Vestibular -Autonomic Interactions

Scientific Review

1. Abstract

The vestibular system contributes to physiological regulation as well as balance, gaze stabilization, spatial orientation, and perception of self-motion. Anatomical studies demonstrate projections from vestibular nuclei to brainstem regions involved in autonomic regulation, and direct human experiments show that vestibular stimulation can modify sympathetic nerve activity and cardiovascular physiology. These responses are not uniform. Their magnitude and direction vary with stimulus characteristics, physiological state, posture, cardiovascular context, and the autonomic output being measured. Different autonomic outputs can also dissociate, making vestibulo-autonomic response inherently multidimensional. [1-9]

Noninvasive physiological measures therefore require constrained interpretation. Heart-rate variability can characterize aspects of cardiac autonomic modulation but does not directly measure vagal or sympathetic nerve traffic; electrodermal activity reflects sympathetic sudomotor physiology rather than global sympathetic activity; and pupil dynamics are influenced by autonomic pathways together with luminance, gaze, arousal, cognition, and other factors. Respiration, posture, visual context, motion sickness, and participant state can modify or mimic candidate autonomic responses and must be considered when interpreting motion-associated physiological change. [10-22]

Disease-specific evidence remains preliminary. In postural orthostatic tachycardia syndrome, recent evidence provides a direct but preliminary bridge between otolith-related vestibular measures and cardiovascular variability. Autism spectrum disorder has a substantial literature describing group-level autonomic differences and altered sensory-autonomic reactivity, but the direct relationship between controlled mechanical vestibular stimulation and autonomic physiology remains insufficiently studied. [23-28]

Taken together, the literature establishes that vestibular input can influence human autonomic physiology through measurable but heterogeneous, stimulus-dependent, state-dependent, and pathway-specific responses. It does not identify a therapeutic vestibular waveform, establish that natural motion improves autonomic regulation, or demonstrate clinical benefit in autism, POTS, or other conditions.

Within the SeaKing Solace research framework, the resulting question is whether characteristics of received natural vestibular motion predict reproducible, temporally structured, and interpretable changes across synchronized physiological measures. Phase 1 is designed to identify and replicate

candidate motion-response relationships while characterizing major competing explanations. Any such relationships would require subsequent controlled reproduction and manipulation before causal, therapeutic, dose-response, or adaptive-control conclusions could be justified.

2. Purpose and Scope

The purpose of this review is to examine the scientific evidence for functional interactions between the vestibular and autonomic nervous systems and to determine what that evidence does, and does not, permit investigators to infer about externally applied natural motion.

This review follows Scientific Review 01: Vestibular System & Motion, which examined how physical motion becomes vestibular input and established the methodological importance of characterizing natural motion as a multidimensional, time-varying exposure. Review 01 also distinguished motion of an external vessel or platform from the head-centered motion actually received by the participant. The present review begins downstream of that physical-input problem and asks what happens physiologically when vestibular input reaches systems involved in autonomic regulation.

The review therefore examines anatomical vestibular access to autonomic circuitry; direct human vestibulo-sympathetic physiology; cardiovascular and respiratory interactions; stimulus and state dependence; cardiac variability, electrodermal activity, and pupil dynamics; motion sickness and sopite syndrome; individual variability and adaptation; and the current disease-specific evidence relevant to POTS and autism. It also considers the interpretive limitations of experimental vestibular paradigms and noninvasive autonomic measurements.

Throughout the review, autonomic physiology is treated as multidimensional rather than as a single continuum between sympathetic and parasympathetic states. Muscle sympathetic nerve activity, skin sympathetic nerve activity, heart rate, arterial pressure, heart-rate variability, respiration, electrodermal activity, pupil dynamics, vascular responses, and symptoms are related but non-equivalent outputs. Likewise, evidence that vestibular input reaches autonomic circuitry or changes a physiological measure does not by itself establish the direction, mechanism, desirability, or clinical significance of that response. [1-6]

The scope is intentionally evidentiary rather than therapeutic. The review does not assume that externally applied motion increases vagal activity, decreases generalized sympathetic activity, produces “autonomic balance,” or improves clinical outcomes. It instead asks which vestibulo-autonomic relationships are established, which remain conditional or uncertain, which measurements can test them appropriately, and which conclusions require controlled experiments beyond the existing literature.

For SeaKing Solace Phase 1, the relevance is methodological. The central question is whether features of received head-centered natural motion can be related reproducibly to synchronized multimodal physiological responses while major competing influences are measured. Phase 1 can identify candidate associations, temporal relationships, state dependence, and within-person reproducibility. It cannot by itself establish therapeutic efficacy, clinical benefit, a specific neural mechanism, an optimal waveform or dose, or the superiority of natural or adaptive motion.

The purpose of this review is therefore to define the scientific foundation and evidentiary boundaries necessary to test the vestibular-autonomic hypothesis without presuming its outcome.

3. From Vestibular Input to Autonomic Control

The vestibular system contributes to more than perception of movement, gaze stabilization, and postural control. Signals arising from vestibular organs also reach neural structures involved in autonomic and cardiovascular regulation. This organization provides a biological pathway through which information about head movement and orientation relative to gravity can influence physiological regulation during movement and postural change. [1-4]

The relationship is not adequately represented as a simple pathway from vestibular input to a single autonomic output. Vestibular signals enter distributed brainstem networks that interact with cardiovascular, sympathetic, parasympathetic, respiratory, and other homeostatic processes. [2-4]

3.1 Anatomical Access to Autonomic Brainstem Circuitry

Anatomical studies provide direct evidence that vestibular nuclei have access to brainstem regions involved in autonomic regulation.

Balaban and Beryozkin demonstrated projections from vestibular nuclear regions to the nucleus tractus solitarius and the dorsal motor nucleus of the vagus. These connections provide anatomical substrates through which vestibular information can enter circuits involved in visceral and cardiovascular regulation. [1]

Additional anatomical work identified projections from the caudal vestibular nuclei to the ventrolateral medulla, which contains neuronal populations important to cardiovascular regulation and sympathetic control. [2]

Gagliuso and colleagues subsequently identified vestibular neurons projecting directly to the solitary nucleus, further supporting pathways capable of conveying vestibular information into brainstem autonomic circuitry. [3]

Together, these findings establish anatomical access. They demonstrate that vestibular signals can reach neural structures participating in autonomic regulation without requiring that relationship to be inferred solely from peripheral changes in heart rate, arterial pressure, or other physiological measures.

Anatomical connectivity does not determine the direction, magnitude, or clinical meaning of the resulting response. A projection to the nucleus tractus solitarius, dorsal motor vagal region, or ventrolateral medulla does not establish that a particular vestibular stimulus will increase parasympathetic activity, decrease sympathetic activity, or produce a beneficial physiological state. Those questions require functional evidence. [1-4]

3.2 Vestibular-Autonomic Pathways Are Distributed

Vestibulo-autonomic control is better understood as a distributed network than as a single “vestibular-to-vagus” pathway.

The nucleus tractus solitarius is an important site of visceral and cardiovascular integration, while regions of the ventrolateral medulla participate in regulation of sympathetic cardiovascular output. Vestibular projections to these regions therefore provide multiple routes through which information about movement and orientation can interact with ongoing autonomic regulation. [2-4]

This distributed architecture has an important physiological implication: different peripheral outputs need not change in parallel. Sympathetic nerve traffic, heart rate, vascular resistance, arterial pressure, respiration, and other measures represent different components or consequences of an

integrated regulatory system. An observed change in one therefore cannot be assumed to define the state of the others or identify the neural pathway responsible. [4]

Anatomical connectivity consequently establishes biological plausibility and structural access, while functional experiments are required to determine how these pathways are recruited under particular conditions.

3.3 Feed-Forward and Feedback Regulation

A proposed function of vestibulo-autonomic pathways is to contribute to cardiovascular adjustment during movement and changes in orientation relative to gravity.

Arterial baroreceptors provide feedback about cardiovascular consequences as they occur. Vestibular information can provide a different form of information: because the vestibular system detects head acceleration and orientation relative to gravity, it can signal a postural or gravitational transition during the transition itself. Vestibular pathways can therefore contribute a feed-forward component to cardiovascular regulation rather than relying exclusively on feedback generated after arterial pressure has changed. [4,29]

These mechanisms do not operate independently. Experimental evidence demonstrates that baroreceptor state modifies human vestibulo-sympathetic responsiveness. Dyckman, Monahan, and Ray found that altering baroreflex loading changed the responsiveness of the vestibulo-sympathetic reflex, demonstrating interaction between vestibular and cardiovascular feedback systems. [9]

The resulting regulatory model is therefore one of interacting signals:

vestibular information about movement and orientation → feed-forward autonomic influence

together with

cardiovascular consequences → baroreceptor feedback → compensatory autonomic influence

These processes converge within an ongoing regulatory network rather than acting as isolated reflexes. [4,9,29]

The narrower conclusion required here is that vestibular signals have established anatomical access to autonomic brainstem circuitry and operate within a distributed regulatory system that interacts with cardiovascular feedback.

The next question is functional: when the human vestibular system is experimentally perturbed, can changes in autonomic nerve traffic actually be measured?

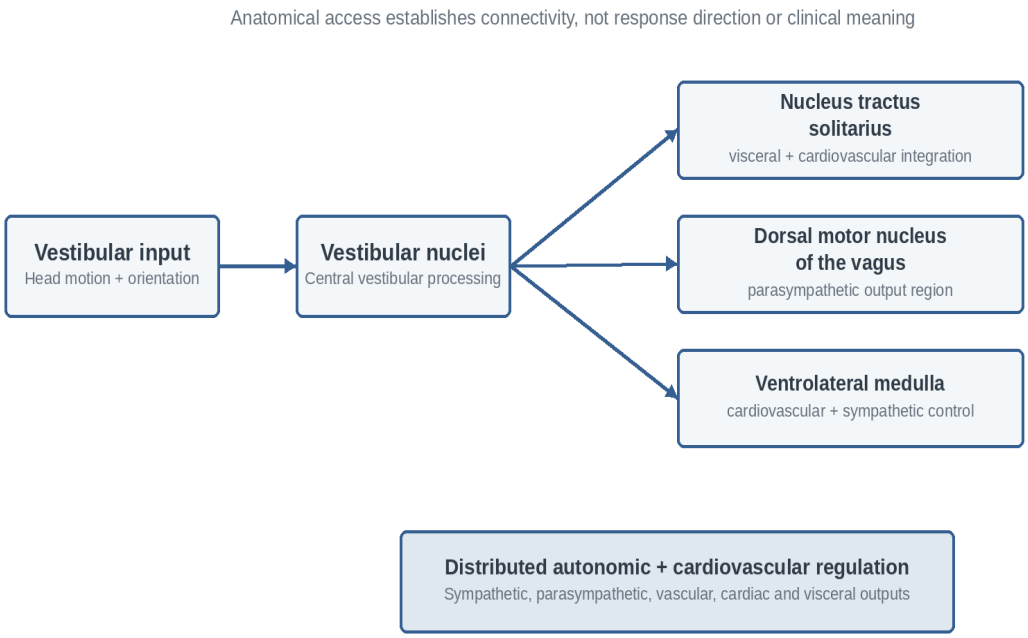

Figure 1. Vestibular access to autonomic circuitry. Conceptual schematic showing established anatomical access from vestibular nuclei to brainstem regions involved in autonomic and cardiovascular regulation. The schematic represents distributed connectivity and does not imply that a particular vestibular stimulus produces a predetermined parasympathetic, sympathetic, or clinical effect. [1-4]

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4. The Human Vestibulo-Sympathetic Reflex

Anatomical connectivity establishes that vestibular signals can reach autonomic regulatory circuitry. Functional evidence requires demonstrating that vestibular perturbation actually changes autonomic output in humans.

Human studies using direct recordings of sympathetic nerve activity provide that evidence. Vestibular stimulation can modify sympathetic nerve traffic in conscious humans, establishing a functional vestibulo-sympathetic reflex. [4-8,30,31]

The established finding is not that vestibular stimulation simply increases or decreases sympathetic activity. The response varies with the stimulus, the sympathetic effector being measured, and physiological context.

4.1 Direct Measurement of Muscle Sympathetic Nerve Activity

Muscle sympathetic nerve activity, or MSNA, provides a direct method for examining sympathetic neural control of the peripheral vasculature in conscious humans. Microneurography records sympathetic bursts from peripheral nerves rather than inferring sympathetic activity from downstream cardiovascular variables.

Bent, Bolton, and Macefield applied sustained sinusoidal galvanic vestibular stimulation and demonstrated modulation of MSNA synchronized with the vestibular stimulus. Earlier work using brief galvanic stimulation had failed to demonstrate a comparable response, indicating that the

detectability of vestibulo-sympathetic coupling depends in part on how vestibular input is delivered. [5,32]

Subsequent work demonstrated frequency dependence. Grewal, James, and Macefield found that changing the frequency of sinusoidal galvanic vestibular stimulation altered the relationship between vestibular input and MSNA. [33]

Mechanical stimulation provides complementary evidence. Controlled low-frequency acceleration capable of activating otolith-related pathways has also produced measurable modulation of MSNA, including responses at low stimulus magnitudes. [34]

These experiments establish that vestibular perturbation can influence sympathetic vasoconstrictor nerve traffic directly. They do not establish a universal direction or magnitude of response.

4.2 Skin Sympathetic Nerve Activity Is Not Equivalent to MSNA

Sympathetic outflow is functionally differentiated.

MSNA is closely associated with vasoconstrictor control in skeletal muscle vascular beds. Skin sympathetic nerve activity, or SSNA, includes activity related to cutaneous vasomotor and sudomotor control and can behave differently from MSNA.

Human vestibular experiments demonstrate this distinction. James, Stathis, and Macefield demonstrated vestibular modulation of SSNA, while Grewal and colleagues reported biphasic modulation of SSNA during low-frequency physiological activation of the utricle. [6,30]

Vestibular input can therefore influence more than one sympathetic effector system.

A change in SSNA should not be assumed to mean that MSNA changed in the same direction or magnitude. Likewise, a downstream electrodermal response should not be interpreted as a measure of generalized sympathetic activation. Different sympathetic outputs can be recruited differently by the same physiological state. [6,30]

This distinction becomes especially important during motion sickness, where sympathetic outputs can dissociate, as considered in Section 12. [20]

4.3 Mechanical Vestibular Stimulation

Galvanic vestibular stimulation permits precise experimental perturbation but is not equivalent to mechanical motion. Evidence from controlled mechanical stimulation is therefore particularly relevant to a natural-motion research program.

Low-frequency mechanical acceleration has been shown to modulate both MSNA and SSNA, supporting the conclusion that vestibulo-sympathetic coupling is not merely an artifact of galvanic stimulation. [7,30]

One sinusoidal linear-acceleration study reported decreased MSNA while heart rate and mean arterial pressure remained relatively stable. [31]

This result establishes two important points. Vestibular stimulation does not necessarily increase sympathetic nerve traffic, and changes in directly measured sympathetic activity need not produce large simultaneous changes in conventional cardiovascular variables.

The appropriate conclusion is therefore narrow: controlled mechanical vestibular stimulation can modify directly recorded sympathetic nerve activity, and that response may not be faithfully represented by heart rate or arterial pressure alone. [7,30,31]

4.4 Direction of Response Is Not Uniform

Human studies do not support a model in which vestibular stimulation consistently moves sympathetic activity upward or downward.

Some experimental conditions produce increases or phase-dependent modulation of sympathetic nerve traffic. Others produce decreases, and some paradigms have produced little detectable response. [5,7,30-32]

These findings indicate that vestibulo-sympathetic coupling is conditional rather than directionally uniform. Stimulus characteristics, experimental paradigm, physiological context, and the sympathetic effector being measured can alter the observed response. [7-9,33]

The more appropriate experimental question is therefore not whether vestibular stimulation activates or suppresses “the sympathetic nervous system,” but:

Under what stimulus and physiological conditions does a particular vestibular input modify a particular sympathetic output, and what is the temporal structure of that response?

The stimulus characteristics underlying this conditionality are examined systematically in Section 6.

4.5 Physiological State Modifies the Reflex

Physiological context also modifies vestibulo-sympathetic responsiveness.

Sauder, Leonard, and Ray demonstrated greater sensitivity of the vestibulo-sympathetic reflex in the upright posture. [8]

Dyckman, Monahan, and Ray demonstrated that baroreflex loading alters vestibulo-sympathetic responsiveness. [9]

These findings establish that the reflex does not operate independently of the cardiovascular state into which vestibular input arrives. The detailed cardiovascular implications of these interactions are considered in Section 5, while broader state dependence is examined later in the review.

The central conclusion of the human nerve-recording literature is therefore specific but important:

vestibular stimulation can directly modify human sympathetic nerve traffic, but the response is effector-specific, stimulus-dependent, and state-dependent.

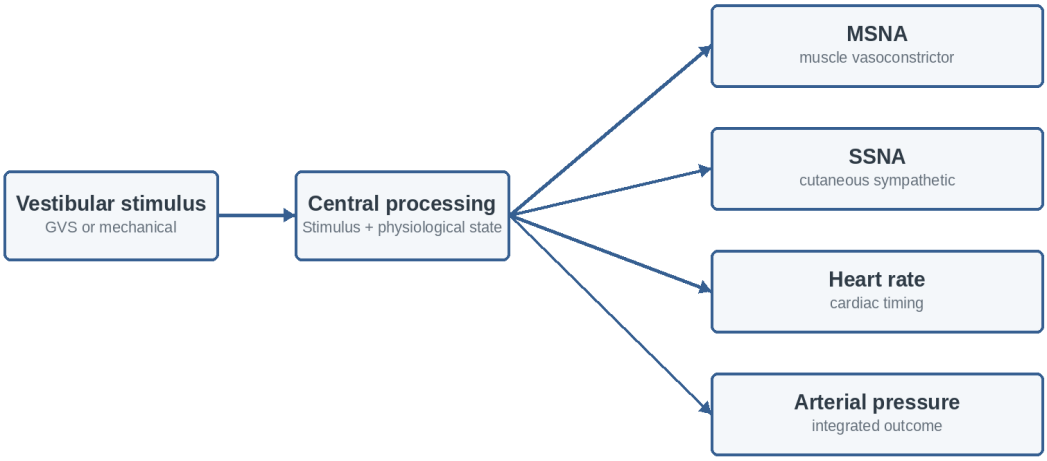

Figure 2. Autonomic output is multidimensional. Direct human studies demonstrate vestibular modulation of muscle and skin sympathetic nerve activity, while cardiovascular outputs may remain comparatively stable or respond differently. The direction and magnitude of response depend on stimulus, effector, posture, and cardiovascular state. [4-9,30,31,33,34]

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5. Vestibular Influences on Cardiovascular Regulation

Direct modulation of sympathetic nerve traffic provides a mechanism through which vestibular input can contribute to cardiovascular regulation. The cardiovascular consequences, however, emerge from an integrated system that simultaneously includes vascular resistance, cardiac activity, baroreflex feedback, posture, respiration, and other physiological influences. [4,9,31]

Accordingly, neither stable cardiovascular variables nor changes in those variables can be interpreted in isolation as proof of the presence or absence of vestibulo-autonomic activity.

5.1 Vestibular Contributions to Vascular Regulation

Changes in posture redistribute blood within the body. Movement toward an upright orientation favors displacement of blood toward dependent regions, creating a need for rapid cardiovascular compensation to maintain arterial pressure and cerebral perfusion.

Sympathetic vasoconstrictor activity is one component of that compensation.

Because the vestibular system detects head acceleration and orientation relative to gravity, vestibular information can contribute to cardiovascular regulation during gravitational transitions. Direct human MSNA studies support this functional relationship, and the sensitivity of the response varies with posture. [4,5,7,8]

Vestibular information should therefore be understood as one input into the broader regulatory network controlling vascular tone and arterial pressure, not as an independent determinant of those variables.

5.2 Interaction With Baroreflex Regulation

As established in Section 3.3, vestibular and baroreflex signals provide complementary information.

Vestibular input can contribute information about movement or orientation during a gravitational transition, while baroreceptors provide feedback about the cardiovascular consequences of that transition. These signals interact rather than functioning as independent reflexes. [4,9,29]

Dyckman, Monahan, and Ray demonstrated this experimentally by showing that baroreflex loading changes vestibulo-sympathetic responsiveness. [9]

The cardiovascular response to vestibular stimulation therefore depends partly on the regulatory state in which the stimulus occurs.

This interaction becomes especially relevant during orthostatic challenge and provides part of the physiological rationale for later considering POTS. It does not, by itself, establish vestibular dysfunction as a cause or vestibular stimulation as a treatment.

5.3 Posture Is a Physiological Variable

Posture provides one of the clearest demonstrations that vestibulo-autonomic responsiveness depends on cardiovascular context.

Sauder, Leonard, and Ray found greater vestibulo-sympathetic reflex sensitivity in the upright posture. [8]

This is consistent with a system whose contribution becomes more relevant when gravitational redistribution of blood creates greater demand for compensatory vascular regulation.

The important experimental conclusion is not that vestibular input becomes an independent controller of arterial pressure when upright. It is that posture changes the strength of measurable vestibulo-sympathetic coupling.

Posture must therefore be treated as a physiological variable rather than merely a feature of experimental setup.

For Phase 1, standardized seated posture reduces a known source of between-session variation, while timestamped departures from that posture can be evaluated as potential contributors to physiological change.

5.4 Stable Heart Rate or Blood Pressure Does Not Mean an Absent Autonomic Response

Successful cardiovascular regulation can conceal the activity responsible for maintaining stability.

If arterial pressure is being actively defended, sympathetic nerve activity or vascular resistance may change while measured arterial pressure changes very little.

Human mechanical vestibular experiments provide a direct example. During sinusoidal linear acceleration, changes in MSNA have been observed while heart rate and mean arterial pressure remained relatively stable. [31]

Had heart rate and arterial pressure been the only measurements, that physiological response could have been missed.

The converse is equally important. A change in heart rate or arterial pressure during vestibular stimulation does not by itself establish a vestibulo-sympathetic mechanism because multiple physiological systems contribute to those outputs.

Continuous cardiovascular measurements should therefore be interpreted as components of a broader physiological record rather than as standalone evidence for or against vestibulo-autonomic activity.

5.5 Cardiovascular Stability Is an Integrated Outcome

The relationship among vestibular input, sympathetic activity, vascular resistance, cardiac activity, and arterial pressure is therefore not one-to-one.

Vestibular input can modify sympathetic neural traffic.

Sympathetic activity can contribute to vascular regulation.

Baroreflex feedback can modify the response.

Posture can alter reflex sensitivity.

Other physiological systems simultaneously contribute to the cardiovascular state.

The observed heart rate or arterial pressure at any moment represents the integrated result of those interacting processes.

For natural-motion research, this means that cardiovascular measurements are valuable both as outcomes and as information about the physiological context in which candidate vestibulo-autonomic responses occur.

It also explains why multimodal measurement is necessary: the absence of a large change in a conventional cardiovascular variable does not establish the absence of physiological regulation beneath it.

The next question is what characteristics of vestibular stimulation determine the response. That stimulus dependence is examined in Section 6.

6. Stimulus Dependence of Vestibulo-Autonomic Responses

The human literature does not support treating vestibular stimulation as a unitary exposure.

Vestibulo-autonomic responses vary with characteristics of the stimulus, including frequency, magnitude, direction, temporal structure, and duration. Physiological state further modifies the relationship between a given stimulus and the resulting response. [5,7-9,31,33]

This dependence is central to the SeaKing Solace research question.

If different motion characteristics produce different physiological responses, then natural motion cannot be represented adequately by a binary condition such as “motion” versus “no motion.” The exposure must be characterized quantitatively.

6.1 Frequency Dependence

Frequency is one of the clearest experimentally demonstrated determinants of vestibulo-autonomic response.

Grewal, James, and Macefield demonstrated that changing the frequency of sinusoidal galvanic vestibular stimulation altered the relationship between vestibular input and MSNA. [33]

Mechanical studies likewise demonstrate physiologically measurable sympathetic responses during low-frequency acceleration. [7,31]

These findings do not establish a universally optimal frequency. They establish the narrower and more important point that frequency can change the physiological response.

For natural-motion research, frequency content should therefore be preserved rather than collapsed into summary measures of overall movement.

6.2 Magnitude and Acceleration

Stimulus magnitude also matters.

Mechanical vestibular experiments demonstrate measurable sympathetic responses at relatively low acceleration magnitudes, indicating that large or provocative movements are not required for vestibulo-sympathetic coupling to occur. [34]

The relationship should not be assumed to be linear.

A larger acceleration does not necessarily imply a proportionally larger autonomic response, nor does a stronger physiological response establish a more desirable one.

Phase 1 should therefore characterize the range and distribution of received acceleration rather than treating magnitude solely as an intensity variable to be maximized.

6.3 Direction, Axis, and Orientation

As established in Scientific Review 01, vestibular stimulation depends on the direction and orientation of motion relative to the head.

The semicircular canals and otolith organs encode different aspects of head movement and orientation. Consequently, mechanically different motion components cannot be assumed to be physiologically interchangeable.

For multidimensional natural motion, this means that heave, surge, sway, pitch, roll, and yaw should not be collapsed prematurely into a single motion magnitude.

The relevant question is empirical:

Do particular components, orientations, or combinations of head-centered motion predict particular physiological responses?

Phase 1 is designed to preserve the physical information required to test that question rather than assuming in advance which axis is most important.

6.4 Temporal Structure

Two exposures can contain similar overall acceleration while differing substantially in temporal organization.

Vestibular input may be periodic, irregular, transient, sustained, or composed of changing combinations of frequencies and axes.

Human studies comparing brief and sustained stimulation demonstrate why this distinction matters. Brief galvanic stimulation has not always produced detectable sympathetic responses, whereas sustained sinusoidal stimulation has demonstrated clear modulation of MSNA. [5,32]

These studies differ in more than duration alone, so they do not isolate temporal structure as the sole explanation. They nevertheless demonstrate that findings obtained with one temporal form of stimulation cannot automatically be generalized to another.

Natural-motion analysis should therefore preserve temporal structure rather than relying only on session-level averages.

6.5 Duration and Exposure History

Duration introduces an additional dimension.

As exposure continues, the physiological response may change even when the physical stimulus remains within a similar range.

Adaptation, habituation, fatigue, motion sickness, and sopite-related physiology may emerge over time. These processes are examined in Sections 12 through 14.

Accordingly, a prolonged natural-motion session should not be treated as one stationary physiological condition.

Responses may emerge, diminish, reverse, or change as exposure continues.

Time since exposure onset and prior exposure history may therefore be relevant alongside the instantaneous characteristics of the motion itself.

6.6 Stimulus Characteristics Interact With Physiological State

Stimulus dependence does not occur independently of the participant.

As established in Sections 4 and 5, posture alters vestibulo-sympathetic reflex sensitivity and baroreflex loading modifies vestibulo-sympathetic responsiveness. [8,9]

The same physical stimulus can therefore produce different measurable responses under different physiological conditions.

This creates an important distinction between the stimulus and the stimulus-response relationship.

A motion waveform may be physically reproducible while its physiological effect varies systematically with posture, cardiovascular state, susceptibility, adaptation, or other participant characteristics.

Such variation should not automatically be classified as noise. If it is reproducible and associated with measurable state variables, it may reveal part of the underlying physiology.

6.7 There Is No Established Universal Vestibulo-Autonomic Dose

The available evidence does not define a universal vestibular “dose.”

No established combination of frequency, magnitude, duration, direction, or temporal structure is known to produce a predetermined autonomic outcome across individuals and physiological states.

Nor does the existing evidence establish which physiological response, if any, should be optimized clinically.

The appropriate discovery-stage objective is therefore to identify reproducible stimulus-response relationships before attempting to define an optimal waveform or dose.

The broader therapeutic implications of this limitation are addressed in Section 20.

6.8 Implications for Natural Multidimensional Motion

Stimulus dependence provides the central methodological rationale for high-resolution characterization of natural motion.

If vestibulo-autonomic responses depend on frequency, magnitude, temporal structure, orientation, duration, and physiological context, then treating a prolonged exposure simply as “on the boat” discards information necessary to evaluate the relationship.

The relevant exposure is not merely the presence of vessel motion.

Nor is vessel motion necessarily identical to the vestibular exposure received by the participant.

As established in Review 01, head-centered motion provides the more proximal physical representation of the participant’s received exposure.

Phase 1 therefore preserves synchronized head-centered 6-DoF motion so that physiological responses can be evaluated against the characteristics of the motion actually received.

This does not assume that every motion dimension will prove physiologically relevant.

It provides the data required to determine which dimensions, if any, are informative.

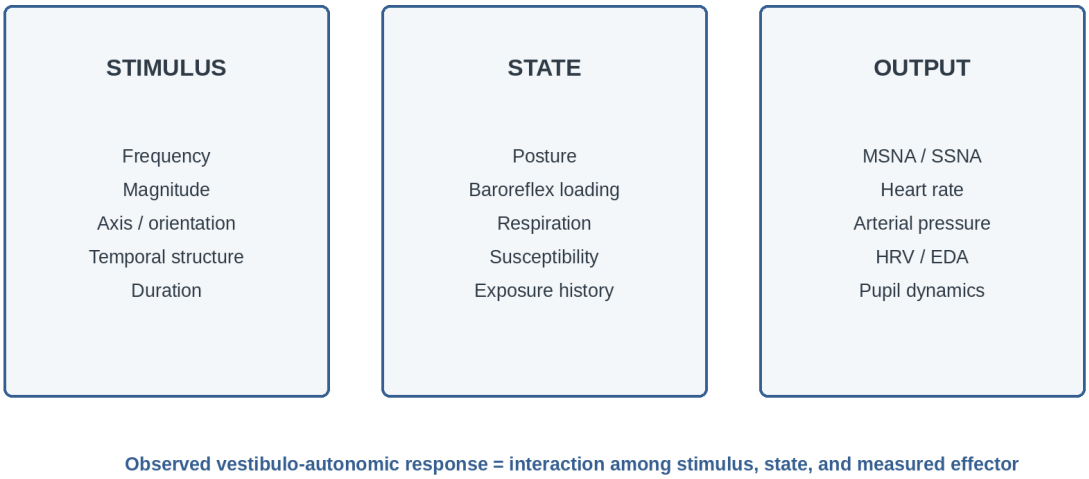


Figure 3. Stimulus, state, and output jointly determine the observed vestibulo-autonomic response. Frequency, magnitude, orientation, temporal structure, and duration interact with physiological state, while different autonomic effectors and downstream measurements need not change in parallel. [5,7-9,31,33,34]

The next question is whether results obtained from existing experimental vestibular paradigms can be transferred directly to such natural multidimensional exposure.

7. Experimental Vestibular Paradigms and Translational Limits

Human vestibulo-autonomic physiology has been studied using several experimental methods, including galvanic vestibular stimulation, head-down rotation, controlled mechanical acceleration, and caloric stimulation.

These paradigms are valuable because they permit controlled perturbation of vestibular function.

They are not interchangeable.

Each produces a different physical or neural input, and none should be assumed to reproduce prolonged natural multidimensional motion.

The existing literature should therefore be used to establish physiological principles while preserving the distinction between the experimental stimulus studied and the natural exposure proposed for Phase 1.

7.1 Galvanic Vestibular Stimulation

Galvanic vestibular stimulation applies electrical current across electrodes positioned near the mastoid processes and alters vestibular afferent signaling in a controlled and temporally precise manner.

GVS has provided important evidence for human vestibulo-sympathetic coupling. Sustained sinusoidal stimulation can modulate MSNA, and changes in stimulation frequency alter that relationship. [5,33]

Its experimental strength is control.

Its translational limitation is that the stimulus is electrical rather than a naturally occurring mechanical head motion.

GVS can therefore establish that perturbing vestibular afferent signaling influences autonomic output.

It cannot establish that a particular mechanical motion will produce the same response.

7.2 Head-Down Rotation

Head-down rotation and related positional paradigms have been used to examine vestibular contributions to sympathetic and cardiovascular regulation.

These methods are useful because they alter head orientation relative to gravity and can engage otolith-related pathways while permitting direct physiological measurement.

They also alter posture and cardiovascular loading.

As Sections 4 and 5 established, posture and baroreflex state themselves modify vestibulo-sympathetic responsiveness. [8,9]

Results from positional paradigms therefore provide evidence about vestibular-autonomic physiology under those conditions but should not be generalized automatically to seated natural motion.

7.3 Controlled Mechanical Linear Acceleration

Mechanical translation is especially relevant because it produces a physical motion stimulus rather than electrical vestibular perturbation.

Controlled low-frequency linear acceleration has been shown to modify directly recorded sympathetic nerve activity. [7,31]

These experiments strengthen the evidence that vestibulo-sympathetic coupling occurs during actual mechanical motion.

Their advantage is stimulus precision.

Their limitation is simplification.

Laboratory translation typically constrains axis, waveform, frequency, magnitude, duration, and participant posture. Natural motion contains changing combinations of these features.

Controlled mechanical experiments therefore establish that defined physical acceleration can produce autonomic responses without establishing how a prolonged multidimensional exposure will behave.

7.4 Caloric Vestibular Stimulation

Caloric stimulation perturbs vestibular function through thermal stimulation of the external auditory canal, producing vestibular responses without reproducing ordinary head motion.

It has long-standing value for vestibular assessment and can provide information about vestibular-autonomic interactions under experimentally induced vestibular activation. [29]

Its relationship to natural mechanical motion is indirect.

Accordingly, caloric findings can contribute to evidence that vestibular perturbation influences physiology, but they should not be treated as equivalent to the physical exposure proposed for Phase 1.

7.5 Experimental Control and Ecological Complexity Answer Different Questions

The difference between laboratory paradigms and natural motion is not simply a limitation of laboratory research.

Controlled and naturalistic exposures answer different questions.

Controlled paradigms are strongest when investigators need to isolate a variable, reproduce a stimulus precisely, or test causal dependence.

Natural motion is potentially useful when the physiologically relevant stimulus characteristics are not yet known and must first be identified within a complex exposure.

The two approaches are therefore complementary.

Naturalistic discovery can identify candidate relationships.

Controlled stimulation can then attempt to reproduce, manipulate, and reduce them.

7.6 Results Should Not Be Generalized Across Paradigms Without Testing

A response demonstrated with GVS should not automatically be expected during mechanical acceleration.

A response demonstrated during a positional maneuver should not automatically be expected during seated natural motion.

A response produced by simplified linear translation should not automatically be expected during multi-axis exposure.

The appropriate inference from the existing literature is narrower:

multiple forms of vestibular perturbation can influence human autonomic physiology, but the response depends on the characteristics and context of the perturbation.

This is sufficient to justify testing natural multidimensional motion.

It is not sufficient to predict its exact physiological effect.

7.7 Implications for the SeaKing Solace Research Sequence

The translational gap between controlled vestibular paradigms and natural motion defines the role of Phase 1.

Phase 1 is not intended to reproduce a published laboratory stimulus aboard a vessel.

It is intended to characterize natural received motion and determine whether reproducible physiological relationships emerge within it.

Candidate relationships can then be carried into controlled mechanical testing.

That sequence avoids two opposite errors:

assuming that a laboratory stimulus already defines the relevant natural exposure;

or assuming that natural complexity is inherently necessary or superior.

The evidence should determine which components survive controlled reproduction and reduction.

Paradigm	Primary strength	Principal translational limit	Phase 1 inference
Galvanic vestibular stimulation (GVS)	Precise, controllable perturbation of vestibular afferent signaling	Electrical rather than natural mechanical head motion	Establishes vestibulo-autonomic coupling; does not specify the response to natural motion. [5,33]
Head-down / positional paradigms	Engage gravity-related vestibular inputs while physiology is measured	Posture and cardiovascular loading change simultaneously	Relevant to vestibular-cardiovascular interaction, but not directly equivalent to seated natural motion. [8,9]
Controlled mechanical linear acceleration	Defined physical motion stimulus with direct sympathetic measurements	Simplified axis, waveform, magnitude, duration, and posture	Shows that actual mechanical acceleration can modify sympathetic nerve activity. [7,31,34]
Caloric vestibular stimulation	Established vestibular perturbation used in human autonomic research	Thermal perturbation does not reproduce ordinary head motion	Supports vestibular-autonomic interaction but has indirect mechanical relevance. [29]
Natural multidimensional motion	Preserves ecological combinations of axes, frequencies, temporal structure, and duration	Many variables change together; causal interpretation is limited	Useful for discovery and system identification; candidate relationships require later controlled reproduction.

Table 1. Experimental vestibular paradigms and their translational limits. Existing paradigms establish physiological principles under controlled conditions, but none can be assumed to reproduce prolonged natural multidimensional head motion. Natural motion and controlled stimulation therefore answer complementary discovery and causal-testing questions. [5,7-9,29,31,33,34]

Before those physiological relationships can be interpreted, however, the measurement outputs themselves require equal discipline.

One of the most important is heart-rate variability.

8. Cardiac Variability and the Limits of "Vagal Tone"

Heart-rate variability is widely used in autonomic research because beat-to-beat variation in cardiac timing contains information about neural and physiological processes influencing the heart. It is noninvasive, can be measured continuously, and is well suited to repeated and prolonged recordings.

These advantages make HRV relevant to Phase 1.

They also make it vulnerable to overinterpretation.

HRV is not a direct recording of vagal nerve activity or sympathetic nerve traffic, and no single HRV metric provides a scalar measure of whole-body "autonomic balance." Its physiological meaning depends on the metric, recording conditions, respiration, heart rate, posture, duration, and analytical question. [10-13]

For this review, HRV is therefore treated as one component of a multimodal physiological record rather than as a standalone measure capable of identifying mechanism or clinical meaning.

8.1 What Heart-Rate Variability Measures

The interval between successive heartbeats is not perfectly constant.

Variation in cardiac timing arises from interacting physiological processes that include autonomic modulation of the sinoatrial node, respiration, baroreflex-related cardiovascular regulation, and other sources of short- and longer-timescale variability.

HRV methods quantify aspects of this beat-to-beat variation.

Standard approaches include time-domain and frequency-domain measures derived from sequences of normal cardiac intervals. The 1996 Task Force standards established widely used definitions and methodological conventions for acquiring and interpreting these measurements. [10]

The distinction between measurement and mechanism is essential.

ECG records cardiac electrical timing.

HRV describes variation in that timing.

Neither directly records the autonomic nerves supplying the heart.

Autonomic influences contribute importantly to HRV, but the observed variability is the downstream product of those influences interacting with respiration, intrinsic cardiac properties, cardiovascular reflexes, and recording conditions. [10,12]

8.2 Respiratory Sinus Arrhythmia and Cardiac Parasympathetic Modulation

Respiratory sinus arrhythmia, or RSA, is rhythmic variation in cardiac timing associated with respiration.

Under many experimental conditions, respiratory-frequency cardiac variability is strongly influenced by parasympathetic modulation of the sinoatrial node and can therefore provide useful information about cardiac vagal modulation. [11,12]

That relationship does not make RSA a direct measurement of vagal nerve activity.

Grossman and Kollai demonstrated important limitations in the relationship among respiration, RSA, and cardiac vagal tone, particularly for comparisons between individuals. Grossman and Taylor

subsequently emphasized the physiological complexity of RSA and the importance of respiratory and cardiovascular context. [11,12]

A change in RSA may therefore be consistent with altered cardiac parasympathetic modulation under appropriate conditions.

It does not establish increased vagal activity throughout the body or activation of a specific vestibulo-vagal pathway.

For this review, cardiac parasympathetic modulation is the more defensible terminology when the measurement and experimental conditions support that interpretation.

8.3 RMSSD

The root mean square of successive differences, or RMSSD, is a commonly used time-domain HRV measure.

RMSSD quantifies short-term beat-to-beat variation by examining differences between successive normal cardiac intervals and is frequently used as a measure sensitive to cardiac parasympathetic modulation. [13]

Its practical advantages include suitability for short-term recordings and less dependence on some assumptions involved in frequency-domain decomposition.

Those advantages do not make RMSSD a direct neural measurement.

Its value can be influenced by recording quality, ectopic beats and artifact handling, heart rate, respiration, posture, participant state, and analytic decisions.

Accordingly, an increase in RMSSD during motion should be reported first as an increase in RMSSD.

Further physiological interpretation requires respiratory and cardiovascular context.

8.4 Respiration Is Part of HRV Interpretation

Respiration is not a minor nuisance variable in short-term HRV analysis.

Respiratory rate and pattern influence respiratory-frequency cardiac variability and can change during motion, speech, altered arousal, sickness, and other participant states. [11,12,16]

A motion-associated change in HRV can therefore reflect altered cardiac autonomic modulation, altered respiration, or interaction between the two.

This is why Phase 1 includes continuous respiratory measurement.

The objective is not simply to “correct” HRV for respiration.

Respiration may itself be part of the physiological response to motion.

Section 9 examines that distinction directly.

8.5 Low-Frequency HRV Is Not a Specific Measure of Sympathetic Activity

Low-frequency HRV has historically been interpreted in some literature as a marker of sympathetic cardiac modulation.

That interpretation is not sufficiently specific.

Low-frequency variability reflects multiple physiological influences, including baroreflex-related processes and contributions from both sympathetic and parasympathetic mechanisms. [14]

LF power should therefore not be labeled “sympathetic tone.”

A change in LF during motion may be physiologically informative, but it does not by itself establish the direction or magnitude of sympathetic nerve activity.

Direct sympathetic recordings such as MSNA and SSNA remain conceptually distinct from HRV-derived measures.

8.6 LF/HF Is Not “Sympathovagal Balance”

The ratio of low-frequency to high-frequency HRV has also been widely described as an index of “sympathovagal balance.”

That interpretation has substantial physiological limitations.

The numerator is not a pure sympathetic measure.

The denominator is not a complete measure of parasympathetic activity.

The two components are not independent opposing quantities whose ratio directly represents the balance of the autonomic nervous system. [15]

For this review, LF/HF should therefore not be used as a direct measure of sympathetic-parasympathetic balance.

If calculated, it should be treated as a derived HRV metric whose interpretation remains constrained by the physiology of its components.

8.7 Heart Rate and HRV Are Related but Not Interchangeable

HRV depends partly on the underlying cardiac rate and interval structure.

Changes in heart rate can therefore alter the mathematical and physiological context in which HRV measures are interpreted. [13]

A motion-associated increase in RMSSD accompanied by a substantial change in mean heart rate may not have the same interpretation as an equivalent RMSSD change occurring at a stable rate.

Phase 1 should therefore preserve both cardiac timing and HRV metrics rather than interpreting variability independently of the mean cardiac state.

8.8 HRV Is Most Informative in a Multimodal Record

The value of HRV increases when it can be interpreted alongside other synchronized measurements.

Respiration helps characterize respiratory contributions.

Beat-to-beat arterial pressure provides cardiovascular context.

EDA provides information about sympathetic sudomotor activity.

Pupil dynamics provide another physiological channel.

Motion measurements define the physical exposure.

Symptoms and event logs help identify competing states.

This does not transform HRV into a direct neural measurement.

It allows candidate cardiac-autonomic changes to be interpreted within the physiological system in which they occurred.

8.9 Implications for Phase 1

Phase 1 should use HRV to answer constrained questions.

Do cardiac interval dynamics change reproducibly in temporal relation to particular characteristics of received motion?

Are those changes reproducible within participants?

How do they relate to respiration, heart rate, arterial pressure, and other measured physiological signals?

Do they persist when major competing explanations are considered?

These questions are scientifically stronger than asking whether motion “increases vagal tone.”

The Phase 1 interpretation should therefore remain at the level supported by the measurement:

motion-associated changes in cardiac interval variability and, where respiratory and methodological context supports it, changes consistent with altered cardiac parasympathetic modulation.

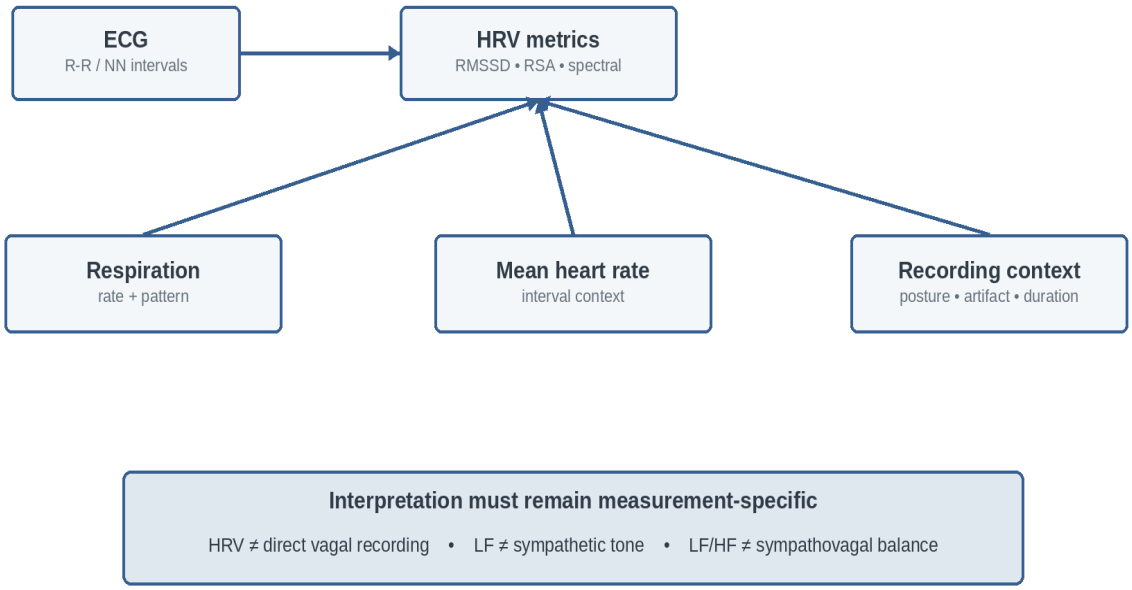


Figure 4. Why heart-rate variability is not simply “vagal tone.” HRV is derived from cardiac interval timing and is influenced by respiration, mean heart rate, recording conditions, and multiple cardiovascular-autonomic processes. Respiratory-frequency variability may provide information about cardiac parasympathetic modulation under appropriate conditions, but HRV is not a direct neural recording; LF-HRV is not a specific measure of sympathetic activity; and LF/HF is not a direct measure of sympathovagal balance. [10-16]

The next section examines respiration not merely as a condition for interpreting HRV, but as a physiological output and potential component of the motion-response pathway in its own right.

9. Respiratory-Autonomic Interactions

Respiration is relevant to vestibulo-autonomic research for more than one reason.

It influences cardiac variability, can change as a physiological response, may participate in pathways linking motion to downstream autonomic measures, and can provide a competing explanation for apparent motion-associated effects.

For Phase 1, respiration should therefore be treated as a physiological signal in its own right rather than merely as a nuisance variable to be corrected during HRV analysis. [11,12,16,20]

9.1 Respiration Modifies Cardiac Variability

Respiration contributes strongly to short-term variation in cardiac timing.

As established in Section 8, respiratory sinus arrhythmia and other respiratory-frequency components of HRV depend on the participant's breathing pattern. Changes in respiratory rate or depth can therefore alter HRV even when the underlying autonomic process of interest has not changed in the manner initially hypothesized. [11,12,16]

This creates an important interpretive constraint.

A motion-associated HRV change cannot be evaluated fully without knowing whether respiration changed at the same time.

Continuous respiratory measurement is therefore necessary for interpreting cardiac variability during prolonged natural motion.

9.2 Respiration Can Be a Physiological Output

Respiration should not be treated solely as a source of contamination.

Vestibular exposure and motion-sickness-related states can themselves alter respiratory behavior. Javaid and colleagues reported respiratory changes together with changes in blood pressure and skin blood flow in participants experiencing motion sickness during sinusoidal galvanic vestibular stimulation. [20]

A respiratory change during motion may therefore be part of the physiological response rather than merely an analytic nuisance.

The appropriate question is not simply whether respiration should be removed statistically.

It is whether respiration changes systematically with received motion and how those changes relate temporally to other physiological signals.

9.3 Respiration as a Potential Mediator

A motion-associated HRV response can have several possible structures.

One possibility is:

motion → altered cardiac autonomic modulation → altered HRV

Another is:

motion → altered respiration → altered HRV

A third is that motion alters both respiration and cardiac autonomic modulation through interacting processes.

These possibilities have different mechanistic implications.

Phase 1 cannot establish mediation from temporal association alone, but synchronized respiratory and cardiac signals can identify candidate pathways for later controlled testing.

Respiration should therefore be retained as a time-resolved signal rather than reduced to a single session-average breathing rate.

9.4 Respiration as a Competing Explanation

Respiratory change can also weaken an otherwise attractive interpretation.

Suppose RMSSD rises during a segment of natural motion.

Without respiratory data, that change might be interpreted as altered cardiac parasympathetic modulation.

If breathing changes substantially during the same interval, the inference becomes less specific.

The cardiac change may still be physiologically meaningful, but respiration provides a plausible contributor or alternative explanation.

This is one reason Phase 1 needs synchronized rather than merely simultaneous measurement.

Timing can help determine whether respiratory changes precede, accompany, or follow candidate cardiac responses.

9.5 Motion Sickness Increases the Importance of Respiratory Measurement

Motion sickness is especially relevant because it can alter respiration as part of a broader physiological state. [20]

A respiratory change occurring during motion may therefore reflect vestibulo-autonomic physiology, sickness-related physiology, or both.

Overt nausea is not required for all motion-related physiological states to become relevant, as discussed in Section 12.

Respiratory interpretation should therefore consider symptoms, behavioral observations, and other physiological channels rather than treating breathing changes as mechanism-specific.

9.6 Behavioral Context Matters

Speaking, posture changes, physical movement, distress, drowsiness, and other participant behaviors are treated as protocol events during active recording because they can alter the respiratory signal being measured and introduce additional behavioral context.

The canonical source set does not establish a precise quantitative effect of each of these behaviors under Phase 1 conditions.

They should therefore be documented rather than assigned predetermined corrections.

This supports the planned timestamped event categories for speaking/social interaction, posture change, anxiety/distress, drowsiness, reduced responsiveness, sensor adjustment, and other protocol deviations.

9.7 Respiratory Inductance Plethysmography in Phase 1

The Phase 1 architecture includes continuous respiratory monitoring using a respiratory belt.

Respiratory inductance plethysmography provides a practical noninvasive method for tracking respiratory timing and pattern during prolonged recording. [35]

Its role is not to provide a complete measurement of pulmonary physiology.

Its role is to supply a synchronized respiratory signal that can be interpreted alongside ECG, beat-to-beat arterial pressure, EDA, pupil dynamics, motion exposure, and participant events.

9.8 Temporal Analysis Is More Informative Than Session Averages

A baseline average, underway average, and recovery average may be descriptively useful, but they can obscure transient structure.

If a candidate physiological response depends on particular motion characteristics, then respiratory changes may occur over shorter timescales.

The continuous respiratory signal permits questions such as:

Does breathing change repeatedly during particular motion conditions?

Do respiratory changes precede cardiac variability changes?

Do respiratory changes emerge with sickness-related symptoms?

Do they persist into recovery?

These relationships do not establish mechanism by themselves, but they help determine which explanations warrant controlled testing.

9.9 What Respiratory Measurement Contributes

Respiratory measurement can document whether breathing changes during vestibular exposure, improve interpretation of HRV, and identify temporal relationships among motion, breathing, cardiac variability, and other physiological outputs. [11,12,16,20,35]

It cannot independently establish a vestibular mechanism or prove mediation.

Its value lies in making a major source of physiological variation observable rather than invisible.

The same principle applies to cutaneous sympathetic physiology.

10. Cutaneous Sympathetic and Sudomotor Physiology

The sympathetic nervous system is functionally differentiated.

As established in Section 4, vestibular stimulation can modulate both muscle and skin sympathetic nerve activity, and those outputs need not behave identically. [6,20,30]

For Phase 1, direct microneurographic recording is not practical during prolonged natural motion. Electrodermal activity therefore provides an accessible noninvasive measure related to sympathetic sudomotor physiology.

Its interpretation must remain effector-specific.

10.1 Skin Sympathetic Nerve Activity

Skin sympathetic nerve activity, or SSNA, contains sympathetic traffic directed toward cutaneous effectors, including sudomotor and vasomotor functions.

Human microneurographic studies demonstrate vestibular modulation of SSNA.

James, Stathis, and Macefield demonstrated modulation of skin sympathetic nerve activity during vestibular stimulation, and Grewal and colleagues reported biphasic modulation during low-frequency mechanical activation of utricular pathways. [6,30]

These findings establish that vestibular influences on sympathetic physiology are not limited to muscle vasoconstrictor pathways.

They also reinforce that sympathetic output should not be treated as a single global variable.

A change in SSNA describes a change in cutaneous sympathetic nerve activity under the conditions studied.

It should not automatically be generalized to MSNA, cardiac sympathetic activity, or global sympathetic state.

10.2 Electrodermal Activity

Electrodermal activity measures changes in the electrical properties of the skin associated principally with sweat-gland activity under sympathetic control.

Because eccrine sweat glands receive sympathetic sudomotor innervation, EDA provides a practical noninvasive signal of sympathetic sudomotor activity. [17]

Unlike microneurography, EDA can be recorded continuously during prolonged naturalistic exposure.

The measurement remains downstream from sympathetic nerve traffic itself.

EDA does not record sympathetic axons directly.

It measures an electrodermal consequence of sudomotor activity.

10.3 EDA Is Not Global Sympathetic Tone

EDA should not be described as a direct measure of total sympathetic activity.

It does not measure MSNA.

It does not measure cardiac sympathetic nerve activity.

It does not quantify sympathetic vascular control throughout the body.

This distinction follows directly from the effector specificity established in the nerve-recording literature.

A participant can show a sudomotor response without an equivalent change in another sympathetic output, and the reverse is also possible.

10.4 Vestibular Stimulation Can Affect Cutaneous Sympathetic Physiology

Direct SSNA studies provide the mechanistic rationale for including a cutaneous sympathetic measure in Phase 1.

Low-frequency vestibular stimulation can modulate SSNA, including during mechanical utricular activation. [6,30]

These findings do not establish that every vestibular stimulus will produce a measurable EDA response.

SSNA and EDA are related to cutaneous sympathetic physiology but are not identical measurements.

Phase 1 therefore uses EDA as a candidate downstream signal whose relationship with natural motion must be demonstrated empirically.

10.5 Motion Sickness Is a Major Competing Interpretation

EDA is particularly relevant to motion research because electrodermal changes have been associated with motion sickness. Warwick-Evans and colleagues reported EDA as an index associated with motion-sickness development. [21]

A rise in EDA during motion may therefore reflect altered sudomotor physiology without identifying why it changed.

The response could relate to vestibular-autonomic coupling, emerging motion sickness, distress, or multiple simultaneous processes.

Section 12 examines sickness-related physiology directly.

10.6 Environmental Conditions Matter

Sudomotor activity is sensitive to environmental conditions.

Temperature and humidity can influence sweating and therefore affect EDA interpretation. [17]

The planned HVAC-controlled participant area reduces this source of variability but does not eliminate it.

Ambient temperature and humidity should therefore still be logged.

The purpose is not to assume that environmental variation explains every EDA change.

It is to make that alternative explanation measurable.

10.7 Behavioral and Technical Context

Posture changes, movement, speaking, distress, sensor adjustment, and other events may coincide with changes in EDA or recording quality.

The source set does not justify assigning fixed physiological effects to each event.

Timestamped event logging therefore provides the appropriate contextual control.

Affected periods can be identified and examined rather than assumed either valid or invalid automatically.

10.8 Preserve Temporal Structure

EDA contains both slower tonic variation and more transient event-related changes.

Reducing the full recording to a single average would lose potentially relevant temporal information.

A gradual electrodermal change developing over an hour may have a different interpretation from repeated transient responses following particular motion features.

Preserving the continuous time series allows those patterns to be compared with motion and symptom timing. [17]

10.9 What EDA Contributes

EDA provides a continuous noninvasive measure of sympathetic sudomotor physiology.

Its strongest value in Phase 1 is as an effector-specific signal that can be aligned with motion, environmental conditions, symptoms, and other physiological measurements.

EDA cannot establish global sympathetic activation, identify a specific vestibular mechanism by itself, or define therapeutic benefit.

Its value lies in the specificity of the physiology it does measure.

The same discipline is required when interpreting the pupil.

11. Pupillary Dynamics and Visual Context

Pupil diameter is influenced by autonomic pathways but is not autonomically specific.

Parasympathetic and sympathetic pathways contribute to pupillary control, while luminance, gaze, visual input, cognitive activity, arousal, fatigue, and motion sickness can also alter the pupil. [18,19,36]

Pupillometry is therefore relevant to Phase 1 as a continuous physiological signal whose interpretation depends strongly on visual and behavioral context.

It should not be treated as a direct measure of sympathetic activation.

11.1 Autonomic Control of the Pupil

Pupil diameter reflects interacting neural influences on the iris.

Parasympathetic pathways contribute importantly to constriction, while sympathetic pathways contribute to dilation.

The resulting pupil size is therefore compatible with autonomic interpretation but does not identify a single autonomic pathway.

An increase in pupil diameter should not automatically be interpreted as increased sympathetic activity.

A decrease should not automatically be interpreted as increased parasympathetic activity.

The same observed change can arise under different physiological and environmental conditions. [18,19]

11.2 Luminance Is a Primary Interpretive Requirement

Luminance is among the strongest determinants of pupil diameter.

Changes in retinal illumination can produce substantial pupil responses independently of the autonomic process being investigated. [18]

This is especially relevant during vessel-based natural motion, where exterior light conditions may vary with cloud cover, vessel orientation, reflections, window exposure, and gaze direction.

A pupil change that coincides with a luminance change cannot be assigned confidently to autonomic physiology without accounting for the visual environment.

For this reason, luminance should be measured independently rather than inferred from pupil size.

11.3 Gaze and Visual Context Matter

Where the participant is looking changes the visual input reaching the eyes.

A wearable eye-tracking system can provide pupil measurements together with gaze and scene information.

This is valuable because a participant may shift between exterior views, the vessel interior, another person, or eye closure during the session.

Those states may differ in luminance and visual content and may also coincide with changes in head position or participant state.

Gaze and visual context therefore provide interpretive information rather than serving merely as ancillary eye-tracking outputs. [18]

11.4 Cognitive and Arousal Influences

Pupil dynamics are also sensitive to cognitive effort and arousal. [19]

A change during motion may therefore reflect altered attention, alertness, distress, or another central state rather than a direct vestibular-autonomic effect.

The canonical source set does not justify assigning a specific quantitative pupillary signature to each such state under Phase 1 conditions.

These influences should therefore be documented and interpreted contextually rather than modeled as predetermined autonomic effects.

11.5 Motion Sickness Is a Competing Pupillary Pathway

Pupillary changes have also been studied in relation to motion sickness. [36]

A pupil response occurring during vestibular exposure can therefore reflect the candidate vestibulo-autonomic relationship, emerging sickness physiology, or another concurrent process.

This is one reason pupil data should be interpreted alongside symptoms and other physiological measures rather than in isolation.

Section 12 examines motion sickness and sopite syndrome as competing physiological states in detail.

11.6 Eye Closure Is Both a Data-Quality and State Event

Eye closure interrupts normal pupil measurement.

It can also provide information about participant state.

Drowsiness, fatigue, discomfort, motion sickness, or a desire to reduce visual input may all coincide with eye closure.

For this reason, periods of eye closure should not simply disappear during preprocessing as unexplained missing data.

The planned RN event category “eyes closing” provides useful temporal context.

The meaning of eye closure should remain descriptive until the broader physiological state is considered.

11.7 Pupil Data Require Preprocessing and Quality Control

Pupillometry is sensitive to blinks, eyelid occlusion, gaze effects, tracking loss, and other measurement artifacts.

Published guidance emphasizes transparent preprocessing and handling of pupil-size data. [18]

Phase 1 should therefore prespecify procedures for blink handling, tracking loss, artifact rejection, baseline definition, and treatment of interpolated data.

The goal is not to force a perfectly continuous trace.

It is to preserve a physiologically interpretable signal with explicit quality-control boundaries.

11.8 Baseline and Recovery Require Visual Context

Baseline normalization can be useful, but baseline pupil diameter is itself dependent on illumination, gaze, and adaptation state.

If the visual environment differs substantially between baseline, underway, and recovery periods, a simple percent change from baseline cannot be interpreted as a pure physiological effect of motion.

Luminance and visual context should therefore accompany pupil measurements across all recording periods.

11.9 Pupil Labs Core and Separate Luminance Measurement

The Phase 1 architecture includes Pupil Labs Core together with a separate measure of luminance or validated luminance context.

The conceptual reason for keeping these measures distinct is straightforward.

Pupil diameter is the physiological response being interpreted.

Luminance is one of the major inputs capable of changing that response.

Independent measurement allows investigators to determine whether candidate pupil responses remain interpretable when visual conditions are considered.

11.10 What Pupillometry Contributes

Pupillometry can provide continuous noninvasive information about pupil dynamics during natural motion.

Its value increases when pupil size is interpreted together with luminance, gaze, recording quality, symptoms, and participant state.

It cannot directly measure sympathetic nerve activity or establish a vestibular mechanism by itself.

A reproducible pupil response that remains evident under comparable visual conditions would represent a candidate physiological association worthy of further testing.

It would still require interpretation within the broader multimodal record.

That broader interpretive problem becomes especially important in the next section, where motion sickness can alter several of the same physiological signals simultaneously.

12. Motion Sickness as a Competing Autonomic Pathway

Motion sickness is a central competing explanation in vestibulo-autonomic research because it can produce changes across many of the same physiological systems used to characterize candidate responses to motion.

Experimental studies demonstrate motion-sickness-related changes in electrodermal activity, respiration, blood pressure, skin blood flow, and sympathetic physiology. [20,21]

Accordingly, a physiological response occurring during motion cannot automatically be attributed to the vestibulo-autonomic mechanism under investigation.

12.1 Motion Sickness Is a Multisystem State

Motion sickness is not defined solely by nausea.

It can involve sweating, pallor, dizziness, respiratory change, vascular responses, altered sympathetic activity, and other physiological changes. [20,21]

This creates a direct interpretive overlap with Phase 1.

The same motion exposure that may engage vestibulo-autonomic pathways can also produce a sickness-related physiological state.

Those processes may occur separately or simultaneously.

The presence of a motion-associated physiological response therefore establishes neither its mechanism nor its desirability.

12.2 Sympathetic Outputs Can Dissociate During Motion Sickness

Motion-sickness physiology reinforces the broader finding that sympathetic output is not uniform.

Different sympathetic effectors can respond differently during sickness-related states. [20]

An electrodermal response therefore does not establish a corresponding change in MSNA, and stable heart rate or blood pressure does not establish absence of sympathetic change.

The same effector-specific interpretation developed in Sections 4 and 10 applies here.

12.3 EDA Is Relevant but Nonspecific

Electrodermal activity has been associated with motion sickness and can provide useful information about changing sudomotor physiology. [21]

It is not a diagnostic marker of motion sickness by itself.

An EDA change during motion may reflect sickness-related physiology, vestibular-autonomic modulation, distress, environmental influence, or multiple simultaneous processes.

Its interpretation depends on the broader physiological and symptom context.

12.4 No Single Physiological Signal Defines Motion Sickness

The existing literature does not establish one objective physiological signal that universally identifies the onset of motion sickness.

EDA, respiration, cardiovascular measures, pupil behavior, and other signals can contribute useful information, but none alone establishes or excludes a sickness-related state.

This is particularly important when symptoms are mild or evolving.

A multimodal approach is therefore more appropriate than a binary physiological threshold.

12.5 Motion-Sickness Susceptibility Is Informative but Imperfect

Individuals differ in their susceptibility to motion sickness.

The revised Motion Sickness Susceptibility Questionnaire provides a standardized method for characterizing historical susceptibility. [37]

This information is useful for Phase 1 but should not be treated as deterministic.

A low susceptibility score does not guarantee absence of sickness-related physiology during a particular exposure, and a high score does not establish that every physiological change during motion reflects sickness. [38]

MSSQ should therefore be treated as a baseline susceptibility variable rather than as a diagnostic gate.

12.6 Prescreening Does Not Eliminate Sickness Physiology

Prescreening improves safety and feasibility but cannot remove motion sickness as a competing explanation.

Participants selected for reasonable motion tolerance may still experience mild, evolving, or subclinical symptoms during prolonged exposure.

The absence of a stop request or overt nausea therefore should not be interpreted as proof that the preceding physiological record is free of sickness-related influence.

Continuous physiological measurement and timestamped symptom observations remain necessary.

12.7 Sopite Syndrome Extends the Problem Beyond Nausea

Sopite syndrome is especially important because it broadens the range of motion-related physiological states that can occur without prominent nausea.

Foster and colleagues demonstrated vestibular modulation of skin sympathetic nerve activity during sopite syndrome induced by low-frequency sinusoidal motion, in a state characterized by drowsiness and fatigue. [22]

This finding has an important interpretive consequence.

A participant exposed to motion may become quieter, less active, drowsy, fatigued, or less responsive.

Those observations cannot automatically be classified as beneficial regulation.

They may be compatible with sopite-related physiology.

This does not mean that every episode of drowsiness represents sopite syndrome.

It means sopite is a plausible competing explanation when those features emerge.

12.8 Behavioral “Calm” Is Not a Mechanism

Naturalistic observation can make behavioral changes appear compelling.

A participant who becomes visibly quieter during rhythmic motion may appear to be experiencing a desirable effect.

That observation may ultimately prove meaningful.

But behavioral appearance alone cannot establish the underlying physiology.

Reduced activity may accompany relaxation, fatigue, drowsiness, sopite syndrome, adaptation, or other state changes.

Phase 1 should therefore record observable behaviors descriptively rather than assigning them a positive or negative autonomic meaning in advance.

12.9 Event Logging Provides Temporal Context

The planned participant-specific RN event logging is particularly important for this reason.

Relevant categories include nausea, warmth or sweating, pallor, dizziness, headache, drowsiness, eyes closing, fatigue or reduced responsiveness, anxiety or distress, posture change, speaking or social interaction, sensor adjustment, requested pause or stop, and other protocol deviation.

These observations do not diagnose motion sickness or sopite syndrome individually.

Their value is temporal.

They allow candidate physiological responses to be examined in relation to the onset and progression of observable symptoms and behavioral changes.

12.10 Time Course Matters

Motion sickness is not necessarily instantaneous.

A participant's physiological state may evolve gradually during prolonged exposure.

A response observed early in a session may occur before any overt symptoms.

The same response later may occur during nausea, sweating, or fatigue.

A different pattern may emerge as drowsiness develops.

This makes time-resolved analysis more informative than treating the entire underway period as one physiological block.

Baseline, active exposure, and recovery together can help characterize how sickness-related physiology evolves and resolves.

12.11 Motion Sickness Can Be a Competing Mechanism or Intermediate State

Motion sickness may occupy different causal roles depending on the question being asked.

It can act as a competing mechanism when a physiological response attributed to vestibulo-autonomic regulation is better explained by sickness.

It may also represent an intermediate state through which motion produces downstream physiological changes.

Or it may be an independent tolerability outcome.

These possibilities should not be collapsed into a single statistical adjustment.

The first task is to identify the state and its timing.

12.12 Tolerability Is Also an Outcome

Motion sickness is relevant not only to interpretation but also to tolerability.

A motion profile that reliably produces a physiological response but also produces substantial nausea, dizziness, distress, or sopite-related impairment has a different translational profile from one that does not.

Phase 1 is not designed to establish a therapeutic dose, but it can characterize tolerability alongside physiological response.

Requested pauses or stops, symptom development, exposure duration, and recovery should therefore remain part of the dataset.

12.13 What Motion-Sickness Physiology Establishes for Phase 1

The motion-sickness literature establishes that:

* motion can produce genuine multimodal autonomic changes;

* EDA and other physiological signals are informative but nonspecific;

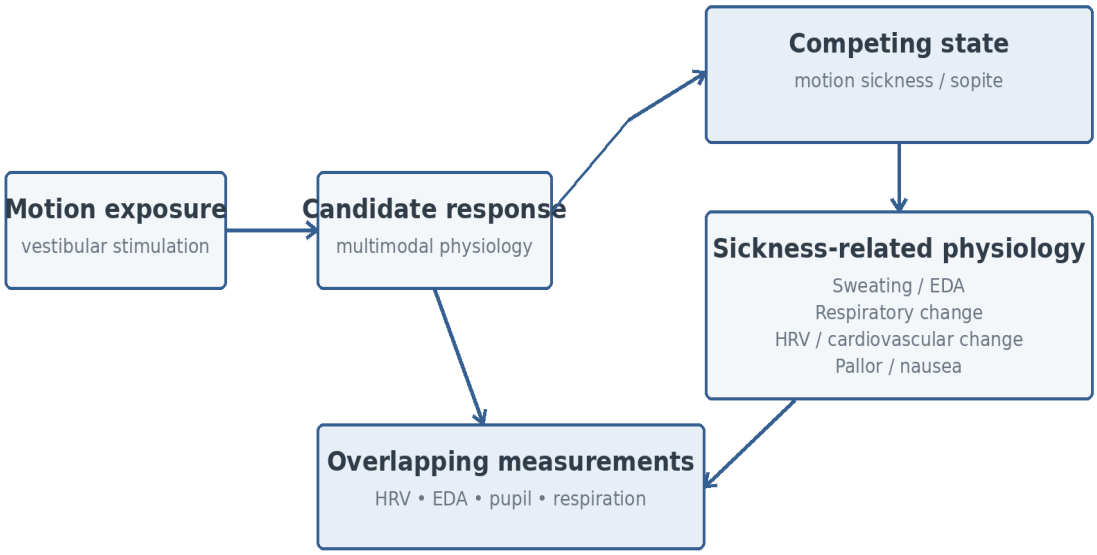
* susceptibility varies and cannot be predicted perfectly;

* different autonomic outputs can dissociate; and

* sopite-related physiology can occur without prominent nausea. [20-22,37,38]

Accordingly, absence of nausea cannot be equated with absence of sickness-related physiology, and drowsiness or reduced responsiveness cannot automatically be equated with beneficial regulation.

Phase 1 therefore needs susceptibility characterization, synchronized physiology, event logging, and recovery measurement so that sickness-related states remain visible rather than silently incorporated into candidate motion-response models.



Behavioral calm, eye closure, or drowsiness does not by itself identify a beneficial physiological state.

Figure 5. Motion sickness and sopite syndrome as competing physiological states. Motion-related sickness can alter several of the same signals proposed for Phase 1 measurement, and sopite syndrome can include drowsiness, fatigue, reduced responsiveness, and autonomic change without prominent nausea. Behavioral calmness or eye closure therefore cannot be assigned a beneficial autonomic meaning without physiological and symptom context. [20-22,37,38]

The next question is how much variability in response reflects systematic differences among participants and physiological states.

13. Individual Variability and State Dependence

Vestibulo-autonomic responses vary across individuals and within the same individual across different physiological states.

This variability is not unexpected.

The preceding literature demonstrates dependence on stimulus characteristics, posture, cardiovascular state, motion-sickness susceptibility, and other contextual factors. [7-9,33,37,38]

The scientific question is therefore not whether variability exists.

It is whether some of that variability is systematic and reproducible.

13.1 The Same Stimulus Need Not Produce the Same Response

A fixed-response model is inconsistent with the human vestibulo-autonomic literature.

The relationship is better represented as:

vestibular exposure + participant state → observed physiological response

rather than:

vestibular exposure → fixed physiological response

A similar physical exposure may therefore produce different measurable responses across participants or across sessions in the same participant.

Reproducibility must be demonstrated rather than assumed.

13.2 Posture Is a State Variable

Posture provides direct evidence of state dependence.

Sauder, Leonard, and Ray demonstrated greater vestibulo-sympathetic reflex sensitivity in the upright posture. [8]

For Phase 1, standardized seated posture therefore serves as an experimental control while departures from that posture remain relevant contextual events.

This point was established physiologically in Sections 4 and 5; here its significance is that posture contributes to participant state.

13.3 Cardiovascular State Matters

Baroreflex loading also modifies vestibulo-sympathetic responsiveness. [9]

The vestibular system therefore does not act upon a physiologically neutral cardiovascular background.

The same motion stimulus may produce different responses when arterial pressure and regulatory state differ.

Continuous cardiovascular measurement thus provides both an outcome and information about the state in which the vestibular stimulus was received.

13.4 Motion-Sickness Susceptibility Is an Individual Difference

Historical susceptibility to motion sickness varies substantially among participants. [37]

That variability is informative but probabilistic.

A susceptibility score can help contextualize subsequent physiology but cannot determine in advance whether a given response will represent sickness-related physiology.

The distinction between susceptibility and observed state should therefore remain explicit.

13.5 Baseline State Matters

Participants also begin sessions from different physiological baselines.

Heart rate, HRV, respiration, arterial pressure, EDA, pupil dynamics, fatigue, and other measures may differ before exposure begins.

Within the same participant, baseline state may vary across sessions.

The baseline recording therefore provides more than a value to subtract from the underway period.

It characterizes the physiological context immediately preceding exposure.

13.6 Medication and Exposure History Are Contextual Variables

Medication use and prior exposure may also contribute to variability.

The Phase 1 intake records medication information and motion-sickness history.

The canonical source set does not establish the specific quantitative effect of every possible medication or prior exposure under Phase 1 conditions.

These variables should therefore be documented and analyzed as context rather than assigned unsupported predetermined effects.

13.7 Within-Person Response Patterns May Be Stable

Individual variability does not necessarily imply random variability.

Cowings and colleagues reported evidence that autonomic response patterns associated with motion-related states can show within-person stability. [39]

This raises an important possibility.

Two participants may respond differently to the same general stimulus while each shows a relatively reproducible personal response pattern across repeated exposures.

If so, averaging across participants could obscure meaningful structure.

13.8 Repeated Measures Can Reveal Participant-Level Structure

The repeated-session Phase 1 design provides an opportunity to test this directly.

If similar received-motion characteristics repeatedly produce similar physiological responses within the same participant, evidence for participant-specific structure strengthens.

If an apparent pattern occurs once and fails to recur, confidence should decrease.

Repeated exposure therefore allows variability itself to become an experimental question.

13.9 Group Means Can Conceal Heterogeneity

A group mean near zero can arise because no systematic response exists.

It can also arise because different participants show reproducible responses in opposite directions.

Those possibilities have very different interpretations.

Participant-level analysis is therefore particularly important in a discovery-stage study.

At the same time, retrospectively identified subgroups can arise by chance.

Any apparent individual response phenotype requires replication.

13.10 State Dependence and Individual Differences Are Distinct

Individual variability and state dependence should not be treated as interchangeable.

Individual variability refers to differences between participants.

State dependence refers to changes associated with temporary physiological conditions within or across exposures.

A participant may have a stable response tendency while its magnitude still depends on posture, cardiovascular state, susceptibility, or exposure history.

The analytical problem is therefore hierarchical:

what motion was received?

what state was the participant in?

how did this participant respond?

13.11 Individualization Must Be Earned

The existence of biological variability does not justify personalized therapy.

Participant-specific response structure becomes scientifically meaningful only if it is sufficiently reproducible to predict future responses better than simpler group-level models.

Phase 1 can test whether such structure exists.

It cannot assume that it does.

13.12 Recovery May Also Vary by Participant

Individual differences may also appear in recovery.

Some participants may return toward baseline quickly, while others may show more persistent changes.

Repeated sessions can determine whether recovery characteristics themselves demonstrate within-person stability.

That question becomes especially relevant when considering adaptation across exposures.

13.13 What Individual Variability Establishes for Phase 1

The current evidence establishes that vestibulo-autonomic responsiveness is conditioned by physiological context and that within-person response patterns may show stability. [8,9,37-39]

It does not establish that every participant has a stable physiological “signature” or that participant-level differences have therapeutic meaning.

The appropriate Phase 1 question is:

Do motion-response relationships exhibit reproducible structure within participants and across measurable physiological states?

If they do, later controlled studies can test whether those relationships are stable, causal, and predictive.

If they do not, the hypothesis of meaningful participant-specific response structure should weaken.

Repeated exposure introduces the next problem: the participant may change as exposure history accumulates.

14. Repeated Exposure, Adaptation, and Habituation

Vestibular and motion-related physiological responses can change with repeated exposure.

This creates both an opportunity and an interpretive challenge for longitudinal research.

Motion-sickness sensitivity may decrease, physiological response magnitude or timing may change, and some individual response characteristics may nevertheless remain stable. [39,40]

The important question is not whether repeated exposure changes the system.

It is how that change should be interpreted.

14.1 Repeated Exposure Can Change Motion Sensitivity

Dai, Raphan, and Cohen demonstrated a prolonged reduction in motion-sickness sensitivity following repeated visual-vestibular interaction. [40]

This establishes that motion susceptibility is not necessarily fixed.

A participant may respond differently during later sessions than during earlier ones even when the physical exposure is similar.

Session number and prior exposure should therefore be retained as relevant variables.

14.2 Habituation Is Not the Same as Therapeutic Improvement

A reduction in sickness or response magnitude across repeated exposure may represent habituation.

That observation should remain specific.

Reduced nausea may indicate increased motion tolerance.

A smaller physiological response may indicate altered responsiveness to repeated stimulation.

Neither establishes improved autonomic regulation.

Habituation does not demonstrate increased vagal tone, reduced sympathetic tone, or clinical benefit.

Those conclusions require separate evidence.

14.3 Exposure History Changes the Meaning of Later Sessions

Repeated-session data cannot be treated as though every exposure occurs in the same physiological context.

A response that appears during early sessions and diminishes later may reflect adaptation.

It may also reflect different received motion, different baseline state, changing sickness susceptibility, measurement variation, or an unstable original association.

Session number should therefore remain an explicit analytical variable rather than pooling all exposures as interchangeable.

14.4 Stable Structure Can Coexist With Adaptation

Adaptation does not necessarily mean that every aspect of a participant's response becomes unstable.

Within-person autonomic response patterns may remain recognizable even while their magnitude changes across sessions. [39]

For example, one participant might repeatedly show predominantly electrodermal and pupillary responses while another repeatedly shows stronger cardiorespiratory changes, even if both responses diminish with exposure.

This distinction between response structure and response magnitude is important for longitudinal analysis.

14.5 Repeated Exposure Helps Separate Signal From Chance

Repeated sessions also provide a direct test of candidate associations.

If a physiological relationship recurs when similar head-centered motion occurs, confidence increases.

If it appears once and does not recur, confidence decreases.

If it changes systematically with exposure history, adaptation becomes a candidate explanation.

Repeated exposure therefore strengthens the study only when change and replication are analyzed explicitly.

14.6 Acute Response, Recovery, and Longitudinal Change Are Different Timescales

Repeated exposure creates several distinct timescales:

acute response during a session

recovery after motion ceases

change across repeated sessions

persistence between sessions

These should not be collapsed.

A response that resolves within minutes of docking differs from one that persists into recovery.

A response that gradually diminishes over multiple sessions differs again.

Preserving these timescales allows adaptation and persistence to be characterized more precisely.

14.7 Adaptation Can Change Motion-Sickness Confounding

If sickness-related physiology diminishes over repeated sessions while another candidate response remains stable, interpretation of that response may strengthen.

If the candidate physiological response diminishes in parallel with sickness symptoms, sickness-related physiology becomes a more plausible contributor.

Repeated exposure can therefore help separate candidate vestibulo-autonomic relationships from sickness-related processes.

14.8 Received Motion Must Still Be Comparable

A longitudinal difference cannot be attributed confidently to adaptation unless the physical exposure itself is characterized.

Natural vessel motion varies between sessions.

Frequency, magnitude, axis combinations, and head-centered exposure may differ.

Therefore:

session 1 response ≠ session 8 response

does not automatically imply adaptation.

The first question is whether sufficiently comparable motion was received.

This is another reason motion must be measured on every session.

14.9 Adaptation May Be Stimulus-Specific

Evidence that motion sensitivity changes under one visual-vestibular adaptation paradigm does not establish that adaptation generalizes across every form of vestibular exposure. [40]

An apparent adaptation should therefore be described in relation to the stimulus actually received.

Claims of generalized “vestibular adaptation” would require evidence of transfer across conditions.

14.10 Adaptation Need Not Be Linear

The canonical evidence does not establish that adaptation during repeated natural motion will follow a simple monotonic trajectory.

Responses may change rapidly and then stabilize.

They may fluctuate.

Some physiological outputs may adapt while others remain stable.

The observed longitudinal pattern should therefore be modeled rather than assumed.

14.11 Recovery Trajectories May Also Change

Repeated exposure may change not only the active response but also recovery.

A participant may return toward baseline more quickly during later sessions, more slowly, or not differently at all.

The planned recovery period provides a standardized window for examining those changes.

It should not be assumed to capture complete recovery from every possible physiological state.

14.12 Adaptation Can Falsify as Well as Support a Candidate Relationship

Changing responses across repeated sessions should not automatically be rescued by labeling them “adaptation.”

If a candidate motion-response relationship appears early and then disappears despite comparable exposure, that may reflect habituation.

It may also indicate that the relationship is not sufficiently stable for the proposed mechanism.

Adaptation itself should be supported by a systematic longitudinal pattern.

14.13 Implications for Future Individualization

If participant-specific response structure persists while predictable adaptation occurs, later models may eventually incorporate exposure history into individualized prediction.

If longitudinal responses remain unstable, individualized control becomes less plausible.

This is an evidence gate for later development, not a conclusion of Phase 1.

14.14 What Repeated Exposure Establishes for Phase 1

The available evidence establishes that motion sensitivity can change with repeated exposure and that within-person autonomic response patterns may show stability. [39,40]

It does not establish that repeated natural motion improves autonomic function or that habituation represents therapeutic benefit.

The Phase 1 questions are therefore:

Do candidate motion-response relationships replicate across sessions?

Do their magnitude, timing, or physiological structure change systematically with exposure history?

Are those changes explained by differences in received motion, baseline state, or sickness susceptibility?

Do participant-specific response patterns remain identifiable over time?

Those questions position repeated exposure as a source of scientific information rather than merely repeated data collection.

The next section applies the vestibular-autonomic framework to its first disease-specific population: POTS.

15. Vestibular-Autonomic Relevance to POTS

Postural orthostatic tachycardia syndrome is relevant to vestibular-autonomic research because the disorder is defined by abnormal cardiovascular responses to upright posture, while vestibular pathways participate in cardiovascular regulation during postural and gravitational change.

That overlap provides a scientific rationale for investigating vestibular-autonomic relationships in POTS.

It does not establish that POTS is caused by vestibular dysfunction or that vestibular stimulation is therapeutic.

The current evidence supports a narrower conclusion: POTS is physiologically heterogeneous, vestibular input participates in normal orthostatic cardiovascular regulation, and recent disease-specific evidence suggests that otolith-related vestibular measures and cardiovascular variability may be altered together in some individuals with POTS. [23,25]

15.1 POTS Is a Heterogeneous Syndrome

POTS should not be treated as a single-mechanism disorder.

Consensus and review literature describe a syndrome characterized by excessive orthostatic tachycardia accompanied by chronic orthostatic symptoms, but multiple physiological mechanisms can contribute to that phenotype. [23]

Reported mechanisms include abnormalities involving blood-volume regulation, peripheral vascular function, autonomic control, and adrenergic signaling.

Raj and colleagues demonstrated a renin-aldosterone paradox and evidence of disturbed blood-volume regulation, reinforcing that POTS cannot be reduced to a simple model of excessive sympathetic activation. [24]

This heterogeneity is central to vestibular interpretation.

Even if altered vestibular-autonomic coupling is demonstrated in a subgroup, that finding would not establish a universal POTS mechanism.

15.2 POTS Is Not Simply "Too Much Sympathetic Activity"

Orthostatic tachycardia does not by itself identify a single autonomic mechanism.

Heart rate is an integrated cardiovascular output influenced by blood volume, vascular resistance, cardiac autonomic regulation, baroreflex function, posture, and other processes.

Some individuals with POTS may show hyperadrenergic features, but that phenotype should not be generalized to the entire syndrome. [23,24]

The relevant disease-specific question is therefore not whether POTS reflects generalized sympathetic excess.

It is whether vestibular-autonomic regulation differs systematically in some individuals with the syndrome.

15.3 Why Vestibular Physiology Is Relevant to Orthostatic Regulation

The relevance begins with normal physiology.

Vestibular signals provide information about head movement and orientation relative to gravity.

Vestibulo-sympathetic pathways participate in cardiovascular regulation during postural change, and their responsiveness varies with posture and baroreflex state. [4,8,9]

Because POTS manifests during upright posture, it is reasonable to test whether those regulatory relationships differ in affected individuals.

A pathway can be relevant to a disorder without being its root cause.

That distinction is especially important in a heterogeneous syndrome.

15.4 Otolith Function Is a Plausible Point of Interest

The otolith organs are particularly relevant because they encode linear acceleration and head orientation relative to gravity.

Mechanical stimulation engaging otolith-related pathways can modulate sympathetic nerve activity in healthy humans. [7,30]

This establishes a physiological bridge between otolith-related vestibular input and autonomic cardiovascular regulation.

The disease-specific question is whether that relationship is altered in POTS.

15.5 Woo et al. Provides Preliminary Direct Disease-Specific Evidence

Woo and colleagues examined vestibulo-sympathetic interaction and otolith function in individuals with POTS.

The study included 47 participants with POTS and 32 controls and evaluated vestibular-evoked myogenic potentials together with cardiovascular variability measures. [25]

The findings provide preliminary direct evidence that otolith-related vestibular measures and autonomic or cardiovascular measures may differ together in POTS.

This is important because it moves the rationale beyond normal physiological plausibility.

It provides a disease-specific signal worth investigating further.

15.6 The Woo Study Does Not Establish Causation

The Woo et al. findings do not establish that otolith dysfunction causes POTS.

Several causal relationships remain possible.

Vestibular abnormalities could contribute to orthostatic dysregulation.

Autonomic or cardiovascular dysfunction could influence vestibular measurements.

Both could reflect another underlying process.

Different POTS subgroups could show different relationships.

Or the association could be physiologically real without being a primary disease mechanism.

The study therefore supports altered vestibular-autonomic association, not causal attribution. [25]

15.7 The Findings Do Not Define a Universal POTS Phenotype

A group-level difference does not mean every participant exhibits the same abnormality.

POTS heterogeneity makes that distinction particularly important. [23,24]

The current evidence does not establish that all individuals with POTS have abnormal otolith function or that one vestibular measure can classify the syndrome.

Independent replication and subgroup characterization remain necessary.

15.8 Vestibular Symptoms Do Not Establish Vestibular Causation

Dizziness and disequilibrium are common reasons vestibular and orthostatic disorders can appear clinically similar.

Symptom overlap does not identify mechanism.

Dizziness may arise from altered cerebral perfusion, cardiovascular dysregulation, vestibular dysfunction, visual factors, medication effects, or other processes.

Therefore:

orthostatic dizziness + vestibular-autonomic physiology does not establish a vestibular cause of POTS.

Disease-specific physiological measurements are more informative than symptom labels, but they still require causal testing.

15.9 Altered Vestibular-Autonomic Function Could Be Primary, Secondary, or Compensatory

Even if altered vestibular-autonomic relationships are replicated in POTS, their biological role would remain uncertain.

They could represent a primary abnormality.

They could develop secondarily to chronic orthostatic dysregulation.

They could represent compensation for another deficit.

Or they could be associated without major causal importance.

Determining which interpretation is correct requires controlled manipulation rather than observational association alone.

15.10 The Existing Evidence Does Not Establish Vestibular Treatment for POTS

The current source set does not demonstrate that vestibular stimulation improves POTS symptoms or normalizes orthostatic physiology.

It does not identify a therapeutic vestibular waveform, frequency, amplitude, duration, or axis combination.

And it does not establish that changing a vestibular-autonomic biomarker improves clinically meaningful outcomes.

The translational rationale is therefore experimental, not therapeutic.

15.11 Why POTS Remains a Strong Translational Candidate

Despite those limitations, POTS is a particularly coherent future population for controlled vestibular-autonomic study.

Vestibular pathways participate in cardiovascular regulation during gravitational challenge.

Posture modifies vestibulo-sympathetic responsiveness.

Baroreflex state modifies the reflex.

POTS is defined by abnormal orthostatic physiology.

And Woo et al. provides preliminary disease-specific evidence linking otolith-related measures with cardiovascular variability. [8,9,23,25]

Together, these findings support the testable question:

Do individuals with POTS exhibit reproducible differences in vestibular-autonomic response to controlled mechanical stimulation compared with appropriate controls?

That question is supported by current evidence.

Whether vestibular stimulation is therapeutic is not yet answered.

15.12 Position Within the SeaKing Solace Research Sequence

Phase 1 does not test POTS.

It is designed first to determine whether natural head-centered motion produces reproducible and interpretable physiological relationships in healthy adults.

If candidate relationships survive replication and controlled mechanical reproduction, disease-specific studies can then ask whether the same stimulus-response relationships differ in POTS.

This sequencing reduces ambiguity.

A later POTS study should not be asked simultaneously to discover the relevant stimulus, establish the mechanism, and prove clinical efficacy.

15.13 What Later POTS Studies Would Need to Determine

A disease-specific program would need to separate several questions:

Does vestibular-autonomic response differ between POTS and controls?

Does any difference vary across POTS phenotypes?

Is the difference associated with otolith-related function?

Does controlled vestibular stimulation alter orthostatic cardiovascular physiology?

Does any physiological change persist?

And does that physiological change correspond to meaningful symptom or functional improvement?

These questions require separate evidentiary steps.

15.14 What the Current POTS Evidence Establishes

The current evidence supports four defensible conclusions.

POTS is a heterogeneous orthostatic syndrome and should not be reduced to generalized sympathetic overactivation. [23,24]

Vestibular pathways contribute to normal cardiovascular regulation during postural and gravitational change. [4,8,9]

Mechanical stimulation engaging otolith-related pathways can modify sympathetic physiology in healthy humans. [7,30]

And Woo et al. provides preliminary direct disease-specific evidence linking otolith-related vestibular measures with autonomic or cardiovascular abnormalities in POTS. [25]

What remains unresolved is causation, universality, therapeutic significance, and whether controlled vestibular manipulation can produce predictable clinically relevant effects.

That makes POTS a justified future mechanistic population, not an established therapeutic indication.

The evidence architecture in autism is different.

16. Vestibular-Autonomic Relevance to Autism

Autism spectrum disorder is relevant to vestibular-autonomic research for a different reason than POTS.

In POTS, disease-specific evidence now provides a preliminary direct bridge between otolith-related vestibular measures and cardiovascular variability.

In autism, the evidence base is broader but less direct.

Meta-analytic, systematic-review, and experimental studies report group-level differences in cardiac autonomic measures, resting autonomic physiology, sensory-autonomic reactivity, pupil responses, and respiratory-autonomic function. [26-28,41,42]

These findings establish autonomic physiology as a relevant domain of autism research.

They do not establish a uniform autonomic phenotype or a direct mechanical vestibular-autonomic abnormality.

The central translational question is therefore:

Does controlled vestibular stimulation produce reproducible autonomic responses in autistic individuals, and do those responses differ systematically from appropriate comparison groups?

That question remains largely untested directly.

16.1 Group-Level Autonomic Differences Have Been Reported

Cheng, Huang, and Huang conducted a meta-analysis of HRV in individuals with autism spectrum disorder and reported group-level differences in cardiac autonomic measures. [26]

This supports the conclusion that cardiac autonomic physiology may differ on average between autistic and comparison groups.

It does not establish that every autistic individual has the same physiological pattern.

Nor should the finding be translated into a universal statement about “low vagal tone.”

As established in Section 8, HRV is not a direct measure of vagal nerve activity.

The appropriate interpretation is therefore population-level difference in cardiac autonomic measures, not a universal defining autonomic signature.

16.2 Resting Autonomic Findings Are Heterogeneous

Arora and colleagues systematically reviewed resting-state autonomic function in autism and emphasized substantial heterogeneity across the literature. [27]

Reported findings vary by physiological measure, participant characteristics, developmental stage, task, medication exposure, and recording conditions.

Some studies report clear differences.

Others report smaller, inconsistent, or context-dependent effects.

The literature therefore does not support the claim that autistic individuals share one universally abnormal resting autonomic state.

That heterogeneity is not peripheral.

It is central to later study design.

16.3 Sensory Stimulation Provides the Strongest Direct Translational Bridge

Schaaf and colleagues demonstrated autonomic dysregulation during sensory stimulation in children with autism spectrum disorder. [28]

This finding is especially important because it moves beyond resting physiology.

It suggests that autonomic reactivity to sensory input may differ in autistic children.

That makes sensory-autonomic coupling relevant to the SeaKing Solace hypothesis.

However, sensory stimulation is not equivalent to vestibular stimulation.

The study supports altered autonomic reactivity to sensory exposure.

It does not establish that mechanically generated vestibular motion produces the same response.

16.4 Sensory-Autonomic Reactivity Is Not Vestibular-Autonomic Coupling

This distinction is the central evidentiary boundary in the autism section.

Sensory paradigms may involve visual, auditory, tactile, proprioceptive, vestibular, or multimodal inputs.

Even when vestibular elements are present within a broader sensory protocol, the resulting physiological response cannot necessarily be attributed specifically to the vestibular component.

The existing sensory-autonomic literature therefore provides a rationale for testing vestibular-autonomic coupling.

It does not establish that coupling directly.

16.5 Pupillary Findings Add Another Physiological Domain

Daluwatte and colleagues reported atypical pupillary light reflex characteristics together with HRV differences in children with autism spectrum disorder. [41]

This provides additional evidence that more than one physiological system may differ at the group level.

The interpretive limits established in Section 11 still apply.

Pupillary differences do not identify a specific sympathetic or parasympathetic abnormality and do not establish how autistic participants would respond to mechanical vestibular stimulation.

Their relevance is physiological and methodological rather than mechanistically conclusive.

16.6 Respiratory and Autonomic Findings Reinforce the Multimodal Picture

Ming and colleagues reported respiratory and autonomic dysfunction in children with autism spectrum disorders. [42]

This is relevant because respiration is both a physiological output and an important determinant of cardiac variability.

Together with the cardiac and pupillary literature, these findings reinforce that autism-related autonomic physiology cannot be summarized adequately by a single measure.

They do not establish that all physiological systems are uniformly abnormal.

16.7 The Evidence Does Not Support a Universal "Low Vagal Tone" Model

A recurring simplification is to describe autism as a state of low vagal tone.

The current evidence does not justify that claim.

HRV meta-analysis demonstrates group-level differences. [26]

Resting-state systematic review demonstrates heterogeneity. [27]

And HRV itself is not direct vagal measurement.

Accordingly, a future increase in RMSSD or another HRV metric during motion could not automatically be interpreted as "correcting low vagal tone."

The physiological measurement and the clinical claim would be different.

16.8 Autonomic Difference Does Not Establish Autonomic Cause

Even reproducible autonomic differences would not establish that autonomic dysfunction causes autism.

Observed differences could contribute to sensory or behavioral phenomena.

They could arise secondarily from other developmental, behavioral, environmental, or physiological factors.

They could represent compensatory responses.

And their meaning may differ among individuals.

The reviewed literature does not establish autism as an autonomic disorder in a unitary causal sense.

Nor does it justify assuming that changing an autonomic biomarker treats the core condition.

16.9 Behavioral Change Cannot Serve as a Surrogate Mechanism

Naturalistic observations of calmness, engagement, reduced distress, or altered communication can provide important reasons to ask scientific questions.

They cannot determine mechanism.

As established in Section 12, reduced activity, eye closure, drowsiness, and fatigue can also occur during sopite-related physiology.

A behavioral observation should therefore remain an observation until the physical exposure, physiological response, temporal structure, and competing explanations are measured.

16.10 Reactivity May Be More Informative Than Resting State

The combination of heterogeneous resting-state findings and altered responses during sensory stimulation raises a useful hypothesis.

The relevant physiological difference in autism may not always be a fixed baseline deficit.

It may involve how autonomic physiology responds to sensory input. [27,28]

That possibility is especially relevant to a vestibular research program because the proposed stimulus is sensory.

The evidence does not establish vestibular reactivity as the specific difference.

It provides a rationale for testing it.

16.11 The Direct Vestibular-Autonomic Evidence Gap

This is the most important unresolved issue.

There is substantial literature on autonomic physiology in autism.

There is substantial literature demonstrating vestibular-autonomic coupling in humans.

And there is evidence of altered sensory-autonomic reactivity in autistic children.

What remains largely untested within the preserved evidence base is the direct relationship between controlled mechanical vestibular stimulation and autonomic response in autism.

Therefore, the following chain cannot yet be treated as established:

autism → altered vestibular-autonomic coupling → therapeutic response to motion

The evidence currently supports the rationale for testing the first relationship.

It does not establish the second or third.

16.12 Contrary Evidence Should Remain Visible

The autism-autonomic literature also includes critical commentary cautioning against overstating the consistency or universality of autonomic dysfunction in autism.

The Barbier et al. article preserved in the source ledger is important because it prevents the review from presenting a heterogeneous literature as unanimous. [43]

Its presence does not negate reported autonomic differences.

It constrains the strength of the conclusion.

The defensible position is:

autonomic differences and altered sensory-autonomic responses have been reported in autism, but their consistency, mechanisms, and individual significance remain heterogeneous and incompletely resolved.

16.13 Why Autism Remains a Justified Translational Population

Despite the direct evidence gap, autism remains a justified future population for mechanistic investigation.

Group-level autonomic differences have been reported. [26,27]

Sensory stimulation can produce different autonomic responses. [28]

Pupillary and cardiorespiratory findings support multimodal physiological characterization. [41,42]

And the broader human literature establishes that vestibular stimulation can modify autonomic physiology.

Together, these findings support the question:

Does controlled vestibular stimulation produce reproducible autonomic responses in autistic individuals, and are those responses systematically different from controls?

That is the justified translational claim.

16.14 Position Within the SeaKing Solace Research Sequence

Phase 1 does not test autism.

It first asks whether natural motion produces reproducible physiological relationships in healthy adults.

If candidate relationships survive replication and controlled mechanical reproduction, later autism studies can test whether those responses differ in magnitude, timing, pattern, tolerability, or state dependence.

Clinical significance must then be tested separately.

This sequencing protects later autism studies from simultaneously having to discover the stimulus, establish the physiology, and prove benefit.

16.15 What the Current Autism Evidence Establishes

The current evidence supports four defensible conclusions.

Group-level differences in cardiac autonomic measures have been reported. [26]

Resting autonomic findings are heterogeneous and context dependent. [27]

Autonomic responses during sensory stimulation can differ in autistic children. [28]

Pupillary and respiratory-autonomic studies provide additional evidence that several physiological domains may be relevant. [41,42]

The evidence does not establish a universal low-vagal-tone phenotype, autonomic causation of autism, altered mechanical vestibular-autonomic coupling, or therapeutic benefit from vestibular stimulation.

The autism rationale is therefore one of converging physiological relevance with a direct experimental gap.

That gap defines the next translational question rather than answering it.

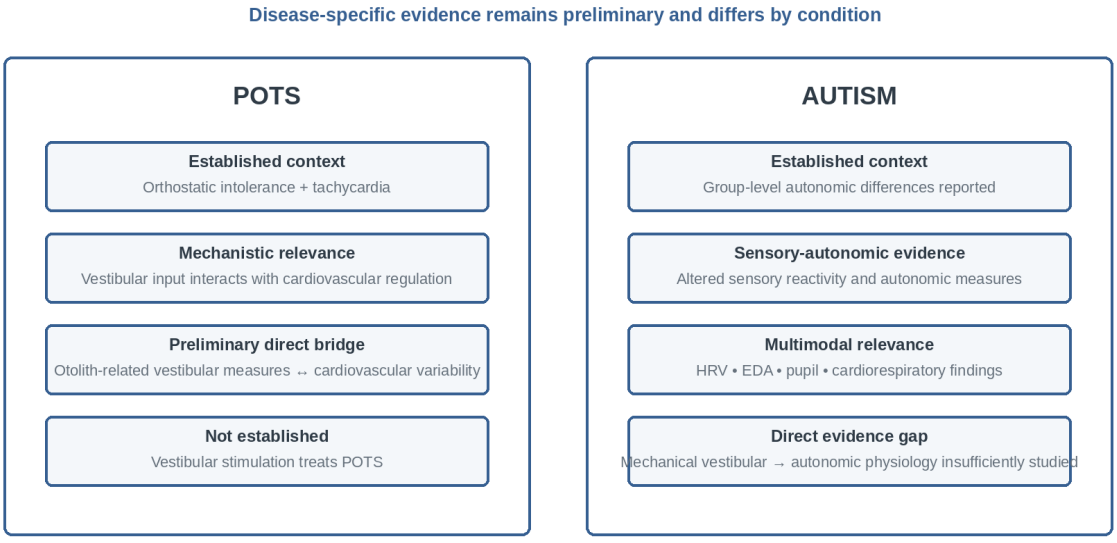


Figure 6. Disease-specific evidence architecture for POTS and autism. POTS has a preliminary direct bridge between otolith-related vestibular measures and cardiovascular/autonomic abnormalities, whereas autism has substantial autonomic and sensory-autonomic literature but a direct experimental gap for controlled mechanical vestibular-autonomic coupling. Neither literature establishes therapeutic benefit from vestibular stimulation. [4,8,9,23-28,41,42]

The review now returns from disease-specific rationale to experimental architecture: if natural motion-response relationships are to be identified without conflating distinct physiological outputs or competing states, multiple synchronized measures are required.

17. Multimodal Measurement Architecture

The preceding sections establish that no single physiological measurement can characterize vestibulo-autonomic response comprehensively or specifically.

Cardiac timing, respiration, arterial pressure, electrodermal activity, and pupil dynamics measure different physiological processes and have different interpretive limitations. Motion sickness, posture, environmental conditions, and participant behavior can further alter those signals.

The experimental response is therefore not to select one variable as the definitive autonomic endpoint.

It is to measure multiple non-equivalent physiological signals synchronously with the physical exposure and the participant's evolving state.

For SeaKing Solace Phase 1, the purpose of multimodal measurement is not simply to collect more biomarkers.

It is to reduce interpretive ambiguity.

17.1 The Experimental Unit Is a Time-Aligned System

The natural-motion experiment can be represented as several interacting layers:

physical environment → vessel motion → head-centered received motion → participant state → physiological response

alongside:

visual and environmental context + symptoms + behavior + protocol events

Each layer contributes information required to interpret the others.

Physiology without physical exposure is difficult to attribute.

Vessel motion without head-centered motion may incompletely represent the received vestibular stimulus.

Cardiac variability without respiration is less interpretable.

Pupil response without luminance and gaze context is less specific.

EDA without environmental and symptom context can be ambiguous.

The experimental unit is therefore the synchronized relationship among exposure, context, state, and physiology rather than any isolated sensor output.

17.2 Physical Exposure Must Be Measured

The first element of the architecture is the motion itself.

As established in Review 01 and Section 6, natural vessel motion is multidimensional and time varying.

Frequency, magnitude, orientation, temporal structure, and duration may all prove relevant to physiological response.

Phase 1 therefore requires continuous quantitative motion measurement rather than simply classifying participants as underway or stationary.

The purpose is to determine what physical exposure occurred and when it occurred.

17.3 Vessel Motion and Head-Centered Motion Are Separate Measurements

Vessel motion does not necessarily equal the motion received at the participant's head.

Participants can move their heads relative to the vessel, change orientation, or compensate behaviorally for vessel movement.

Two individuals aboard the same vessel may therefore receive different head-centered motion.

Phase 1 includes 6-DoF measurement at both the vessel and participant level so that this distinction can be tested rather than assumed.

One important analysis can therefore ask:

Does head-centered motion explain or predict physiological response better than vessel motion alone?

If not, the added value of participant-level motion measurement should be reconsidered.

17.4 ECG Provides the Cardiac Timing Reference

Continuous ECG supplies the beat-to-beat cardiac timing required for heart-rate and HRV analysis.

Its role within the architecture is temporal as much as physiological.

Cardiac changes can be aligned with motion, respiration, arterial pressure, EDA, pupil dynamics, and participant events.

The interpretive limitations of HRV established in Section 8 remain unchanged.

ECG and HRV provide information about cardiac timing and cardiac autonomic modulation; they do not directly record autonomic nerve activity.

17.5 Respiration Provides Both Context and Response Information

Continuous respiratory measurement is required because breathing influences cardiac variability and may itself change during motion.

As established in Section 9, respiration can function as context, physiological output, possible intermediate process, or competing explanation.

Its value within the architecture is therefore to preserve the temporal relationship among breathing, cardiac timing, motion exposure, and other physiological responses.

17.6 Beat-to-Beat Arterial Pressure Adds Cardiovascular Dynamics

Continuous beat-to-beat arterial pressure provides information unavailable from intermittent blood-pressure measurements.

Transient pressure changes can be examined in relation to motion, cardiac timing, respiration, and other physiological signals.

This is particularly important because changes in directly recorded sympathetic activity can occur without large changes in mean arterial pressure, as established in Sections 4 and 5.

For Phase 1, beat-to-beat pressure therefore provides both an outcome and information about the cardiovascular state in which the vestibular stimulus is being received. [44]

17.7 Baroreflex-Related Coupling Can Be Examined, but Not Overclaimed

Simultaneous ECG and beat-to-beat arterial pressure permit analysis of spontaneous relationships between arterial pressure and cardiac timing.

These methods can provide information about baroreflex-related cardiovascular coupling. [45]

Their interpretation must remain constrained.

They do not directly record baroreceptor afferent activity, measure the entire baroreflex system, or establish that a vestibular response operates through a specific baroreflex pathway.

Their value is comparative.

Investigators can ask whether candidate motion-response periods are accompanied by reproducible changes in pressure-heart-period relationships and whether those relationships depend on participant state or exposure history.

17.8 EDA Adds an Effector-Specific Sympathetic Signal

EDA contributes information from a sympathetic effector domain different from cardiac timing or blood pressure.

As established in Section 10, EDA reflects sympathetic sudomotor physiology rather than global sympathetic activity. [17]

Its inclusion is useful precisely because autonomic outputs can dissociate.

An EDA response may occur with or without parallel changes in cardiac or vascular measures.

Those patterns can help characterize the physiological response without requiring every measure to move together.

17.9 Pupillometry Adds Another Non-Equivalent Physiological Window

Pupil dynamics provide an additional continuous physiological signal.

Pupil Labs Core also supplies gaze and visual-context information relevant to interpretation.

As established in Section 11, pupil diameter is influenced by autonomic pathways but also by luminance, gaze, arousal, cognition, fatigue, and motion sickness. [18,19,36]

Pupillometry therefore contributes another non-equivalent physiological view rather than another generic sympathetic marker.

17.10 Luminance and Environmental Context Are Measurements

Natural environments contain variables capable of changing physiological signals independently of the motion being studied.

Luminance is particularly important for pupil interpretation.

Temperature and humidity are relevant to sudomotor physiology and EDA.

The participant area is planned to be HVAC controlled, which reduces variation but does not guarantee invariance.

Relevant environmental variables should therefore be measured or logged where practical.

The principle is straightforward:

when a plausible competing influence can be measured, measurement is preferable to assuming constancy.

17.11 Behavioral and Symptom Events Supply Context Sensors Cannot Provide

Continuous physiological sensors cannot identify every relevant participant event.

A participant may report nausea, become pale, close the eyes, become drowsy, change posture, begin speaking, show distress, adjust a sensor, or request that the session stop.

These events can materially change interpretation.

Phase 1 therefore includes participant-specific timestamped RN event logging.

The event stream complements the physiological sensors by documenting observable or reported state changes that cannot be inferred reliably from the sensor record alone.

17.12 Standardization Reduces Avoidable Variation

Multimodal measurement does not eliminate the need for experimental standardization.

Participants are planned to remain seated in a standardized posture, minimize unnecessary head movement, and avoid unnecessary social interaction while sensors are active.

The participant area is environmentally controlled as practical.

These controls reduce avoidable variation while preserving the natural-motion exposure that Phase 1 is intended to characterize.

Departures from those conditions should be documented rather than assumed absent.

17.13 Baseline, Active Exposure, and Recovery Form One Continuous Record

The Phase 1 sequence includes a static pre-exposure baseline, prolonged underway exposure, and static post-docking recovery period.

These periods provide useful experimental anchors.

They should not be treated as merely three averages.

The underway exposure is nonstationary.

Motion changes over time.

Participant state may evolve.

Sickness-related physiology, adaptation, and transient responses may appear and disappear.

The primary data structure should therefore remain continuous and time resolved, with baseline, active exposure, and recovery defining contextual periods within that record.

17.14 Synchronization Is a Core Experimental Requirement

The value of the architecture depends on temporal alignment.

If motion, physiology, environmental variables, and participant events are recorded on poorly aligned clocks, the experiment cannot determine confidently whether a physiological change preceded, followed, or coincided with a candidate motion exposure.

Synchronization must therefore include attention to clock alignment, drift, latency, and event timing. [46]

The relevant streams include:

* vessel motion;

* head-centered motion;

* ECG;

* respiration;

* beat-to-beat arterial pressure;

* EDA;

* pupil and gaze;

* luminance and environmental context; and

* participant-specific event logging.

Synchronization is part of the scientific design, not merely a data-engineering convenience.

17.15 Temporal Order Can Constrain Mechanistic Interpretation

A synchronized dataset permits investigators to examine temporal order.

A motion feature may repeatedly precede a physiological response.

Respiration may change before HRV.

A pupil response may coincide with a luminance change.

EDA may change only after sickness-related symptoms emerge.

Such timing can strengthen or weaken different interpretations.

Temporal precedence does not prove causality.

But without temporal alignment, even those distinctions cannot be tested.

17.16 Convergence and Dissociation Are Both Informative

Multimodal measurement should not be designed around the assumption that all signals will move together.

A candidate response may involve several physiological domains simultaneously.

That convergence can strengthen evidence that the participant entered a coherent physiological state.

But dissociation can be equally informative.

EDA may change without measurable HRV change.

Cardiac timing may change while arterial pressure remains stable.

Pupil dynamics may change independently of other outputs.

The direct human literature shows that autonomic effectors can dissociate.

The objective is therefore to characterize the pattern of response rather than force all signals into agreement.

17.17 No Composite "Autonomic Score" Is Established

The presence of multiple measurements does not justify combining them into a single autonomic-regulation score.

HRV, EDA, blood pressure, respiration, and pupil dynamics represent different physiological processes, operate on different timescales, and have different confounds.

There is also no established universal direction in which each should move to define a beneficial state.

Phase 1 should therefore preserve individual signals and their relationships unless a composite measure is independently justified and validated.

The goal is not to rank participants from "dysregulated" to "regulated."

It is to characterize reproducible stimulus-response structure.

17.18 The Architecture Enables Falsification

The multimodal design strengthens Phase 1 because it gives alternative explanations opportunities to outperform the preferred hypothesis.

If vessel motion predicts physiology but head-centered motion adds no information, the proposed importance of participant-level exposure weakens.

If an HRV association is explained by respiration, a direct cardiac-autonomic interpretation weakens.

If pupil changes track luminance, the candidate autonomic interpretation weakens.

If EDA changes occur primarily during sickness-related events, motion sickness becomes a stronger explanation.

If candidate relationships fail to replicate, their evidentiary weight decreases.

A strong architecture should make preferred explanations easier to challenge, not merely easier to support.

17.19 The Phase 1 Measurement Sequence

The planned workflow operationalizes this architecture.

Participants complete intake, including motion-sickness susceptibility, medication information, and baseline state.

Sensors are applied for ECG, EDA, respiration, continuous beat-to-beat finger-cuff blood pressure, Pupil Labs Core, vessel and head-centered 6-DoF motion, and relevant environmental measures.

Participants assume the standardized seated posture.

After acclimation consideration, a five-minute silent static baseline is recorded.

The vessel then begins an approximately two-hour natural-motion exposure while physical and physiological measurements remain synchronized.

The RN records participant-specific symptoms, observations, and protocol events using timestamped event logging.

After docking, participants remain instrumented for a ten-minute static recovery recording.

The resulting dataset is intended to represent, on a common timeline:

what motion each participant received;

what physiological state the participant was in;

what changed physiologically;

and

what relevant contextual events occurred around those changes.

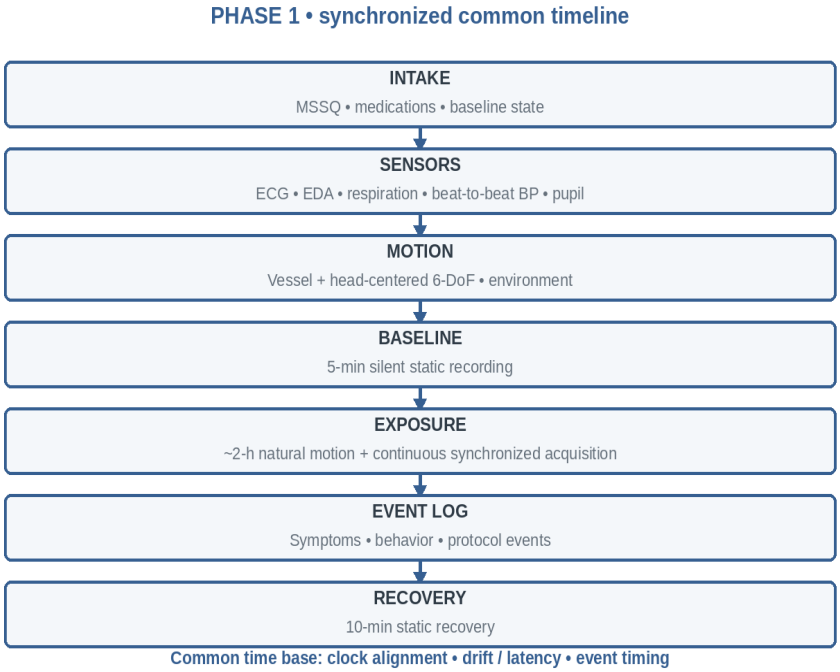


Figure 7. Phase 1 multimodal measurement architecture. Vessel and head-centered motion, ECG/HRV, respiration, beat-to-beat arterial pressure, EDA, pupil/gaze, luminance/environmental context, symptoms, behavior, and protocol events are acquired as a synchronized time-resolved system spanning baseline, natural-motion exposure, and recovery. Synchronization is necessary to evaluate temporal order and competing explanations. [10,17,18,35,43-46]

17.20 What the Architecture Can Provide

The Phase 1 architecture can support analysis of whether characteristics of natural motion are associated with reproducible changes across multiple physiological domains.

It can test whether head-centered exposure adds information beyond vessel motion.

It can characterize temporal relationships among motion, cardiac timing, respiration, arterial pressure, EDA, pupil dynamics, symptoms, and behavior.

It can make several major competing explanations measurable rather than invisible.

It cannot by itself establish vestibular causality or therapeutic benefit.

Those boundaries are addressed formally in Sections 19 and 20.

The immediate purpose is narrower:

to create a sufficiently synchronized and physiologically interpretable record to determine whether reproducible motion-response structure exists.

The next section examines how competing explanations within that record should be distinguished as confounds, mediators, modifiers, or competing mechanisms.

18. Competing Explanations in Natural Motion

Natural motion is physiologically rich.

That is one of its scientific advantages and one of its principal interpretive challenges.

During prolonged vessel motion, vestibular input changes alongside respiration, visual input, posture, participant behavior, cardiovascular state, motion-sickness susceptibility, environmental conditions, and exposure history. Several of these processes can alter the same physiological measurements used to identify candidate vestibulo-autonomic responses.

The analytical problem is therefore not simply to identify correlations between motion and physiology.

It is to determine which explanations remain plausible after the measured context is considered.

18.1 Not Every Alternative Explanation Is a Confound

The terms confound, mediator, modifier, and competing mechanism describe different causal roles and should not be used interchangeably.

A confound is a factor associated with both the apparent exposure and outcome that can create or distort the observed relationship.

A mediator lies along a possible causal pathway between exposure and outcome.

A modifier changes the magnitude or direction of the relationship between exposure and outcome.

A competing mechanism provides an alternative physiological process capable of producing the observed response.

These distinctions matter because the appropriate analytical response differs.

A confound may need adjustment or stratification.

A mediator should not automatically be adjusted away if the objective is to understand the pathway through which motion produces the response.

A modifier may define the conditions under which a relationship occurs.

A competing mechanism may require additional measurements or later experimental manipulation to distinguish it from the preferred explanation.

Phase 1 can characterize these roles provisionally.

It cannot determine the complete causal structure from observational temporal data alone.

18.2 Respiration Can Occupy More Than One Role

Respiration illustrates why these categories matter.

As established in Sections 8 and 9, breathing strongly influences respiratory-linked cardiac variability.

Suppose a particular motion feature is followed by slower respiration and increased RMSSD.

Respiration could be part of the pathway:

motion → respiratory change → altered cardiac variability

It could accompany a broader physiological response without mediating the cardiac change.

Or respiratory variation could explain an apparent HRV association that otherwise might be attributed more directly to cardiac autonomic modulation.

The appropriate interpretation depends on timing, reproducibility, and later controlled testing.

Respiration should therefore be measured and modeled rather than automatically removed as "noise."

18.3 Visual Context Can Produce Competing Pupillary Explanations

Pupil dynamics provide a second example.

A pupil response occurring during motion may reflect autonomic or central-state change.

But if luminance or gaze changes simultaneously, the visual explanation becomes more plausible.

If pupil changes repeatedly track a particular head-centered motion feature while luminance and gaze remain sufficiently comparable, that competing explanation weakens.

The purpose of luminance and gaze measurement is therefore not to prove that a pupil response is autonomic.

It is to test whether major non-autonomic explanations account for the observed signal.

18.4 Motion Sickness Can Be a Competing Mechanism or Intermediate State

Motion sickness presents a more complex problem.

As established in Section 12, sickness-related states can alter respiration, EDA, cardiovascular physiology, sympathetic output, pupil behavior, and participant behavior. [20-22]

Suppose a candidate motion profile is followed by increased EDA, altered respiration, pupil change, and drowsiness.

Those findings could represent the vestibulo-autonomic response of interest.

They could instead represent emerging sickness or sopite-related physiology.

Or the motion could first produce a sickness-related state that then generates the downstream physiological changes.

Simply deleting every interval associated with symptoms could remove biologically meaningful information.

Ignoring sickness would create the opposite error.

The state should first be identified and characterized, after which its relationship to the candidate motion-response pattern can be tested.

18.5 Posture and Cardiovascular State Can Modify the Response

Posture and baroreflex state differ from simple measurement artifacts because human experiments show that they can modify vestibulo-sympathetic responsiveness. [8,9]

A motion-response relationship may therefore be stronger under one physiological state than another.

This is effect modification rather than necessarily confounding.

Phase 1 standardizes posture where practical and measures cardiovascular state continuously, allowing investigators to determine whether candidate relationships depend systematically on those conditions.

18.6 Participant Behavior Can Change Both Exposure and Physiology

Participant behavior is particularly important because it can alter both sides of the proposed relationship.

A head movement changes received vestibular exposure.

Speaking changes respiration.

Postural adjustment can change cardiovascular loading.

Eye closure changes visual input.

Distress or drowsiness can alter several physiological measures.

These events should therefore be timestamped rather than treated as unexplained variance.

Their presence may identify periods requiring sensitivity analysis, provide state information, or reveal why nominally similar vessel motion produced different head-centered exposures.

18.7 Environmental Variables Can Produce Measurement-Specific Alternatives

Environmental conditions do not affect every physiological signal equally.

Luminance is particularly relevant to pupil diameter.

Temperature and humidity are relevant to sudomotor activity and EDA.

Environmental variation therefore creates measurement-specific competing explanations rather than a generic environmental confound.

Where practical, these variables should be measured so their relationship to candidate responses can be examined directly.

18.8 Exposure History Can Modify Later Responses

Repeated exposure introduces another possible modifier.

As established in Section 14, motion sensitivity and physiological response can change with repeated exposure. [39,40]

A candidate association that changes across sessions may therefore reflect adaptation, changing sickness susceptibility, changing baseline state, differences in received motion, or instability of the original relationship.

Session number and prior exposure should remain explicit variables rather than assuming all sessions are exchangeable.

18.9 Temporal Order Helps Constrain Explanations

Synchronization allows competing explanations to be compared using temporal structure.

If a motion feature repeatedly precedes a physiological response, an exposure-response interpretation becomes more plausible than if the physiological change consistently precedes the motion feature.

If luminance changes before the pupil response, visual explanation strengthens.

If respiratory change consistently precedes an HRV change, respiration becomes more relevant to interpretation.

If sickness-related symptoms emerge before a multimodal physiological shift, sickness becomes a stronger competing mechanism.

Temporal precedence does not establish causality.

It narrows the set of plausible explanations.

18.10 Multimodal Convergence Does Not Automatically Establish Mechanism

Several physiological signals changing together may provide stronger evidence for a coherent state transition than one isolated biomarker.

It still does not identify the mechanism automatically.

Motion sickness itself can produce multimodal physiological change.

Respiration can influence cardiac variability while another process changes EDA.

Luminance can alter the pupil during the same interval.

The value of multimodal convergence therefore depends on whether the pattern is reproducible and whether major competing explanations remain plausible.

18.11 Competing Models Should Be Compared Explicitly

Phase 1 should not be structured around a single preferred explanatory model.

Candidate models may include:

Model A: head-centered motion predicts physiological response directly.

Model B: vessel motion predicts response adequately without participant-level head motion.

Model C: respiratory change accounts for an apparent cardiac-variability relationship.

Model D: visual conditions account for an apparent pupil response.

Model E: sickness or sopite-related physiology accounts for a multimodal response.

Model F: participant state modifies the relationship between motion and physiology.

Model G: no reproducible motion-response relationship exists.

The preferred interpretation should be the one that best survives comparison with plausible alternatives, not simply the one most consistent with the initial hypothesis.

18.12 Residual Uncertainty Will Remain

No observational natural-motion study can measure every variable capable of affecting physiology.

Unmeasured influences and measurement error will remain.

Accordingly, even a highly reproducible Phase 1 association should be treated as a candidate relationship requiring controlled reproduction.

The role of Phase 1 is to reduce uncertainty enough to identify what should be tested next, not to eliminate uncertainty entirely.

18.13 Implications for Phase 1 Analysis

The analytical objective is therefore to ask:

Does a candidate relationship replicate?

Does head-centered motion predict the response better than vessel motion alone?

Does the relationship remain when respiration, visual context, environmental conditions, sickness-related state, posture, and relevant participant events are considered?

Does participant state modify the relationship systematically?

Does exposure history change its magnitude or structure?

Do plausible competing models explain the data better?

A candidate relationship becomes more compelling as it survives these challenges.

A relationship that disappears when a major competing explanation is considered should weaken accordingly.

This is the analytical bridge between multimodal measurement and the specific questions Phase 1 is designed to test.

19. What Phase 1 Is Designed to Test

Phase 1 is a discovery and system-identification study.

Its purpose is to determine whether characteristics of naturally occurring head-centered motion are associated with reproducible and interpretable physiological responses in healthy adults under measured conditions.

It is not necessary for Phase 1 to establish mechanism or therapeutic benefit to succeed.

Its scientific success depends on whether it can identify sufficiently robust stimulus-response structure to justify controlled reproduction.

19.1 Whether Natural Motion Contains Physiologically Relevant Structure

The first question is whether characteristics of natural motion predict physiological response better than a simple distinction between motion and no motion.

Candidate dimensions include frequency, magnitude, axis or orientation, temporal structure, duration, and combinations of these features.

Phase 1 can determine whether particular measured motion characteristics repeatedly coincide with or precede physiological changes.

A finding that physiology differs simply between docked and underway periods would be less informative than a reproducible relationship with defined features of the received motion.

19.2 Whether Head-Centered Motion Adds Explanatory Value

Review 01 established that vessel motion and received head-centered motion are not necessarily equivalent.

Phase 1 can test the empirical importance of that distinction.

If participant-level head-centered motion predicts physiological response better than vessel motion alone, the evidence for characterizing received exposure strengthens.

If it does not, the proposed importance of head-level measurement should be revised accordingly.

This is a directly falsifiable component of the research architecture.

19.3 Whether Responses Are Temporally Structured

A meaningful stimulus-response relationship should contain temporal information.

Phase 1 can determine whether candidate physiological changes occur repeatedly during or after particular motion characteristics and whether their latency and duration show reproducible structure.

Temporal relationships do not prove causation.

They help distinguish candidate exposure-response relationships from slower unrelated drift.

19.4 Whether Candidate Relationships Replicate Within Participants

Repeated sessions allow candidate associations to be tested for recurrence.

If similar received-motion characteristics repeatedly produce similar physiological patterns within the same participant, confidence in participant-level structure increases.

If an association appears once and does not recur, confidence should decrease.

Replication is therefore part of discovery rather than something deferred entirely to later phases.

19.5 Whether Candidate Relationships Generalize Across Participants

Phase 1 can also determine whether some relationships recur across participants.

A group-level relationship may exist even when effect magnitude varies.

Alternatively, reproducible participant-specific patterns may exist without a strong common group-average direction.

Both are scientifically informative.

The analysis should determine which structure the data support rather than requiring one in advance.

19.6 Whether Participant State Modifies the Response

Because vestibulo-autonomic responsiveness is state-dependent, Phase 1 can test whether candidate relationships vary with measured participant conditions.

Relevant variables include posture, cardiovascular state, baseline physiology, motion-sickness susceptibility, symptoms, exposure history, and other recorded contextual factors.

Evidence that a relationship occurs only under particular states would not invalidate it.

It would define its boundary conditions.

19.7 Whether Responses Are Multidimensional

Phase 1 can determine whether candidate motion features are associated with changes across one or several physiological domains.

Some relationships may appear primarily in cardiac timing.

Others may involve respiration, arterial pressure, EDA, pupil dynamics, or combinations of signals.

Different outputs need not move in the same direction.

The objective is to characterize response structure rather than require a predetermined composite autonomic pattern.

19.8 Whether Major Competing Explanations Account for the Relationship

As developed in Section 18, Phase 1 can test whether candidate associations remain interpretable after major measured alternatives are considered.

An HRV relationship that disappears when respiration is modeled has a different evidentiary status from one that remains.

A pupil response explained by luminance has a different interpretation from one reproducible under comparable visual conditions.

A multimodal response occurring only during sickness-related states has a different interpretation from one observed independently of those states.

Phase 1 can therefore rank competing explanations even when it cannot resolve causality completely.

19.9 Whether Responses Change With Repeated Exposure

Repeated sessions permit longitudinal questions.

Candidate responses may strengthen, diminish, remain stable, or change structure across exposures.

Phase 1 can determine whether those changes relate systematically to exposure history while accounting for differences in received motion and baseline state.

This can identify adaptation or habituation as hypotheses for later controlled testing.

19.10 Whether Recovery Contains Reproducible Information

The post-exposure recovery period allows investigators to determine whether candidate physiological changes resolve rapidly, persist after major vessel motion ceases, or show participant-specific recovery trajectories.

Persistence does not establish therapeutic carryover.

It establishes temporal persistence of a measured physiological state.

That distinction should remain explicit.

19.11 Whether Candidate Relationships Are Strong Enough for Controlled Reproduction

The most important Phase 1 output is not a declaration that motion “works.”

It is a set of candidate relationships sufficiently specific to test under controlled conditions.

A useful candidate should ideally identify:

the relevant characteristics of received motion;

the physiological output or pattern associated with them;

the temporal relationship;

the conditions under which the relationship occurs;

its within-person reproducibility;

its between-person structure;

and the major competing explanations that remain.

That information provides the experimental specification for the next stage.

19.12 What a Positive Phase 1 Result Would Establish

A strongly positive Phase 1 could establish that:

measured characteristics of natural head-centered motion are associated with reproducible, temporally structured physiological responses in healthy adults under the studied conditions;

some relationships replicate within participants and potentially across participants;

the response depends on identifiable motion characteristics or participant states;

head-centered exposure may provide predictive information beyond vessel motion alone;

major measured competing explanations can be characterized and, in some cases, made less plausible;

and

specific candidate motion-response relationships are sufficiently defined to justify controlled mechanical reproduction.

That would be a meaningful scientific result.

It would demonstrate that natural vestibular exposure and human physiology contain reproducible input-output structure worthy of causal testing.

The conclusions beyond that boundary belong to later experiments.

Phase 1 question	Finding that strengthens the candidate	Finding that weakens or redirects it
Does natural motion contain physiologically relevant structure?	Defined motion features predict physiology repeatedly.	Only docked-versus-underway differences or no reproducible feature relationship.

Phase 1 question	Finding that strengthens the candidate	Finding that weakens or redirects it
Does head-centered motion add explanatory value?	Head motion predicts response beyond vessel motion.	Vessel motion performs equivalently or head measurement adds no stable information.
Is the response temporally structured?	Motion features repeatedly precede or align with defined physiological changes.	Timing is inconsistent or physiology precedes the proposed exposure relationship.
Does the relationship replicate?	Within-person recurrence across sessions and, where applicable, across participants.	One-off associations or unstable participant patterns.
Does participant state modify the response systematically?	Posture, cardiovascular state, susceptibility, or exposure history explain reproducible effect modification.	State dependence is inconsistent or overwhelms the candidate relationship.
Do competing explanations account for the result?	Candidate persists after measured respiratory, visual, environmental, sickness, and event context are considered.	A competing model explains the response better.
Is the candidate defined well enough for Phase 2?	Exposure-response relationship can be represented for controlled mechanical reproduction.	No sufficiently stable or interpretable stimulus-response structure emerges.

Table 2. Phase 1 evidence tests and decision consequences. Phase 1 is designed to identify reproducible stimulus-response structure and to weaken or redirect candidates when replication, temporal structure, head-centered exposure, or competing explanations do not support the preferred model. This table summarizes the manuscript's prespecified discovery logic; it does not add a new therapeutic endpoint or causal claim.

20. What Phase 1 Cannot Establish

Phase 1 is defined not only by the questions it can answer but by the conclusions that remain outside its design.

Even a strong, reproducible, multimodal natural-motion association would remain observational with respect to the specific causal mechanism responsible.

The following boundaries therefore apply even if Phase 1 is strongly positive.

20.1 It Cannot Establish Therapeutic Efficacy or Clinical Benefit

Phase 1 is not a treatment trial.

It studies healthy adults and focuses on physiological stimulus-response relationships rather than clinical outcomes.

A reproducible physiological response therefore cannot be described as therapeutic benefit.

Nor can its direction be assumed to be beneficial.

Changes in HRV, arterial pressure, respiration, EDA, pupil dynamics, or combinations of those signals have physiological meaning only within context.

Clinical efficacy requires separate studies in relevant populations using prospectively defined clinical outcomes and appropriate comparators.

20.2 It Cannot Establish a Specific Neural Mechanism

Natural motion changes several interacting sensory and physiological processes simultaneously.

A temporal association between head-centered motion and physiology does not prove that the vestibular system caused the response or identify the neural pathway through which it occurred.

Anatomical access and prior human vestibular experiments establish biological plausibility.

They do not convert a naturalistic association into mechanistic proof.

Controlled reproduction and manipulation are required to test causal dependence.

20.3 It Cannot Establish Increased "Vagal Tone"

As established in Section 8, HRV is not a direct recording of vagal nerve activity.

RMSSD and respiratory-linked cardiac variability can provide information consistent with changes in cardiac parasympathetic modulation under appropriate conditions. [11-13]

They do not quantify global vagal activity.

Similarly, anatomical projections between vestibular and autonomic brainstem regions establish access, not activation of a particular vagal efferent pathway during a natural-motion exposure. [1,3]

Phase 1 should therefore not report an HRV change as proof that motion "stimulated the vagus nerve."

20.4 It Cannot Establish Reduced or Increased Global Sympathetic Tone

Phase 1 does not directly record MSNA or SSNA.

EDA provides information about sympathetic sudomotor physiology, not generalized sympathetic activity.

Heart rate and arterial pressure are integrated cardiovascular outputs rather than direct sympathetic nerve recordings.

As established in Sections 4 and 10, different sympathetic effectors can dissociate.

Phase 1 therefore cannot convert changes in EDA, heart rate, blood pressure, or HRV into claims of generalized sympathetic activation or suppression.

20.5 It Cannot Establish "Autonomic Balance"

The autonomic nervous system is not represented by one validated scalar continuum in which sympathetic and parasympathetic activity move reciprocally.

The physiological measures used in Phase 1 represent different effector systems and regulatory processes.

There is no established combination of HRV, EDA, pupil diameter, respiration, heart rate, and arterial pressure that defines a universal state of "autonomic balance."

Phase 1 can characterize patterns.

It cannot label them globally balanced or dysregulated without independent validation.

20.6 It Cannot Establish That Natural Motion Is Superior

Phase 1 studies natural motion because the relevant stimulus characteristics are not yet known.

A positive natural-motion association would demonstrate that useful physiological structure can be identified in that environment.

It would not establish that natural vessel motion is necessary, optimal, or superior to simpler controlled stimulation.

Later reduction experiments may show that only a small subset of the natural stimulus is required.

That possibility is central to the research sequence rather than contrary to it.

20.7 It Cannot Establish an Optimal Waveform or Dose

Discovery of an association does not establish optimal stimulation parameters.

Phase 1 may identify candidate frequency ranges, magnitudes, axes, temporal structures, durations, or combinations associated with particular physiological responses.

Natural exposure does not manipulate those parameters independently.

It therefore cannot determine necessity, sufficiency, dose-response shape, minimum effective stimulus, optimal stimulus, or tolerability boundaries for a controlled intervention.

Those questions require controlled manipulation.

20.8 It Cannot Establish Causality From Dose-Response-Like Natural Variation

Natural motion may contain apparent relationships in which larger or more frequent stimulus features are associated with larger physiological responses.

Such gradients are scientifically useful.

They are not equivalent to experimentally controlled dose-response relationships because other characteristics of the exposure and participant state may vary simultaneously.

A formal dose-response claim requires deliberate manipulation under controlled conditions.

20.9 It Cannot Establish Effects in POTS or Autism

Phase 1 participants are healthy adults.

Its findings therefore cannot establish that the same responses occur in POTS, autism, or any other clinical population.

Sections 15 and 16 provide rationales for later disease-specific investigation, not permission to extrapolate Phase 1 effects directly to those populations.

Any disease-specific mechanism, tolerability profile, physiological response, or clinical effect requires direct study.

20.10 It Cannot Establish That Adaptation Is Therapeutic

Repeated exposure may change physiological response or motion-sickness susceptibility.

As established in Section 14, such changes may represent adaptation or habituation.

They do not establish improved autonomic function or clinical benefit.

A response that becomes smaller across sessions is not automatically a better response.

A participant who becomes more tolerant of motion is not thereby shown to have improved autonomic regulation.

20.11 It Cannot Establish That Behavioral Calmness Is Beneficial Regulation

Behavioral changes during motion may be important observations.

They are not mechanistically specific.

Reduced activity, eye closure, drowsiness, or reduced responsiveness can occur during sopite-related states, as discussed in Section 12. [22]

Phase 1 therefore cannot use apparent calmness as a surrogate for beneficial autonomic regulation.

Behavior and physiology should remain separately measured outcomes until their relationship is established.

20.12 It Cannot Establish a Validated Participant-Specific Prescription

Repeated measurements may reveal participant-specific response patterns.

That does not establish a clinically useful individualized motion prescription.

Individualization requires prospective evidence that participant-specific models predict future responses reliably and outperform simpler population-level approaches.

Phase 1 can identify candidate heterogeneity.

It cannot yet convert that heterogeneity into personalized dosing.

20.13 It Cannot Justify Closed-Loop Adaptive Control

Closed-loop control requires more than a measurable physiological response.

A controller needs a validated target, an interpretable response variable, known stimulus-response dynamics, acceptable latency, established tolerability constraints, and evidence that changing the stimulus in response to the measured state improves the desired outcome.

Phase 1 provides none of those elements conclusively.

It may identify candidate inputs and candidate outputs from which such a system could eventually be studied.

Adaptive control therefore remains an evidence-gated future objective.

20.14 It Cannot Eliminate Residual Confounding

The multimodal architecture measures several major competing influences.

It cannot measure every possible determinant of human physiology.

Unmeasured behavioral, psychological, environmental, and biological factors will remain.

Statistical adjustment cannot convert an observational natural-motion exposure into a fully controlled causal experiment.

Residual uncertainty should therefore remain explicit even when associations are strong.

20.15 It Cannot Replace Controlled Reproduction

This is the central evidentiary boundary.

A natural-motion association becomes mechanistically stronger only if the candidate stimulus can be reproduced under controlled conditions and the physiological response recurs.

Subsequent experiments can then manipulate, remove, simplify, or vary components to test necessity, sufficiency, interaction, and dose-response behavior.

Phase 1 identifies what should be reproduced.

It does not substitute for reproduction.

20.16 The Appropriate Evidentiary Ceiling

A successful Phase 1 can support the conclusion that:

specific characteristics of received natural motion are reproducibly associated with specific physiological responses under defined conditions and warrant controlled experimental testing.

It cannot support the conclusion that:

the motion is therapeutic, the response is beneficial, a particular autonomic pathway caused it, a clinical population will respond similarly, or an optimal treatment waveform has been identified.

Maintaining that distinction protects the scientific value of a positive discovery result.

The next section therefore states the SeaKing Solace vestibular-autonomic hypothesis in explicitly testable form, including the conditions under which the hypothesis should be weakened or rejected.

21. The SeaKing Solace Vestibular-Autonomic Hypothesis

The preceding evidence supports a testable research hypothesis rather than a therapeutic conclusion.

The SeaKing Solace hypothesis is that measurable characteristics of received vestibular motion may produce reproducible, stimulus-dependent changes in human physiology relevant to autonomic regulation, and that sufficiently robust natural motion-response relationships can be carried forward into controlled mechanical testing.

This hypothesis is evidence-gated.

Each stage depends on findings from the preceding stage, and failure at an earlier gate should weaken, modify, or stop progression toward later claims.

The sequence therefore moves from naturalistic association toward controlled mechanism testing only as the evidence permits.

21.1 H1: Natural Motion-Response Association

H1: Quantifiable characteristics of naturally occurring motion are associated with reproducible changes in measured physiological signals.

This is the foundational Phase 1 hypothesis.

Relevant physiological outputs include cardiac timing and HRV, respiration, beat-to-beat arterial pressure, electrodermal activity, pupil dynamics, and other prespecified measures.

H1 does not predict that every signal will change or that all signals will change in the same direction.

It does not assign therapeutic meaning to the response.

Support for H1 requires more than a difference between docked and underway conditions.

Measured characteristics of motion must provide reproducible information about physiological change.

If physiology changes during the voyage but those changes cannot be related reproducibly to measured motion, H1 is weakened.

21.2 H2: Head-Centered Exposure

H2: Head-centered received motion predicts physiological response more effectively than vessel motion alone.

Review 01 established that vessel motion and participant head motion are not necessarily equivalent.

H2 tests whether that distinction matters physiologically.

Support requires participant-level head-centered motion to provide meaningful explanatory or predictive information beyond vessel-level motion.

If vessel motion performs equivalently, the hypothesis that head-centered measurement is necessary for subsequent modeling should be weakened.

H2 therefore makes the proposed exposure architecture itself falsifiable.

21.3 H3: Parameter Dependence

H3: Physiological response depends systematically on measurable characteristics of received motion rather than on motion exposure as a unitary condition.

Candidate characteristics include frequency content, acceleration magnitude, axis or orientation, temporal structure, duration, and combinations of those features.

This hypothesis follows from the controlled human literature demonstrating stimulus-dependent vestibulo-autonomic responses. [7,31,33]

Support for H3 requires identifiable motion characteristics to predict reproducible differences in physiological response.

It does not require identification of an optimal waveform.

Parameter dependence establishes structure in the input-output relationship, not therapeutic optimization.

21.4 H4: State Dependence

H4: The relationship between received motion and physiological response is modified systematically by measurable participant state.

Human vestibulo-autonomic physiology is known to depend on context including posture and baroreflex state, while respiration, motion-sickness susceptibility, baseline physiology, and exposure history can further affect interpretation. [8,9,11,37,40]

Support for H4 requires state variables to explain reproducible differences in the motion-response relationship.

State dependence should not be invoked simply to explain inconsistent data after the fact.

It must itself demonstrate structure.

Repeated sessions are especially important here because they allow investigators to determine whether candidate relationships replicate under comparable states and whether changing state modifies those relationships systematically.

Participant-specific patterns may also emerge, but individualization should remain descriptive until those patterns predict future responses reliably.

21.5 H5: Controlled Reproduction

If H1 through H4 identify sufficiently strong candidate relationships, the next hypothesis becomes testable:

H5: A physiological response associated reproducibly with natural motion can be reproduced using controlled mechanical stimulation approximating the relevant received-motion characteristics.

H5 represents the critical transition from naturalistic association toward causal testing.

A candidate motion pattern identified during Phase 1 can be reconstructed under controlled conditions.

If the physiological response recurs, confidence in the physical stimulus-response relationship increases.

If it does not, the original association may depend on unmeasured elements of the natural environment, incorrect characterization of the relevant stimulus, or an unstable original relationship.

Successful reproduction therefore strengthens the hypothesis.

Failure of reproduction weakens or redirects it.

21.6 H6: Reduction and Component Testing

If controlled reproduction succeeds:

H6: The reproduced stimulus can be simplified and experimentally manipulated to identify which motion components are necessary, sufficient, or functionally relevant to the physiological response.

This stage tests the components of the candidate stimulus.

Frequency can be varied.

Magnitude can be varied.

Axes can be removed or isolated.

Temporal structure can be altered.

Duration can be changed.

Simpler waveforms can be compared with more complex ones.

The objective is not to preserve natural complexity by default.

It is to determine the minimum stimulus structure required to reproduce the response.

A component that can be removed without materially changing the response should not be retained merely because it was present in the original vessel motion.

Reduction is therefore a mechanistic test, not an engineering compromise.

21.7 H7: Adaptive Control, Only if Justified

If reproducible stimulus-response relationships, meaningful physiological targets, and participant-specific predictive structure are established:

H7: Real-time physiological feedback may improve control of the motion stimulus compared with a fixed protocol.

H7 is intentionally downstream.

Closed-loop control would require:

a validated physiological target;

a reproducible relationship between controllable motion parameters and that target;

a response timescale compatible with feedback;

sufficient signal quality to distinguish response from artifact and competing physiology;

and evidence that adaptation improves a prespecified outcome compared with a fixed or simpler protocol.

Technical feasibility alone would not support H7.

A fixed waveform or small number of predefined protocols may ultimately perform as well as or better than adaptive control.

Closed-loop stimulation must therefore earn its complexity empirically.

21.8 H8: Explicit Failure Condition

H8: If reproducible motion-response structure cannot be demonstrated, does not survive major competing explanations, or cannot be reproduced under controlled mechanical stimulation, the corresponding vestibular-autonomic hypothesis should be weakened, revised, or abandoned.

This is an explicit falsification condition for the research program.

Examples include:

* no reproducible physiological relationship with measured natural motion;

* head-centered motion providing no meaningful information beyond vessel motion;

* no systematic dependence on identifiable motion parameters;

* candidate responses explained more convincingly by respiration, visual context, motion sickness, or another measured process;

* failure of candidate relationships to replicate;

* failure of controlled mechanical reproduction;

* failure of component manipulation to produce predicted changes; or

* failure of later physiological targets to correspond to meaningful clinical outcomes.

Negative evidence is therefore not treated as an obstacle to be explained away.

It determines where the model should change.

21.9 Replication Is a Requirement Across the Hypothesis Chain

Replication is not a separate endpoint confined to one stage.

It is a requirement throughout the architecture.

Natural associations must recur.

State dependence must recur.

Participant-specific patterns must predict subsequent responses.

Controlled reproduction must reproduce the candidate physiology.

Component manipulations must generate repeatable changes.

A striking single observation therefore carries less evidentiary weight than a smaller but repeatedly observed relationship.

This principle prevents discovery-stage findings from advancing solely because they are large or statistically interesting.

21.10 Individualization Is Conditional, Not Assumed

Participant heterogeneity may prove important.

Some individuals may demonstrate reproducible response patterns distinct from group-level averages.

That does not automatically justify personalized stimulation.

Individualization becomes scientifically meaningful only if participant-specific information improves prediction of future response beyond simpler models.

The evidence sequence is therefore:

observe heterogeneity → demonstrate within-person reproducibility → predict future response → test whether individualized stimulus selection adds value.

Without predictive improvement, individual differences remain descriptive rather than prescriptive.

21.11 The Evidence Gates Form a Dependency Chain

The SeaKing Solace hypothesis can be summarized as:

H1 — Association

Natural motion characteristics predict physiological change.

↓

H2 — Exposure specificity

Head-centered received motion improves prediction beyond vessel motion.

↓

H3 — Parameter dependence

Specific characteristics of received motion predict specific responses.

↓

H4 — State dependence

Measurable participant state systematically modifies those relationships.

↓

H5 — Controlled reproduction

Candidate responses can be recreated under controlled mechanical stimulation.

↓

H6 — Reduction

Relevant stimulus components can be isolated, manipulated, and simplified.

↓

H7 — Adaptive control, if justified

Physiological feedback improves performance compared with simpler fixed approaches.

Alongside the entire sequence:

H8 — Failure condition

If a relationship fails the relevant evidentiary gate, the corresponding hypothesis weakens or stops progressing.

The sequence describes dependency, not inevitability.

21.12 The Architecture Prevents Premature Optimization

The hypothesis chain also establishes when optimization becomes scientifically meaningful.

A stimulus cannot be optimized before the relevant response has been identified.

A participant-specific stimulus cannot be justified before stable individual response structure has been demonstrated.

A feedback controller cannot be meaningful before both the target and the controllable stimulus-response relationship are validated.

The progression is therefore:

discover → replicate → characterize state dependence → reproduce → reduce → validate → optimize → individualize or adapt only if justified

Optimization is downstream of understanding.

21.13 Biomarker Discovery and Clinical Validation Remain Separate

The physiological variables measured during Phase 1 are candidate response measures.

They are not yet validated therapeutic biomarkers.

A physiological signal may predict motion exposure accurately without predicting clinical benefit.

A reproducible physiological difference in a disease population may not be causal.

And manipulating a biomarker may not improve symptoms or function.

Disease-specific physiology and later clinical outcomes are therefore separate evidence gates downstream of mechanistic reproduction.

21.14 The Hypothesis Should Become Narrower as Evidence Improves

The initial hypothesis is intentionally broad:

some measurable characteristics of natural motion may predict reproducible physiological responses.

If evidence accumulates, the hypothesis should become more specific.

A narrower frequency range may emerge.

Certain acceleration magnitudes may matter.

One or more axes may prove relevant.

A particular temporal pattern may reproduce the response.

Specific participant states may modify it.

A simpler controlled waveform may eventually replace the complex natural-motion representation.

That narrowing is a desired scientific outcome.

The objective is not to preserve natural-motion complexity indefinitely.

It is to identify the smallest defensible stimulus-response model supported by the evidence.

21.15 The Evidence-Gated Hypothesis

The full SeaKing Solace vestibular-autonomic hypothesis can therefore be stated as follows:

Natural multidimensional motion may contain measurable head-centered vestibular stimulus characteristics associated with reproducible physiological responses relevant to autonomic regulation. If those relationships demonstrate parameter dependence, temporal reproducibility, and interpretable state dependence, they can be tested through controlled mechanical reproduction and reduction. If specific controllable stimulus-response relationships are subsequently established, their disease-specific and clinical relevance can be evaluated. Adaptive or individualized control should be considered only if participant-specific information and real-time feedback demonstrably improve prediction or outcome. If the relationships fail at any of these evidentiary gates, the hypothesis should be weakened or revised accordingly.

Every stage is conditional.

The architecture does not assume that the entire chain will be supported.

It defines the sequence of experiments required to determine how far the evidence permits the hypothesis to progress.

Section 22 therefore turns this hypothesis chain into the practical progression from discovery to controlled testing.

22. From Discovery to Controlled Testing

The SeaKing Solace research program is intentionally staged.

Natural motion is used first because the physiologically relevant components of the exposure are not yet known.

Controlled mechanical stimulation comes later because simplification is most informative after candidate relationships have been identified.

Disease-specific and clinical testing come later still because a physiological response should not be treated as therapeutic before its reproducibility, mechanism, and clinical relevance have been established.

The progression is:

characterize → measure → associate → replicate → challenge competing explanations → reproduce → manipulate and reduce → establish dose-response → test target populations → evaluate clinical significance → consider individualization or adaptive control if justified

Each stage answers a question that the preceding stage cannot.

22.1 Characterize the Natural Exposure

The first requirement is to describe the physical exposure quantitatively.

Natural vessel motion is multidimensional and time varying, and vessel motion does not necessarily equal the motion received at the participant's head.

Phase 1 therefore begins with synchronized measurement of vessel and head-centered 6-DoF motion.

This preserves candidate characteristics such as frequency, magnitude, temporal structure, orientation, duration, and combinations of motion components.

At this stage, investigators should not decide in advance which component is the relevant stimulus.

The initial question is simply:

What motion did the participant actually receive?

Without that information, later physiological associations cannot be tied to a sufficiently defined exposure.

22.2 Acquire Synchronized Multimodal Physiology

The physical exposure must then be aligned with a sufficiently broad physiological record.

As established in Section 17, ECG, respiration, beat-to-beat arterial pressure, EDA, pupil dynamics, gaze and luminance context, environmental measurements, symptoms, and behavioral events provide complementary information.

The objective is not to create a composite autonomic score.

It is to determine which physiological systems change, when they change, and whether those changes occur in reproducible temporal relationship with the measured motion.

The question at this stage is:

What happened physiologically while that motion was being received?

22.3 Identify Candidate Motion-Response Relationships

Once exposure and physiology are synchronized, investigators can search for candidate relationships.

These may involve specific frequencies, acceleration magnitudes, temporal patterns, axes, combinations of axes, exposure durations, or participant states.

They may appear in one physiological channel or across several.

Discovery analysis should identify relationships that are sufficiently structured to deserve further testing.

At this stage, the finding remains an association.

The relevant question is:

Which characteristics of received motion, if any, predict measurable physiological change?

22.4 Replicate Before Advancing

A candidate association should not progress solely because it is statistically striking.

It should recur.

Repeated participant sessions allow investigators to determine whether similar received-motion characteristics are associated with similar physiological responses.

Replication can be examined within participants and, where appropriate, across participants.

A relationship that appears once and fails to recur under comparable conditions should receive less evidentiary weight.

A relationship that recurs gains credibility.

Replication is therefore an evidence gate between discovery and further development.

22.5 Challenge Major Competing Explanations

Replication alone does not establish mechanism.

A reproducible relationship may still reflect respiration, motion sickness or sopite-related physiology, posture, visual context, environmental change, participant behavior, adaptation, or another measured process.

The multimodal architecture therefore permits candidate motion-response models to be compared with plausible alternatives.

The question becomes:

Does received motion still provide explanatory information when the major measured alternatives are considered?

A relationship becomes stronger if it remains interpretable after those processes are characterized.

It becomes weaker if another measured pathway explains the response more convincingly.

22.6 Reproduce the Candidate Exposure Mechanically

If Phase 1 identifies a sufficiently strong and interpretable candidate relationship, the next step is controlled mechanical reproduction.

A simulator or motion platform can approximate the relevant physical exposure under more controlled conditions.

The first objective is reproduction, not immediate optimization.

The question is:

If the candidate motion exposure is recreated mechanically, does the physiological response recur?

A positive result strengthens the physical stimulus-response relationship.

A negative result suggests that the naturalistic association may depend on unmeasured features of the original exposure, incorrect characterization of the relevant stimulus, or an unstable original finding.

Controlled reproduction is therefore the critical bridge between discovery and stronger causal inference.

22.7 Manipulate and Reduce the Stimulus

Once a response can be reproduced, the stimulus can be decomposed experimentally.

Frequency can be varied.

Magnitude can be varied.

Axes can be removed, isolated, or recombined.

Temporal structure can be simplified.

Duration can be altered.

The central questions are:

Which components are necessary?

Which are sufficient under the tested conditions?

Which alter the response predictably?

This stage converts an observed natural association into a manipulable experimental system.

The objective should be to identify the minimum sufficient controllable stimulus rather than preserve natural complexity by default.

If a simpler waveform reproduces the same response, simplification represents scientific progress.

22.8 Establish Parameter and Dose-Response Relationships

Only after relevant stimulus components have been identified does formal dose-response testing become meaningful.

Vestibular “dose” is multidimensional.

It may involve frequency, magnitude, duration, axis, temporal structure, or combinations of these variables.

Controlled manipulation can determine whether changes in those parameters produce systematic changes in the physiological response.

A dose-response relationship should not be assumed to mean that more stimulation is better.

The response may be nonlinear.

A stronger stimulus may increase motion sickness or reduce tolerability.

The purpose is to characterize the response surface, not to maximize physiological change automatically.

22.9 Validate the Physiological Target Before Optimization

Optimization requires a meaningful target.

A reproducible HRV change is not automatically therapeutic.

An EDA response is not automatically desirable.

A pupil response is not automatically beneficial.

A multimodal physiological pattern may be scientifically robust without having clinical significance.

The research sequence must therefore distinguish:

reproducible physiological response

from

validated therapeutic target.

Only after disease-specific and clinical relevance are established does therapeutic optimization become justified.

22.10 Test Disease-Specific Physiology

Once a controllable stimulus-response relationship has been established in healthy participants, target populations can be studied more interpretabily.

For POTS, later studies can test whether vestibular-autonomic responses differ from controls and whether controlled stimulation alters relevant orthostatic cardiovascular physiology.

For autism, later studies can test whether controlled vestibular stimulation produces reproducible autonomic responses and whether those responses differ from appropriate comparison groups.

The first disease-specific question is therefore:

Does the candidate physiology behave differently in the target population?

That is distinct from the later question of whether changing that physiology improves symptoms or function.

22.11 Test Clinically Meaningful Outcomes

At the therapeutic stage, physiology alone is no longer sufficient.

A candidate intervention must ultimately improve outcomes that matter clinically.

A reproducible autonomic change may be mechanistically interesting without producing meaningful benefit.

Clinical studies therefore require prospectively defined outcomes appropriate to the target disorder, together with suitable comparators and tolerability assessment.

Only then can the physiological response begin to be interpreted as a therapeutic biomarker rather than simply a reproducible physiological effect.

22.12 Test Individualization Only if It Adds Predictive Value

Participant-specific response patterns may emerge during discovery and controlled testing.

Individualization should be pursued only if those patterns improve prediction or outcome beyond simpler approaches.

A fixed protocol may perform adequately.

A small number of stratified protocols may outperform fully personalized stimulation.

Or participant-specific models may add substantial value.

The relevant question is not whether people differ.

It is:

Does using participant-specific information improve prediction or outcome enough to justify additional complexity?

22.13 Adaptive Control Comes Last

Real-time adaptive control represents the furthest downstream stage of the current concept.

A closed-loop system would require:

* a validated physiological target;

* a reproducible controllable stimulus-response relationship;

* adequate signal quality;

* a response timescale suitable for feedback;

* defined tolerability constraints; and

* evidence that adaptation improves outcome compared with a fixed or simpler protocol.

Technical feasibility does not establish scientific necessity.

If fixed stimulation performs as well as adaptive stimulation, the simpler approach should remain preferred.

Closed-loop control should therefore earn its complexity through comparative evidence.

22.14 Each Stage Has a Stop Rule

The research program should not be interpreted as an inevitable progression toward a commercial device.

Each stage creates a decision point.

If no reproducible natural motion-response relationship appears, waveform development lacks a strong basis.

If candidate relationships are better explained by respiration, visual context, or sickness-related physiology, the model should change.

If controlled reproduction fails, the naturalistic relationship should be reconsidered.

If component manipulation shows that presumed elements are unnecessary, the stimulus should simplify.

If no meaningful dose-response emerges, optimization may not be justified.

If target populations do not show relevant physiology, disease-specific development should weaken.

If physiological changes do not correspond to meaningful clinical outcomes, therapeutic development should stop or redirect.

If adaptive control does not outperform fixed protocols, it should not be adopted merely because it is technologically possible.

These stop rules operationalize the falsification principle established in Section 21.

22.15 Discovery and Control Answer Different Questions

Naturalistic discovery and controlled stimulation should not be viewed as competing approaches.

They serve different scientific functions.

Natural motion is useful because investigators do not yet know which stimulus features matter.

Controlled stimulation is useful because candidate features can then be reproduced, isolated, and manipulated.

Discovery without control risks remaining associative.

Control without adequate discovery risks selecting the wrong stimulus in advance.

The two stages are complementary.

22.16 The Discovery-to-Control Progression

The full pathway can therefore be summarized as:

1. Characterize natural physical exposure
↓

2. Acquire synchronized multimodal physiology
↓

3. Identify candidate motion-response associations
↓

4. Replicate those associations
↓

5. Challenge major competing explanations
↓

6. Reproduce candidate exposure under controlled mechanical conditions
↓

7. Remove and manipulate stimulus components
↓

8. Establish parameter and dose-response relationships
↓

9. Test disease-specific physiology
↓

10. Test clinically meaningful outcomes
↓

11. Test individualization if participant-specific information adds predictive value

↓

12. Test adaptive closed-loop control only if it outperforms simpler fixed approaches

This progression is the operational form of the evidence-gated hypothesis developed in Section 21 and the canonical SeaKing Solace research architecture.

Its purpose is not to move every candidate forward.

It is to determine which observations survive increasingly demanding tests.

A candidate that fails at one stage should be weakened, revised, or stopped.

A candidate that survives becomes progressively more specific, controllable, and scientifically interpretable.

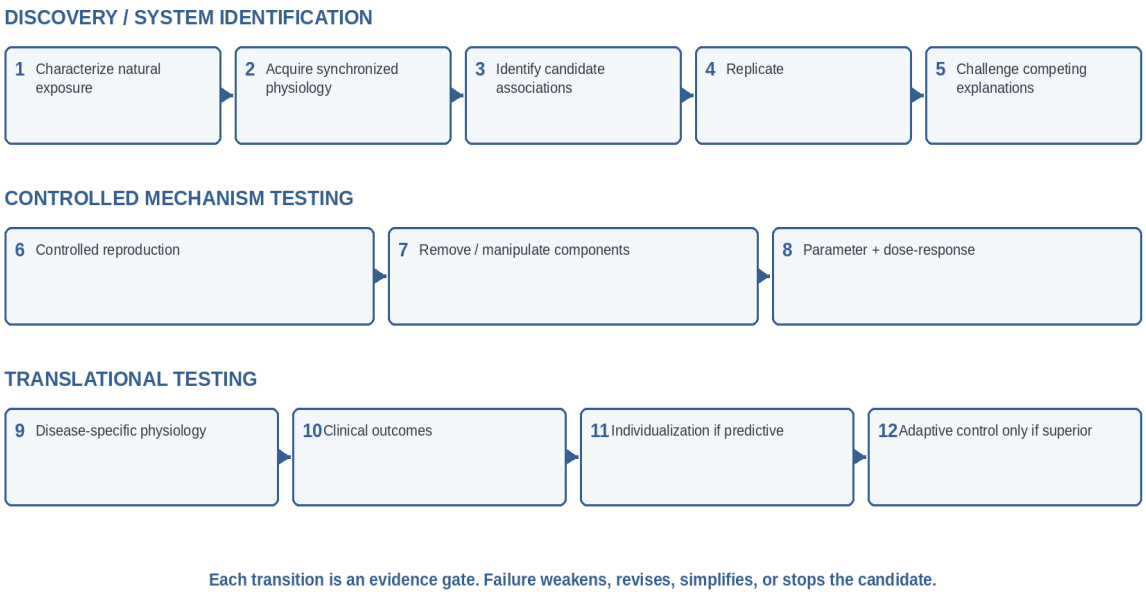


Figure 8. Discovery-to-control research progression. Natural characterization and synchronized physiology are followed by candidate identification, replication, challenge by competing explanations, controlled reproduction, stimulus reduction and manipulation, dose-response testing, disease-specific physiology, clinical outcomes, and only then individualization or adaptive control if each preceding evidence gate is satisfied. The sequence is conditional rather than inevitable.

The central principle is therefore:

the current evidence is sufficient to justify testing the hypothesis, but not to presume its endpoint.

The next section examines the limitations of the evidence base supporting this progression.

23. Limitations of the Current Evidence

The literature reviewed here establishes that vestibular input can influence human autonomic physiology.

It does not yet provide a complete account of how prolonged natural multidimensional motion interacts with autonomic regulation, nor does it establish the clinical significance of such interactions.

The limitations arise from the structure of the evidence base itself: many studies are small mechanistic experiments in healthy adults, experimental paradigms differ substantially, physiological

endpoints are heterogeneous, motion sickness can produce overlapping responses, naturalistic exposure limits causal inference, and disease-specific evidence remains incomplete.

These limitations do not negate the established physiology.

They define the questions that prospective research must still answer.

23.1 Much of the Direct Human Literature Uses Small Mechanistic Samples

Many of the strongest human vestibulo-autonomic studies use techniques such as microneurography that permit unusually direct physiological measurement but are technically demanding and resource intensive.

Consequently, sample sizes are often relatively small.

Small mechanistic studies can provide strong evidence that a physiological phenomenon exists, particularly when the stimulus is controlled and the output is measured directly.

They are less suited to estimating population heterogeneity, identifying stable subgroups, characterizing uncommon responses, or determining how broadly an effect generalizes.

This is particularly relevant to a system already known to be stimulus- and state-dependent.

23.2 Healthy Adults Dominate the Strongest Mechanistic Evidence

Much of the direct human evidence for vestibulo-sympathetic coupling comes from healthy adults.

That is appropriate for establishing basic physiology.

It limits disease-specific inference.

A vestibular-autonomic response demonstrated in healthy participants cannot be assumed to occur identically in POTS, autism, or another clinical population.

Baseline physiology, medication exposure, cardiovascular regulation, sensory processing, tolerability, and other participant characteristics may differ.

Healthy-adult studies therefore establish mechanistic plausibility and physiological capability, not clinical generalizability.

23.3 Experimental Paradigms Are Simplified and Heterogeneous

The literature uses multiple forms of vestibular perturbation, including galvanic stimulation, mechanical acceleration, positional paradigms, and caloric stimulation.

These approaches provide experimental control.

They are not physiologically interchangeable.

Frequency, magnitude, direction, duration, temporal structure, posture, and the manner in which vestibular pathways are engaged differ among paradigms.

As established in Sections 6 and 7, the response can depend on those differences.

The literature therefore supports general principles of vestibulo-autonomic coupling without providing one standardized stimulus-response function that can be transferred directly to prolonged natural motion.

23.4 Natural Prolonged Multidimensional Motion Is Poorly Represented in the Existing Literature

Controlled laboratory studies deliberately reduce complexity.

Natural vessel motion does the opposite.

It contains changing combinations of linear and angular acceleration, gravitational orientation, head movement, visual context, participant behavior, and prolonged exposure.

The current literature does not sufficiently characterize how autonomic physiology behaves under that complete exposure.

This is one of the central empirical gaps motivating Phase 1.

Existing mechanistic studies justify asking the question.

They do not answer it in advance.

23.5 Physiological Endpoints Are Heterogeneous and Non-Equivalent

Different studies measure different outputs.

Some record MSNA or SSNA directly.

Others measure heart rate, arterial pressure, HRV, respiration, EDA, skin blood flow, pupil dynamics, symptoms, or combinations of these variables.

These endpoints represent related but non-equivalent physiological processes.

A change in one cannot automatically be generalized to another.

Consequently, apparently different findings across studies may reflect both genuine physiological variation and differences in what was measured.

This heterogeneity limits attempts to describe vestibulo-autonomic response as one uniform phenomenon.

23.6 The Direction of Response Is Not Uniform

The current literature does not support a simple directional model.

Vestibular stimulation can produce different sympathetic, cardiovascular, and other physiological responses depending on the experimental conditions. [5,7-9,31,33]

This means that the evidence cannot presently support a universal claim that vestibular stimulation increases parasympathetic activity, decreases sympathetic activity, or shifts physiology toward a uniformly favorable state.

Direction must be interpreted in relation to the stimulus, effector, and participant state.

23.7 Noninvasive Autonomic Measurements Have Important Interpretive Limits

Several practical measures relevant to natural-motion research are indirect.

As established in Section 8, HRV is not a direct recording of vagal or sympathetic nerve activity, LF-HRV is not a specific measure of sympathetic tone, and LF/HF is not a direct measure of sympathovagal balance. [11,12,14,15]

Respiration materially affects interpretation of cardiac variability. [11,12,16]

EDA reflects sympathetic sudomotor physiology rather than global sympathetic activity. [17]

Pupil dynamics are influenced by autonomic pathways together with luminance, gaze, arousal, cognition, fatigue, and other factors. [18,19]

These measurements remain useful.

Their limitations mean that mechanistic conclusions require multimodal context rather than biomarker relabeling.

23.8 Motion Sickness Can Produce Overlapping Physiology

Motion sickness is a major source of interpretive ambiguity because it is itself a multisystem physiological response to motion.

Changes can occur in electrodermal activity, respiration, blood pressure, skin blood flow, sympathetic activity, symptoms, and behavior. [20,21]

Sopite syndrome further demonstrates that drowsiness, fatigue, reduced alertness, and autonomic changes can occur without prominent nausea. [22]

Accordingly, the absence of overt nausea does not establish that motion-related sickness physiology is absent.

Any natural-motion study that does not characterize sickness-related state risks attributing overlapping physiology to another mechanism.

23.9 Repeated Exposure Changes the System Being Studied

Repeated sessions improve the ability to test replication.

They also introduce adaptation.

Motion-sickness susceptibility can change over time, and autonomic response patterns may change or retain participant-specific structure. [39,40]

A difference between early and later sessions can therefore reflect adaptation, different received motion, altered baseline state, changing sickness susceptibility, or measurement variation.

Repeated exposure strengthens inference only when these possibilities are distinguished.

23.10 Natural-Motion Studies Have Fundamental Causal Limits

Natural exposure is valuable for discovery precisely because it preserves complex motion.

That complexity also limits causal inference.

Vestibular input, visual information, posture, respiration, participant behavior, environmental conditions, and sickness-related physiology can change together.

A statistical association between head-centered motion and physiology therefore does not establish that the vestibular component caused the response.

Multimodal measurement can narrow alternative explanations.

Temporal order can strengthen or weaken them.

Statistical modeling can improve prediction.

None fully substitutes for controlled manipulation.

The transition from association to stronger causal inference therefore requires controlled reproduction and component testing, as developed in Sections 21 and 22.

23.11 High-Dimensional Discovery Creates a Multiplicity Problem

Natural-motion datasets can contain many candidate predictors and outcomes.

Motion can be represented across multiple axes, frequency bands, magnitudes, temporal features, and derived metrics.

Physiological recordings add additional high-dimensional signals.

Participant state and contextual variables add still more.

With enough candidate relationships, apparently significant findings can arise by chance.

Discovery analyses must therefore remain distinguishable from confirmatory evidence.

Candidate relationships should be ranked, replicated, validated, and ultimately challenged under controlled conditions rather than accepted on the basis of an isolated statistical association.

23.12 Prediction Is Not Mechanism

Sophisticated statistical or machine-learning models may identify motion features that predict physiology accurately.

Predictive success does not establish that those features are causal.

A model can exploit correlated visual, respiratory, sickness-related, behavioral, or other features without distinguishing the biological pathway responsible.

Prediction is valuable for identifying candidate structure.

Mechanism requires experimental manipulation.

These should remain separate evidentiary outcomes.

23.13 Disease-Specific Evidence Remains Limited

The translational evidence is uneven.

POTS has preliminary direct evidence linking otolith-related vestibular measures with cardiovascular variability, but the findings do not establish causation, universality, or treatment efficacy. [23-25]

Autism has substantial literature describing group-level autonomic differences and sensory-autonomic reactivity, but the direct controlled mechanical vestibular-autonomic bridge remains largely untested. [26-28,41,42]

Neither literature currently establishes that vestibular stimulation produces clinically meaningful benefit.

23.14 Physiological Difference Does Not Establish a Therapeutic Target

Even when disease-specific physiological differences are identified, their biological role may remain uncertain.

A difference may be causal.

It may be compensatory.

It may be secondary to another process.

Or it may be clinically unimportant.

Changing a physiological marker therefore does not establish that the patient has improved.

A candidate autonomic response becomes a therapeutic target only when manipulation of that response is shown to influence outcomes that matter clinically.

23.15 Clinical Significance Has Not Been Established

This is the principal translational limitation of the current evidence.

The literature reviewed here does not establish that prolonged natural vestibular motion treats POTS, autism, or another clinical condition.

It does not identify a validated autonomic biomarker that mediates therapeutic benefit from such motion.

It does not establish an optimal therapeutic waveform or dose.

And it does not demonstrate that adaptive motion control improves clinical outcomes.

Those questions remain downstream of the current evidence.

23.16 The Appropriate Interpretation of the Evidence

Taken together, the evidence is strong enough to support a research program but not a therapeutic conclusion.

Vestibular-autonomic coupling is anatomically supported and directly measurable in humans.

Its expression is conditional on stimulus characteristics, physiological state, and the output being measured.

The literature is fragmented across paradigms, endpoints, and populations.

Prolonged natural multidimensional motion remains incompletely characterized as an autonomic exposure.

Disease-specific relevance is preliminary.

Clinical significance is unknown.

The current evidence therefore makes the SeaKing Solace hypothesis scientifically grounded but unresolved.

That distinction is the basis for prospective testing.

24. Conclusions

The evidence reviewed in this paper supports a clear and bounded conclusion:

vestibular-autonomic coupling is established human physiology, but the autonomic consequences of prolonged natural multidimensional motion remain insufficiently characterized to support causal or therapeutic conclusions.

Anatomical studies demonstrate vestibular access to brainstem autonomic circuitry, and direct human experiments demonstrate that vestibular stimulation can modify sympathetic nerve activity. Cardiovascular and other physiological studies further show that these responses interact with

posture, baroreflex state, stimulus characteristics, and the specific autonomic effector being measured. [1-9]

The unresolved question is not whether vestibular and autonomic systems interact.

It is how that interaction behaves under the natural exposure relevant to the SeaKing Solace research program.

24.1 What Is Established

The current literature establishes several findings relevant to that question.

Vestibular nuclei have anatomical access to brainstem regions involved in autonomic and cardiovascular regulation. [1-4]

Vestibular stimulation can modify directly recorded sympathetic nerve activity in humans. [5-7,30]

The resulting response is stimulus-dependent and state-dependent rather than uniformly directional. [7-9,33]

Different autonomic and physiological outputs can dissociate. [6,20]

And motion sickness, sopite syndrome, respiration, visual context, posture, participant state, and exposure history can overlap with or modify candidate responses. [20-22,40]

These findings provide the biological and methodological foundation for prospective study.

24.2 What Remains Unresolved

The existing literature does not establish how prolonged natural multidimensional head-centered motion maps onto human autonomic physiology.

It does not identify which motion characteristics, if any, are most physiologically informative.

It does not establish whether candidate natural motion-response relationships replicate within or across participants.

It does not determine whether natural complexity is necessary or whether a simpler controlled stimulus could reproduce any identified response.

And it does not establish the clinical meaning of the resulting physiological changes.

These are empirical questions.

24.3 Disease-Specific Relevance Is Plausible but Incomplete

POTS and autism illustrate two different translational rationales.

In POTS, normal vestibular participation in orthostatic cardiovascular regulation and preliminary disease-specific otolith-autonomic findings justify further mechanistic study. [23,25]

In autism, group-level autonomic differences and sensory-autonomic reactivity provide a rationale for investigating vestibular-autonomic response directly, but that direct mechanical bridge remains largely untested. [26-28]

Neither evidence base currently establishes treatment efficacy from vestibular stimulation.

Disease-specific physiological testing therefore remains a downstream experimental step.

24.4 Phase 1 Addresses the Natural-Motion Evidence Gap

Phase 1 is designed to determine whether measurable characteristics of received natural head-centered motion predict reproducible and temporally interpretable changes across synchronized physiological measures.

The study does not require every physiological signal to move together.

Nor does it assume a preferred direction of response.

Its central task is to determine whether reproducible input-output structure exists and whether major measured competing explanations account for that structure.

A positive result would identify candidate motion-response relationships suitable for controlled reproduction.

A negative result would weaken or redirect the hypothesis.

Both outcomes are scientifically informative.

24.5 Controlled Reproduction Is the Critical Next Evidence Gate

Naturalistic association cannot establish the complete causal mechanism.

If Phase 1 identifies reproducible candidate relationships, they must next be recreated under controlled mechanical conditions.

Successful reproduction would strengthen the physical stimulus-response relationship.

Subsequent manipulation and reduction could determine which components are necessary, sufficient, or functionally relevant.

Failure of reproduction would require reconsideration of the naturalistic interpretation.

Controlled testing is therefore the bridge from discovery toward mechanism.

24.6 Clinical Translation Requires Additional Evidence Gates

Even successful controlled reproduction would remain a physiological result.

Later work would still need to establish parameter and dose-response relationships, disease-specific physiology, tolerability, clinically meaningful outcomes, and whether participant-specific or adaptive approaches add value beyond simpler fixed protocols.

The research sequence therefore remains:

natural-motion discovery → replication → controlled reproduction → reduction and manipulation → dose-response → disease-specific physiology → clinical outcomes → individualization or adaptive control only if justified

No stage substitutes for the next.

24.7 Current Evidentiary Position

The state of the evidence can therefore be summarized in three categories.

Established: vestibular input has anatomical access to autonomic circuitry; vestibular stimulation can modify human autonomic physiology; responses are stimulus-, state-, and effector-dependent; and several candidate physiological measurements have known interpretive limitations.

Scientifically plausible and testable: prolonged natural head-centered motion may contain measurable characteristics that predict reproducible multimodal physiological responses, and sufficiently robust relationships may be reproducible under controlled mechanical stimulation.

Not established: that natural motion produces beneficial autonomic regulation; that it increases generalized vagal activity or decreases generalized sympathetic activity; that multi-axis natural motion is superior; that an optimal therapeutic waveform or dose exists; that vestibular stimulation treats POTS or autism; or that adaptive control improves clinical outcomes.

This distinction defines the appropriate present claim.

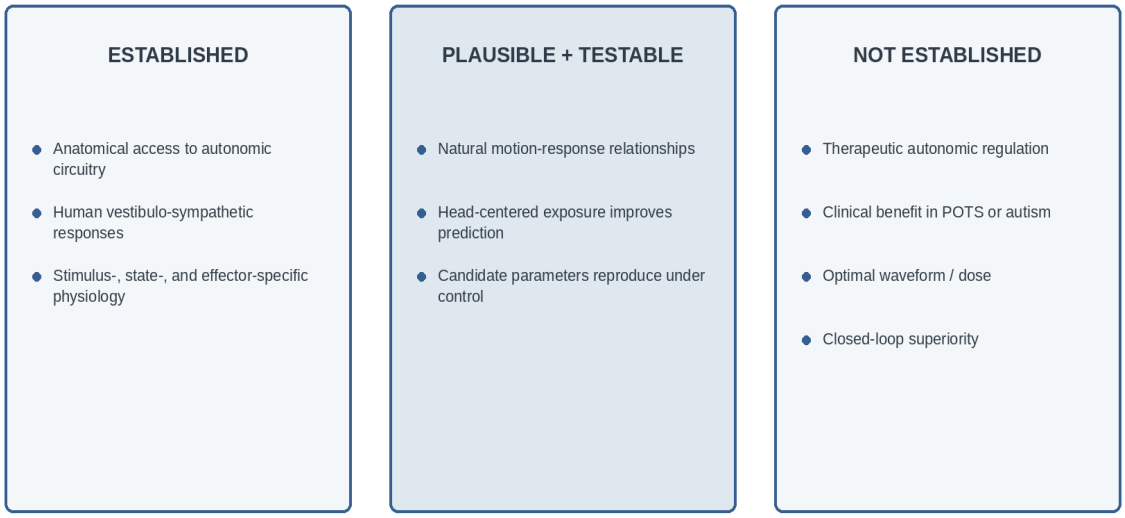


Figure 9. Current evidentiary position. Established science supports anatomical vestibular access to autonomic circuitry and measurable human vestibulo-autonomic responses with stimulus-, state-, and effector-dependence. It is scientifically plausible and testable that natural head-centered motion may contain reproducible physiological structure. Therapeutic benefit, generalized vagal or sympathetic effects, superiority of natural or multi-axis motion, an optimal therapeutic waveform or dose, treatment of POTS or autism, and benefit from adaptive control remain unestablished.

24.8 Final Conclusion

The SeaKing Solace vestibular-autonomic hypothesis is supported by established anatomy and direct human physiology, but its proposed natural-motion application remains unproven.

The current science is sufficient to justify a falsifiable experimental program.

It is not sufficient to presume the outcome of that program.

The central question is therefore:

Do measurable characteristics of the natural motion actually received by a participant predict reproducible, temporally structured, and physiologically interpretable responses that survive competing explanations and controlled reproduction?

If they do, the relevant stimulus can be progressively reproduced, simplified, manipulated, and tested for disease-specific and clinical significance.

If they do not, the hypothesis should weaken or change.

That is the present evidentiary position:

vestibular-autonomic coupling is established; the SeaKing Solace translational hypothesis is scientifically grounded and experimentally tractable; its clinical implications remain to be demonstrated.

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