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Are evolutionary hypotheses for motion sickness "just-so" stories?[1]

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Abstract. Vertebrates have evolved rapidly conditionable nausea and vomiting reflexes mediated by gut and brainstem receptors, clearly as a defense against neurotoxin ingestion. In 1977 Treisman proposed that sensory orientation linkages to emetic centers evolved for the same reason, and that motion sickness was an accidental byproduct. It was an "adaptationist" explanation for motion sickness, since it assumed that evolution has shaped all phenotypic traits for survival advantage. Treisman's "poison" theory is plausible, and frequently cited as the accepted scientific explanation for motion sickness. However, alternative explanations have been proposed. The creation of hypotheses is an essential part of science – provided they are testable. This paper reviews the evidence for the Poison theory and several other adaptationist explanations. These hypotheses are certainly not "just-so stories", but supporting evidence is equivocal, and contradictory evidence exists Parsimony suggests an alternative "pluralistic" view: The vertebrate reticular formation maintains oxygenated blood flow to the brain, discriminates unexpected sensory stimuli- including postural disturbances, and detects and expels ingested neurotoxins. The three systems share neuroarchitectural elements but normally function independently. Brainstem sensory conflict neurons normally discriminate brief postural disturbances, but can be abnormally stimulated during prolonged passive transport (e.g. by boat, beginning about 150–200 generations ago). Sensory conflict signals cross couple into the neurotoxin expulsion and avoidance system, producing an arguably maladaptive emetic phenotype.

Keywords: Motion sickness, nausea, vomiting, toxicosis, vestibular, evolution, adaptationism, pluralism

1. Introduction

What mechanisms evolved in humans and animals as a defense against ingested neurotoxins? How strong is the evidence that sensory orientation-emetic linkages evolved as an additional defense mechanism? Are there alternative evolutionary explanations for motion sickness that are verifiable and falsifiable?

Many plants, animals and microorganisms have evolved a wide variety of toxins that are used for predation or self-defense, and which act on the target species through absorption or ingestion. When vertebrates ingest toxins, they act locally in the gastrointestinal (GI) tract, or may be transmitted to other organs via the bloodstream. However vertebrates have also evolved mechanisms to detect and expel ingested toxins and prevent re-ingestion: Chemoreceptors in GI tract mucosa send signals via vagal and dorsal root afferents to the brainstem nucleus tractus solitarius (NTS) and dorsal vagal complex (DVC) [2,30,31]. Bloodstream toxins are detected by a brainstem chemoreceptor trigger zone (CTZ) and relayed to the NTS. Either type of chemoreceptive input acts on brainstem centers to trigger strongly aversive sensations (e.g. nausea in hu-

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mans). In most animals it also activates a retching and vomiting reflex, which expels the previously ingested food. Regions of the limbic amygdala and forebrain associate the smell and taste of the ingested food with the aversive sensation, even if the nausea sensation does not develop until several hours after ingestion. When the same smells or tastes are encountered again, the aversive reaction is triggered, even after a single trial – the phenomenon of conditioned taste (a.k.a. flavor) aversion [16]. The various GI, CTZ, olfactory and gustatory chemoreceptors, coupled through vomiting and limbic associative learning mechanisms, thus form multiple lines of defense against toxicosis, even in animals (e.g. rodents) who are physically incapable of vomiting. The evolutionary survival advantage of such mechanisms seems self-evident. It is not surprising that in the modern era, cancer chemotherapeutic agents or high radiation doses that also stimulate GI mucosal vagal afferents also cause nausea and vomiting. Opiates, nicotine and some surgical anesthetics also cause nausea and vomiting, but act centrally. It has been noted that women who experience nausea and vomiting during the first trimester of pregnancy have fewer miscarriages, and suggested that morning sickness and strong food cravings and aversions could have evolved to reduce maternal ingestion of pathogenic microorganisms or teratogens [29,58]. Some epidemiological and anthropological evidence supports the explanation [67].

The phenomenon of motion sickness is harder to explain in an evolutionary context. Why should certain real or apparent body motions or vertigo caused by vestibular disease lead to nausea and vomiting? Apparently only animals who completely lack vestibular function are completely immune. Susceptibility is not limited to humans, cats and dogs. Anecdotally a wide variety of vertebrate species, including birds and fish can be made motion sick [9,48]. Nausea and vomiting are physically disabling, so what possible survival advantage could be gained? Several different alternative explanations have been proposed. Perhaps the most widely known is the "Poison Theory", originally briefly suggested by Claremont [10], and later formally elaborated by evolutionary psychologist Michel Treisman [70]. Treisman asserted that motion sickness is "so obviously disadvantageous that, if there were no positive reason for its presence, natural selection should have acted strongly to eliminate it." He noted that "in some situations, for example, survivors on ocean rafts, it has certainly contributed to many deaths". To explain the mechanism, he invoked a variant of the conflict theory for motion sickness: "the systems involved in controlling movement, including eye movements, and determining the location of the body in space are complex, almost continually in action and are highly susceptible to even a minor degree of disruption. They constitute an ideal warning system for detecting early central effects of neurotoxins when these have not activated more basic levels of defense", particularly in unspecialized feeders who eat both plants and carrion. He postulated that a spatial orientation-emetic linkage provided survival value, and that nausea and vomiting in response to motion was "an accidental byproduct of this system". Treisman acknowledged that motion sickness could be "a neutral side effect of a beneficial gene or genes". Nevertheless he believed that motion sickness "implies the existence of direct or indirect pathways between the visual and vomiting centers which represent a biological investment that is difficult to think of as arising as an accident."

Treisman's 1977 Science article has since been widely cited as the evolutionary explanation for motion sickness in the popular literature. Evolutionary psychologist Steven Pinker [57] – an advocate of testable evolutionary hypotheses – explained that motion sickness could be like "the problem faced by Ingrid Bergman in *Notorious*: when you've eaten poison, how do you know? Your judgment would be addled, but that would affect your judgment about whether your judgment has been addled! How can a malfunction detector distinguish between the brains malfunctioning and its accurately registering an unusual situation? (Old bumper sticker: the world is experiencing technical difficulties. Do not adjust your mind). Gravity, of course, is the most stable, predictable feature of the world. If two parts of the brain have different opinions about it, chances are that one or both are malfunctioning. . . The rule would be: if you think gravity is acting up, you've been poisoned: jettison the rest of the poison now".

Treisman's poison hypothesis is plausible, but is it testable? If so, how compelling is the evidence? Are there alternative evolutionary explanations for motion sickness that should be considered? Are these verifiable and falsifiable?

2. Adaptatationism, pluralism, and just-so stories

In *Origin*, Charles Darwin [13] cautioned: "We may sometimes attribute importance to characters [phenotypes] which are really of very little importance, and which have originated from quite secondary causes, independently of natural selection. . . If green woodpeck-

ers alone had existed, and we did not know that there were many black and pied kinds, I dare say that we should have thought that the green color was a beautiful adaptation to hide this tree-frequenting bird from its enemies"

"Adaptationism" is the hypothesis that natural selection is the only important factor driving the evolution of morphologic, physiologic, or behavioral traits. The alternative view, "pluralism", accepts natural selection as a major factor driving evolution, but argues that developmental constraints and nonadaptive side consequences of genetic change determine many important traits. These terms derive from scientific debates beginning in the 1860s, later notably involving pluralist S. Wright [75], and adaptationist R.A. Fisher [15]. Many contemporary vestibular physiologists may be unaware of the debate. Adaptationism was a foundational concept in the fields of evolutionary psychology and sociobiology in the 1970s. However, critics in the fields of paleontology, evolutionary biology and genetics, notably S.J. Gould [20,21] argued against doctrinaire adaptationism and for a pluralist approach. In retrospect, it seems clear that Darwin was a pluralist. The evidence for the theory of natural selection comes from the breadth of the evidence for it. In a recent review of the debate, Orzack and Forber [56] note that we can't legitimately reverse the theory and conclude that natural selection necessarily drove the evolution of a particular trait just because we have some plausible hypothesis in mind. Certainly the generation of alternative plausible evolutionary hypotheses is an essential part of science. Any valid scientific hypothesis – adaptationist or pluralist – should be potentially verifiable and falsifiable. Unfortunately, finding evidence can be difficult, because we largely lack access to evolutionary history. Hence evolutionary hypotheses are typically underdetermined (in the mathematical sense) by the available evidence. Competing hypotheses are often empirically indistinguishable given the facts available. Sometimes a hypothesis will explain portion of the evidence, but not all of it.

Adaptationist hypotheses that do not meet this test of verifiability/falsifiability are arguably naïve speculation [20] and are frequently called "just-so stories", after Rudyard Kipling's fanciful children's tales [37] (e.g. "How the leopard got his spots"). For a testable hypothesis to be accepted as proven, it should have ample supporting evidence, and no strong contradictory evidence should exist. Thirty five years after Treisman proposed it, how compelling is the evidence for the "Poison Theory"? Are there alternative explanations for motion sickness which are verifiable and falsifiable?

2.1. Supporting evidence

There is evidence that susceptibility to motion sickness has a genetic basis. Experiments show susceptibility is higher in Asians [38,68]. Surveys suggest susceptibility runs in families [1]. Heritability in identical twins is around 57% [3,18,61]. Increased human autonomic response to motion sickness and other stresses has been correlated with polymorphism of a chromosome 10 gene encoding brain stem alpha 2 adrenergic receptors [14]. On the other hand, the fact that motion sickness has a genetic basis is not evidence for vestibular involvement in the emetic response to poisons.

Treisman offered several lines of evidence in support of the poison hypothesis. One was that "infants and young puppies appear not to be susceptible [to motion sickness]. This is consistent [with the poison theory] since young mammals are fed on milk or preselected food which is unlikely to be toxic, and also often exposed to random movements when carried." While the lack of susceptibility of younger animals is consistent with the theory, it hardly proves it. The lack of susceptibility in infants could alternatively be attributed simply to the immaturity of the infant's spatial orientation mechanisms [60].

A second point of evidence was that vesibulectomy renders humans and animals immune to motion sickness. Money and Cheung [47] pursued this experimentally by performing an experiment in seven dogs to see whether vestibulectomy rendered them immune to intramuscular injections of five different poisons, as well as to swing tests of motion susceptibility. Vestibulectomy rendered the dogs immune to swinging, and did increase the latency time to vomiting for three of the drugs (lobeline, levodopa, and nicotine). Money and Cheung argued by analogy that "if a foot were surgically removed and it was observed that walking was then impaired, it could be concluded that the foot is part of the normal mechanism for walking. . . ". They therefore concluded "the inner ear is part of the normal mechanism for vomiting in response to poisons". Nevertheless, does this evidence "prove" the poison theory? Why were two of the agents evaluated (pilocarpine and apomorphine) ineffective? It was not shown that physiologic doses of the agents tested affect the discharge rate or sensitivity of primary vestibular neurons [74], or that they respond much more quickly than CTZ or gut receptors, as posited by the Poison hypothesis. Note also that labyrinthectomy did not abolish vomiting in any dog to any of the poisons used. Therefore, in all cases, vomiting must have been partially due to

non-vestibular emetic pathways. The removal of tonic vestibular emetic input could simply be disfacilitating central emetic neuronal circuitry [76].

2.2. Contradictory evidence

If the ingestion of poisonous plants or animals by humans and animals causes nausea and vomiting due to early direct effects on the vestibular organs, then nausea and vomiting also ought to be relatively consistently associated with symptoms and signs specifically attributable to the vestibular system (e.g. vertigo, nystagmus, circling and falling) as opposed to lightheadedness and nonspecific dizziness (e.g. due to histamine poisoning), or muscle weakness and ataxia (e.g. due to blocking of muscle neuromuscular junctions by botulinum toxin). Auditory symptoms e.g. tinnitus or hearing loss might also be anticipated, since the auditory and vestibular systems are homologous, sharing common hair cell transduction and encoding mechanisms. National authorities track food borne illnesses in humans and animals, and considerable data is available on food borne viruses, bacteria, fungi, algae and protozoans, how they are spread in food in water, and the toxins and symptoms they produce [44]. Also, poisonous plant searchable online databases have become available for medical and veterinary use [39,50,71]. Ingestion of poisonous plants by humans and animals readily causes a constellation of symptoms directly attributable to gut and CTZ chemoreceptor inputs to the NTS vomiting pathways. These include nausea, food aversion, vomiting, fatigue, chills, lightheadedness, headache, flushing, cold sweating. A second constellation of symptoms commonly results due to direct neurotoxic effects on organ or circulatory systems: diarrhea, abdominal cramps, facial tingling and numbness, fever, tremor, double vision, muscular pain and weakness, respiratory and kidney failure, convulsions, hallucinations, coma, and death. Of all the symptoms in these two categories, nausea, vomiting, diarrhea, cramping and fever are by far the most common. A third constellation of symptoms attributable to vestibular stimulation – nystagmus, true vertigo, spinning, falling are rare, sometimes reported after reef or shellfish poisoning or ingestion of certain mushrooms. Symptoms generally occur late in the progression. Tinnitus is not reported. The general absence of specific vestibular and auditory symptoms after poisonous food ingestion by humans and animals thus does not support Treisman's Poison Theory.

2.3. Alternative adaptationist theories

Since the evidence supporting the Poison Theory is not compelling, are there alternative evolutionary explanations for motion sickness, and are these distinguishable, verifiable and falsifiable?

Several authors have proposed what can be termed "negative reinforcement" theories: Watt [74] noted that certain types of sustained active motions, such as rapid rhythmic voluntary rotation of the entire torso, head and gaze together through large angles elicited motion sickness within many subjects within a half hour. Transient aftereffects included transient oscillopsia, postural instability and VOR gain changes. Watt argued that the disordered postural, locomotor and gaze control strategies induced by these motions would be hazards to survival, and that motion sickness susceptibility evolved specifically to discourage such motions. Nausea arguably has survival value in a manner analogous to pain, in that it provides negative reinforcement for the activity that causes it. Why nausea rather than pain was elicited, or whether all other stimuli that cause motion sickness also transiently disorder postural, locomotor or gaze control strategies were not considered. Guedry [23] argued that motions which produced vestibular sensory conflict were "inefficient" and that motion sickness susceptibility evolved so such movements would be avoided. However, no evidence on this point was offered. Bowins [8] subsequently proposed a similar idea, arguing that postural instability due to sensory conflict or inner ear disease increases the risk of injury or vulnerability to predators. He also hypothesized that prostration due to motion sickness is protective – though he offered no evidence to this debatable [76] assertion. Bowins noted that infants are unsusceptible to motion sickness, because they lack the capacity to remove themselves from motion. As a putative test of the theory, Bowins predicted that motion sickness susceptible humans or animals will elect to voluntarily terminate provocative motions earlier than the non-susceptible. The prediction is plausible – indeed almost inescapable. However, it doesn't seem a valid test of the evolutionary aspect or the hypothesized relationship between postural instability and predation. Riccio and Stoffregen [62] found evidence that motion sickness and postural instability were causally related, though they deliberately chose not to speculate on why the symptoms of motion sickness are what they are. Whether postural instability is in fact necessary or sufficient to account for motion sickness has been debated [6,73].

Rupert [65] recently proposed an "intestinal contraction" theory, observing that normal movement of food through the small intestine is critical for survival, and hypothesized that digestion is critically disturbed by whole body accelerations at frequencies of 9–12/min, which happen to be the normal segmental contraction frequencies in the ileum and duodenum, respectively. He speculated that the otolith organs may act as a sentinel for motion at these frequencies, slowing emptying and eventually causing vomiting. He noted that 9–12 cycles/min is also the frequency of maximum motion sickness susceptibility to ship motion. Whether or how digestion proceeds among sailors adapted to motion these frequencies was not addressed. The "intestinal contraction" hypothesis does not account for motion sickness produced by semicircular canal or visual stimulation alone.

To illustrate another plausible adaptationist alternative to Treisman's theory, I once offered a "rock-a-bye, baby" hypothesis [51]: In adult humans, drowsiness ("sopite syndrome") is sometimes the earliest manifestation of motion sickness, and often the only one during long low level motion exposure [22]. Throughout history, parents have successfully rocked their babies to sleep. Why should rocking make newborns sleepy? One plausible explanation is that human fetuses begin to make self-generated movements during in the first trimester. The developing fetal nervous system learns to anticipate the vestibular and haptic consequences of its own head and body movements. Presumably this would be far easier when the mother was not moving herself. If mechanisms involved in movement control and sensorimotor learning in the developing fetus (e.g. the sensory-motor conflict mechanisms reviewed in the next section) also linked to reticular formation centers driving hypothalamic sleep switch neurons, so that the fetus tended to be awake and moving primarily when the mother was asleep, it would promote sensorimotor learning. Fetal activity is indeed in opposite daily phase to that of the mother [36]. This "rock-a-bye, baby" hypothesis plausibly could account for sopite syndrome during passive motion in the adults as a vestige of this fetal developmental phenotype. However it does not readily explain nausea and vomiting in the adult, i.e. as an adaptationist explanation, it can only account for the drowsiness component of the adult phenotype.

2.4. *Sensory-motor conflict theory: A pluralistic alternative*

Most early physicians presumed that motion sickness was due to mechanical stimulation of visceral organs or motion induced changes in cerebral blood flow [60]. Beginning in the 1880s, the essential nature of vestibular sensory input and the contributory role of visual cues were acknowledged [32,34]. Since normal body movements never make people sick, Claremont proposed that the essential stimulus was "due to the unaccustomed conflict between sensations normally combined in other ways" [10]. Such "inter-modality" conflict ideas explained – at least in a notional way – why wearing vision distorting spectacles or watching a wide screen movie could make some people nauseous [60]. Nevertheless , Reason [59] subsequently rejected the "inter-modality" conflict theory, noting that the signals from the eyes and inner ear were inherently coded differently, and that inter-modality theories could not account for the relative immunity of drivers and pilots as compared to their passengers. Building on von Holst and Mittelstaedt's "reafference principle [28] and Held's "sensory rearrangement" theory [26], Reason [59] hypothesized that each time a movement is made, the brain consults a "neural store" of previously experienced movement command and sensory afference "trace pairs". The afferent trace that was closest to the current motor command (corresponding to the "efference copy" signal of von Holst), was neurally subtracted from incoming sensory afferent information. It cancelled the "reafferent" component of sensory input due to self-generated movement, leaving only the "exafferent" or "sensory conflict" signal, coding the motorically unanticipated component of sensory information. Hence if head movements are made under conditions of "sensory rearrangement" (e.g. living in weightlessness, hypergravity or a rotating environment, or wearing prism glasses) which change the rules normally relating body movement and sensory return, it should create sensory conflict and hence motion sickness. Reason argued that a "neural mismatch" signal proportional to sensory conflict had the functional purpose of initiating sensory-motor learning. If this mismatch signal was large and sustained, motion sickness resulted. This would only happen under conditions of sustained passive movement (e.g. in boats, cars, and airplanes) or sensory rearrangement (e.g. when in weightlessness or a rotating environment). Reason acknowledged Treisman's theory, but noted that "motion sickness is not an inevitable consequence of the human condition: if we had remained as self-propelled animals content to stay within our normal Earth gravity environment, the problem would not have arisen". Treisman hypothesized that the essential conflict was determined by the "previously established correlation" between sensory

inputs rather than "between the present pattern of input and past experience" as argued by Reason. Of course Treisman's "correlation" must have its origin in past experience, so Treisman's and Reason's hypotheses were fundamentally similar.

In 1982 [52], I extended Reason's "neural mismatch" theory to a formal bio-mathematical model that also included emetic linkage mechanisms. The model posited the existence of three classes of sensory neurons: 1) sensory afferents, 2) neurons coding sensory conflict early in the sensory processing pathway, and 3) internal model interneurons, coding various aspects of head and body orientation, and driven by sensory conflict neurons. I argued on control theoretic grounds that internal model interneurons normally drove both perceptions and motor outflow, and that the functional purpose of sensory conflict neurons was to detect external disturbances to movement. Conflict neurons add a corrective component to internal model interneuron responses, thereby also initiating corrective motor outflow [52–55]. The internal model interneurons also predict the reafferent component of sensory information, which subtractively cancels incoming sensory afferent signals. High levels of sensory conflict modify internal model neuron responses to subsequent sensory stimuli, mimicking Reason's sensory-motor learning scheme. Sensory conflicts would be produced not only by conditions of sensory rearrangement, as Reason proposed, but also by any unanticipated disturbance to head movement. Since the model proposed that the primary functional role of sensory conflict signals was in body movement control, rather than in creation of motion sickness, it has since become known as the "sensory-motor conflict theory". From a control/estimation theory perspective, sensory conflict neurons and internal model interneurons function as a body orientation estimator ("Observer"). The Observer modeling approach defined in [52,54] was subsequently extended to predict multi-sensory orientation in a variety of experiments [7, 25,45,46,72].

At the time, there was no physiological evidence that sensory conflict neurons actually existed. Based on the theory, in 1990 I enumerated the response properties that sensory conflict neurons should have, such that a physiologist who compared active and passive responses could look for them [53]. In those days, animal studies of vestibular nucleus neurons utilized only passive motion stimuli, so it was not surprising that neurons in the first two classes (conflict neurons and internal model interneurons) could not be experimentally distinguished from each other in the brainstem. I noted that efference copy neurons that exactly cancelled sensory reafference (as von Holst had proposed [28]) might not be found, since the cancellation effect could be distributed across several parallel neural pathways [52]. Although Reason suggested that visual and haptic sensory conflict neurons might exist, I noted that visual or haptic afferent stimuli could produce vestibular sensory conflicts indirectly [53]. Debate continued as to whether the essential conflict causing motion sickness was the result of cancellation of incoming sensory signals, as von Holst, Reason and I had proposed. Others argued that the essential conflict could equivalently be between competing internal estimates of orientation [7, 70,79], motor outputs, or that all conflict notions were unproven reifications [69].

Fortunately, the important question of whether brainstem sensory conflict neurons actually exist is now being resolved. Beginning a decade ago, several laboratories began to compare responses of vestibular afferent and brainstem vestibular nucleus neurons during active and passive movement [43,63]. The findings have important implications for understanding vestibular function at all levels. It was demonstrated that reafferent cancellation of semicircular canal [12] and otolith [33] input did not take place via efferent cancellation in the vestibular periphery itself. It makes sense to look for sensory conflict neurons in the early stages of sensory processing in the brainstem reticular formation, since this region is part of the vertebrate attention and arousal system, where unanticipated sensory signals are discriminated from irrelevant stimuli. Cullen and coworkers have recently demonstrated a class of semicircular canal [11,64] and otolith (Cullen, personal communication) driven second order "vestibular only" ("VO") neurons in Rhesus vestibular nucleus that respond during passive head movement but not during corresponding active motions. Passive head movements typically result from external disturbances to posture or locomotion gait and normally require a corrective response. Cullen et al. argue [64] that reafference must be cancelled by signals originating in an internal model – which they speculate may be located partly in the cerebellum. Numerous anatomical connections from vestibular nucleus to NTS are known to exist [4]. However, we do not yet have a physiological definition of motion sickness, since it has not yet been shown that Cullen's specific VO sensory conflict neurons project to NTS emetic control regions, and that when these VO neurons are directly stimulated, emesis results.

Other vestibular nucleus interneurons code head orientation and gravitoinertial acceleration, and contribute

to a second major homeostatic function of the reticular formation: maintaining adequate oxygenated blood flow to the brain during changes in body posture. These can thus be classified as internal model interneurons rather than sensory conflict neurons, since they must respond during both active and passive movement. They project to brainstem cardiovascular and respiratory control neurons in the nucleus of the solitary tract (NTS) and contribute to orthostatic regulation [4]. Receptors from skin, muscle and viscera contribute to this process as well [35].

Brainstem pattern generators normally produce rhythmic signals for breathing, swallowing, and movement. What are the characteristics of the vestibular-emetic linkage? The sensory-motor conflict theory posits that brainstem pattern generator cell groups are stimulated by sensory conflict neurons by an as-yet-unidentified overload coupling mechanism, and when sufficiently stimulated, the pattern generators switch from normal mode and become vomiting pattern generators. The pattern generators alter the phase of their drive to respiratory motor neurons, co-contracting the diaphragm, intercostal and abdominal muscles and closing the glottis during expulsion to prevent aspiration of vomitus [42]. Conversely, respiratory motor neurons apparently influence vomiting pattern generators, since regular controlled breathing can somewhat delay symptom onset [77].

Since the CNS internal model's prediction of reafferent sensory input is doubtless imperfect, some low level of sensory-conflict is presumably always present in daily life, and does not elicit motion sickness symptoms. Larger conflicts arise each time an animal unexpectedly stumbles or falls, but these intervals last seconds or less. Only in the rare situation where an animal is moved passively for many minutes and conflict signals are sustained at high levels is the emetic NTS neurocircuitry somehow activated. To account for the absence of symptoms for the brief sensory conflicts of normal life, for the delayed appearance and symptom crescendo under conditions of prolonged conflict, and for increased sensitivity to repeated intervals of nauseogenic stimulation [5,19], the vestibular-emetic linkage portion of the formal model included a nonlinear "leaky integrator" followed by a threshold. These emetic linkage elements were a "black box" model, but could correspond to abnormal neurotransmitter leakage at high conflict levels only encountered during sustained passive (real or apparent) movement. The peripheral autonomic response pattern associated with motion sickness is abnormal also: it does not fit the normal "fight or flight vs. rest and digest" autonomic synergy seen in other responses to stress [66].

It is significant that drugs which have proven effective against motion sickness are relatively ineffective against other stimuli, and conversely. Exposure to radiation and cancer chemotherapeutic agents release serotonin which stimulates the NTS directly via vagal afferents and the CTZ by blood-borne transmission. Selective 5-HT3 receptor antagonists (e.g. ondanestron, palonosetron) and/or Substance-P/Neurokinin$_1$ receptor antagonists (e.g. aprepitant) are effective against these stimuli, but have little effect against motion sickness [27,31,41]. Effective anti-motion sickness drugs include centrally acting antihistamines (e.g. dimenhydrinate, meclizine, promethazine), muscarinic anticholinergics (e.g. scopolamine) and certain sympathomimetics (e.g. amphetamine, ephedrine) [76]. The implication is that the vestibular conflict linkage to the vomiting pattern generators acts downstream of the serotonergic NTS and CTZ emetic inputs. Associative learning mechanisms involving serotonin release due to toxins in the GI system are ubiquitous – and not unique to vertebrates. Even the soil nematode C. Elegans modifies its feeding preferences after exposure to pathogeneic bacteria via a serotonergic associative learning mechanisms [78]. After repeated nauseogenic motion exposure, humans can develop anticipatory nausea and vomiting ("I feel sick at the sight of a boat"), but this syndrome is driven by association centers in amygdala and forebrain, and presumably does not activate vestibular sensory conflict pathways. Thus the spatial orientation dependent and toxin dependent drives to the emetic system apparently evolved using largely different sensory neurotransmitter systems.

The foregoing ideas are summarized in Fig. 1. The top half of the diagram schematizes the neurotoxin defense system, where toxins act on serotonergic gut receptors and the brainstem CTZ to activate vomiting mechanisms and produce nausea. Amygdala and forebrain centers can retrigger nausea and vomiting when olfactory and gustatory stimuli previously associated with toxin ingestion are reencountered. The lower half of the diagram depicts how motion cues normally act through vestibular and other sense organs and a cerebellar internal model to create brief vestibular sensory conflicts, and in concert with the internal model, determine orientation perception and create the appropriate ocular, postural muscle and cardiorespiratory autonomic responses to maintain brain blood flow. Portions of these two neurotoxin defense and movement control systems are anatomically collocated in the brainstem

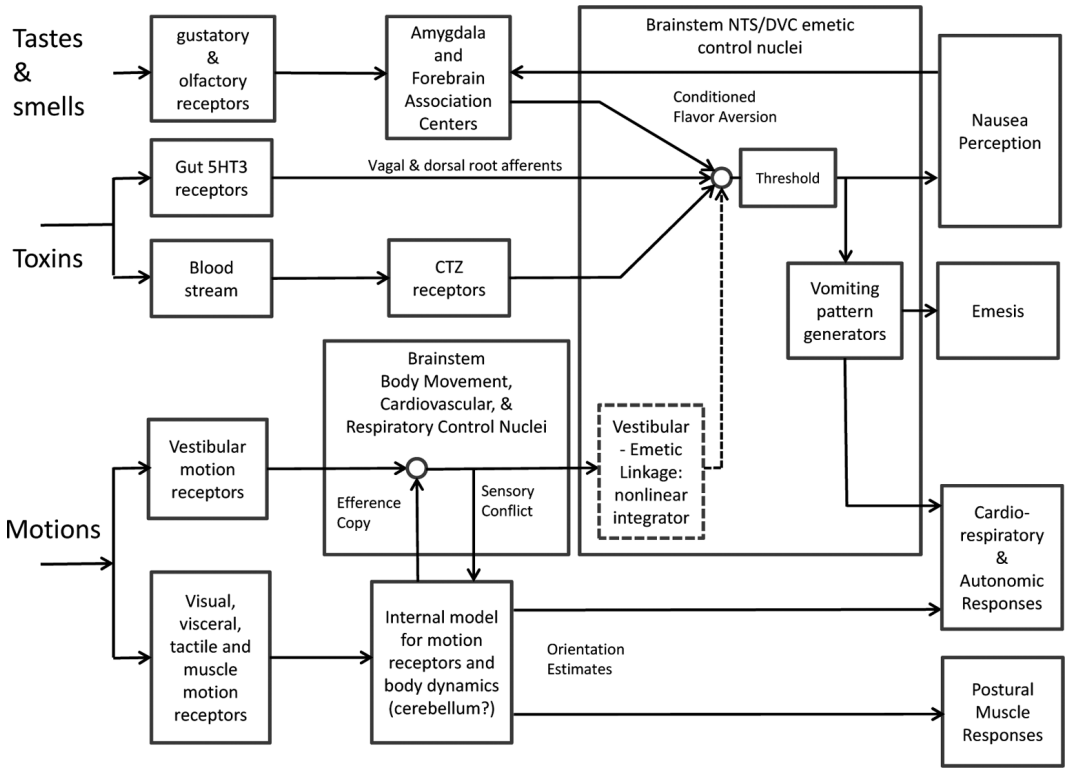

Fig. 1. Schematic of the interactions between limbic/forebrain associative learning centers, the brainstem neurotoxin defense mechanisms, and the body movement and cardiorespiratory control systems. The vestibular-emetic linkage (dotted box and line) is activated at abnormal levels only during prolonged periods of unnatural passive body movement. See text for details.

reticular formation, but normally function separately. Each conveys a separate survival advantage. Sustained exposure to passive motion was arguably first encountered by humans 3000–5000 years (150–200 generations) ago after humans invented boats and began to ride domesticated animals. Today we encounter it frequently in trains, autos and aircraft. The model postulates that vestibular conflict always stimulates the emetic system, but at sub threshold level. When conflict level is sustained for several minutes, the threshold is exceeded and vomiting pattern generators are stimulated. The vestibular-emetic linkage is shown as the dotted path in Fig. 1. The emetic drives are assumed to share a common threshold, since individual susceptibility to chemotherapy, anesthesia, morning sickness, migraine and motion sickness are moderately correlated (e.g. [17,40,49]) and aversive smells and tastes or toxins act to intensify motion sickness, and vice versa. The emetic linkage threshold level is high enough so that sickness does not occur during the normal active body movements of everyday life. Anti-motion sickness drugs do not modify vestibular afferent responses – they probably act on the vestibular -emetic linkage or raise the overall emetic threshold. Unfortunately none are sufficiently effective to make most people completely immune to strong stimulation. There is considerable evidence (e.g. [24,60]), that the most important component of motion sickness adaptation is achieved via continued exposure to sensory rearrangement and sensory-motor learning, which presumably gradually alters internal model neuron responses and reduces vestibular sensory conflict.

The sensory-motor conflict theory for motion sickness reflects a pluralistic viewpoint: Today's animals are not the perfect end products of a perpetually constant environment; they continue to evolve in response to environmental changes and competitive survival pressures.[1] Genetic changes are typically pleiotropic, influencing multiple phenotypic traits, some adaptive and some not. Today's successful vertebrates nonetheless share many phenotypic flaws. For example, the

[1] Darwin, Origin of Species, 6$^{\text{th}}$ Ed, Chapter 6, p. 86: "Natural selection tends only to make each organic being as perfect as, or slightly more perfect than, the other inhabitants of the same country with which it has to struggle for existence."

co-location of the larynx and esophagus in the pharynx in many land animals renders them susceptible to death by choking on food. Rodents and rabbits are unable to vomit, and horses and other ruminants rarely do so, partly due to their highly adapted stomach anatomy. Instead they must rely on conditioned taste aversion. Humans and other bipeds are notoriously susceptible to low back pain and disabling injury due to the lordosis of the lumbar spine, a vestige of their quadrupedal progenitors. Vertebrates also share a common basic vestibulo-autonomic regulatory and movement control system central neural architecture. The motion sickness phenotype – not present in normal life – reveals an analogous architectural flaw.

3. Conclusions

Returning now to the title question: are adaptationist evolutionary theories for motion sickness naïve "just-so stories"? I conclude most are not, since they are potentially experimentally verifiable and falsifiable. Experiments such as those of Money and Cheung are useful. However, the experimental evidence in favor of Treisman's well-known Poison Theory – including Money and Cheung's – seems at best equivocal. Common human and animal symptoms of food poisoning – including nausea, vomiting, diarrhea, cramping, and fever – can be parsimoniously attributed to activation of serotonergic receptors in the gut and CNS, and to direct effects of toxins on organ systems. Vestibular or auditory symptoms would be expected, but are rarely mentioned in the clinical and veterinary food poisoning literature. Drugs that are effective for nausea and vomiting due to cytotoxins are relatively ineffective against motion sickness. On the basis of the limited experimental evidence, it is difficult to distinguish the poison theory from several other adaptationist explanations (e.g. a "negative reinforcement" theory).

On the other hand, pluralist theories accept the possibility that certain phenotypes are neutral or even potentially maladaptive. The sensory-motor conflict theory for motion sickness, reviewed as an example of a pluralistic theory, and supported by recent physiological evidence, accepts the survival value of the chemoreceptive emetic reflexes and conditioned taste aversion, but postulates that brainstem sensory conflict signals have important functional roles in everyday movement control and autonomic regulation that covey survival advantage – normally without making animals motion sick.

Most of the evidence that non-human vertebrates are susceptible to motion sickness in non-experimental situations is anecdotal, and come from observations when animals are being passively transported by boats, auto, or airplane (e.g. [9,48]). Eventually it may become technically possible to monitor how frequently animals are actually exposed to prolonged passive movement during their natural lives in their normal environment, whether motion sickness is rarely or frequently produced, and whether they are more subject to predation or injury as a result. Until then it is seems parsimonious to assume adaptationist hypotheses such as Treisman's Poison Theory remain unverified. Acknowledging that the survival value of sensory conflict mechanisms is likely in movement control, based on the available evidence, it seems equally likely that motion sickness represents an overload coupling between the neurotoxin defense and movement control systems due to unnatural motions, a phenotype rarely manifest during vertebrate evolution.

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