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Prolonged Exposure to Microgravity Increases Susceptibility to Traumatic Brain Injury

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PROLONGED EXPOSURE TO MICROGRAVITY INCREASES SUSCEPTIBILITY TO TRAUMATIC BRAIN INJURY

by

Ryan Baskerville

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LIST OF ABBREVIATIONS

SANS – Spaceflight Associated Neuro-Ocular Syndrome

VIIP – Visual Impairment and Intracranial Pressure

ICP – Intracranial pressure

CSF – Cerebrospinal fluid

MRI – Magnetic resonance imaging

NASA – National Aeronautics and Space Administration

TBI – Traumatic brain injury

HDBR – Head-down bedrest

DAI – Diffuse axonal injury

CSDM – Cumulative strain damage measure

MPS – Maximum principal strain

THuMS – Toyota Model for Human Safety

FEM/FEA – Finite element modelling/finite element analysis

HIC – Head injury criteria

BrIC – Brain injury criteria

ATD – Anthropomorphic test device

CEV – Crew exploration vehicle

CSV – Comma-separated value

ABSTRACT

With the prospect of semi-permanent and permanent habitable fixtures on the moon and Mars, the complications associated with long-term exposure to microgravity should be investigated exhaustively. Spaceflight Associated Neuro-Ocular Syndrome (SANS), a group of neurological and ocular effects resulting from prolonged exposure to microgravity, is characterized by significant fluid shifts into the cranium, namely cerebrospinal fluid and blood, and an upward shift of the brain relative to the skull. This syndrome, along with its immediate effects on visual acuity, cognitive ability, and motor function are recognized by NASA, but its effects on susceptibility to traumatic brain injury have yet to be studied. Using a biofidelic human body model (Toyota Human Model for Safety, or THuMS) along with a structural finite element analysis software (LS-Dyna), we were able to replicate the effects of microgravity on cerebral structures and subject the SANS-altered models to a variety of loading events. An unmodified THuMS model was used as a control for each injury event. Here we report that the pre-strained condition associated with an influx of CSF into the third and lateral ventricles results in an increased risk of traumatic brain injury according to four injury metrics. This data serves as a preliminary study into the effects of microgravity on susceptibility to traumatic brain injury. As the promise of creating a spacefaring society becomes more realistic, steps may be required to mitigate the effects of long-term microgravity exposure on susceptibility to traumatic brain injury.

INTRODUCTION

WHAT IS SANS?

Spaceflight Associated Neuro-Ocular Syndrome (SANS), (formerly called Visual Impairment and Intracranial Pressure [VIIP] Syndrome), is a group of structural changes to the brain and eye which is associated with long-term exposure to microgravity. The underlying etiology remains uncertain in the medical community but is thought to be an upward fluid shift (cerebrospinal fluid and blood) caused by the prolonged absence of Earth's gravity causing a slight increase in intracranial pressure [1]. The elevated intracranial pressure (ICP) as a result of fluid influx to the head results in expansion of the ventricles and cerebrospinal fluid (CSF) spaces. While the combination of ocular changes negatively affects near-field visual acuity, the structural changes to the brain could be responsible for reported decrements in cognitive function, along with other neurological symptoms associated with spaceflight. These deficits and their related physiological changes are shown in Figure 1, below.

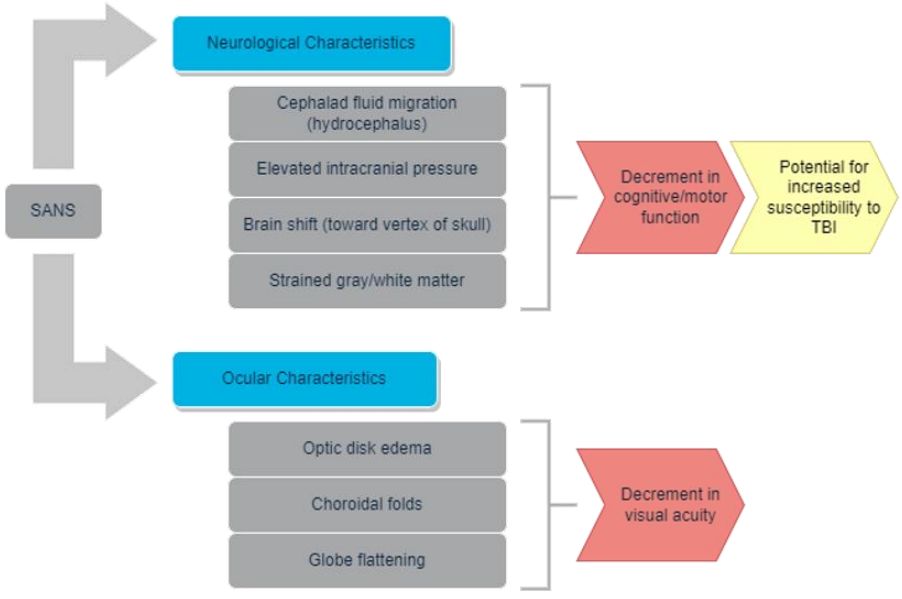


Figure 1: Ocular and neurological characteristics and manifestations of SANS.

Exposure to microgravity not only induces a cephalad (superior direction) shift of CSF and blood, but also perturbs biological processes such as CSF production, circulation, and resorption. According to Ludwig *et al.,* "microgravity and associated attenuation of hydrostatic pressures are likely to diminish [these] downward dynamics, so that the resulting prevalence of upward CSF flow may enhance net flow volumes into the head and thereby enlarge intracerebral CSF spaces" [2], causing (at least in part) the structural changes to the brain seen on MRI.

Due to the invasive nature of tests used to measure intracranial pressure, such as lumbar punctures and intraparenchymal pressure microsensors, no data has been collected on subjects *during* exposure to microgravity, but elevated ICP seems to be the driving force for many of the neuro-ocular symptoms experienced by astronauts and cosmonauts. Superior fluid shifts are also regarded as the root cause of the structural changes evident in magnetic resonance images of astronauts upon return from long-term missions. The structural alterations, or cerebral remodeling, detailed in the following section manifest themselves in many ways, affecting astronauts' vision, orthostatic tolerance, behavior, memory, and judgement [1].

IMPACT OF SANS (PROJECT IMPORTANCE)

Since the 1960s, with the conception of the Mercury program, The United States has had a profound interest in the opportunity of space travel. Sixty years later, NASA (National Aeronautics and Space Administration), along with private aerospace companies like SpaceX and Virgin Galactic, have ambitious plans to construct a permanent presence on the Moon, and eventually Mars [3]. While plans to create a spacefaring society offer solutions to many problems we face here on Earth, they also spawn new challenges of their own.

Humans have evolved to live in homeostasis on Earth. Drastic changes to our environment, like the ones experienced in space, are known to cause significant changes to the human body. Loss of bone density, muscle mass, and visual acuity are a few well-documented effects of long-term spaceflight [4]. An overall decrement in the body's ability to autoregulate can put astronauts at risk for a wide variety of SANS-related physical manifestations.

According to NASA's Human Research Program, the risks currently associated with SANS (short-term or long-term vision alterations, cognitive effects, or other deleterious health effects) require mitigation before deep space exploration and habitation, as well as planetary travel, as seen in Figure 2 [5]. Elevated intracranial pressure and ventricular expansion induce substantial strains in the brain's gray and white matter. While NASA have addressed the cognitive and ocular deficits associated with SANS, they have not yet addressed the possibility of increased susceptibility to traumatic brain injury (TBI). Before extending the duration of spaceflight to previously unprecedented lengths the likelihood, consequence, and risk disposition of TBI due to these manifestations should

be analyzed and understood. Given that SANS affects brain tissue on the macroscale (induced strains to white and gray matter, elevated ICP, ventricular expansion) it is paramount to determine the macroscale effects of microgravity on brain tissue compliance and injury tolerance.

Risk Ratings and Dispositions per Design Reference Mission (DRM) Category

DRM Categories	Mission Type and Duration	Operations		Long-Term Health	
		LxC	Risk Disposition *	LxC	Risk Disposition *
Low Earth Orbit	Short (<30 days)	3x1	Accepted	3x2	Accepted
	Long (30 days-1 year)	3x2	Accepted	3x3	Accepted
Lunar Orbital	Short (<30 days)	3x1	Accepted	3x2	Accepted
	Long (30 days-1 year)	3x2	Accepted	3x3	Accepted
Lunar Orbital + Surface	Short (<30 days)	3x1	Accepted	3x2	Accepted
	Long (30 days-1 year)	3x2	Accepted	3x3	Accepted
Mars	Preparatory (<1 year)	3x2	Accepted	3x3	Accepted
	Mars Planetary (730-1224 days)	3x4	Requires Mitigation	3x4	Requires Mitigation

Note: LxC is the likelihood and consequence rating. The information above was last approved by the Human System Risk Board in 4/2020.

Figure 2: Risk ratings and dispositions for SANS according to NASA's Human Research Roadmap [5].

Traumatic brain injury has extensive epidemiological impacts here on earth, with TBI-related hospitalizations in the United States topping 2.5 million annually. In addition, over 5 million Americans currently live with TBI-related disabilities [6]. In space, the problems associated with traumatic brain injury are further exacerbated due to the lack of advanced medical equipment and specialized personnel. Such injuries can have severe and long-lasting consequences when sustained on Earth, but could be more severe and difficult to treat, and adversely affect astronaut cognition/performance when sustained in space. By providing an understanding of mechanisms that increase injury risk, steps can be taken to

mitigate exposures and implement appropriate medical interventions, thereby protecting the long-term health of astronauts.

Relevant Neuroanatomy

The brain is one of two main parts of the central nervous system (the other being the spinal cord). It is responsible for nearly all our actions, feelings, and thoughts. The brain is comprised of two types of tissue, referred to as gray matter and white matter, and is surrounded by cerebrospinal fluid, or CSF [7].

Gray matter, which is comprised mostly of cell bodies and dendrites, is responsible for the regulation of emotion, movement, and memory. It makes up the outer surface of the brain, including the folds or grooves known as sulci. Erosion/degradation of gray matter, such as that resulting from common gray matter diseases such as Alzheimer's, result in hindrance or loss of memory and/or motor function. During trauma, gray matter is also susceptible to damage via intracerebral hemorrhage, which can result in cell death [8].

White matter is a type of brain cell that is associated with the brain signaling, or connectivity within the brain. White matter tracts can transport signals within a hemisphere or between the brain's hemispheres. Its composition, in contrast to gray matter, is mostly axons and myelin [9]. Mechanically, individual axons are damaged or broken by excess shear or tensile deformation, resulting in impaired or lost axonal transport [10]. Figure 3 shows the structures which comprise a neuron and a cross-section

of the brain which identifies white and gray matter, as well as the third and lateral ventricles.

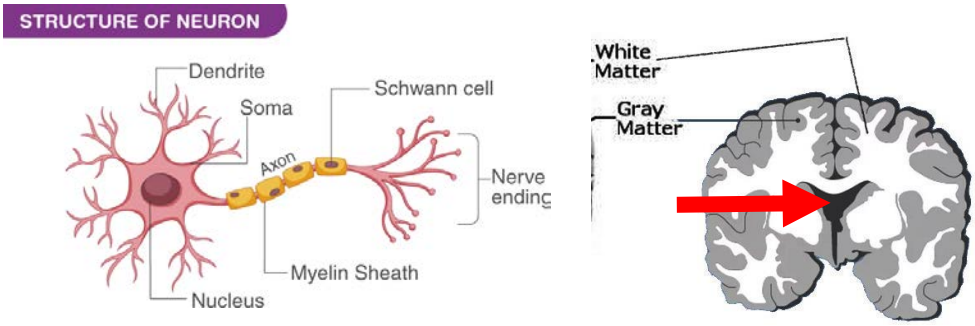


Figure 3: Diagram depicting the anatomy of a neuron (left), and a coronal cross-section of gray and white matter. Ventricular spaces are shown by the red arrow [8].

Cerebrospinal fluid is a liquid that fills the brain's ventricles and subarachnoid spaces. It is produced primarily by the ventricles and secreted by the choroid plexus before circulating throughout the brain (through the ventricles and to the subarachnoid spaces) and being resorbed by the arachnoid villi. Due to its circulatory nature, CSF can nourish and remove waste from the brain, keeping the brain's interstitial fluid composition constant. Blockage in the flow of- or increase in the production of- CSF can result in a condition called hydrocephalus, in which the ventricles expand. This condition can cause headaches, nausea, and mental deterioration, and is typically associated with intracranial hypertension (elevated intracranial pressure) [11].

Cerebrospinal fluid also plays a key role in injury biomechanics. It acts as a mechanical damper between the brain and skull during impacts or impulses, reducing the contact force between the two. Due to the buoyant force created by CSF, mechanical injury is further inhibited by reducing the effective weight of the brain inside the skull (thus reducing the loading experienced by the brain tissue (parenchyma) during impact). [11]. Taken together, it is apparent that the brain's ability to tolerate impacts or sudden acceleration may be altered by excess quantities of CSF or changes in the location and distribution of CSF. Figure 4 below shows ventricular and extra-ventricular CSF pathways.

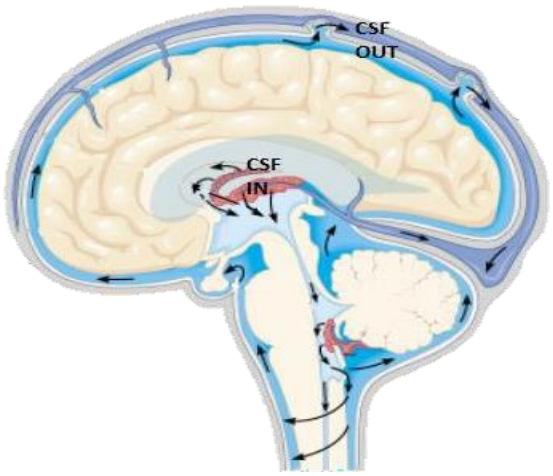


Figure 4: Cerebrospinal fluid production in ventricles; circulation, and resorption through subarachnoid spaces [34].

BRAIN-STRUCTURE CHANGES ASSOCIATED WITH MICROGRAVITY [1]

Recently, two classical approaches have emerged to examine the effects of microgravity on the brain. Firstly, MRI images have been collected for astronauts before and after long-term missions. Secondly, due to the small sample size of persons who have experienced long-term spaceflight (>60 days), an analog environment to microgravity has been developed. Subjects, when exposed to six-degree head down bedrest (HDBR), exhibit neurological changes which accurately reflect those which happen in space [13].

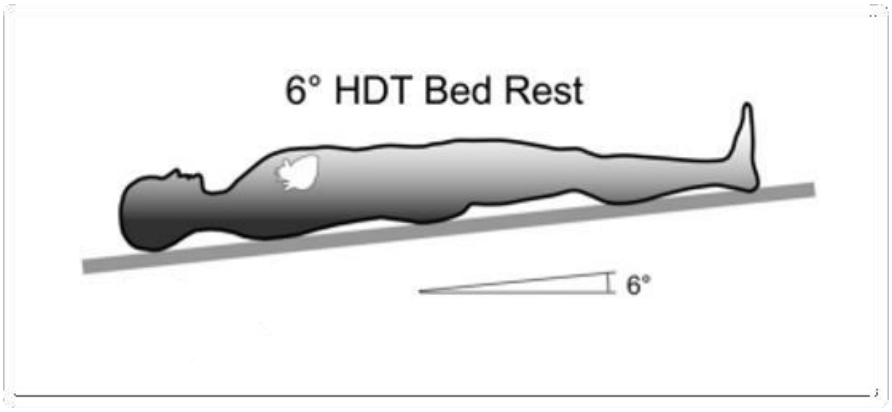


Figure 5: 6-degree head down bed rest depiction.

A study by Li, *et al.* using a terrestrial analog for microgravity (six-degree head down bed rest) indicate macroscale changes to brain tissue, including regional volumetric changes of gray and white matter. Most notably, however, this study indicates a decline in Fractional Anisotropy in white matter tracts after HDBR, indicating that accumulation of stresses and strains in the brain could potentially cause a decline in cognitive function [12].

[1] Any reference to 'structure changes' or 'cerebral remodeling' refers to mechanical deformation to elements and is not indicative of structural changes in a medical context

In a similar HDBR study, a significant cephalad shift, along with a marginally significant anterior-to-posterior shift and a significant posterior rotation of the brain about the medial-lateral axis have been identified and quantified – the results of which can be seen in Figure 6, below [13]. This brain-shift analysis demonstrates that the brain moves upward relative to the skull, reducing the gap between the brain and skull near the vertex. For impacts to the top of the skull, it is apparent that there is less CSF to cushion the brain from impacting the skull.

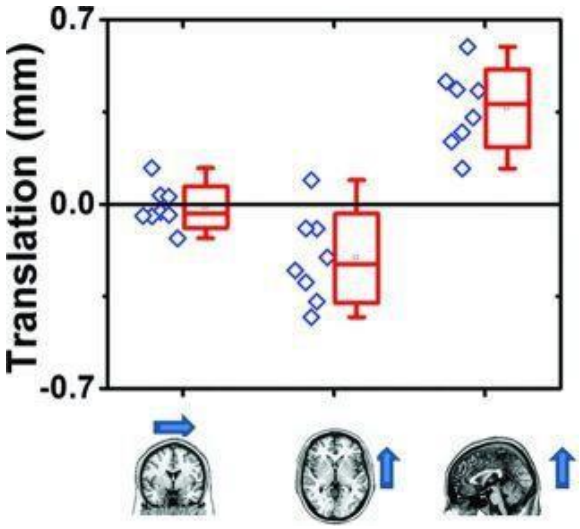


Figure 6: Translational results from brain-shift analysis performed by Roberts, et al.

Roberts *et al.* collected pre- and post-spaceflight MRI images which indicated a prominent cephalad shift of the brain for all 12 astronauts with long-term microgravity exposure. Further, 17 out of 18 subjects with long-term exposure showed narrowing of sulci, especially the central sulcus, as seen in Figure 5, below [14]. Narrowing of extracerebral cerebrospinal fluid spaces was apparent in almost all test subjects (both short-term and long-term exposure to microgravity). Figure 7 contains an example of an MRI showing the narrowing of the sulci after long-term spaceflight.

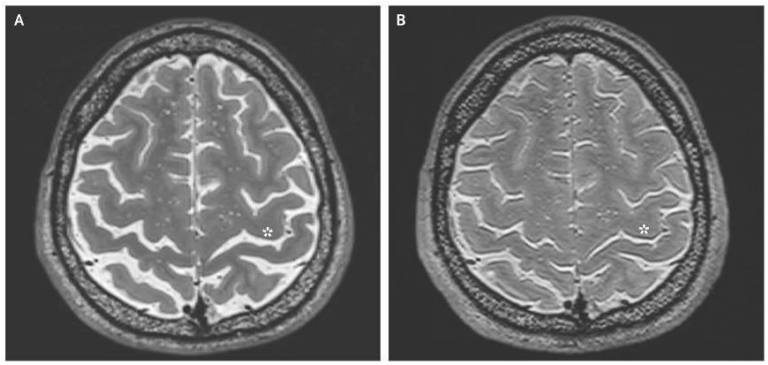


Figure 7: Pre-flight MRI (A) compared to post-flight MRI (B), note the narrowing of the grooves (or sulci), specifically the central sulcus [14].

The work of Van Ombergen, *et al.*, who analyzed the volumetric changes of white matter, gray matter, and cerebrospinal fluid using voxel-based morphometry on pre- and post-flight MRI data from ten cosmonauts (n=10) indicates broadly distributed volumetric decrements in gray matter, along with local increase in white matter and various changes to the volume of CSF in different areas of the brain, particularly the CSF-filled ventricles. Van Ombergen notably reported increased volume of ventricular CSF spaces – maximally 12.9% in the third ventricle, along with a decrease in CSF volume near the vertex (top) of the skull, likely due to the upward migration of the brain and associated downward displacement of fluid [15]. The results of Van Ombergen's work is shown in Figure 8, below.

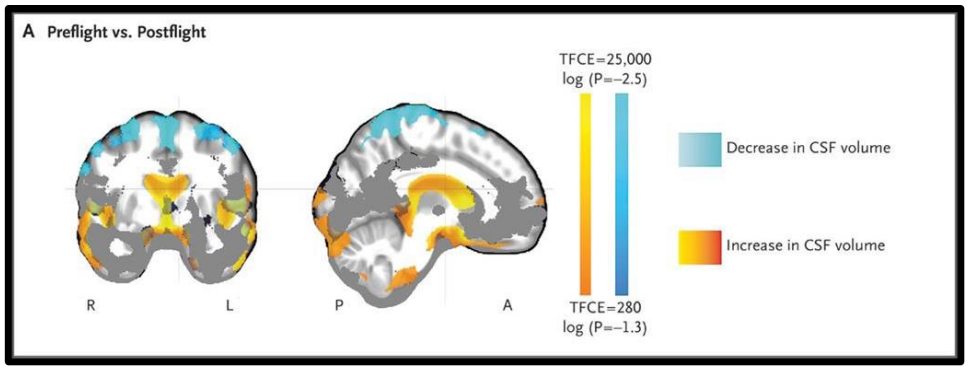


Figure 8: Regional changes in gray matter and CSF volume as indicated by Van Ombergen et al.

In a more recent van Ombergen study, significant increases in volume of the third and lateral ventricles, along with a significant increase in total ventricular volume were reported (13.3%, 10.4%, and 11.6%, on average, respectively), as seen in Figure 9 [16].

Lastly, as part of this thesis, a novel set of MRI data following long-term

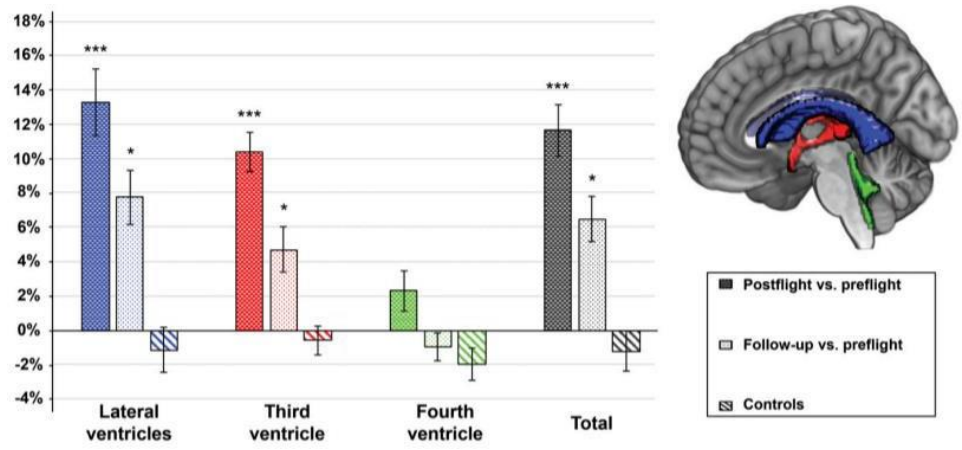


Figure 9: Pre-flight versus post-flight ventricular volume data via MRI data as indicated by Van Ombergen et al..

spaceflight was analyzed. This data, provided by NASA (and attached as an appendix) indicate a significant expansion of the lateral ventricle and total ventricular volume. The data provided therein (summarized in Appendix A) also indicates significant lateral and third ventricular expansion, maximally 20.9%.

Taken together, all available works regarding the macroscale effects of long-term exposure to microgravity or its analogs draw three very similar conclusions: (1) the brain migrates upward, (2) the ventricles expand, and (3) extra-ventricular CSF spaces become narrowed.

Traumatic Brain Injury

Traumatic brain injury, commonly known as TBI, is the result of impact to, or sudden acceleration/deceleration of, the head. Closed brain injuries occur when the skull is not fractured or punctured and are caused by relative movement of the brain inside the skull. These types of injuries are often manifested by microtears and bruises in the tissues of the brain. Penetrating injuries are classified by a breakage or penetration of the skull.

Traumatic brain injury is a term that covers a variety of pathologies arising from impact or acceleration-deceleration to the head. The brain and other intracranial tissues develop deformation and stresses in response to loading, and injury occurs when the capacity of tissue to withstand the applied load is exceeded. TBI can include focal lesions/contusion, which typically arise from impact to the head causing contact between the brain and skull, or diffuse damage to brain tissue, which is more commonly associated rapid-acceleration-deceleration of the head.

A common type of closed brain injury is called Diffuse Axonal Injury (DAI). This type of injury, which primarily affects the white matter tracts, occurs due to shearing forces in the brain which can cause damage to axons. It is not uncommon for intracranial hypertension to be documented during treatment of severe DAI [17]. Diffuse Axonal Injuries affect large proportions of the brain and are typically the result of abrupt rotation of the head/brain. While DAI is characterized by damage to a significant proportion of the

brain's tissue (specifically axons), other injury types are characterized by more focalized mechanical damage.

Focal brain injury, often associated with intracerebral hemorrhage and contusion, is commonly caused by impact to the head [18]. Unlike DAI, focal brain injury is mechanically represented by small proportions of highly strained tissue.

One commonality between all types of traumatic brain injury is that they all occur as a result of stresses and strains exceeding the physiological limits of the brain's tissue. For this reason, mechanical tools such as finite element modeling are well-suited for this type of injury analysis. Traumatic brain injuries can be replicated using a combination of finite element modeling and an appropriate injury criterion [19, 20, 21]. Analyses of closed brain injuries commonly utilize injury metrics such as Cumulative Strain Damage Measure (CSDM), Maximum Principal Strain (MPS), or other finite element-based injury metrics along with a biofidelic human body model [20]. CSDM is typically used as an indicator of DAI, while MPS can be used as a predictor of concussion or mild TBI [21].

Such stresses and strains can be experienced in brain tissue as a result of contact/impact or inertial (acceleration-deceleration) mechanisms. These types of events are known to occur (or could easily happen) during space flight – such as from launch, re-entry, landing, or minor accident events. In that SANS is associated with development of excessive intracranial pressure (therefore pre-stressing and pre-straining brain structures) as well as migration of the brain towards the vertex of the skull (reducing the space between the skull and the brain at that region), we hypothesize that the brain will be made more susceptible to focalized mechanical injury due to SANS-related morphological

changes. Such a phenomenon must be investigated and understood such that appropriate precautions and interventions can be established and implemented.

Biomechanical Implications of SANS

The upward migration of CSF, blood, and brain parenchyma combine to create a 'pre-strained' condition in the brain, which may be responsible for some cognitive deficits reported as a result of SANS (headache, orthostatic intolerance, memory lapse, etc.). While these symptoms may be independently detrimental to an individual's ability to perform on a mission, we hypothesize that a pre-strained brain could also prove to be more susceptible to TBI during or immediately following a mission.

In a mechanical sense, it is plausible that the viscoelastic tissue in the brain is subject to a superposition effect, where the strains from an impact or impulse to the head are imposed upon strains from the equilibrated, steady strain-state of SANS-related boundary conditions. The underlying mechanisms behind brain injury and the stress/strain state of the brain following long-term exposure to microgravity are highly comparable (accumulation of stresses and strains in brain tissue). This raises concern that long-duration spaceflight could put astronauts at higher risk for TBI. It is likely that the pre-strained condition of the brain caused by microgravity-induced geometric abnormalities may increase the susceptibility to- and severity of- traumatic brain injuries in astronauts.

Finite Element Modeling

The use of finite element modelling (FEM) for predicting injury to the human body is a well-established practice in the field of biomechanics [23, 24]. The finite element method uses iterative approximations to find approximate solutions to complex differential equations [25]. Using finite element analysis, a computer-driven form of the finite element method, high-rate dynamic models with complex geometries and non-linear material models can be simulated. The results of interest for a finite element analysis are

typically element stresses and strains or nodal displacements and accelerations – quantities that cannot be obtained using any other approach, but that are closely associated with known injury mechanisms for cerebral tissue.

THUMS MODEL

The THuMS AM50 model (Total Human Model for Safety, Adult Male, 50th Percentile) is a validated human body finite element model representing a 50th percentile adult male. The model has been validated for translational head impacts and combined translational/rotational head impacts [22]. Its most recently released iteration includes highly accurate models for internal organs, and an improved brain model with more nodes and elements (the whole-body model contains 760,000 nodes and 1.9 million elements) [22]. Its main use is to simulate the kinetics and kinematics of a human body to study the effects of car crashes and the efficacy of safety equipment. The full body AM50 model, and a detail showing the head parts, is shown in Figure 10, below [22].

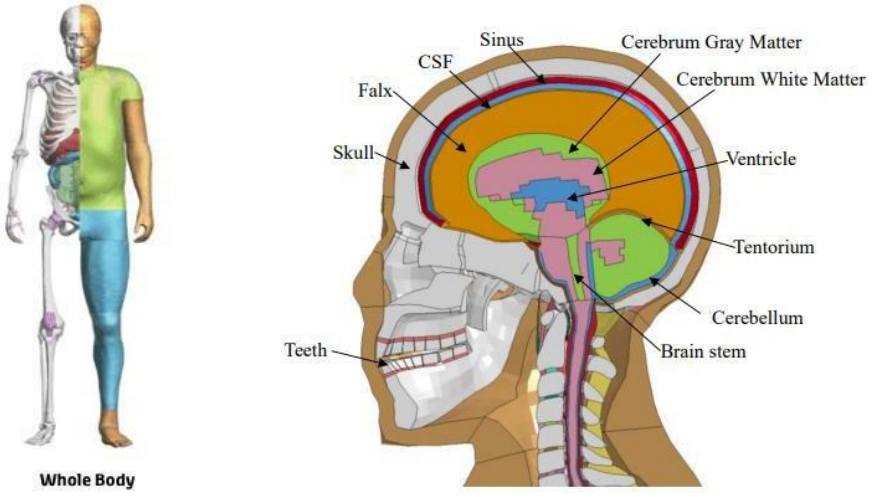


Figure 10: The full-body (left) and head (right) diagram for the THuMS model [22].

The skull has been modelled using a combination of shell and solid elements with material properties defined by an isotropic elasto-plastic material keyword input

(MAT_24: MAT_PIECEWISE_LINEAR_PLASTICITY). The gray matter, white matter, and CSF are all modelled as hexagonal solid elements; the CSF has fluid-like behavior in that the deviatoric portion of the stress tensor is zero. Both the gray and white matter are defined by a viscoelastic material input (MAT61: MAT_KELVIN-MAXWELL_VISCOELASTIC), while the CSF is modelled as an elastic material (MAT_1: MAT_ELASTIC_FLUID). The nodes at the interface of the brain and skull are connected into common nodes [22]. The THuMS model contains all necessary anatomic structures to replicate SANS in a simulated environment (CSF, white and gray matter, ventricles, skull, etc.)

As the THuMS model contains many individual parts meshed independently. This allows the user to be very precise with the application of boundary conditions, the selection of output data, and, when necessary, the truncation of unneeded portions of the model. For the simulations contained in this study, the head as been isolated from the rest of the model for improved efficiency. This method is used throughout the validation of THuMS as seen in its documentation. Users also have full control over what output data is produced by THuMS and LS-Dyna. Force, acceleration, deflection, stress, and strain are all available for collection.

Finite Element-Based Injury Prediction

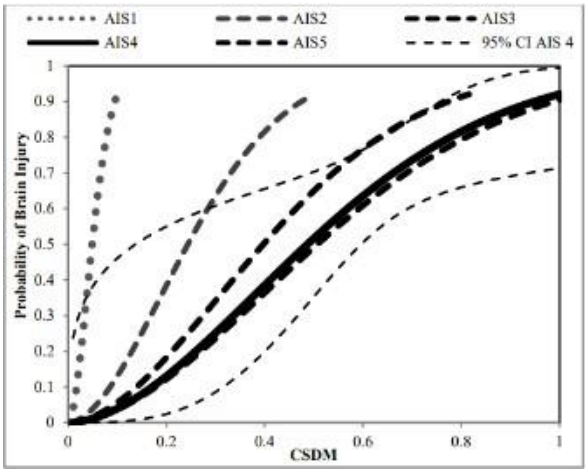
Macroscale kinematic-based injury metrics such as HIC (Head Injury Criterion) and BrIC (Brain Injury Criterion) use the linear and rotational kinematics of the center of gravity of the whole head (typically using an anthropomorphic test device to measure linear and rotational accelerations) to predict macroscale injury likelihood. These metrics and methods are good indicators of injury risk but lack adaptability and fidelity. ATDs

and ATD finite element models focus solely on the kinematics of the head as a whole and give little insight into the stress and strain behavior of the brain tissue. By nature, HIC and BrIC are unable to detect a difference in injury risk resulting from pre-strained brain tissue.

In contrast, we can gain more insight into the location, severity, and type of brain injury resulting from a given scenario using more advanced models such as THuMS (Toyota Human Model for Safety). By using THuMS in lieu of a more rudimentary ATD model, we can analyze stresses and strains in individual elements or regions of the brain, providing context into the mechanism behind injuries. This study uses LS-Dyna and Toyota's THuMS model to comparatively analyze pre- and post- spaceflight injury risk using two metrics, CSDM and MPS.

CSDM (Cumulative Strain Damage Measure) calculates the total volume fraction of the brain which exhibits a first principal strain above a critical value over the course of a potentially injurious event. When used in conjunction with a biofidelic human body model, such as Toyota's THuMS, the Cumulative Strain Damage Measure can predict the likelihood of Diffuse Axonal Injury (DAI) in an impact or acceleration event by calculating the volume fraction of brain tissue that has experienced a tensile strain over 15% - at which axonal swelling and loss of axonal transport are evident. Takhounts *et al.* suggest that there is a 50% probability of DAI when 55% of the brain tissue elements experience a maximum principal strain greater than or equal to 0.15 [26]. For less severe load cases, the use of lower strain thresholds may be used to describe potential injury risk (i.e.., CSDM-5 or CSDM-10) [24].

CSDM values can be applied to real-life injury assessments, as seen in the Figure below. In this example, CSDM-15 has been correlated to injuries on the Abbreviated Injury Scale, which is used in clinical settings to classify injury type and score injury severity [27]. For reference, AIS Scores and their related symptoms/characteristics are also provided in Figure 11.



AIS	Head injury
1	Headache or dizziness
2	Unconscious less than 1 h; linear fracture
3	Unconscious 1 – 6 h; depressed fracture
4	Unconscious 6 – 24 h; open fracture
5	Unconscious more than 24 h; large hematoma
6	Non-survivable

Figure 11: Abbreviated Injury Scale probability for CSDM-15 values (left). Abbreviated Injury Scale symptoms and characteristics (right). [26] [35].

Maximum Principal Strain (MPS) can be used as an indicator of Diffuse Axonal Injury, vascular rupture, or concussion when implemented accordingly (using different tolerance levels for each type of injury). Kleiven indicates that MPS over 0.21 is a predictor of DAI, while a conservative predictor of vascular rupture is a strain over 0.60. Kleiven's work also states that an MPS of 0.10 is indicative of reversible damage to axons and can be used as a conservative injury metric for concussion [28].

METHODS

SANS ALTERATIONS

The SANS-altered models were created by adding an upward gravity load of one G to all gray and white matter elements to induce an upward migration of the brain inside the skull, along with a prescribed volumetric expansion of the CSF contained within the third and lateral ventricles. The SANS boundary conditions, in the absence of an injury event, converged to a steady-state equilibrium in a matter of 50ms. Despite this, it was discovered in early iterations of impact simulations that the elements behaved more ideally when the model was allowed to converge for a longer period before the models were subjected to any external loading. For this reason, each injury simulation included at least 300ms of convergence time, as quantified by two mechanical criteria - maximum principal strain and resultant velocity. Maximum principal strain was considered to have converged when all elements reached a steady, nonzero strain state. (The vast majority of gray and white matter elements exhibit resultant velocities much less than 1 mm/s after 300 ms).

VALIDATION OF BOUNDARY CONDITIONS

The creation and validation of the boundary conditions which were applied to replicate the effects of long-term exposure to microgravity was a lengthy iterative process. Multiple variations and magnitudes of thermal expansion (to produce a volumetric expansion of the third and lateral ventricles) conditions were created and tested before deciding which condition best represented the effects of SANS-related structural changes. Initial attempts exacerbated poorly meshed areas of the THuMS model, causing unpredictable behavior of elements near the cerebellum.

By altering the boundary conditions to which the THuMS model is subjected, the macroscale effects of long-term microgravity exposure can be well approximated via finite element modelling. To replicate the upward migration of CSF (enlargement of ventricular spaces) along with elevation of intracranial pressure, a thermal expansion was added to the ventricles along with an associated temperature perturbation (since the simulation was run as a structural-only analysis, the effects of the thermal expansion and temperature perturbation should not affect the results of the injury analysis and are only evident as geometric changes).

The pre-impact boundary conditions selected for propagation throughout the study were a 0.05 coefficient of thermal expansion assigned to the third and lateral ventricles, along with a temperature perturbation of 1 K, and an upward (+z, toward the vertex of the skull) gravity load of 1 G. The resulting equilibrium state of the brain (seen in Figure 12, below) is both qualitatively and quantitively consistent with the available literature and MRI data on this condition.

As discussed previously, ventricular volume data provided by NASA (summarized in Appendix A) indicated an average total ventricular expansion of 10.88% (and a maximum of 20.8%). A similar study performed on Russian cosmonauts by van Ombergen, et. al indicate a mean ventricular expansion of 11.6%, while the expected volumetric expansion of the third and lateral ventricles was approximately 15%. A slight but measurable narrowing of the central sulcus is also evident in the microgravity-analog FEM model, qualitatively corroborated by MRI data collected by Roberts et. al. [14].

In Figure 12, below, the FE model (bottom) very closely resembles the ventricular volume changes indicated by Van Ombergen *et al*. The reason the FE model does not

portray regional volumetric changes to gray and white matter is because we chose to model the driving force of elevation of ICP - expansion of the ventricles, instead of forcing the model to conform precisely to documented behavior. We have chosen to model the mechanism behind the brain's structural changes instead of simply replicating the volumetric changes in various parts of the brain. By driving the pre-strained condition of the brain with volumetric expansion of the third and lateral ventricles, we have intuitively modelled the mechanical effects of elevated ventricular volume as a primary cause of elevated strains in the gray and white matter from SANS.

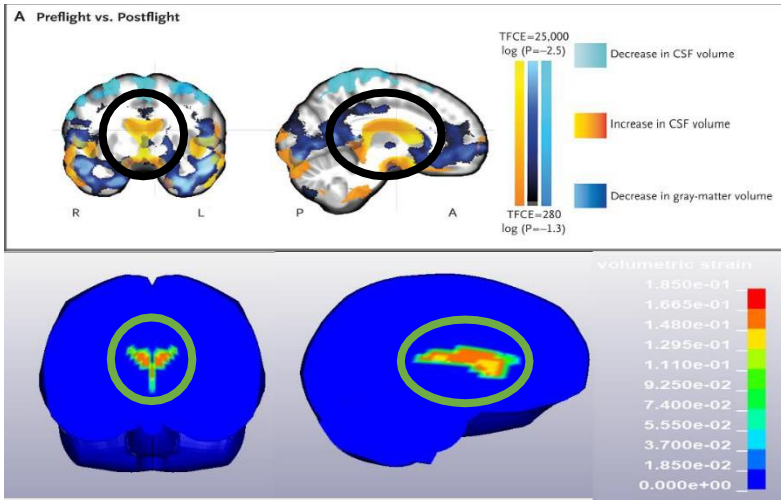


Figure 12: Qualitative validation of volumetric expansion in third and lateral ventricles (circled).

In order to replicate the absence of Earth's gravity, as well as induce the superior shift of the brain (towards the vertex of the skull), as indicated by Roberts et al., a 1G gravity in the superior direction was added to the THuMS model. The resulting upward migration, and slight rearward rotation, can be seen in Figure 13 below, accompanied by the results of Roberts' brain shift analysis following HDBR. By using a validated human body model (THuMS), a robust and industry-accepted finite element solver (LS-Dyna), and boundary conditions which adequately reflect available MRI data, the data which has

been produced is as reliable as possible. Note that the Roberts brain-shift analysis likely quantifies the rigid body displacement of the brain inside the skull, whereas the finite element model calculates the displacement of each element in the brain. However, most elements, especially in the area of interest near the vertex of the skull, reflect the Roberts data, with most elements in that area shifting upwards between 0.285 mm and 0.7 mm. While only marginally significant, the rearward rotation of the brain (clockwise from the given perspective) is apparent since the front of the brain translates upward more than the rear.

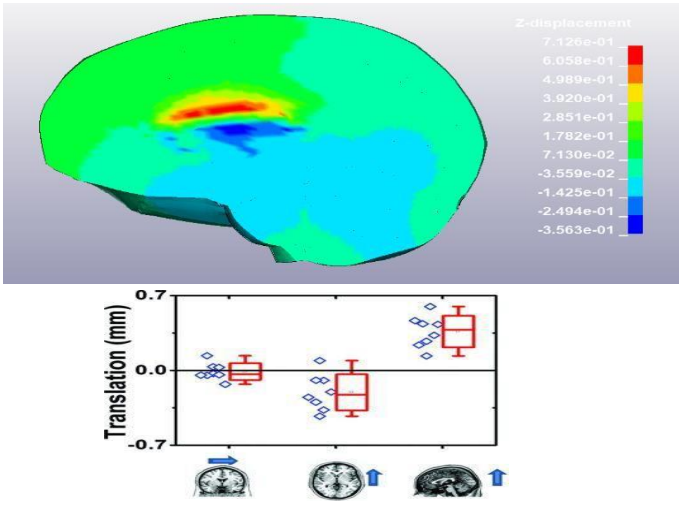


Figure 13: Quantitative validation of negative gravity boundary condition.

Further validation of the selected boundary conditions comes from measuring the space between the vertex of the skull and the brain. As previously stated, this distance is known to shrink due to the absence of gravity. By plotting the z-displacement time history of a node near the vertex of the skull (such as in Figure 14), we have confirmed that the behavior of the model qualitatively matches the effects of SANS. While we currently have no directly applicable quantitative data to compare with, the phenomenon has been replicated with a 1G upward gravity condition.

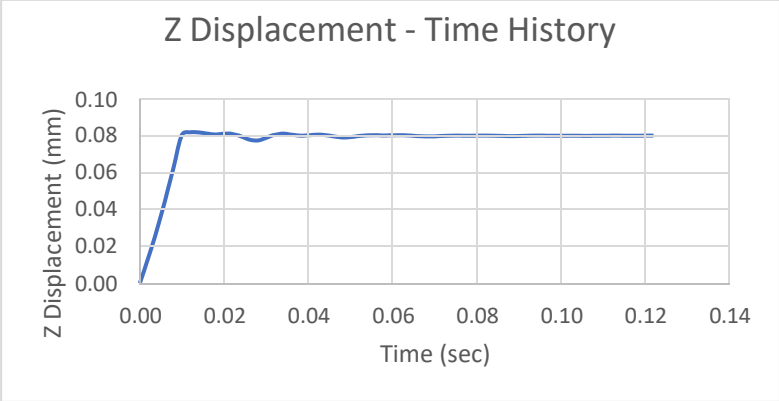


Figure 14: Z Displacement time history of a node near the vertex of the skull. Note that a positive displacement represents motion toward the vertex of the skull, thereby narrowing the extra-ventricular CSF space in that area.

Ultimately, the application of SANS-related boundary conditions puts some brain tissue in a pre-strained, displaced state. Figure 15 below shows the distribution of elevated maximum principal strain in a coronal and sagittal cross-section (note the accumulation of strains immediately surrounding the ventricles). Also shown (bottom) is the resultant displacement of the white and gray matter in the same cross sections. This shows the migration of elements away from the ventricles caused by ventricular expansion.

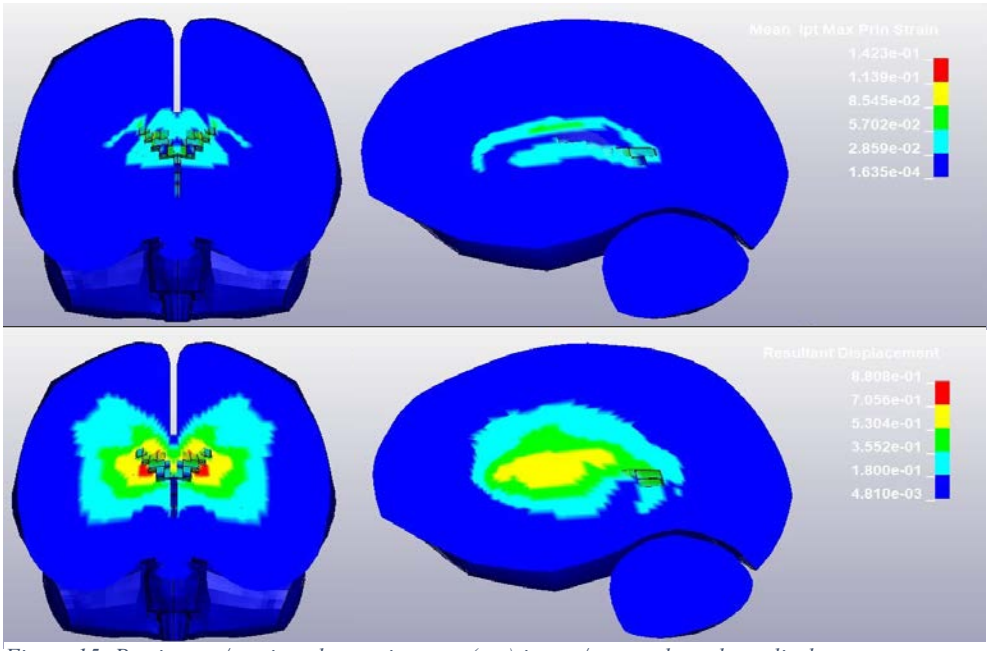


Figure 15: Pre-impact/pre-impulse strain state, (top) in mm/mm, and resultant displacement, (bottom) in mm, state of gray/white matter. The model has converged to steady-state strains and displacements in the figure.

SELECTING INJURY EVENTS

The full suite of completed simulations consists of four injury events with and without SANS-related alterations, in addition to one model which allowed the SANS boundary conditions to converge without an injury event (for a total of 9 simulations). Each of the nine variations were run in LS Dyna using the SMP Single-Precision solver. The first and second injury events simulate a steel impactor (3.6 kg) striking the vertex of the skull with initial velocities of 8 and 20 meters per second, respectively. The third and fourth are a 10G and 20G sinusoidal acceleration impulse applied over the course of 300 ms in the fore-aft direction. Two versions of each event were run (with and without SANS-alterations), resulting in a total of 8 injury simulations for analysis. A baseline dataset was first gathered with no additional boundary conditions/perturbations to the THuMS head form for each injury event.

Injury events were selected based on general relevance to spaceflight. Instrumented tests of Crew Exploration Vehicle (CEV) landing modules [29] indicate that vehicle landing could produce accelerations in the range of 10-20 g's peak, in an approximate sinusoidal shape with durations ranging from 200-300 ms. In accordance with this information, 'moderate' and 'severe' acceleration impulses were selected for simulation (10G and 20G sinusoidal acceleration impulses over 300 ms).

As no predictions can be made as to the magnitude and location of blunt force impacts to the head in space, the 8 m/s and 20 m/s parietal bone impacts were chosen to parallel the 'moderate' and 'severe' impulses chosen previously. Since the 8 m/s parietal bone impact has been validated during the creation of THuMS, we are confident that this simulation is especially robust.

Modelling Injury Events

The 8 m/s baseline impact is based on the Yoganandan Parietal Impact validation set provided with the THuMS documentation (the STRFLG option must be changed from 0 to 1 in the ELOUT ASCII output to access the strain data for post-processing). The 20 m/s baseline impact required a modification of the initial velocity generation keyword input, and the subsequent parametric variations required additional keyword inputs to impose thermal expansion of the ventricles and a negative gravity condition inside the skull.

For each of the parietal impact simulations, a solid, rigid sphere with properties of steel was situated above the vertex of the head. It was given an initial velocity (in accordance with its simulation) and an initial velocity start time of 1 second to allow the boundary conditions to converge to a steady strain state.

To create the acceleration impulse models, the steel ball impactor mesh was removed from the simulation, along with its associated velocity generation and contact inputs. The nodes at the base of the occipital bone were constrained to allow movement exclusively in the anterior/posterior direction (x-axis). Two simple acceleration impulses were created (10G and 20G Peak Linear Acceleration) to be applied to the nodes of the skull in the x- direction. All simulations were run using a timestep of 2 milliseconds. The acceleration impulse models were also allowed to converge to steady state before the impulse was applied.

Using the ELOUT ASII output allowed access to a strain time-history for every element in the gray and white matter. After the analyses were complete, CSDM and global maximum principal strain were retrieved for use as both comparative indicators of increased susceptibility, and injury prediction methods.

POST-PROCESSING

Upon completion of each simulation, the Maximum Principal Strain ASCII output was accessed and saved as a single CSV (comma-separated value) file. This CSV file contains the MPS value for each element at every timestep throughout the simulation. The large CSV was split evenly into 119 smaller CSV containing 1000 elements each, and a MATLAB script was written to post-process the data.

To appropriately identify changes in susceptibility to brain injury in both moderate and severe injury events, CSDM values were calculated at three critical strain values: 5%, 10%, and 15%. While risk of lethal injury is relatively low at 5% and 10% maximum principal strain, this method of calculating CSDM at low strain thresholds has been used for injury prediction in equestrian sports and other mild TBI prediction studies [28, 24].

Each 1000-column CSV was systematically scanned for values over the critical strain threshold, and three counter variables tallied the quantity of damaged elements present at each threshold. Calculation of CSDM was performed by dividing the number of damaged elements by the total number of elements in the gray and white matter (118,840). The post-processing script also determined the global Maximum Principal Strain - the highest strain experienced by any element throughout the duration of the simulation.

The data were compiled into groups of 3 simulations containing the convergence model (without an injury event), a baseline model injury event (unaltered THuMS brain), and a SANS-altered injury event (with boundary conditions). The data is presented in this manner to determine the effects of boundary conditions - in conjunction with, and in the absence of – a potentially injurious event on injury risk.

RESULTS

The application of SANS boundary conditions produced notable strains in the gray and white matter (in fact, individual elements exhibited steady state strains on the same order of magnitude as impact/impulse models). Allowing the boundary conditions to converge in the absence of an impact/acceleration event yielded a CSDM-5 value of 0.0087 (0.87% of the brain's gray and white matter elements experienced a maximum principal strain over 5% after the elements had reached a steady state condition), and a CSDM-10 value of 5.05e-5.

The 8 m/s baseline impact caused strains slightly higher, on average, than the SANS-only model (SANS boundary conditions without an external injury event). As hypothesized, the application of SANS boundary conditions in conjunction with the 8 m/s impact elevated strains even higher. A 3.6kg impactor with a velocity of 8 m/s striking the parietal bone of the baseline THuMS model (no SANS boundary conditions) resulted in a CSDM-5 value of 0.00645, while the impact was not severe enough to register on either the CSDM-10 or CSDM-15 scales. Once the THuMS model was altered to replicate the effects of long-term exposure to microgravity (SANS-modified model), the CSDM-5 value increased by 849% to 0.0613 and registered on the CSDM-10 scale at a value of 0.0113. The altered impact was still not measurable using a critical strain threshold of 15%. Global maximum principal strain increased from 0.094 to 0.340 from the baseline to SANS-altered impacts (261% increase). Kernel distribution curves have been presented in Figure 14 for both sets of parietal impact simulations.

A similar, less severe, increase in injury metrics was observed for the 20 m/s parietal bone impact. The same impactor striking the parietal bone of the standard THuMS model at 20 m/s yielded CSDM-5, CSDM-10, and CSDM-15 values of 0.124, 0.016, and 0.0043. This impact on the SANS-modified THuMS model showed increases in CSDM-5, -10, and -15 of 15.5% (to 0.143), 58% (to 0.0256), and 55.8% (to 0.0067), respectively. Kernel distributions for each parietal impact simulation are provided in the figure below.

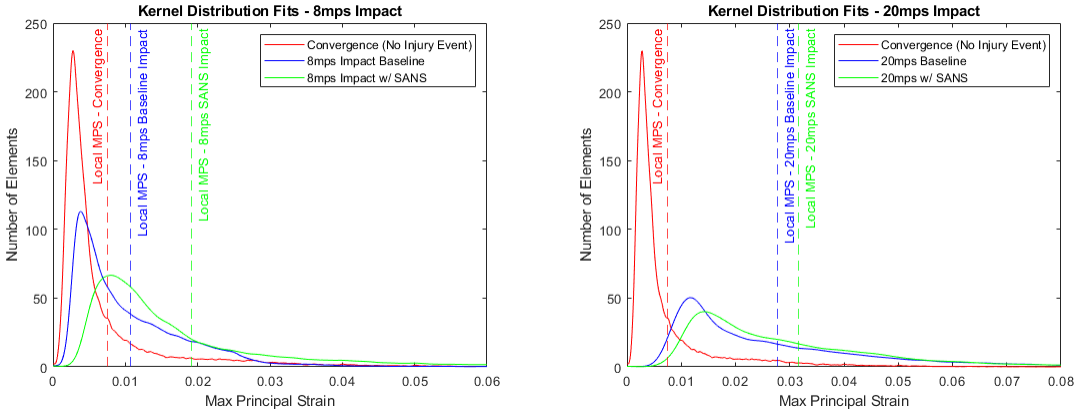


Figure 16: Kernel distribution fits of parietal bone impacts (8 m/s left, 20 m/s right). Average local MPS is represented by the dotted lines.

The baseline THuMS model, when subjected to a 10G acceleration impulse in the anterior-posterior direction, did not register any maximum principal strains over 5% - meaning the baseline event did not register on any of the three injury prediction scales. However, the SANS-modified model registered on all three scales, with CSDM values of 0.0458, 0.008, and 0.0023 (CSDM-5, CSDM-10, and CSDM-15, respectively).

The final simulation results come from the 20G impulse in the anterior-posterior direction. In parallel with the other simulations, there was an increase in average maximum principal strain, all CSDM levels, and MPS. The results for the acceleration impulses are provided in the figure below. Figure 18 shows calculated injury metrics for MPS (left) and CSDM (right).

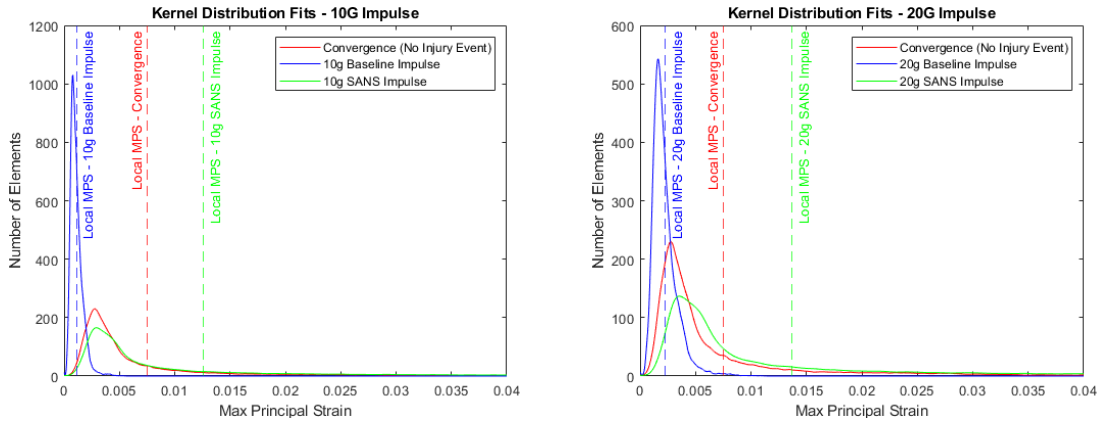


Figure 17: Kernel distribution fits of acceleration impulses (10G left, 20G right). Average local MPS is represented by the dotted lines.

	Injury Metric			
Event	**CSDM-5**	**CSDM-10**	**CSDM-15**	**MPS**
Boundary Condition Convergence (No Injury Event)	0.0087	5.05E-05	0	0.1423
Baseline 8 m/s Impact	0.0065	0	0	0.0943
SANS 8 m/s Impact	0.06125	0.01139	0.00345	0.3399
Baseline 20 m/s Impact	0.1236	0.0162	0.0043	0.2339
SANS 20 m/s Impact	0.1427	0.0256	0.0067	0.3632
Baseline 10g Impulse	0	0	0	0.0055
SANS 10g Impulse	0.0458	0.008	0.0023	0.2802
Baseline 20G Impulse	0	0	0	0.0113
SANS 20G Impulse	0.0507	0.0086	0.0022	0.2827

Table 1: Tabulated injury metrics for each event Orange cells indicate 'injurious' classification.

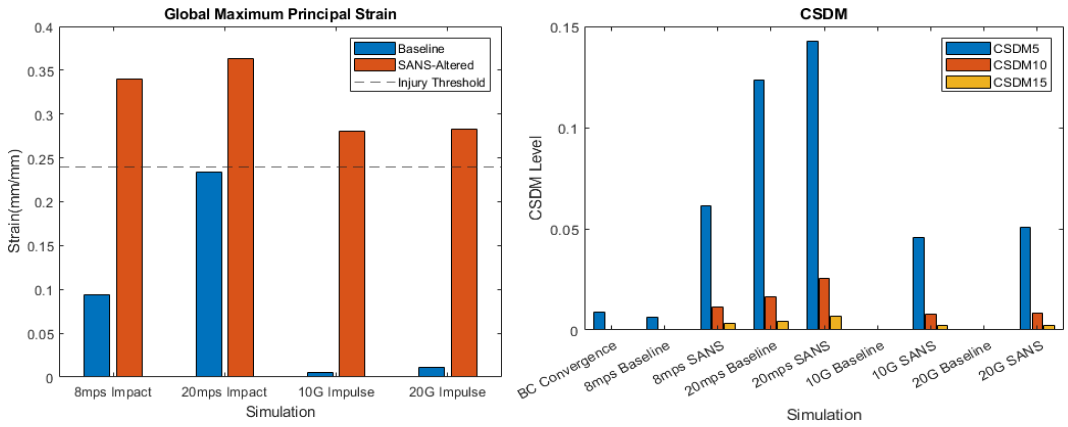


Figure 18: Baseline and SANS-altered global Maximum Principal Strain for each injury event (left). CSDM values for each injury event (right).

DISCUSSION

Migration of blood and CSF to the head due to exposure to microgravity causes an elevated strain state in the gray and white matter. The strain state of the brain caused by the microgravity-related boundary conditions is not expected to be injurious in the absence of external loads to the head. While transient accumulation of high strains may not be mechanically injurious in and of themselves, the superposition of strains caused by impact or acceleration upon pre-strained tissue (by SANS) elevates injury risk across the board. This is evident in the increase of each of the selected injury prediction criteria from the baseline to SANS-altered models. The potential for an individual to experience a brain injury during an event such as an impact or spacecraft landing may be drastically increased as a result of the pre-strained brain tissue. It is apparent that the application of SANS-related boundary conditions produces a significant shift in skew when plotting CSDM kernel plots (the mean local MPS increases with every injury event because of the boundary conditions). This is a positive indication that long-term spaceflight related brain changes do, in fact, increase susceptibility to traumatic brain injury.

Traumatic brain injury is commonly simulated using finite element analysis and a combination of relevant FE-based injury predictors. Most notably, stresses, strains, and intracranial pressure are often used to determine whether a certain scenario may cause TBI [26]. Since fluid influx and accumulation in the cranium produce elevated intracranial pressure along with significant stresses and strains in the brain matter, each of these injury metrics will likely be affected by SANS effects. In fact, the data herein show increased injury risk across the board – for all injury events and all tested injury metrics. While CSDM levels remain non-injurious according to collected injury tolerance levels [23] [19], MPS levels changed classification from 'non-injurious' to 'injurious' (MPS > 0.24) in all four injury events (8 m/s parietal impact, 20 m/s parietal impact, 10G impulse, 20G impulse) due to the SANS boundary conditions [24].

While this research focuses specifically on altered brain geometry (expansion, compression, or distortion of individual elements) resulting from exposure to microgravity, there are a host of other scenarios in which an individual may have altered brain geometry. Terrestrial disorders such as hydrocephalus or idiopathic intracranial hypertension are associated with persistent elevated ICP [2] [11]. Hydrocephalus, specifically in the context of spina bifida, is associated with expansion of cerebral (third and lateral) ventricles, like the effects of SANS [30]. Therefore, the results presented in this study suggest that persons affected by these disorders may also be more prone to traumatic brain injury due to these symptoms.

PROJECT LIMITATIONS

Fluid shifts to the cranium are the primary driving force for structural changes in brain matter after long-term exposure to microgravity, but other studies have also found cellular-level damage to brain tissue [31]. Finite element models are currently incapable of replicating cell/neuron function, which are thought to be disrupted by SANS-related changes. Similarly, a coupled fluid-structural analysis of these fluid shifts and impact tolerance would extremely computationally expensive. Dysfunctional cells, along with damaged neurons and the possibility of further elevation of ICP due to microbleeds, could further increase susceptibility to primary brain injury, or compound into serious complications including secondary brain injury. The potential for compounding adverse effects resulting from SANS-related structural changes to the brain should be investigated more thoroughly before a final conclusion is to be made on the overall safety of permanent extraterrestrial habitations.

Exposure to microgravity is known to cause cellular-level changes to many parts of the body. Muscle and bone atrophy are commonly reported complications from space travel. Impediments to the production, circulation, and resorption of cerebrospinal fluid have also been pointed out. Since the THuMS model is constructed using solid elements for CSF, a coupled fluid-structure analysis cannot be reasonably created to analyze the effects of fluid production, resorption, flow, and hydrostatic pressures on susceptibility to injury. Also, this study accurately reproduces some of the structural changes to the brain using only two driving factors (ventricular volumetric expansion and upward gravity). This simplifies the simulations by isolating the mechanical response to microgravity as an independent variable but may not fully capture the true change in susceptibility to, and

severity of, brain injury. On all accounts, it is probable that omitting cellular and fluid responses to microgravity produces a conservative calculation of injury risk.

As the gray and white matter are modelled as viscoelastic, they exhibit some stress-relaxation behavior. SANS-related brain changes occur over a period of 2 months or more; however, they were simulated in just one second. The dynamic response of viscoelastic materials can get quite complex, but the model was allowed to settle for at least two time constants before and after being subject to an external load case to allow for stress-relaxation and any potential delay between stress input and strain reaction. Two time constants should allow adequate time for convergence, stress-relaxation, or creep to occur before external loads were applied.

FUTURE WORKS

Being the first study of its kind, it is important to first understand the basic effects of altered brain structure on injury susceptibility and severity before simulating a large variety of impact and impulse events. While this study focuses on a small number of injury events, it provides a solid foundation for future works to build upon.

Moving forward, it would be logical to subject the SANS-altered brain model to a host of other injury events – perhaps some spaceflight-specific events such as takeoff, entry, descent, and landing (both ideal and emergency) impulses. The impulses tested in this paper are loosely representative of crewed spacecraft landings in which astronauts are seated in a reclined position. Different landing modules may have astronauts positioned differently, which would require acceleration impulses in different directions, for example.

A more comprehensive set of injury events would be beneficial to fully comprehend the effects of SANS-related changes on traumatic brain injury. For example, it is understood that the risk of head/neck injuries is slightly higher for lateral car impacts than frontal impact [32]. An examination on the magnitude of SANS effects on injury tolerance for lateral impacts, and other trauma events, would provide further support for our results, and potentially guide future design for landing modules.

Additionally, given the wide range of ventricular volume data throughout literature and provided by NASA, patient specific injury tolerance analysis would be extremely insightful into the scope and magnitude of this phenomenon. By obtaining pre- and post-flight magnetic resonance images of astronauts who have been exposed to microgravity, FE models could be derived to precisely model the changes in the brain's structure. Subjecting these models to a variety of injury events, similar to what has been done here, would detail an exact change in injury response for a given individual as opposed to using mean data. Determining whether certain demographics are more sensitive or resilient to SANS-related brain changes and fluid shifts could prove valuable for astronaut selection in the future.

Further research must be done, in addition, to determine the effects of cellular changes of brain tissue on its injury tolerance. Changes in cell shape, size, volume, and adherence have been documented because of microgravity exposure, creating the need to analyze whether these changes have a significant effect on the brain's injury response [33]. Microscale structural changes to the cells in the brain, as well as macroscale structural changes to the brain itself, may compound to further amplify the apparent increase in injury risk. If that were the case, the results contained in this paper (concerning as they

may be) would be a very conservative estimate of the effects of microgravity on susceptibility to traumatic brain injury.

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APPENDIX A:

Tabulated summary of pre- and post-flight ventricular volume data provided by NASA.

	Preflight			Postflight		
Subject ID	Lateral Ventricle Volume (mL)	Total Ventricular Volume (mL)	Extra-ventricular CSF Volume (mL)	Lateral Ventricle Volume (mL)	Total Ventricular Volume (mL)	Extra-ventricular CSF Volume (mL)
1975	29.9	36.9	285	36.2	44.6	281
2171	39.1	44.9	312	41	47.5	309
6717	27.1	34.3	341	28.7	36.6	339
7673	14	19.9	379	15.7	22.1	363

Mean Changes (mL)		
2.875	3.7	-6.25
Mean Changes (%)		
10.44504995	10.88235294	-1.898253607

VITA

Ryan Baskerville graduated with a Bachelor of Science in Mechanical Engineering from the University of North Florida in 2020. He expects a to receive a Master of Science in Mechanical Engineering from the University of North Florida in May of 2022. Dr. Grant Bevill serves as Ryan's thesis advisor and committee chairperson, along with fellow committee members Dr. Alexandra Schonning and Dr. Jutima Simsiriwong. Ryan has accumulated 4 years of internship experience in the raw materials manufacturing and aerospace fields. He is currently employed as an intern-level mechanical engineer at Drone Aviation Corp. in Jacksonville, Florida.

Ryan's current professional/academic interests include injury biomechanics, safety optimization, and finite element analysis. He also has interests in small-batch manufacturing, electric vehicles, and aerospace engineering. He is proficient in the use of modeling/analysis software such as SolidWorks, Siemens NX, and ANSYS LS-Dyna, as well as programming language/logic through experience with MATLAB.