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"Vomiting center" reanalyzed: an electrical stimulation study

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Electrical stimulation of the brainstem of 15 decerebrate cats produced stimulus-bound vomiting in only 4 animals. Vomiting was reproducible in only one cat. Effective stimulating sites were located in the solitary tract and reticular formation. Restricted localization of a "vomiting center", stimulation of which evoked readily reproducible results, could not be obtained.

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The neural correlates of motion sickness, a widespread and potentially serious problem, are unfortunately not well understood<sup>10,11,13</sup>. Essential to our knowledge of motion sickness is an understanding of the control of vomiting. The present concept of the "vomiting center" is based on studies by Borison and Wang who showed that vomiting can be produced by electrical stimulation of a region of the brainstem of unanesthetized, decerebrate cats<sup>3</sup> and that large lesions in this region render dogs refractory to emetic agents<sup>14,15</sup>. Their effective stimulating sites were located in the region of the solitary tract and nucleus and nearby lateral reticular formation, over a rostral-caudal distance of about 4.5 mm. As a first step in studying the connections of the "vomiting center", we sought to localize effective stimulating sites to a more restricted anatomical region. Unexpectedly, vomiting proved difficult to obtain when stimulating in the region described above and was usually non-reproducible in a single animal.

Studies were performed on 15 adult cats (Table I). Experimental procedures were varied in an attempt to produce vomiting. Animals were allowed food and fluids ad libitum. Most were also given 50-100 ml of milk via a stomach tube during the experiment. Gaseous anesthesia (halothane/nitrous oxide or ether) was used for all cats except one. The trachea was cannulated in the first seven experiments; an endotracheal tube was used in later animals. Anesthesia was discontinued following intracollicular decerebration. One cat was anesthetized with Nembutal (40 mg/kg i.p.) and decerebrated on the day prior to stimulation, by which time it exhibited normal decerebrate rigidity (exp. 14). Thoracic pressure was measured in one experiment using catheters inserted into the superior vena cava and thoracic cavity<sup>8</sup>. The cat's head was held in a stereotaxic

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frame; most animals were also supported using hip pins and a spinal clamp placed at T1. The caudal cerebellum was exposed by removing part of the overlying occipital bone; the caudal-medial cerebellum was also removed in the first four experiments to allow visualization of the brainstem. Despite the vestibulocerebellum's importance for the development of motion sickness, its removal does not hinder animals' ability to vomit<sup>1,17</sup>. Exposed nervous tissue was kept moist with warm saline. An ace bandage was wrapped around the cat's abdomen and thorax in experiments 12 and 13 to simulate the pneumographs used by Borison and Wang<sup>3</sup>. Rectal temperature was maintained between 36-38 degrees C and blood pressure was monitored to ensure that the animals remained in good condition.

At least two hours elapsed between decerebration and the start of brainstem stimulation. A total of 296 tracks was made in grid-like patterns from 2 mm caudal to the obex to 6 mm rostral to it. This area encompasses the effective region previously described by Borison and Wang as extending from about the level of the obex rostrally for approximately 4.5 mm<sup>3</sup>. Eighty-one percent of our tracks were in this narrower region. Typically, several tracks were made in a frontal plane at 0.5 mm intervals before proceeding to a new rostral-caudal level. Stimuli were applied at depth intervals of 0.5 mm or less in each track. Any stimulus effects were noted at the time. Regions from which prodromal symptoms of vomiting were obtained were more thoroughly explored. Current was applied using a constant current stimulator and either glass micropipettes filled with 2M NaCl and fast green dye (exp. 1-5), pairs of enameled covered, side-by-side tungsten electrodes (exp. 6-12), or enameled bipolar nichrome wire electrodes (exp. 13-15). The latter electrodes were provided by Dr. H. L.

Borison and are identical to those used by Borison and Wang<sup>3</sup>. A variety of stimulus conditions was used: 0.15-0.5 ms pulses, 10-500 Hz, 30-2000  $\mu$ amp, pulse trains of 60-70 ms duration repeated once every 500 ms or trains of continuous pulses usually lasting at least 10-15 sec.

To make it more likely that electrical stimulation would produce vomiting, the opiate antagonist naloxone (Endo Lab.; 1.3-3.0 mg/kg i.v.) was administered during the last half of the stimulation phase of 7 experiments. Naloxone has been shown to increase cats' susceptibility to motion sickness (Crampton and Daunton, personal communication; Miller and Wilson, unpublished observations).

At the experiment's end, the animal's brain was fixed in 10% formalin, and frontal sections (100  $\mu$ m) of the brainstem were stained with thionin. The locations of stimulating sites were reconstructed in relation to electrode tracks and either fast green dye marks<sup>12</sup> or small electrolytic lesions made at known depths.

Most attempts to produce vomiting, as defined by the expulsion of gastric contents, proved unsuccessful: vomiting occurred during electrical stimulation of the brainstem in only three out of fifteen cats (Table I; exp. 2,6,8). Emesis was obtained during long trains of pulses at frequencies of 66 and 333 Hz (train duration greater than 30 sec; exact timing not documented due to infrequent occurrence of vomiting). It was not possible to produce more than one emetic event during repeated excitation of a previously effective stimulating site. In two experiments, vomiting could not be produced until after naloxone was given, even though stimulation had been applied earlier in the experiment in the same region as the effective site. Naloxone also produced later episodes of

spontaneous vomiting in one of these cats. However, since spontaneous vomiting started 23 minutes after the first emetic event and then occurred at relatively short intervals of 3-11 minutes, the vomiting observed during electrical stimulation may well represent a genuine stimulus effect rather than merely the first episode of spontaneous vomiting.

The sites at which vomiting was produced during stimulation were not restricted to a single anatomical structure; they were located in the solitary tract and reticular formation ventral to it, from 0.5-2 mm rostral to the obex (Fig. 1). In contrast to these three instances in which vomiting occurred, numerous additional attempts to produce emesis by stimulating in this same region proved unsuccessful, both in cats that vomited and in other animals. Electrical stimulation in or near the area postrema, the chemoreceptor trigger zone for emesis<sup>2,16</sup>, failed to produce vomiting when tested in nine experiments.

In addition to the three cats that vomited during stimulation, emesis occurred reproducibly in a fourth animal immediately after the stimulus was turned off (exp. 14). The electrode was in the reticular formation about 3.5 mm rostral to the obex and 2.5 mm ventral to the descending vestibular nucleus. A fifth animal vomited while the current was turned off and the electrode was being re-positioned.

Prodromal signs such as salivation, swallowing, mouth opening, or retching were observed at stimulating sites where emesis was elicited as well as at other nearby locations in almost all experiments. Vomiting-like or retching-like behavior without actual expulsion of gastric contents occurred during stimulation in two experiments (Fig. 1). In another experiment in which vomiting-like behavior was elicited when the stimulus

was turned off, changes in thoracic pressure usually indicative of expulsion were simultaneously recorded without expulsion occurring (i.e., there was a sudden reversal in intrathoracic pressure from negative to positive (cf.<sup>8,9</sup>)). These pressure changes occurred at the same location from which vomiting was later obtained (exp. 14, described above).

The use of naloxone during 7 experiments had limited usefulness due to the inconsistent results obtained. The same dose (2 mg/kg i.v.) produced episodes of spontaneous vomiting in one cat while it had no obvious effect on three others. Only in one animal did stimulation after giving naloxone produce emesis without the occurrence of spontaneous vomiting. Naloxone did not appear to affect the occurrence or severity of prodromal symptoms.

Although we were able to confirm the finding reported by Borison and Wang in 1949 that vomiting can be produced by electrical stimulation of the brainstem of unanesthetized decerebrate cats<sup>3</sup>, our results differ from theirs in at least four respects despite our efforts to replicate their experimental conditions. First, Borison and Wang produced vomiting in 55% of their cats (11 out of 20). Their percentage of successful experiments was actually higher because some of their nine negative experiments should probably be discounted from their total for various reasons which they mention (e.g., animals died early). In contrast, we only obtained stimulus-bound vomiting in 4 out of 15 cats, including two in which emesis occurred only after giving naloxone and a third that vomited when the stimulus was turned off. Second, Borison and Wang produced vomiting within 10-15 seconds of the onset of stimulation whereas we only obtained vomiting either after longer stimulus periods or when the stimulus was turned off. Third, they never observed prodromal signs when emesis was produced whereas



we always did. Fourth, Borison and Wang reported that several emetic responses could be obtained by repeated excitation of an effective site. We could not produce more than one vomiting sequence during repeated stimulation in any one animal, even after giving naloxone.

The stimulating sites at which vomiting was obtained in our experiments were located in the solitary tract and reticular formation, in the effective region described by Borison and Wang<sup>3</sup>. Ikeda and colleagues have also stimulated this region in decerebrate dogs and obtained vomiting-like behavior as measured by pressure changes in a balloon placed in the stomach<sup>5</sup>. In addition, they obtained vomiting-like behavior by stimulating the area postrema<sup>6</sup> or the midline of the brainstem slightly caudal to the obex<sup>5</sup>. Neither Borison and Wang nor we were able to produce vomiting by stimulating the area postrema. The midline region of Ikeda and Yamanaka<sup>5</sup> received only cursory attention in our experiments; it is unclear how thoroughly Borison and Wang studied it. There is some question, however, whether the pressure changes recorded by Ikeda and colleagues should be considered synonymous with expulsion since large abdominal pressure changes occur during retching<sup>8,9</sup> and retching does not always lead to vomiting, at least during electrical stimulation.

Borison and Wang concluded that the "vomiting center" is situated in that part of their responsive region which is neither afferent nor efferent to the "center"<sup>3</sup>. They considered that the "center by itself does not carry out the function of vomiting but it coordinates the activities of other neural structures in its immediate vicinity to produce a complicated patterned response." We suggest that there is not a well localized coordinating center for emesis since electrical stimulation of such a

structure would be expected to produce vomiting more reliably than we found. Another possible explanation for our result is that vomiting was difficult to obtain due to the state of the preparation. This seems unlikely since six of our animals vomited for various reasons and since it is well known that decerebrate animals can vomit in response to an appropriate stimulus<sup>1,8,9</sup>. Our results are more consistent with the concept that neurons involved in the control of vomiting are diffusely distributed in the effective region described by Borison and Wang.

Another means by which electrical stimulation may elicit emesis is by directly exciting descending pathway(s)<sup>4</sup> that could produce coordinated activation of the musculature responsible for vomiting. One such pathway is the solitary-spinal tract which projects bilaterally to the region of phrenic motoneurons in the C4-C6 ventral horn and to the thoracic ventral horn<sup>7</sup> and may thus be able to activate the respiratory muscles that produce the pressure changes required for expulsion<sup>8,9</sup>.

In summary, we have shown that vomiting is difficult to produce by electrical stimulation of the brainstem of unanesthetized, decerebrate cats. Furthermore, we have provided evidence that a discretely localized "vomiting center" does not exist.

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TABLE I

Observations made during electrical stimulation of the brainstem

Abbreviations: mo, mouth opening; retch, retching; sal, salivation; swal, swallowing. Exp. 14 was carried out with Drs. H. L. Borison and L. E. McCarthy at Dartmouth Medical School, Hanover NH.

Naloxone dose		
Exp	(mg/kg i.v.)	Observations
1	0	vomited spontaneously
2	0	sal,swal,retch,vomited
3	0	sal,swal,mo
4	0	sal,swal,retch
5	0	swal,mo
6	2	swal,mo; stimulus-bound vomiting after naloxone
7	2	swal,mo
8	3	swal,mo; stimulus-bound vomiting after naloxone; naloxone also caused vomiting
9	2	mo
10	2	swal,mo,retch; naloxone caused vomiting
11	1.3	swal,mo
12	2	swal,mo
13	0	swal,mo
14	0	swal,mo; vomited when stimulus turned off
15	0	swal,mo

Fig. 1. Vomiting was produced once during electrical stimulation in each of 3 cats. The sites are shown by filled circles on frontal sections of the brainstem, at indicated distances rostral to the obex. Vomiting-like or retching-like behavior, without expulsion of gastric contents, was obtained in 2 other animals at sites marked with X. Abbreviations: AMB, n. ambiguus; AP, area postrema; CUN, cuneate n.; CX, external cuneate n.; DMV, dorsal motor n. of vagus; FTL, lateral tegmental field; INT, n. intercalatus; IO, inferior olive; LRN, lateral reticular n.; PR, paramedian reticular n.; SL, lateral solitary n.; SM, medial solitary n.; ST, solitary tract; VIN, descending vestibular n.; 5SP, spinal trigeminal n.; 12, hypoglossal n.

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