Reafference Cancellation in Brainstem Vestibular Neurons: Implications for Motion Sickness Etiology

Charles M. Oman and Kathleen E. Cullen
Massachusetts Institute of Technology, Cambridge , MA 02139 USA and
Department of Physiology, McGill University, Montreal, Quebec, Canada

Supported in part by the National Space Biomedical Research Institute through NASA NCC 9-58

❖ Summary

Traditional theories attributed motion sickness to vestibular overstimlation or intermodality sensory conflict (Reason & Brand, 1975, Fig 1). However, in formal models now referred to as the "sensory-motor conflict theory", Reason,(1978, Fig 2) and Oman (1982, Fig 3) argued that the essential conflict must be between actual and anticipated sensory cues. Vestibular expectancy conflict signals could also result from compelling visual stimulation (e.g. Cinerama sickness), and serve as error signals in head and body postural control pathways, quickly triggering corrective reflexes in response to passive movement (e.g. ship motion). Sustained conflicts were hypothesized to initiate sensory-motor learning via cerebellar internal model updating. A vestibular-emetic linkage was postulated, but with dynamics too slow to be activated during normal active movements. The theory (Oman, 1990) predicted that vestibular conflict neurons exhibiting reafference cancellation would eventually be found in brainstem or cerebellum. Although the theory has been widely accepted, ecological psychologists (e.g. Stoffregen, 1991) debated the existence of internal models and expectancy conflict signals. Others argued the essential conflict was not at the first stage of vestibular processing, but related to conflicts between the sensed and perceived vertical (Bles,1998) .

Recent physiological studies in alert behaving rhesus primates comparing the responses of vestibular units in brainstem and cerebellum (Figs 4-6, Cullen and coworkers, 2001, 2004, 2009, 2012, 2013) have shown that during active movement, vestibular input ("reafference", von Holst, 1950) is cancelled at the first stage of brainstem processing, In the brainstem, the cancellation is believed to result from "efference copy" signals originating in a cerebellar "internal model" (Fig 7.) that normally predicts the vestibular sensory consequences of self-generated movement. These neurons are believed to participate in reflex stabilization of the head and body during passive movement, whereas the reafference cancellation permits unimpeded active movement. They also project to vestibular thalamus and on to cortex and may contribute to orientation and motion perception. Other classes of brainstem and cerebellar vestibular neurons have been identified that help stabilize gaze, and contribute to autonomic orthostatic regulation, but they do not exhibit the same type of reafference cancellation.

In the context of the motion sickness sensory-motor conflict theory, it makes sense to propose that prolonged stimulation of these units also causes nausea and vomiting. We expect that other types of "sensory rearrangements" can be shown to activate these neurons. Ultimately it will be essential to show that they project to adjacent brainstem areas implicated in nausea and vomiting (e.g. PBN and LTF, Yates and coworkers, 2012,), and assuming they do, what the physiology and purpose of the linkage is.

Fig. 1: Intermodality Sensory Conflict Hypothesis (Reason and Brand, 1975).

TABLE 6
Some Everyday and Laboratory Examples of the Six Kinds of Sensory Rearrangement that can Provoke Motion Sickness

	Visual (A)–Inertial (B)	*Canal (A)–Otolith (B)*
Type 1 (A and B)	1. Watching waves over the side of a ship. 2. Looking out of the side or rear windows of a moving vehicle. 3. Making head movements while wearing some optical device that distorts vision.	1. Head movements made about some axis other than that of bodily rotation—cross-coupled angular accelerations (see text). 2. Low frequency oscillations: between 0·1-0·5 Hz. (? see text).
Type 2 (A not B)	1. "Cinerama sickness" (see text). 2. Operating a fixed-base vehicle simulator with a moving visual display—"simulator sickness". 3. "Haunted-Swing" type of fairground device.	1. Weightless flight—"space sickness". 2. Calorific stimulation of the outer ear. 3. Positional alcoholic nystagmus associated with alcohol and heavy water (see text).
Type 3 (B not A)	1. Reading a map in moving vehicle. 2. Riding in a vehicle without external visual reference. 3. Being swung in an enclosed cabin.	1. Rotation about an Earth-horizontal axis. 2. Any rotation about an off-vertical axis. 3. Counter-rotation (see text).

Fig. 2: "Neural Mismatch" Motion Sickness Model (Reason 1978) based on Reafference Principle (Von Holst, 1950) and a schema proposed by Held (1961).

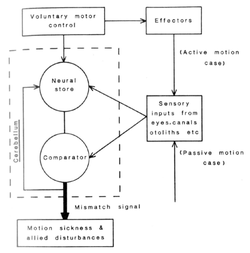


Fig. 3: Computable "Observer" Model for Postural Control, Sensory Expectancy Conflict and Emetic Linkage (Oman,1990, 1991).

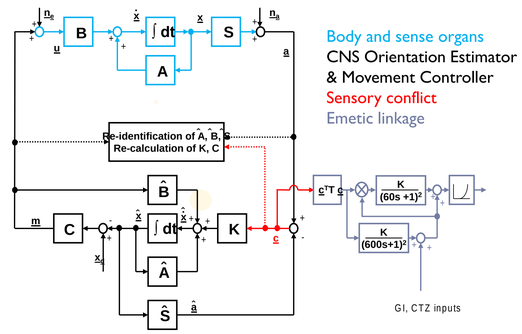


Fig 4: Reafference Cancelation in Rhesus Brainstem Semicircular Canal VO ("Vestibular Only") Neurons (Cullen et al 2009)

Cullen et al (1999, 2004, 2009) showed that active and passive responses of rhesus monkey

- semicircular canal afferents (left column) are identical, but
- brainstem "Vestibular-Only" (VO) neurons (right column) respond only to passive movement.

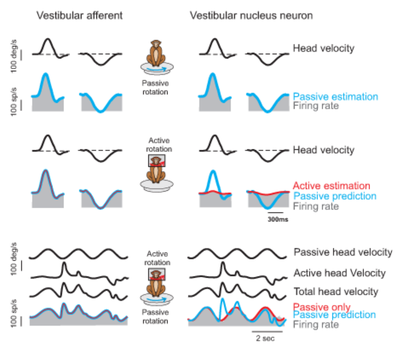


Fig 5: Reafference Cancelation in Rhesus Brainstem Otolith VO Neurons (Carriot & Cullen, 2013)

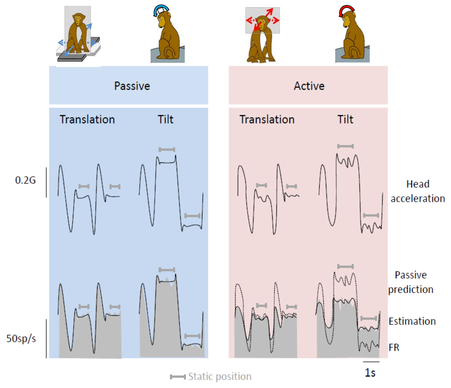


Fig 6: Reafference Cancelation in Rhesus Cerebellar Rostral Fastigial Nucleus Unimodal Cells (Brooks & Cullen 2013)

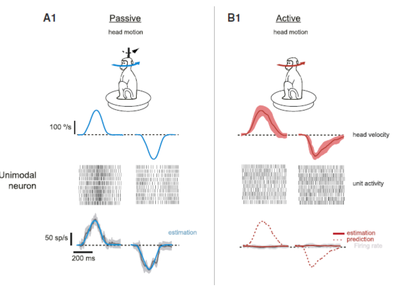
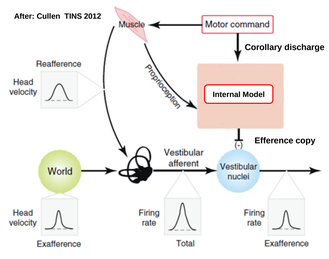


Fig 7: Hypothesized Mechanism for Reafference Cancelation via cerebellar internal model (Cullen, 2012)

Neural mechanism for vestibular reafference cancellation:

Motor command to neck muscle causes neck proprioceptor and vestibular reafference.

Internal model employs proprioceptive cues and motor command to predict expected vestibular signal (efference copy).



Efference copy cancels reafference, so VO neurons primarily respond to passive component of body movement ("exafference").

References

- Bles, W., J. E. Bos, B. de Graff, E. L. Groen and A. H. Wertheim (1998). "Motion sickness: only one provocative conflict ?" Brain Res Bull 47(5): 481-487.
- Brooks, J. X. and K. E. Cullen (2013). "The primate cerebellum selectively encodes unexpected self-motion." Current Biology 23(11): 947-955.
- Carriot, J and Cullen K, Selective encoding of unexpected head tilt by the vestibular nuclei. Poster D2, Sensing Motion for Action Symposium, McGill University, July 13, 2013.
- Cullen, K. E. (2004). "Sensory signals during active versus passive movement." Current Opinion in Neurobiology 14: 698-706.
- Cullen, K. E. (2012). "The vestibular system: multimodal integration and encoding of self-motion for motor control." Trends in Neurosciences 35(3): 185-196.
- Held, R. M. (1961). "Exposure history as a factor in maintaining stability of perception and coordination." J. Nerv. Ment. Dis. 132: 26-32.
- Moy, J. D., D. J. Miller, M. F. Catanzaro, B. M. Boyle, S. W. Ogburn, L. A. Cotter, B. J. Yates and A. A. McCall (2012). "Responses of neurons in the caudal medullary lateral tegmental field to visceral inputs and vestibular stimulation in vertical planes." Am J Physiol Regul Integr Comp Physiol 303: R929-R940.
- Oman, C. M. (1982). "A heuristic mathematical model for the dynamics of sensory conflict and motion sickness." Acta Otolaryngologica (Stockholm)(Suppl 392).
- Oman, C. M. (1990). "Motion sickness: a synthesis and evaluation of the sensory conflict theory." Can. J. Physiol. Pharmacol. 68: 294-303.
- Oman, C. M. (1991). Sensory conflict in motion sickness: an Observer Theory approach. Pictorial communication in real and virtual environments. S. Ellis. London, Taylor and Francis: 362-367.
- Oman, C. M. and K. E. Cullen (2012). "Brainstem processing of vestibular sensory reafference: implications for motion sickness etiology (Abstract 245)." Aviation Space and Environmental Medicine 83(3): 279.
- Reason, J. T. (1978). "Motion sickness adaptation: a neural mismatch model." J. R.. Soc. Med. 71: 819-829.
- Reason, J. T. and J. J. Brand (1975). Motion Sickness. London, Academic Press.
- Roy, E. A. and K. E. Cullen (2001). "Selective processing of vestibular reafference during self-generated head motion." J. Neuroscience 21(6): 2131-2142.
- Stoffregen, T. A. and G. E. Riccio (1991). "An ecological critique of the sensory conflict theory of motion sickness." Ecological Psychology 3(3): 159-194.
- Suzuki, T., Y. Sugiyama and B. J. Yates (2012). "Integrative responses of neurons in parabrachial nuclei to a nauseogenic gastrointestinal stimulus and vestibular stimulation in vertical planes." Am J Physiol Regul Integr Comp Physiol 302: R965-975.
- von Holst, E. and H. Mittelstaedt (1950). The Reafference Principle. The Behavioral Physiology of Animals and Man: The Selected Papers of Erich von Holst. R. Martin. London, Methuen & Co. 1: 139-173.