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Appendix Materials

Relationship between IBS and dizziness

Hair cells in the semicircular canals of the inner ear monitor head position and g-force acceleration by detecting shifts in gravity-dependent endolymph. Together with the vestibular nucleus and its projections to the cerebellum, the vestibular system enables upright balance in the setting of gravity.

However, the vestibular system does far more than track head position; it also informs our sense of physical embodiment.[1] Without precisely timed signals from the inner ear, the brain may question whether it owns the body to which it is connected. The result of vestibular dysfunction is a peculiar sense of Cartesian dualism, where the mind can feel separated from the body, leading to depersonalization, derealization, severe anxiety, or panic[i]; it is notable that all these symptoms have been reported in patients with IBS.

It is this insight—that the gravity-tracking inner ear informs our sense of self—that helps to explain why vestibular pathology might cause anxiety in addition to vertigo and disequilibrium. A meta-analysis of over thirty studies linking inner ear dysfunction with mental distress concluded that some cases of anxiety and panic are triggered by vestibular stimuli being misinterpreted as imminent physical danger.[2] The authors further proposed that mistimed inner ear signals can activate a false alarm in the locus coeruleus, an area of the brain known to be dysregulated in IBS that synthesizes and stores norepinephrine.[3] It is possible that another consequence of peripheral sensitization in IBS is having a low threshold to detect and misinterpret subtle endolymph movements, leading to an inappropriately timed discharge of norepinephrine and sympathetic overdrive.

Despite the high prevalence of vestibular symptoms among patient with IBS, there is little research examining differences in vestibular sensitivity, benign positional vertigo, nystagmus, or benefits of head tilt maneuvers in patients with IBS vs. controls (particularly among those who

report dizziness). Of note, patients with Ménière disease, a disabling inner ear condition marked by vertigo and ear fullness, often report GI symptoms, show evidence of autonomic dysregulation, and have altered intestinal permeability.[4] It is unclear if these findings have relevance to IBS, but they further illustrate the far-reaching impact of the inner ear beyond merely tracking head position.

However, the literature does indicate a role of the cerebellum—a critical gravity management body—in determining responsiveness to and persistence of GI symptoms in IBS.[5] Furthermore, the cerebellum helps to regulate cognitive functions, emotions, social cognitions, autonomic functions, and pain perception.[6] In addition, altered connections of the cerebellum with other brain structures, such as the insula and prefrontal cortex, have been associated with somatic symptom level in IBS. Given the high prevalence of vestibular and cerebellar symptoms in IBS, further research in this area is warranted.

Relationship between IBS, disordered sleep, and hypothalamic-pituitary-adrenal (HPA) axis

Disordered sleep in IBS likely results from a combination of disruptive abdominal pain and diarrhea together with comorbid stress, anxiety, and depression. In return, disordered sleep can lead to abnormalities in the HPA axis—especially dysregulated cortisol—which directly impacts immune function, gut function, and musculoskeletal function. In this manner, disordered sleep promotes a viscous cycle that undermines biopsychosocial health and worsens IBS.

It has been speculated that sleep evolved, in part, as an adaptation to minimize gravity-dependent regional ischemia in the brain.[7] Unlike other vital organs that benefit from mobility and shock absorbency, the brain is encased in bone, rendering it immobile and uniquely vulnerable to g-forces. Although the meninges and cerebrospinal fluid (CSF) lessen the effects of gravity, the brain nonetheless remains susceptible to compression against the skull. In the upright position, downward pull upon the brain's mass results in "regional gravitational ischemia" of its ventral surface in the absence of repositioning, a phenomenon likened to the risk of pressure ulcers among bedbound patients who are not frequently turned.[110] The pituitary gland is especially vulnerable to gravitational pressure given its location upon the hard floor of the sphenoid and within the bony sella turcica, itself situated directly beneath the brain's mass. Sustained horizontal sleep is thought to reposition the brain and restore perfusion to the

dependent ventral structures, including the hypothalamus and pituitary. It is also notable that CSF production and flow, along with intracranial pressure (ICP), are highly dependent upon gravity and vary at different altitudes and with spaceflight (e.g., astronauts in microgravity often develop new onset migraine headaches).[8,9]

Although it remains speculative, the regional gravitational ischemia hypothesis implies a physiologic sequence that could potentially occur for some IBS patients, as follows: GI symptoms and comorbidities disrupt sleep, manifesting with less time spent in the horizontal position; lack of prolonged and restful sleep leads to diminished time reperfusing the gravity-dependent hypothalamus and pituitary; HPA function is undermined and cortisol cycles are dysregulated; abnormalities in cortisol directly impact GI physiology and alter gut microbiology; a dysregulated microbiome leads to increased production of bacterial metabolites which cause peripheral sensitization of afferent visceral nerves, ultimately leading to worsened IBS symptoms. Of course, stress itself can directly alter the HPA axis independent of sleep, but the gravity hypothesis offers an additional mechanism that seeks to accommodate the links between cerebrovascular blood flow, CSF flow, ICP, and gravity. As of this writing, there is little research measuring differences in gravitational ischemia, CSF fluid dynamics, ICP measurements, meningeal structures, or arachnoid anatomy between IBS patients and controls (particularly those with disordered sleep and/or headaches, or those living at different altitudes). Just as primary abnormalities in mesodermal GI support systems could generate IBS symptoms and lead to sleep disruptions, primary abnormalities in mesodermal and fluidic support systems of the brain could work in reverse, causing sleep disruptions, headaches, disrupted HPA axis, and altered GI physiology that culminate in visceral sensitization and IBS symptoms in the susceptible host. Table 2 lists research questions that could help to investigate this intriguing but unproven possibility.

Further details about serotonin as a gravity-management substance

Beyond the GI tract, serotonin supports gravity management across body systems. In the cardiovascular system, serotonin is critical for maintaining vascular tone and blood pressure, regulating heart rate, and mediating the baroreceptor reflex.[10] These jointly allow blood to pump against gravity. Serotonin is also upregulated in the cardiac ventricles to increase stroke volume in the setting of heart failure thereby acting as a compensatory mechanism to support blood flow

as pump function fails.[11] Serotonin is also found in the vestibular nerve and nucleus where it plays a vital role in maintaining balance.[12] This becomes evident when some patients who discontinue selective serotonin reuptake inhibitors (SSRIs) develop disabling vertigo from a rapid reduction in vestibular serotonin.[13] Elsewhere, serotonin coordinates upward contractions in the uterus that promote sperm transport from the cervix to the oviduct, literally pumping against gravity.[14] Cerebrospinal fluid production, which is itself dependent in part on altitude, is regulated by serotonin in the choroid plexus.[15] There is even evidence that changes in g-force can alter serotonin expression in mice,[86] suggesting that serotonin levels may change in relation to the gravitation field experienced by the organism.

Embodied cognitions and gut-brain communication

The "gut-brain" theory of IBS, which is widely accepted and intrinsic to the gravity hypothesis, is itself based upon the more general theory of embodied cognitions.[87] According to this theory, our emotional and cognitive lives emerge not only because we have a brain, but also because the brain is connected to the rest of our body. The body is an extracranial extension of the brain that collects signals from around and within us and transmits them to the CNS for processing and integration. This not only generates symptoms, but also shapes what we think about, what we know and understand, and how we feel. For example, baroreceptors not only sense and regulate blood pressure but also impact pain perception, sleep, consciousness, and even cognitions.[16] We have seen how the same applies to the vestibular system, which not only tracks head position but also shapes mental health. These examples illustrate that our mind depends on the state of our body.

The gut and the brain are also engaged in constant bidirectional dialogue. Physiologic and microbial alterations in the gut shape emotions, cognitions, and behaviors that emerge from the brain.[17] Conversely, we have seen that events in the brain directly affect GI physiology and microbiology through the ANS and HPA axis. The brain can also directly modify visceral pain through descending inhibitory pathways.[18] Details regarding the mechanisms of gut-brain crosstalk are beyond the scope of this article and can be reviewed elsewhere.[19] For our purposes here, it is sufficient to acknowledge the expansive literature demonstrating dynamic interactions between the gut and the brain.

Cognitive embodiment of "up is good" and "down is bad"

It is both intrinsic to our language and embedded in our neuropsychology that moving up against gravity is "good" and moving down with gravity is "bad." The table, below, provides a list of common English-language idioms that link an emotional valance to verticality. Although there are idioms that decouple "up" from good, and vice versa (e.g., "an uphill battle"; "enjoy some down time"), these tend to be exceptions to the idiomatic rule.

Example "Up is Good" Idioms	Example "Down is Bad" Idioms
• Aim high • Floating on a cloud • In high spirits • Living the high life • On cloud nine • On top of the world • Over the moon • Things are looking up • Thumbs up • Up in heaven • Walking on air • Wish upon a star	• Bogged down • Cast (one's) eyes down • Chill running down (one's) spine • Down and out • Down in the dumps • Down in hell • Down on (one's) luck • Feeling down • Hanging (one's) head • Have a sinking feeling • In low spirits • Things are looking down

Research indicates that these concepts are not merely turns of phrase but are more deeply rooted as embodied cognitions. For example, Meier et al. found that emotionally neutral objects are rated more positively when they are placed upward in vertical space. The same investigators also discovered that research subjects could recognize positive words that appear at the top of a screen faster than the same words displayed at the bottom of a screen, and vice vera for negative words.[20] In addition, people more quickly identify words with a positive moral valence when they are at the top of a screen.[21] The same applies to the vertical position of "God-related" vs. "devil-related" words.[22] Meyers-Levey et al. found that rooms with high ceilings generate feelings of freedom, whereas those with low ceilings trigger thoughts of confinement.[23] Deng and colleagues revealed that when an object is placed in a low position, it is perceived to

be heavier than the same object located in a higher position. The authors posit that this judgment relates to experiences with gravity, as heavy objects pull downwards whereas objects lighter than air, like a balloon, float upward.[24]

Even body posture affects emotional valence and self-confidence. Wilson and colleagues revealed that when people stand in a purposefully upright posture, they are more able to recall positive thoughts.[25] Nair et al. also discovered that people experience higher self-esteem and a positive mood when they sit straight up rather than slouching down.[26] In a similar vein, Ostinelli et al. found that when people imagine moving upward, they simultaneously feel greater self-worth compared to imagining a downward movement.[27]

Clinical approach to the eight "g-force cube" profiles

The g-force cube indicates that IBS susceptibility is determined by three factors displayed in Figure 1: (1) g-force resistance; (2) g-force detection; and (3) g-force vigilance. These factors jointly define eight IBS susceptibility profiles. Here, we discuss clinical implications of the gravity hypothesis in relation to each profile.

Profile 1: Very low risk

G-force resistance: durable
G-force detection: normosensitive
G-force vigilance: unconcerned

People with durable GI support systems, lack of peripheral sensitization, and low threat vigilance are very unlikely to develop IBS. Even if someone with this profile transiently experiences gravity strain, they will remain unlikely to experience chronic pain or GI symptoms since they are not peripherally sensitized to nociception or hypervigilant to perceived threats.

Profile 2: Moderate risk

G-force resistance: vulnerable
G-force detection: normosensitive
G-force vigilance: unconcerned

People with this profile inherit and/or develop mechanical vulnerabilities in their GI support structures. For example, they may inherit a maladapted mesentery, have abnormal collagen deposition in their connective tissues, or sustain a spinal injury that affects their

"abdominal crane." These mechanical issues can negatively impact the form and function of the peritoneal viscera, including the intestines, leading to dysmotility and/or altered gut microbiome. However, despite their mechanical vulnerabilities, people in this profile have not yet sensitized their PNS and are not hypervigilant. Although it is possible for gravity strain to cause peripheral and central sensitization over time, people in profile 2 remain at only moderate risk of IBS. Treatment should focus on addressing mechanical vulnerabilities using the approaches outlined in Table 2 (e.g., exercise, weight management, etc.)

Of note, if someone in this profile were to experience an early adverse life event or PTSD, for example, then it could lead to primary hypervigilance (rather than secondary hypervigilance resulting from IBS symptoms). In the setting of pre-existing mechanical vulnerabilities, heightened CNS vigilance could directly alter GI function through the HPA axis and ANS, leading to a higher risk of IBS symptoms compared to someone without pre-existing structural vulnerabilities. In this manner, the IBS gravity hypothesis accommodates the possibility that IBS symptoms can arise from CNS hypervigilance in the susceptible host, rather than always having to arise directly from the GI tract.

Profile 3: Moderate risk

G-force resistance: durable
G-force detection: hypersensitive
G-force vigilance: unconcerned

People in this profile have durable g-force resistance but a hypersensitive PNS. If gravity strain begins to affect body systems, such as the GI tract, then the hypersensitive PNS may quickly generate symptoms and increase the risk of central sensitization and hypervigilance. For example, if an individual with this profile developed acute gastroenteritis, then they might be at increased risk of developing post-infectious IBS (PI-IBS) compared to someone without pre-existing PNS sensitization, even if they have otherwise durable g-force resistance. Because they have a sensitized PNS, changes in the gut microbiome, inflammation, or epithelial permeability from infection may lead to enhanced visceral nociception and trigger rapid symptom generation at a lower threshold than in people without pre-existing PNS sensitivity. It is important to

maintain mechanical durability in someone with this profile because even a modest increase in nociception may generate symptoms.

Profile 4: High risk

G-force resistance: vulnerable
G-force detection: hypersensitive
G-force vigilance: unconcerned

In this common scenario, the GI support systems are mechanically vulnerable and the PNS is sensitized, but there is not yet evidence of central sensitization or threat hypervigilance. This situation is common because when someone possesses a physically vulnerable body, they may compensate by becoming more sensitive to g-forces as a natural result of unabated nociception, as described in the accompanying paper. However, there is still an opportunity in this instance to slow the transition from peripheral to central sensitization and lower the risk of developing g-force hypervigilance. In addition to strengthening the body through physical fitness, people in profile 4 may benefit from techniques to reduce peripheral sensitization, such as PNS neuromodulation, altering gut serotonin levels, modifying the gut microbiome, and other treatments listed in Table 2.

Profile 5: Moderate risk

G-force resistance: durable
G-force detection: normosensitive
G-force vigilance: hypervigilant

In this scenario, there is durable g-force resistance and normosensitive g-force detection—both protective features. However, there is also evidence of g-force hypervigilance, which increases IBS susceptibility. People in profile 5 have little g-force strain on their body and appear physically acclimated to living in a 1g world. There is minimal PNS nociception, and therefore no evidence of PNS sensitization. However, this profile exhibits primary CNS hypervigilance due to high native threat detection and/or accumulation of stressful life events. Importantly, someone in this category could still develop IBS if they experience a change in their g-force resistance, which could occur with a spinal injury, weight gain, aging, abdominal surgery, or change in the gut microbiome (among other possibilities). For example, if someone in this

profile developed acute gastroenteritis, then they might be at higher risk of developing PI-IBS compared to another person without hypervigilance. This is supported by data indicating that pre-existing psychological disorders is an independent risk factor of developing PI-IBS after a bout of acute gastroenteritis. Therefore, treatment for this patient should include maintaining good physical fitness to support g-force durability and treatments to shift away from hypervigilance, such as cognitive behavioral therapy, meditation, or sleep therapy, among others in Table 2.

Profile 6: High risk

G-force resistance: vulnerable
G-force detection: normosensitive
G-force vigilance: hypervigilant

This category is like profile 5, but here there is a higher risk of IBS because of vulnerabilities in g-force resistance. Although the PNS is not yet sensitized, it is likely to become sensitized soon, indicating that profile 6 is more of a transient state than a destination. Patients in this category should be managed in the same way as profile 5: with physical activity to bolster GI resistance, and with treatments to lower CNS hypervigilance.

Profile 7: High risk

G-force resistance: durable
G-force detection: hypersensitive
G-force vigilance: hypervigilant

People in this category are at high risk for developing IBS because they have a hypersensitive PNS and hypervigilant CNS, albeit durable g-force support systems. As with profile 5, patients in this category may develop IBS if they experience any perturbation in their G-force resistance systems. They should be managed with prophylactic physical fitness, cognitive behavioral therapy, and strategies to lower PNS sensitivity, as outlined in Table 2.

Profile 8: Very high risk

G-force resistance: vulnerable
G-force detection: hypersensitive
G-force vigilance: hypervigilant

This is the highest risk category for IBS. Here, patients need to be shifted down along all three axes by reducing g-force vulnerability, lowering PNS sensitivity, and minimizing g-force hypervigilance, where possible. All the treatments in Table 2 may be considered depending on the unique circumstances and preferences of the patient.

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