®*. 2016-11-04 2016;475(5):1499-1504. doi:doi:10.1007/s11999-016-5133-4
22. Zavvarian MM, Hong J, Fehlings MG. The Functional Role of Spinal Interneurons Following Traumatic Spinal Cord Injury. *Frontiers in cellular neuroscience*. 2020;14:127. doi:10.3389/fncel.2020.00127
23. Kozlowska K, McLean L, Walker P, Carrive P. Fear and the Defense Cascade: Clinical Implications and Management. *Harvard Review of Psychiatry*. 2015;23(4):263-287. doi:10.1097/HRP.0000000000000065
24. Asmus SE, Parsons S, Landis SC. Developmental changes in the transmitter properties of sympathetic neurons that innervate the periosteum. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(4):1495-504.
25. AbuAlrob MA, Tadi P. Neuroanatomy, Nucleus Solitarius. Text. 2021/07/31 2021;doi:https://www.ncbi.nlm.nih.gov/books/NBK549831/
26. Breit S, Kupferberg A, Rogler G, Hasler G. Frontiers | Vagus Nerve as Modulator of the Brain–Gut Axis in Psychiatric and Inflammatory Disorders | Psychiatry. 2022;doi:doi:10.3389/fpsyt.2018.00044
27. Sparks M, Crowley S, Gurley S, Mirotsou M, Coffman T. Classical Renin-Angiotensin system in kidney physiology. *Comprehensive Physiology*. 2014 Jul 2014;4(3)doi:10.1002/cphy.c130040
28. Miller A, Arnold A. The renin-angiotensin system in cardiovascular autonomic control: recent developments and clinical implications. *Clinical autonomic research : official journal of the Clinical Autonomic Research Society*. 2019 Apr 2019;29(2)doi:10.1007/s10286-018-0572-5
29. Rodrigues Prestes T, Rocha N, Miranda A, Teixeira A, Simoes-E-Silva A. The Anti-Inflammatory Potential of ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Evidence from Basic and Clinical Research. *Current drug targets*. 2017 2017;18(11)doi:10.2174/1389450117666160727142401
30. Cowley A. Long-term control of arterial blood pressure. *Physiological reviews*. 1992 Jan 1992;72(1)doi:10.1152/physrev.1992.72.1.231
31. Kurtz A. Renin release: sites, mechanisms, and control. *Annual review of physiology*. 2011 2011;73doi:10.1146/annurev-physiol-012110-142238
32. Morganti A, Lopez-Ovejero J, Pickering T, Laragh J. Role of the sympathetic nervous system in mediating the renin response to head-up tilt. Their possible synergism in defending blood pressure against postural changes during sodium deprivation. *The American journal of cardiology*. 1979 Mar 1979;43(3)doi:10.1016/0002-9149(79)90019-5
33. Gideon A, Sauter C, Fieres J, Berger T, Renner B, Wirtz P. Kinetics and Interrelations of the Renin Aldosterone Response to Acute Psychosocial Stress: A Neglected Stress System. *The Journal of clinical endocrinology and metabolism*. 03/01/2020 2020;105(3)doi:10.1210/clinem/dgz190
34. Marías Jn, Appelbaum S, Strowbridge CC. *History of philosophy*. New York : Dover Publications, [1967]; 1967.
35. Clarke DM. Descartes's theory of mind. 2003 2003;
36. Feuerstein G, Wilber K. The yoga tradition : its history, literature, philosophy, and practice. ©1998 1998;
37. Kim J. Mind in a physical world : an essay on the mind-body problem and mental causation. ©1998 1998;
38. James W. *The Emotions, Vol 1*. Williams and Wilkins Co; 1922.

39. Porges SW. *The polyvagal theory : neurophysiological foundations of emotions, attachment, communication, and self-regulation*. 1st ed. ed. The Norton series on interpersonal neurobiology. W.W. Norton; 2011.
40. Thayer J, Lane R. A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of affective disorders*. 2000 Dec 2000;61(3)doi:10.1016/s0165-0327(00)00338-4
41. Jain NB, Ayers GD, Peterson EN, et al. Traumatic Spinal Cord Injury in the United States, 1993-2012. *JAMA : the journal of the American Medical Association*. 2015;313(22):2236. doi:10.1001/jama.2015.6250
42. Lasfargues JE, Custis D, Morrone F, Carswell J, Nguyen T. A model for estimating spinal cord injury prevalence in the United States. *Paraplegia*. 1995;33(2):62-8.
43. Ding W, Hu S, Wang P, et al. Spinal Cord Injury: The Global Incidence, Prevalence, and Disability From the Global Burden of Disease Study 2019. *Spine*. 11/01/2022 2022;47(21)doi:10.1097/BRS.0000000000004417
44. National Spinal Cord InjuryStatistical C. Spinal Cord Injury Facts and Figures at a Glance. *The journal of spinal cord medicine*. 2014;37(3):355-6.
45. Center NSCIS. Traumatic Spinal Cord Injury (SCI) Facts and Figures at a Glance 2023. https://www.nscisc.uab.edu/Public/Facts%202015.pdf
46. Wecht J, Krassioukov A, Alexander M, et al. International Standards to document Autonomic Function following SCI (ISAFSCI): Second Edition. *Topics in spinal cord injury rehabilitation*. Spring 2021 2021;27(2)doi:10.46292/sci2702-23
47. McKinley WO, Jackson AB, Cardenas DD, DeVivo MJ. Long-term medical complications after traumatic spinal cord injury: a regional model systems analysis. *Archives of physical medicine and rehabilitation*. 1999;80(11):1402-10.
48. Cragg J, Noonan V, Krassioukov A, Borisoff J. Cardiovascular disease and spinal cord injury: results from a national population health survey. *Neurology*. 08/20/2013 2013;81(8)doi:10.1212/WNL.0b013e3182a1aa68
49. Wu JC, Chen YC, Liu L, et al. Increased risk of stroke after spinal cord injury: a nationwide 4-year follow-up cohort study. *Neurology*. 2012;78(14):1051-7. doi:10.1212/WNL.0b013e31824e8eaa
50. Krassioukov A, Weaver L. Episodic hypertension due to autonomic dysreflexia in acute and chronic spinal cord-injured rats. *The American journal of physiology*. 1995 May 1995;268(5 Pt 2)doi:10.1152/ajpheart.1995.268.5.H2077
51. Eldahan K, Rabchevsky A. Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. *Autonomic neuroscience : basic & clinical*. 2018 Jan 2018;209:1-17. doi:10.1016/j.autneu.2017.05.002
52. Holmes G, Blanke E. Gastrointestinal dysfunction after spinal cord injury. *Experimental neurology*. 2019 Oct 2019;320doi:10.1016/j.expneurol.2019.113009
53. Karlsson A. Autonomic dysreflexia. *Spinal cord*. 1999 Jun 1999;37(6)doi:10.1038/sj.sc.3100867
54. Krassioukov A, Bunge R, Pucket W, Bygrave M. The changes in human spinal sympathetic preganglionic neurons after spinal cord injury. *Spinal cord*. 1999 Jan 1999;37(1):6-13. doi:10.1038/sj.sc.3100718
55. Krassioukov A, Weaver L. Morphological changes in sympathetic preganglionic neurons after spinal cord injury in rats. *Neuroscience*. 1996 Jan 1996;70(1)doi:10.1016/0306-4522(95)00294-s
56. Ravensbergen H, de Groot S, Post M, Slootman H, van der Woude L, Claydon V. Cardiovascular function after spinal cord injury: prevalence and progression of dysfunction

during inpatient rehabilitation and 5 years following discharge. *Neurorehabilitation and neural repair*. Mar-Apr 2014 2014;28(3)doi:10.1177/1545968313504542
57. Collins H, Rodenbaugh D, DiCarlo S. Spinal cord injury alters cardiac electrophysiology and increases the susceptibility to ventricular arrhythmias. *Progress in brain research*. 2006 2006;152:275-288. doi:10.1016/S0079-6123(05)52018-1
58. Alexander M, Marson L. The neurologic control of arousal and orgasm with specific attention to spinal cord lesions: Integrating preclinical and clinical sciences. *Autonomic neuroscience : basic & clinical*. 2018 Jan 2018;209:90-99. doi:10.1016/j.autneu.2017.01.005
59. Hou S, Rabchevsky A. Autonomic consequences of spinal cord injury. *Comprehensive Physiology*. 2014 Oct 2014;4(4)doi:10.1002/cphy.c130045
60. Gwak Y, Hulsebosch C. Neuronal hyperexcitability: a substrate for central neuropathic pain after spinal cord injury. *Current pain and headache reports*. 2011 Jun 2011;15(3):215-222. doi:10.1007/s11916-011-0186-2
61. Anderson KD. Targeting Recovery: Priorities of the Spinal Cord-Injured Population. *Journal of Neurotrauma*. 2004;21(10):1371-1383.
62. Popa C, Popa F, Grigorean VT, Onose G, Sandu AM, Popescu M. Vascular dysfunctions following spinal cord injury. *Journal of medicine and life*. Jul-Sep 2010 2010;3(3):275-285.
63. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology*. 1996-05-01 1996;46:1470. doi:10.1212/WNL.46.5.1470
64. Krassioukov A, Eng J, Warburton D, Teasell R. A systematic review of the management of orthostatic hypotension after spinal cord injury. *Archives of physical medicine and rehabilitation*. 2009 May 2009;90(5)doi:10.1016/j.apmr.2009.01.009
65. Hainsworth R, Al-Shamma YMH. Cardiovascular responses to upright tilting in healthy subjects. *Clinical Science*. 1988;74(1):17-22.
66. Claydon VE, Steeves JD, Krassioukov A. Orthostatic hypotension following spinal cord injury: understanding clinical pathophysiology. Review. *Spinal Cord*. Jun 2006;44(6):341-51. doi:10.1038/sj.sc.3101855
67. Calaresu F, Yardley C. Medullary Basal Sympathetic Tone. review-article. *Annual Reviews in Physiology*. 2003-11-28 1988;50:511-524. doi:10.1146/annurev.ph.50.030188.002455
68. Krassioukov A. Autonomic function following cervical spinal cord injury. *Respiratory physiology & neurobiology*. 2009;169(2):157-64. doi:10.1016/j.resp.2009.08.003
69. Curt A, Nitsche B, Rodic B, Schurch B, Dietz V. Assessment of autonomic dysreflexia in patients with spinal cord injury. *Journal of neurology, neurosurgery, and psychiatry*. 1997 May 1997;62(5):473-477. doi:10.1136/jnnp.62.5.473
70. Krassioukov AV, Furlan JC, Fehlings MG. Autonomic dysreflexia in acute spinal cord injury: an under-recognized clinical entity. Research Support, Non-U.S. Gov't. *J Neurotrauma*. Aug 2003;20(8):707-16. doi:10.1089/089771503767869944
71. Wanner A, Castillo C, Torres R, Terson de Paleville D. Asymptomatic Autonomic Dysreflexia After Postural Changes in SCI. *Journal of Clinical Exercise Physiology*. 2023;12((s1)):11.
72. Mathias CJ, Christensen NJ, Frankel HL, Spalding JM. Cardiovascular control in recently injured tetraplegics in spinal shock. *The Quarterly journal of medicine*. 1979 Apr 1979;48(190):273-287.
73. Biering-Sørensen F, Biering-Sørensen T, Liu N, Malmqvist L, Wecht JM, Krassioukov A. Alterations in cardiac autonomic control in spinal cord injury. *Autonomic neuroscience : basic & clinical*. 2018 Jan 2018;209:4-18. doi:10.1016/j.autneu.2017.02.004

74. Lopes P, Figoni S, Perkash I. Upper limb exercise effect on tilt tolerance during orthostatic training of patients with spinal cord injury. *Archives of physical medicine and rehabilitation*. 1984 May 1984;65(5)
75. Faghri P, Yount J. Electrically induced and voluntary activation of physiologic muscle pump: a comparison between spinal cord-injured and able-bodied individuals. *Clinical rehabilitation*. 2002 Dec 2002;16(8)doi:10.1191/0269215502cr570oa
76. Helmi M, Lima A, Gommers D, van Bommel J, Bakker J. Inflatable external leg compression prevents orthostatic hypotension in a patient with a traumatic cervical spinal cord injury. *Future cardiology*. 2013 Sep 2013;9(5)doi:10.2217/fca.13.60
77. Young T, Mathias C. The effects of water ingestion on orthostatic hypotension in two groups of chronic autonomic failure: multiple system atrophy and pure autonomic failure. *Journal of neurology, neurosurgery, and psychiatry*. 2004 Dec 2004;75(12)doi:10.1136/jnnp.2004.038471
78. Ten Harkel A, Van Lieshout J, Wieling W. Treatment of orthostatic hypotension with sleeping in the head-up tilt position, alone and in combination with fludrocortisone. *Journal of internal medicine*. 1992 Aug 1992;232(2)doi:10.1111/j.1365-2796.1992.tb00563.x
79. Schwartz M, Andrasik, F. *Biofeedback, Fourth Edition*. 2022.
80. Tan G, Shaffer F, Lyle R, Teo I. *Evidence-based Practice in Biofeedback and Neurofeedback - Google Books*. AAPB; 2016.
81. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs Drug Treatment for Urge Urinary Incontinence in Older Women: A Randomized Controlled Trial. *JAMA : the journal of the American Medical Association*. 2022;280(23):1995-2000. doi:10.1001/jama.280.23.1995
82. Rice KM, Blanchard EB, Purcell M. Biofeedback treatments of generalized anxiety disorder: Preliminary results. OriginalPaper. *Biofeedback and Self-regulation*. 2022;18(2):93-105. doi:doi:10.1007/BF01848110
83. Gevensleben H, Holl B, Albrecht B, et al. Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. *Journal of child psychology and psychiatry, and allied disciplines*. 2009 Jul 2009;50(7)doi:10.1111/j.1469-7610.2008.02033.x
84. Corrado P, Gottlieb H, Abdelhamid LH. The Effect of Biofeedback and Relaxation Training on Anxiety and Somatic Complaints in Chronic Pain Patients. *American Journal of Pain Management*. 2003;13:133-9.
85. Bassotti G, Chistolini F, Sietchiping-Nzepa F, Roberto Gd, Morelli A, Chiarioni G. Biofeedback for pelvic floor dysfunction in constipation. 2004-02-12 2004;doi:10.1136/bmj.328.7436.393
86. Linden W, Moseley JV. The Efficacy of Behavioral Treatments for Hypertension. OriginalPaper. *Applied Psychophysiology and Biofeedback*. 2006-03-25 2006;31(1):51-63. doi:doi:10.1007/s10484-006-9004-8
87. Stout C, Toscano W, Cowings P. Reliability of Psychophysiological Responses Across Multiple Motion Sickness Stimulation Tests - IOS Press. Text. 2022;
88. Karavidas MK, Tsai P-S, Yucha C, McGrady A, Lehrer PM. Thermal Biofeedback for Primary Raynaud's Phenomenon: A Review of the Literature. OriginalPaper. *Applied Psychophysiology and Biofeedback*. 2006-10-03 2006;31(3):203-216. doi:doi:10.1007/s10484-006-9018-2
89. Crider A, Glaros AG, Gevirtz RN. Efficacy of Biofeedback-Based Treatments for Temporomandibular Disorders. OriginalPaper. *Applied Psychophysiology and Biofeedback*. 2022;30(4):333-345. doi:doi:10.1007/s10484-005-8420-5
90. Sokhadze TM, Cannon RL, Trudeau DL. EEG Biofeedback as a Treatment for Substance Use Disorders: Review, Rating of Efficacy, and Recommendations for Further Research.

ReviewPaper. *Applied Psychophysiology and Biofeedback*. 2008-01-24 2008;33(1):1-28. doi:doi:10.1007/s10484-007-9047-5
91. Young LD, Bradley LA, Turner RA. Decreases in health care resource utilization in patients with rheumatoid arthritis following a cognitive behavioral intervention. OriginalPaper. *Biofeedback and Self-regulation*. 2022;20(3):259-268. doi:doi:10.1007/BF01474517
92. Jablon SL, Naliboff BD, Gilmore SL, Rosenthal MJ. Effects of Relaxation Training on Glucose Tolerance and Diabetic Control in Type II Diabetes. OriginalPaper. *Applied Psychophysiology and Biofeedback*. 2022;22(3):155-169. doi:doi:10.1023/A:1026259725197
93. Solomon MJ, Pager CK, Rex J, Roberts R, Manning J. Randomized, Controlled Trial of Biofeedback With Anal Manometry, Transanal Ultrasound, or Pelvic Floor Retraining With Digital Guidance Alone in the Treatment of Mild to Moderate Fecal Incontinence. OriginalPaper. *Diseases of the Colon & Rectum*. 2022;46(6):703-710. doi:doi:10.1007/s10350-004-6643-9
94. Andorfer R. Extending the Efficacy of a Thermal Biofeedback Treatment Package to the Management of Tension-type Headaches in Children - Arndorfer - 2001 - Headache: The Journal of Head and Face Pain - Wiley Online Library. 2022;doi:10.1046/j.1526-4610.2001.111006183.x
95. NIH Technology Assessment Panel on Integration of Behavioral and Relaxation Approaches into the Treatment of Chronic Pain and Insomnia. *Journal of the American Medical Association*. 1996;276:313-18.
96. Hammond D. Can LENS Neurofeedback Treat Anosmia Resulting from a Head Injury? research-article. *http://dxdoiorg/101300/J184v11n01_06*. 8 Sep 2008 2008;doi:Journal of Neurotherapy, Vol. 11, No. 1, 2007: pp. 57–62
97. Van Kampen M, de Weerdt W, al e. Effect of Pelvic Floor Re-Education on Duration and Degree of Incontinence After Radical Prostatectomy: a randomised control trial. *Lancet*. 2000;355:98-102.
98. Glazer H. Treatment of Vulvar Vestibulitis Syndrome With... : Obstetrical & Gynecological Survey. *Journal of Reproductive Medicine*. 1995;40:283-90.
99. Miller N, Dollard J. *Social Learning and Imitation*. 1941.
100. Brucker B, Ince L. Biofeedback as an experimental treatment for postural hypotension in a patient with a spinal cord lesion. *Archives of physical medicine and rehabilitation*. 1977 Feb 1977;58(2):49-53.
101. Ince L. Biofeedback as a Treatment for Postural Hypotension. *Psychosomatic Medicine*. 1985;47, No2:182-188.
102. Miller N. Learning of Visceral and Glandular Responses. *Science*. 1969;163:434-435.
103. Pramanik T, Pudasaini B, Prajapati R. Immediate effect of a slow pace breathing exercise Bhramari pranayama on blood pressure and heart rate. *Nepal Medical College journal : NMCJ*. 2010;12(3):154-7.
104. Maheshkumar K, Dilara K, Ravishankar P, Julius A. Immediate Effects of Bhramari Pranayama on Resting Cardiovascular Parameters in Healthy Adolescents. *Journal of Clinical and Diagnostic Research*.10(5):CC17-CC19. doi:10.7860/JCDR/2016/19202.7894
105. Stancák A, Jr., Kuna M, Srinivasan, Vishnudevananda S, Dostálek C. Kapalabhati--yogic cleansing exercise. I. Cardiovascular and respiratory changes. *Homeostasis in health and disease : international journal devoted to integrative brain functions and homeostatic systems*. 1991;33(3):126-34.
106. MacInnis M, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity. *The Journal of physiology*. 05/01/2017 2017;595(9)doi:10.1113/JP273196
107. Navarrete-Opazo A, Vinit S, Dougherty BJ, Mitchell GS. Daily acute intermittent hypoxia elicits functional recovery of diaphragm and inspiratory intercostal muscle activity after acute

cervical spinal injury. *Experimental neurology*. Feb 14 2015;266C:1-10. doi:10.1016/j.expneurol.2015.02.007
108. Smit A, Timmers H, Wieling W, et al. Long-term effects of carotid sinus denervation on arterial blood pressure in humans. *Circulation*. 03/19/2002 2002;105(11)doi:10.1161/hc1102.105744
109. Stasieńko A, Sarzyńska-Dluglosz I. Virtual Reality in Neurorehabilitation. *Advances in Rehabilitation v30 n4 (20161201): 67-75*. 2022;doi:10.1515/rehab-2015-0056
110. LaViola J. A Discussion of Cybersickness in Virtual Environments. *ACM SIGCHI Bulletin*. 2000;32:47-56.
111. Kourtesis P, Collina S, Doumas L, MacPherson S. Frontiers | Technological Competence Is a Pre-condition for Effective Implementation of Virtual Reality Head Mounted Displays in Human Neuroscience: A Technological Review and Meta-Analysis | Human Neuroscience. 2022;doi:doi:10.3389/fnhum.2019.00342
112. Ma H, Bian, Y, Wang, Y, Zhou, C. Exploring the effect of virtual reality relaxation environment on white coat hypertension in blood pressure measurement | Elsevier Enhanced Reader. *J Biomed Inform*. 2022;doi:10.1016/j.jbi.2021.103721
113. Allebach JP, Rogowitz BE, Stark LW, et al. How virtual reality works: illusions of vision in "real" and virtual environments. SPIE; 1995:277-287.
114. Dentico D, Cheung B, Chang J, et al. Reversal of cortical information flow during visual imagery as compared to visual perception. *NeuroImage*. 10/15/2014 2014;100doi:10.1016/j.neuroimage.2014.05.081
115. Kosunen I, Salminen M, Järvelä S, Ruonala A, Ravaja N, Jacucci G. RelaWorld Neuroadaptive and Immersive Virtual Reality Meditation System. 2016 2016;doi:10.1145/2856767.2856796
116. Hoffman HGP, Chambers GTRN, Meyer WJMDP, et al. Virtual Reality as an Adjunctive Non-pharmacologic Analgesic for Acute Burn Pain During Medical Procedures. *Annals of Behavioral Medicine*. 2011;41(2):183-191. doi:10.1007/s12160-010-9248-7
117. Austin PD, Siddall PJ. Virtual reality for the treatment of neuropathic pain in people with spinal cord injuries: A scoping review. *The Journal of Spinal Cord Medicine*. 2021;44(1):8-18. doi:10.1080/10790268.2019.1575554
118. Cheung KLM, Tunik EPTPD, Adamovich SVPD, Boyd LA. Neuroplasticity and Virtual Reality. *Virtual Reality for Physical and Motor Rehabilitation*. New York, NY : Springer New York : Springer; 2014:5-24. *Virtual Reality Technologies for Health and Clinical Applications 2199-4692*.
119. Luthe W, Schultz JH. *Autogenic therapy*. Grune & Stratton; 1969.
120. Frank DL, Khorshid L, Kiffer JF, Moravec CS, McKee MG. Biofeedback in medicine: who, when, why and how? *Mental health in family medicine*. 2010 Jun 2010;7(2):85-91.
121. Cowings PS, Toscano WB. Autogenic-feedback training exercise is superior to promethazine for control of motion sickness symptoms. *Journal of clinical pharmacology*. 2000;40(10):1154-65.
122. Scott JM, Warburton DE, Williams D, Whelan S, Krassioukov A. Challenges, concerns and common problems: physiological consequences of spinal cord injury and microgravity. *Spinal Cord*. Jan 2011;49(1):4-16. doi:10.1038/sc.2010.53
123. LeBlanc A, Rowe R, Schneider V, Evans H, Hedrick T. Regional muscle loss after short duration spaceflight. *Aviation, space, and environmental medicine*. 1995 Dec 1995;66(12)
124. Trappe S, Costill D, Gallagher P, et al. Exercise in space: human skeletal muscle after 6 months aboard the International Space Station. *Journal of applied physiology (Bethesda, Md : 1985)*. 2009 Apr 2009;106(4)doi:10.1152/japplphysiol.91578.2008

125. LeBlanc A, Schneider V, Shackelford L, et al. Bone mineral and lean tissue loss after long duration space flight. *Journal of musculoskeletal & neuronal interactions*. 2000 Dec 2000;1(2)
126. Wilmet E, Ismail A, Heilporn A, Welraeds D, Bergmann P. Longitudinal study of the bone mineral content and of soft tissue composition after spinal cord section. *Paraplegia*. 1995 Nov 1995;33(11)doi:10.1038/sc.1995.141
127. de Groot PC, van Dijk A, Dijk E, Hopman MT. Preserved cardiac function after chronic spinal cord injury. *Arch Phys Med Rehabil*. Sep 2006;87(9):1195-200. doi:10.1016/j.apmr.2006.05.023
128. Perhonen M, Franco F, Lane L, et al. Cardiac atrophy after bed rest and spaceflight. *Journal of applied physiology (Bethesda, Md : 1985)*. 2001 Aug 2001;91(2)doi:10.1152/jappl.2001.91.2.645
129. Whitson P, Pietrzyk R, Morukov B, Sams C. The risk of renal stone formation during and after long duration space flight. *Nephron*. 2001 Nov 2001;89(3)doi:10.1159/000046083
130. Favazza T, Midha M, Martin J, Grob B. Factors influencing bladder stone formation in patients with spinal cord injury. *The journal of spinal cord medicine*. 2004 2004;27(3)doi:10.1080/10790268.2004.11753756
131. Cruse J, Keith J, Bryant M, Lewis R. Immune system-neuroendocrine dysregulation in spinal cord injury. *Immunologic research*. 1996 1996;15(4)doi:10.1007/BF02935314
132. Mills P, Meck J, Waters W, D'Aunno D, Ziegler M. Peripheral leukocyte subpopulations and catecholamine levels in astronauts as a function of mission duration. *Psychosomatic medicine*. 2001 Nov-Dec 2001;63(6)doi:10.1097/00006842-200111000-00006
133. Ivanenko Y, Poppele R, Lacquaniti F. Distributed neural networks for controlling human locomotion: lessons from normal and SCI subjects. *Brain research bulletin*. 01/15/2009 2009;78(1)doi:10.1016/j.brainresbull.2008.03.018
134. Clément G, Reschke M, Wood S. Neurovestibular and sensorimotor studies in space and Earth benefits. *Current pharmaceutical biotechnology*. 2005 Aug 2005;6(4)doi:10.2174/1389201054553716
135. Cowings PS, Toscano WB, Miller NE, et al. Autogenic-feedback training: a potential treatment for orthostatic intolerance in aerospace crews. *J Clin Pharmacol*. Jun 1994;34(6):599-608.
136. Rashed H, Cowings P, Toscano W, et al. NASA biofeedback training exercise as an alternative method in treating patients with chronic GI symptoms. Abstract. *American Journal Of Gastroenterology*. 09/01/online 2000;95:2470. doi:10.1111/j.1572-0241.2000.02560.x
137. De Couck M, Caers R, Musch L, Fliegauf J, Giangreco A, Gidron Y. How breathing can help you make better decisions: Two studies on the effects of breathing patterns on heart rate variability and decision-making in business cases. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*. 2019 May 2019;139doi:10.1016/j.ijpsycho.2019.02.011
138. Van Hedel HJA, Wirth B, Dietz V. Limits of locomotor ability in subjects with a spinal cord injury. OriginalPaper. *Spinal Cord*. 2005-05-31 2005;43(10):593-603. doi:doi:10.1038/sj.sc.3101768
139. Tandon S, Kambi N, Lazar L, Mohammed H, Jain N. Large-Scale Expansion of the Face Representation in Somatosensory Areas of the Lateral Sulcus after Spinal Cord Injuries in Monkeys. 2009-09-23 2009;doi:10.1523/JNEUROSCI.2118-09.2009
140. Wrigley PJ, Press SR, Gustin SM, et al. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain*. 2009;141(1-2):52-59. doi:10.1016/j.pain.2008.10.007

141. Berger M, Kimpinski K, Currie K, Nouraei H, Sadeghi M, Krassioukov A. Multi-Domain Assessment of Autonomic Function in Spinal Cord Injury Using a Modified Autonomic Reflex Screen. *Journal of neurotrauma*. 09/15/2017 2017;34(18)doi:10.1089/neu.2016.4888
142. Vaschillo E, Lehrer P, Rishe N, Konstantinov M. Heart rate variability biofeedback as a method for assessing baroreflex function: a preliminary study of resonance in the cardiovascular system. *Applied psychophysiology and biofeedback*. 2002 Mar 2002;27(1)doi:10.1023/a:1014587304314
143. Bandura A. Social Cognitive Theory of Self-Regulation. *Organizational Behavior and Human Decision Processes*. 1991;50(2):248. doi:10.1016/0749-5978(91)90022-L
144. Resick PA, Schnicke MK. Cognitive Processing Therapy for Sexual Assault Victims. *Journal of consulting and clinical psychology*. 1992;60(5):748-56.
145. Sakaki M, Yoo HJ, Nga L, Lee T-H, Thayer JF, Mather M. Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults. *NeuroImage*. 2016;139:44-52. doi:10.1016/j.neuroimage.2016.05.076
146. Mather M, Thayer J. How heart rate variability affects emotion regulation brain networks. *Current opinion in behavioral sciences*. 2018;19:98-104. doi:10.1016/j.cobeha.2017.12.017
147. Patañjali, Hartranft C. *The Yoga-Sūtra of Patañjali : a new translation with commentary*. Shambhala pocket library. Shambhala Publications, Inc.; 2019.
148. Blizard DA, Cowings P, Miller NE. Visceral responses to opposite types of autogenic-training imagery. *Biological Psychology*. 1975;3(1):49-55. doi:10.1016/0301-0511(75)90005-8
149. Miller R. *The iRest program for healing PTSD : a proven-effective approach to using Yoga nidra meditation and deep relaxation techniques to overcome trauma*. New Harbinger Publications; 2015.
150. Brewer J, Worhunsky P, Gray J, Tang Y, Weber J, Kober H. Meditation experience is associated with differences in default mode network activity and connectivity. *Proceedings of the National Academy of Sciences of the United States of America*. 12/13/2011 2011;108(50)doi:10.1073/pnas.1112029108
151. Oku K, Ishida H, Okada Y, Hiraoka K. Facilitation of corticospinal excitability during motor imagery of wrist movement with visual or quantitative inspection of EMG activity. *Perceptual and motor skills*. 2011;113(3):982-94.
152. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation*. 1991 Aug 1991;84(2)doi:10.1161/01.cir.84.2.482
153. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein D. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Clinical autonomic research : official journal of the Clinical Autonomic Research Society*. 2011 Jun 2011;21(3)doi:10.1007/s10286-010-0098-y
154. Taylor J, Carr D, Myers C, Eckberg D. Mechanisms underlying very-low-frequency RR-interval oscillations in humans. *Circulation*. 08/11/1998 1998;98(6)doi:10.1161/01.cir.98.6.547
155. Akselrod S, Gordon D, Ube lF, Shannon D, Berger A, Cohen R. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science (New York, NY)*. 07/10/1981 1981;213(4504)doi:10.1126/science.6166045
156. Bonaduce D, Marciano F, Petretta M, et al. Effects of converting enzyme inhibition on heart period variability in patients with acute myocardial infarction. *Circulation*. 1994 Jul 1994;90(1)doi:10.1161/01.cir.90.1.108
157. Torres R, Rashed H, Mathur P, Castillo C, Abell T, Terson de Paleville D. Autogenic biofeedback training improves autonomic responses in a participant with cervical motor

complete spinal cord injury- case report. *Spinal cord series and cases*. 07/12/2023 2023;9(1)doi:10.1038/s41394-023-00593-3
158. Thomas G. Neural control of the circulation. *Advances in physiology education*. 2011 Mar 2011;35(1)doi:10.1152/advan.00114.2010
159. Furness J. Types of neurons in the enteric nervous system. *Journal of the autonomic nervous system*. 07/03/2000 2000;81(1-3)doi:10.1016/s0165-1838(00)00127-2
160. Squair J, Dhaliwal R, Cragg J, Charbonneau R, Grant C, Phillips A. National Survey of Bladder and Gastrointestinal Dysfunction in People with Spinal Cord Injury. *Journal of neurotrauma*. 06/15/2019 2019;36(12)doi:10.1089/neu.2018.5967
161. Sharif S, Jazaib Ali M. Outcome Prediction in Spinal Cord Injury: Myth or Reality. *World neurosurgery*. 2020 Aug 2020;140doi:10.1016/j.wneu.2020.05.043
162. Waddimba A, Jain N, Stolzmann K, et al. Predictors of cardiopulmonary hospitalization in chronic spinal cord injury. *Archives of physical medicine and rehabilitation*. 2009 Feb 2009;90(2)doi:10.1016/j.apmr.2008.07.026
163. Winslow E, Lesch M, Talano J, Meyer P. Spinal cord injuries associated with cardiopulmonary complications. *Spine*. 1986 Oct 1986;11(8)doi:10.1097/00007632-198610000-00014
164. White A, Holmes G. Anatomical and Functional Changes to the Colonic Neuromuscular Compartment after Experimental Spinal Cord Injury. *Journal of neurotrauma*. 05/01/2018 2018;35(9)doi:10.1089/neu.2017.5369
165. Frias B, Phillips A, Squair J, Lee A, Laher I, Krassioukov A. Reduced colonic smooth muscle cholinergic responsiveness is associated with impaired bowel motility after chronic experimental high-level spinal cord injury. *Autonomic neuroscience : basic & clinical*. 2019 Jan 2019;216doi:10.1016/j.autneu.2018.08.005
166. den Braber-Ymker M, Lammens M, van Putten M, Nagtegaal I. The enteric nervous system and the musculature of the colon are altered in patients with spina bifida and spinal cord injury. *Virchows Archiv : an international journal of pathology*. 2017 Feb 2017;470(2)doi:10.1007/s00428-016-2060-4
167. Brading A, Ramalingam T. Mechanisms controlling normal defecation and the potential effects of spinal cord injury. *Progress in brain research*. 2006 2006;152doi:10.1016/S0079-6123(05)52023-5
168. Holmes G. Upper gastrointestinal dysmotility after spinal cord injury: is diminished vagal sensory processing one culprit? *Frontiers in physiology*. 07/17/2012 2012;3doi:10.3389/fphys.2012.00277
169. Mathias C, Christensen N, Corbett J, Frankel H, Goodwin T, Peart W. Plasma catecholamines, plasma renin activity and plasma aldosterone in tetraplegic man, horizontal and tilted. *Clinical science and molecular medicine*. 1975 Oct 1975;49(4)doi:10.1042/cs0490291
170. Logan A, Freeman J, Pooler J, et al. Effectiveness of non-pharmacological interventions to treat orthostatic hypotension in elderly people and people with a neurological condition: a systematic review. *JBI evidence synthesis*. 2020 Dec 2020;18(12)doi:10.11124/JBISRIR-D-18-00005
171. Muth ER. Motion and space sickness: intestinal and autonomic correlates. *Autonomic neuroscience : basic & clinical*. Oct 30 2006;129(1-2):58-66. doi:10.1016/j.autneu.2006.07.020
172. LaCount LT, Barbieri R, Park K, et al. Static and dynamic autonomic response with increasing nausea perception. *Aviation, space, and environmental medicine*. Apr 2011;82(4):424-33.

173. Cowings PS, Ames Research C. *Autogenic-feedback training : a potential treatment for post-flight orthostatic intolerance in aerospace crews*. NASA technical memorandum ; 108785. National Aeronautics and Space Administration, Ames Research Center ;

[National Technical Information Service, distributor]; 1994.
174. Rashed H, Cutts T, Abell T, et al. Predictors of response to a behavioral treatment in patients with chronic gastric motility disorders. *Dig Dis Sci*. May 2002;47(5):1020-6.
175. Shine A, Mathur P, Ahmed S, et al. Low-Resolution Electrogastrogram at Baseline and Response to Temporary Gastric Electrical Stimulation-A Comparison of Cutaneous With Mucosal Recordings. *Neuromodulation : journal of the International Neuromodulation Society*. 2022 Dec 2022;25(8)doi:10.1016/j.neurom.2021.12.008
176. Phillips A, Krassioukov A, Ainslie P, Cote A, Warburton D. Increased central arterial stiffness explains baroreflex dysfunction in spinal cord injury. *Journal of neurotrauma*. 06/15/2014 2014;31(12):1122-1128. doi:10.1089/neu.2013.3280
177. Dorlas J, Nijboer J. Photo-electric plethysmography as a monitoring device in anaesthesia. Application and interpretation. *British journal of anaesthesia*. 1985 May 1985;57(5):524-530. doi:10.1093/bja/57.5.524
178. Naef AC, Jeitziner M-M, Knobel SEJ, et al. Investigating the role of auditory and visual sensory inputs for inducing relaxation during virtual reality stimulation. OriginalPaper. *Scientific Reports*. 2022-10-12 2022;12(1):1-11. doi:doi:10.1038/s41598-022-21575-9
179. Pearson J, Naselaris T, Holmes E, Kosslyn S. Mental Imagery: Functional Mechanisms and Clinical Applications. *Trends in cognitive sciences*. 2015 Oct 2015;19(10):590. doi:10.1016/j.tics.2015.08.003
180. Yucha C, Clark L, Smith M, Uris P, LaFleur B, Duval S. The effect of biofeedback in hypertension. Text. 2001 2001;doi:https://www.ncbi.nlm.nih.gov/books/NBK68765/
181. Nolan R, Floras J, Harvey P, et al. Behavioral neurocardiac training in hypertension: a randomized, controlled trial. *Hypertension (Dallas, Tex : 1979)*. 2010 Apr 2010;55(4)doi:10.1161/HYPERTENSIONAHA.109.146233
182. Yu L, Lin I, Fan S, Chien C, Lin T. One-Year Cardiovascular Prognosis of the Randomized, Controlled, Short-Term Heart Rate Variability Biofeedback Among Patients with Coronary Artery Disease. *International journal of behavioral medicine*. 2018 Jun 2018;25(3)doi:10.1007/s12529-017-9707-7
183. Lüddecke R, Felnhofer A. Virtual Reality Biofeedback in Health: A Scoping Review. ReviewPaper. *Applied Psychophysiology and Biofeedback*. 2021-12-03 2021;47(1):1-15. doi:doi:10.1007/s10484-021-09529-9
184. Martens M, Antley A, Freeman D, Slater M, Harrison P, Tunbridge E. It feels real: physiological responses to a stressful virtual reality environment and its impact on working memory. *Journal of psychopharmacology (Oxford, England)*. 2019 Oct 2019;33(10)doi:10.1177/0269881119860156
185. Park J, Marvar PJ, Liao P, et al. Baroreflex dysfunction and augmented sympathetic nerve responses during mental stress in veterans with post-traumatic stress disorder. *J Physiol*. Jul 15 2017;595(14):4893-4908. doi:10.1113/JP274269
186. Cui J, Wilson TE, Crandall CG. Baroreflex modulation of muscle sympathetic nerve activity during cold pressor test in humans. *American journal of physiology Heart and circulatory physiology*. 2002 May 2002;282(5)doi:10.1152/ajpheart.00899.2001
187. Ishai A, Sagi D. Common mechanisms of visual imagery and perception. *Science (New York, NY)*. 06/23/1995 1995;268(5218)doi:10.1126/science.7792605

188. Koenig-Robert R, Pearson J. Why do imagery and perception look and feel so different? *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 2021 Feb 2021;376(1817)doi:10.1098/rstb.2019.0703
189. Anticevic A, Hu X, Xiao Y, et al. Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 01/07/2015 2015;35(1)doi:10.1523/JNEUROSCI.2310-14.2015
190. Bhasin MK, Denninger JW, Huffman JC, et al. Specific Transcriptome Changes Associated with Blood Pressure Reduction in Hypertensive Patients After Relaxation Response Training. *J Altern Complement Med*. May 2018;24(5):486-504. doi:10.1089/acm.2017.0053
191. Dusek JA, Chang BH, Zaki J, et al. Association between oxygen consumption and nitric oxide production during the relaxation response. *Medical science monitor : international medical journal of experimental and clinical research*. 2006 Jan 2006;12(1)
192. Benson H, Beary JF, Carol MP. The relaxation response. *Psychiatry*. 1974 Feb 1974;37(1)doi:10.1080/00332747.1974.11023785
193. Sluyter D. *Natural Meditation*. Tarcher Perigee; 2015.
194. Bhasin MK, Dusek JA, Chang BH, et al. Relaxation response induces temporal transcriptome changes in energy metabolism, insulin secretion and inflammatory pathways. *PloS one*. 05/01/2013 2013;8(5)doi:10.1371/journal.pone.0062817
195. Thorin E, Atkinson J. Modulation by the endothelium of sympathetic vasoconstriction in an in vitro preparation of the rat tail artery. *British journal of pharmacology*. 1994 Jan 1994;111(1)doi:10.1111/j.1476-5381.1994.tb14067.x
196. Toda N, Kitamura Y, Okamura T. Neural mechanism of hypertension by nitric oxide synthase inhibitor in dogs. *Hypertension (Dallas, Tex : 1979)*. 1993 Jan 1993;21(1)doi:10.1161/01.hyp.21.1.3
197. MacLean MR, Graham J, McGrath JC. Endogenous nitric oxide modulates vasopressor responses, but not depressor responses, to spinal sympathetic nerve stimulation in pithed rats. *Journal of cardiovascular pharmacology*. 1994 Feb 1994;23(2)
198. Vanhoutte PM, Rubanyi GM, Miller VM, Houston DS. Modulation of vascular smooth muscle contraction by the endothelium. *Annual review of physiology*. 1986 1986;48doi:10.1146/annurev.ph.48.030186.001515
199. Tomasino B, Fabbro F. Editorial: Neuroimaging and Neuropsychology of Meditation States. *Frontiers in psychology*. 11/19/2015 2015;6doi:10.3389/fpsyg.2015.01757
200. Cambridge Dictionary. In: Press CU, editor. 2020.
201. Association AP, ed. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth ed. 2013.
202. Li BJ. (PDF) A Public Database of Immersive VR Videos with Corresponding Ratings of Arousal, Valence, and Correlations between Head Movements and Self Report Measures. 2022;doi:http://dx.doi.org/10.3389/fpsyg.2017.02116
203. Lewis T. Studies of the relationship between respiration and blood-pressure: Part II. Facts bearing on the relationship of different factors in the production of respiratory curves of blood-pressure. *The Journal of physiology*. 08/12/1908 1908;37(3)doi:10.1113/jphysiol.1908.sp001267
204. Berntson G, Norman G, Hawkley L, Cacioppo J. Cardiac autonomic balance versus cardiac regulatory capacity. *Psychophysiology*. 2008 Jul 2008;45(4)doi:10.1111/j.1469-8986.2008.00652.x
205. Dekker J, Schouten E, Klootwijk P, Pool J, Swenne C, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged

and elderly men. The Zutphen Study. *American journal of epidemiology*. 05/15/1997 1997;145(10)doi:10.1093/oxfordjournals.aje.a009049
206. Tsuji H, Venditti F, Manders E, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation*. 1994 Aug 1994;90(2)doi:10.1161/01.cir.90.2.878
207. Ruddle R, Lessels S. For efficient navigational search, humans require full physical movement, but not a rich visual scene. *Psychological science*. 2006 Jun 2006;17(6)doi:10.1111/j.1467-9280.2006.01728.x
208. Chrastil E, Warren W. Active and passive spatial learning in human navigation: acquisition of survey knowledge. *Journal of experimental psychology Learning, memory, and cognition*. 2013 Sep 2013;39(5)doi:10.1037/a0032382
209. Huffman D, Ekstrom A. A Modality-Independent Network Underlies the Retrieval of Large-Scale Spatial Environments in the Human Brain. *Neuron*. Nov 6, 2019 2019;104(3):611-622.
210. Novak P. Quantitative autonomic testing. *Journal of visualized experiments : JoVE*. 07/19/2011 2011;(53)doi:10.3791/2502
211. Spinal Cord Injury (SCI) 2016 Facts and Figures at a Glance. *J Spinal Cord Med*. Jul 2016;39(4):493-4. doi:10.1080/10790268.2016.1210925
212. Mei N. Recent studies on intestinal vagal afferent innervation. Functional implications. *Journal of the autonomic nervous system*. 1983 Oct 1983;9(1)doi:10.1016/0165-1838(83)90141-8
213. Denton D, Shade R, Zamarippa F, et al. Neuroimaging of genesis and satiation of thirst and an interoceptor-driven theory of origins of primary consciousness. *Proceedings of the National Academy of Sciences of the United States of America*. 04/27/1999 1999;96(9)doi:10.1073/pnas.96.9.5304
214. Jänig W. Neurobiology of visceral afferent neurons: neuroanatomy, functions, organ regulations and sensations. *Biological psychology*. 01/05/1996 1996;42(1-2)doi:10.1016/0301-0511(95)05145-7
215. Shinder M, Newlands S. Sensory convergence in the parieto-insular vestibular cortex. *Journal of neurophysiology*. 06/15/2014 2014;111(12)doi:10.1152/jn.00731.2013
216. Craig A. How do you feel--now? The anterior insula and human awareness. *Nature reviews Neuroscience*. 2009 Jan 2009;10(1)doi:10.1038/nrn2555
217. Avery J, Drevets W, Moseman S, Bodurka J, Barcalow J, Simmons W. Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biological psychiatry*. 08/01/2014 2014;76(3)doi:10.1016/j.biopsych.2013.11.027
218. Simmons A, Strigo I, Matthews S, Paulus M, Stein M. Initial evidence of a failure to activate right anterior insula during affective set shifting in posttraumatic stress disorder. *Psychosomatic medicine*. 2009 May 2009;71(4)doi:10.1097/PSY.0b013e3181a56ed8
219. Kanoski S, Grill H. Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms. *Biological psychiatry*. 05/01/2017 2017;81(9)doi:10.1016/j.biopsych.2015.09.011
220. Guest J, Datta N, Jimsheleishvili G, Gater D. Pathophysiology, Classification and Comorbidities after Traumatic Spinal Cord Injury. *Journal of personalized medicine*. 07/11/2022 2022;12(7)doi:10.3390/jpm12071126
221. Porges S. Polyvagal Theory: A Science of Safety. *Frontiers in integrative neuroscience*. 05/10/2022 2022;16doi:10.3389/fnint.2022.871227
222. Diagnostic and Statistical Manual of Mental Disorders 5th ed. American Psychiatric Association, 2013.

223. Cao Y, Li C, Newman S, Lucas J, Charlifue S, Krause J. Posttraumatic stress disorder after spinal cord injury. *Rehabilitation psychology*. 2017 May 2017;62(2)doi:10.1037/rep0000135
224. Foley J, DuBois F. Quantitative Studies of the Vagus Nerve in the Cat. *The Journal of comparative neurology*. 1937;67(1)
225. Hsia C, Schmitz A, Lambertz M, Perry S, Maina J. Evolution of air breathing: oxygen homeostasis and the transitions from water to land and sky. *Comprehensive Physiology*. 2013 Apr 2013;3(2)doi:10.1002/cphy.c120003
226. Scandola M, Aglioti S, Lazzeri G, Avesani R, Ionta S, Moro V. Visuo-motor and interoceptive influences on peripersonal space representation following spinal cord injury. *Scientific reports*. 03/20/2020 2020;10(1)doi:10.1038/s41598-020-62080-1
227. Tulsky DS, Kisala PA, Tate DG, Spungen AM, Kirshblum SC. Development and psychometric characteristics of the SCI-QOL Bladder Management Difficulties and Bowel Management Difficulties item banks and short forms and the SCI-QOL Bladder Complications scale. *The journal of spinal cord medicine*. 2015;38(3):288-302. doi:10.1179/2045772315Y.0000000030
228. Gee C, West C, Krassioukov A. Boosting in Elite Athletes with Spinal Cord Injury: A Critical Review of Physiology and Testing Procedures. *Sports medicine (Auckland, NZ)*. 2015 Aug 2015;45(8)doi:10.1007/s40279-015-0340-9
229. Sherwood A, Dimitrijevic M, McKay W. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. *Journal of the neurological sciences*. 1992 Jul 1992;110(1-2)doi:10.1016/0022-510x(92)90014-c
230. West CR, Gee CM, Voss C, et al. Cardiovascular control, autonomic function, and elite endurance performance in spinal cord injury. *Scandinavian Journal of Medicine & Science in Sports*. 2015;25(4):476-485. doi:10.1111/sms.12308
231. Neves M, Cunha A, Cunha M, Gismondi R, Oigman W. The Role of Renin-Angiotensin-Aldosterone System and Its New Components in Arterial Stiffness and Vascular Aging. *High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension*. 2018 Jun 2018;25(2)doi:10.1007/s40292-018-0252-5
232. Duprez D. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: a clinical review. *Journal of hypertension*. 2006 Jun 2006;24(6)doi:10.1097/01.hjh.0000226182.60321.69
233. Mathias C, Frankel H, Davies I, James V, Peart W. Renin and aldosterone release during sympathetic stimulation in tetraplegia. *Clinical science (London, England : 1979)*. 1981 Apr 1981;60(4)doi:10.1042/cs0600399
234. Wecht J, Radulovic M, Weir J, Lessey J, Spungen A, Bauman W. Partial angiotensin-converting enzyme inhibition during acute orthostatic stress in persons with tetraplegia. *The journal of spinal cord medicine*. 2005 2005;28(2)doi:10.1080/10790268.2005.11753806

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Name: Rachel Torres

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Education: MS Clinical Exercise Physiology
University of Louisville 2020

BA English
University of Kentucky 1992

PhD Dissertation Research:

NASA Doctoral Fellow, University of Louisville and Frazier Rehabilitation Institute Neuroscience Collaborative Center: *Autonomic Regulation in People with Spinal Cord Injuries* dissertation research study, 2021-2024, funded by NASA Kentucky Space Consortium

Doctoral Lab Rotations:

Magnuson Lab, University of Louisville, cryostat histology, murine neurosurgery, 2021

Inpatient Clinical Rounds with Dr. Camilo Castillo, Assistant Professor, Department of Neurosurgery, Frazier Rehabilitation Institute, Louisville 2021

Abell Lab, University of Louisville, autonomic measurement, Frazier Rehabilitation and Neuroscience Center

Research Coordinator and Instructor:

University of Louisville and Frazier Rehabilitation Institute Neuroscience Collaborative Center: *Cardiopulmonary Function and Quality of Life through Yoga and Exercise in People with Spinal Cord Injuries*, 2019-2020

Research Assistant:

University of Louisville: Minds-In-Motion, Motor Proficiency, Academic Achievement, and Behavior of Culturally Diverse Elementary School Students 2016

Clinical Internships:

Neurorehabilitation for Stroke and Traumatic Brain Injury, Summer Shadowing Rotation, Frazier Rehabilitation Institute, Louisville, 2021

Cardiac and Pulmonary Rehabilitation Baptist Health Hospital Louisville, KY, 2019

Certifications and Awards:

Outstanding Graduate Student Award in Exercise Physiology University of Louisville 2020

Ellis J. Mendelsohn Award for significant contributions in service to the University, Community, and Profession, University of Louisville 2020

American College of Sports Medicine Certified Inclusive Fitness Trainer, 2020

iRest Level 1 Meditation Instructor 2020

500-hour Certified Yoga Instructor Yoga East Louisville, KY 2018

Certified Yoga Therapist International Association of Yoga Therapists 2017

Trauma-Informed Yoga for PTSD Certified Instructor Yoga Warriors 2010

Professional Affiliations:

Society for Neuroscience

American Spinal Injury Association

American Physiological Society

International Association of Yoga Therapists

Yoga Alliance Continuing Education Provider

Publications:

Torres, R., Castillo, C., Terson de Paleville, D. (2024) (in review) *Biofeedback using Virtual Reality, Conscious Interoception, and Breathing Exercises Modulates Blood Pressure and Heart Rate Variability in People with and without Cervical Spinal Cord Injury*

Torres, R., Castillo, C., Terson de Paleville, D. (2024) (in review) *A Comparison of Virtual Reality and Mental Biofeedback for Blood Pressure Modification in People with and without Spinal Cord Injury*

Torres, R., Rashed, H., Mathur, P., Castillo, C., Abell, T., Terson de Paleville, D. July 2023 *Autogenic Biofeedback Training Improves Autonomic Responses in a Participant with Cervical Motor Complete Spinal Cord Injury- case report.* Spinal Cord Series and Cases.

Torres, R., Immekus, J., Castillo, C., Terson de Paleville, D. (in preparation). *Effects of Yoga on Pulmonary Function and Quality of Life in People with Chronic Spinal Cord Injuries.*

Torres, R., Castillo, C; Wanner, A, Kozlowski, K; Terson de Paleville, D. (2023*). Guided Breathing Exercise Modulates Blood Pressure for People with Spinal Cord Injury.* (published abstract) *Journal of Clinical Exercise Physiology.* 12 (s1): 13.

Wanner, A, Castillo, C; **Torres, R**.; Terson de Paleville, D. (2023) *Asymptomatic Autonomic Dysreflexia After Postural Changes in SCI.(*published abstract*) Journal of Clinical Exercise Physiology* 12 (s1): 11.

Invited Lecturer:

Best Practices for Yoga in a Neurorehabilitation Setting Frazier Rehabilitation Hospital staff continuing education class, 2023

Yoga for Neurorehabilitation yoga teacher training, Yoga Alliance Continuing Education and Gathering Strength, 2021

Brain Injury Alliance of Kentucky: *Integrative Health Approaches for Brain Injury Recovery: Yoga for Stroke and Brain Injury*, UofL Health Rudd Heart and Lung Center 2020

Presentations:

Torres, R. Rashed, H. Mathur, P. Castillo, C. Abell, T. Terson de Paleville, D. Society for Neuroscience, Louisville Chapter, poster presentation: *Autogenic Feedback Training Exercise to Attenuate Orthostatic Intolerance* April 2022.

Sithu, T **Torres, R.** Putman, S Castillo, C Terson de Paleville D. Society for Neuroscience, Louisville Chapter, poster presentation: *Comparison of Virtual Reality to Mental Imagery In Blood Pressure Biofeedback* April 2022.

Torres, R. Rashed, H. Mathur, P. Castillo, C. Abell, T. Terson de Paleville, D. *Autogenic Feedback Training for Orthostatic Hypotension in People with Spinal Cord Injuries* poster presentation, American Spinal Injury Association Annual Scientific Meeting, May 18-20, 2022, New Orleans, LA

Torres, R. Rashed, H. Mathur, P. Castillo, C. Abell, T, Terson de Paleville, D. *Biofeedback with Virtual Reality to Improve Blood Pressure for Individuals with Spinal Cord Injury: a proof-of-concept study* poster presentation, Neuromodulation Conference July, 2022, Louisville, KY

Torres, R.; Castillo, C; Wanner, A, Kozlowski, K; Terson de Paleville, D. (2023) *Guided Breathing Exercise Modulates Blood Pressure for People with Spinal Cord Injuries*. Clinical Exercise Physiology Association (CEPA) 2023 annual meeting.

Wanner, A, Castillo, C; **Torres, R**.; Terson de Paleville, D. (2023). *Asymptomatic Autonomic Dysreflexia After Postural Changes in SCI*. Clinical Exercise Physiology Association (CEPA) 2023 annual meeting.

Torres, R.; Castillo C, Wanner A, Kozlowski K, Terson de Paleville, D. (February 2023) *Modified Autogenic Feedback Training Exercise Modulates Blood Pressure in People with Spinal Cord Injuries.* NASA Human Research Program Investigators Workshop, Galveston, TX.

Kozlowski, K **Torres R**, Wanner A, Castillo C, Terson de Paleville, D *Mental Imagery and Virtual Reality's Impact on Blood Pressure Regulation For People with Spinal Cord Injury* Posters at the Capitol, March 2, 2023 Frankfort, KY

Torres, R., Castillo, C., Wanner, A., Fish, J., Terson de Paleville, D., *Modified Autogenic Feedback Training Exercise Modulates Blood Pressure in People with Spinal Cord Injury* KSCHIRT Conference May 11, 2023 Lexington, KY

Lee, J., Ballard, A., Thompson, E., **Torres, R**., Carll, A., Schuschke, D., Maldonado, C., Terson de Paleville, D., *The Principles of Electrocardiogram and the Effects of Vape Use: An Outreach Program to the Health Academy of*

Pleasure Ridge Park High School poster presentation, University of Louisville Neuroscience Day, Louisville, KY, April 12, 2024