Enhanced recognition memory following vagus nerve stimulation in human subjects

Kevin B. Clark[1], Dean K. Naritoku[2], Douglas C. Smith[1], Ronald A. Browning[3] and Robert A. Jensen[1]

[1] *Program for the Biopsychology of Learning and Memory, Department of Psychology, Southern Illinois University, Carbondale, Illinois 62901-6502, USA*

[2] *Departments of Neurology and Pharmacology, Southern Illinois University School of Medicine, Springfield, Illinois 62794-9230, USA*

[3] *Department of Physiology, Southern Illinois University, Carbondale, Illinois 62901-6512, USA*

Correspondence should be addressed to R.A.J. (rajensen@siu.edu)

Neuromodulators associated with arousal modulate learning and memory, but most of these substances do not freely enter the brain from the periphery. In rodents, these neuromodulators act in part by initiating neural messages that travel via the vagus nerve to the brain, and electrical stimulation of the vagus enhances memory. We now extend that finding to human verbal learning. We examined word-recognition memory in patients enrolled in a clinical study evaluating the capacity of vagus nerve stimulation to control epilepsy. Stimulation administered after learning significantly enhanced retention. These findings confirm in humans the hypothesis that vagus nerve activation modulates memory formation similarly to arousal.

Physiological and psychological events can either strengthen or weaken the formation of memories. Some of these events, such as arousal, may occur immediately before or during the perception of a salient stimulus, enabling an organism to better attend to the stimulus and thus learn about it more efficiently[1]. In contrast, arousal may also occur shortly following a learning experience (that is, during memory consolidation), modulating the storage, rather than the acquisition, of information[2–6]. Memory storage is influenced by arousal and by neuromodulators such as adrenal catecholamines and peptide hormones, released into systemic circulation during aroused states[2–6]. Moderate levels of arousal or associated circulating neurohormones tend to enhance the formation of memory, whereas low and high levels of arousal or neurohormones typically cause relatively poor retention performance[3,4], as reflected in the inverted-U-shaped function of the Yerkes–Dodson curve[7–9]. However, it remains unclear how various neurohormones associated with arousal influence memory storage, as they do not cross the blood-brain barrier in substantial quantities.

The vagus nerve carries most information about viscerosensory states to the brain. Subdiaphragmatic vagotomy[10–13] or reversible inactivation of the nucleus of the solitary tract[14], the primary relay site of vagal afferents in the brain, attenuates the memory modulation produced by peripherally acting neurohormones. Furthermore, electrical stimulation of the vagus nerve, delivered after an aversive learning experience, improves later retention performance in rats[15]. Reversibly inactivating the vagus below the point of stimulation showed that this memory enhancement results from the activation of vagal afferents and not from stimulation of vagal efferents[16]. Taken together, these findings suggest that arousal leads to the release of hormonal substances that activate peripheral receptors, which initiate signals carried by the vagus nerve to the brain, resulting in the modulation of memory storage.

To determine whether vagus nerve stimulation can modulate memory in humans, we modified a protocol used in our laboratory to demonstrate that arousal induced by muscle tension enhances human verbal memory[17] and that antihypertensive beta-blockers attenuate this enhancement, presumably by antagonizing peripheral catecholamine receptors[6]. In this protocol, subjects read a series of paragraphs and later identify words that were highlighted in the text. It reliably produces memory performance at retention intervals of 0.5 to 2.0 hours comparable to that found in other tasks that use retention intervals of 24 hours or longer[17]. Here we report that subjects had better memory retention for highlighted words in paragraphs followed by vagal stimulation than in control paragraphs, suggesting that vagus nerve activation enhances memory in humans.

Results

In each experimental session, subjects silently read two blocks of seven unfamiliar, emotionally neutral paragraphs. Different paragraphs were used for each test session, and their order of presentation was counterbalanced across subjects. Each block of paragraphs began with a practice paragraph, followed by six test paragraphs, three of which each contained seven highlighted nouns (see **Table 1** for presentation order). During one block of test paragraphs, a chronically implanted stimulation device (Cyberonics, Inc.) delivered vagal stimulation for 30 seconds beginning approximately 2 minutes after subjects finished reading of each of the 3 paragraphs in that block containing highlighted words. Sham stimulation followed the reading of paragraphs with highlighted words in the other test block. We hypothesized that if vagal activation in humans can

Table 1. Summary of the presentation of narrative paragraphs.

	1	2	3	4	5	6	7	BREAK	8	9	10	11	12	13	14
1.	X	a	B	c	D	e	F		X	g	H	i	J	k	L
2.	X	b	A	d	C	f	E		X	h	G	j	I	I	K
3.	X	a	B	c	D	e	F		X	g	H	i	J	k	L
4.	X	b	A	d	C	f	E		X	h	G	j	I	I	K

Letters A-L represent the twelve presented experimental paragraphs, and X corresponds to the two practice paragraphs; rows correspond to the four different orders of paragraph presentation. Lower case indicates the presence of highlighted words; white letters indicate the administration of vagus nerve stimulation.

modulate memory storage processes, then highlighted words from those paragraphs that were followed by stimulation should be more readily recognized in a long list of distractor nouns than highlighted words from similar paragraphs read without vagal stimulation.

Vagal stimulation administered after learning, during memory consolidation, caused intensity-dependent enhancement of word-recognition performance relative to sham stimulation. When subjects from Groups A (Visit 2) or B (Visit 4; **Table 2**) received 0.50-mA stimulation after reading paragraphs with highlighted words, word recognition was significantly enhanced (t (9) = 2.78, $p < 0.025$; **Fig. 1**). No such improvement was observed for higher stimulation intensities (0.75 to 1.50 mA; t (9) = 0.76, p = n.s.), replicating our work with rats[15,16]. Additionally, no difference in retention performance (t (8) = –0.837, p = n.s.) was found when the 0.50-mA stimulation was delivered before reading (Group A, Visit 2; Group B, Visit 4). This suggests that the observed enhancement was not due to practice or expectancies, as Group B had experienced two additional test sessions before the test session in which the 0.50-mA stimulation was given.

These within-subjects comparisons demonstrate that stimulation at 0.50 mA enhances word-recognition performance compared to sham stimulation. Both examiner and subjects were blinded to stimulation parameter information, and the examiner did not know whether his actions delivered stimulation or not. Subjective factors such as expectations are unlikely to have influenced the improvement in memory performance observed with 0.50-mA vagal stimulation.

A split ANOVA comparison between those patients that received time-locked stimulation (Group A) and those that received sham stimulation (Group B) at Visits 2 and 3 was calculated to determine whether time effects and expectation may have influenced retention performance. No overall significant difference in recognition of highlighted words was observed between groups (F (1,8) = 1.024, p = n.s.) or across time (F (1,8) = 0.754, p = n.s). The lack of a significant time effect suggests that practice and cumulative stimulation effects did not influence recognition performance. In addition, trend analysis of recognition scores from Visit 2 showed that subjects in Group A, who only received stimulation at 0.50 mA, showed some memory improvement compared to subjects in Group B, who received sham stimulation (F (1,8) = 5.169, $p < 0.053$). Although significant, this finding is somewhat weaker than that found for the within-subjects comparison that assessed the effects of 0.50-mA stimulation versus sham stimulation on word recognition (Group A, Visit 2 combined with Group B, Visit 4; **Table 2**), probably because of the smaller number of subjects ($\omega 2 = 0.294$) in the split analysis.

Vagal stimulation comparable to the higher intensities used in this investigation (0.75–1.50 mA) maximally activates unmyelinated C fibers in laboratory animals[16], and these stimulation intensities are most effective in reducing the severity and frequency of seizures in animal models of convulsive seizures[18–21] as well as pharmacologically resistant forebrain epilepsies in humans[22–24]. Correlations between self-reported number of seizures and memory scores at both 0.50 mA (r = –0.366) and higher current intensities (r = –0.631) suggest that any general cognitive improvement that might have resulted from a decreased number, duration or strength of epileptic episodes experienced by these patients did not contribute to the observed improvement in retention performance.

Discussion

Most studies seeking to evaluate the effects of various modulators on memory storage use simple one-trial avoidance learning tasks in rodent models of memory (for review, see refs 3, 4). Using such tasks and models, we have shown that subdiaphragmic vagotomy attenuates the memory-enhancing properties of 4-OH amphetamine[10], as well as the amnestic properties of leu-enkephalin[11], when administered after learning, during memory consolidation. Because neither compound freely enters the brain, these findings suggest that these and possibly other substances modulate emotional memory through the activation of peripheral receptors that, in turn, send messages about autonomic states to the central nervous system via the vagus nerve. In support of this hypothesis, vagus nerve stimulation delivered

Table 2. Study time course.

		Group A (n = 5)	Group B (n = 5)
Visit 1	**Week 0**	Baseline test; subjects familiarized with testing procedure	
	Week 1	Implantation of vagus nerve stimulation device	
Visit 2	**Week 3**	0.50-mA VNS paired with reading paragraphs	Sham stimulation paired with reading paragraphs
		Six-week period between test visits	
Visit 3	**Week 9**	0.75–1.50-mA VNS paired with reading paragraphs	Sham stimulation paired with reading paragraphs
		Eight-week period between test visits	
Visit 4	**Week 17**	0.75–1.50-mA VNS paired with reading paragraphs	0.50-mA VNS paired with reading paragraphs
		Eight-week period between test visits	
Visit 5	**Week 25**	0.75–1.50-mA VNS paired with reading paragraphs	0.75–1.50-mA VNS paired with reading paragraphs

See Methods for details of stimulation parameters used during and between test visits. VNS, vagus nerve stimulation.

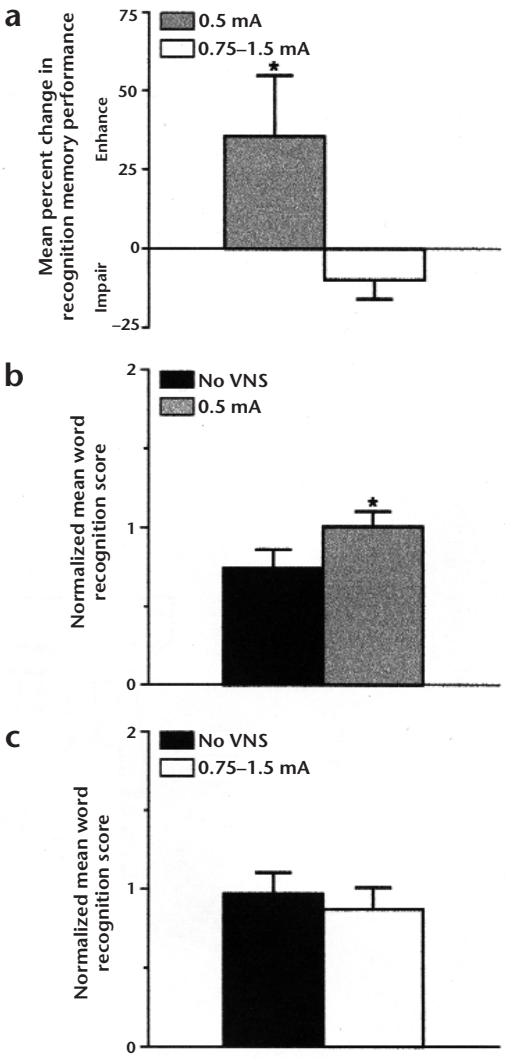

Fig. 1. Intensity-dependent modulation of word-recognition performance. **(a)** Vagus nerve stimulation delivered at 0.50 mA (recognition performance data from Group A, Visit 2 combined with data from Group B, Visit 4) facilitated word recognition as demonstrated by a mean percent increase of 35.6% (± percent change of standard error). In contrast, stimulation administered at intensities between 0.75 and 1.5 mA (Group A, Visit 3 combined with Group B, Visit 5) slightly impaired recognition performance (–10.0%). **(b, c)** Mean percent change in memory performance, calculated from the mean word-recognition scores. These scores were normalized to correct for recency effects specific to paragraph blocks. Recognition scores had a significantly higher normalized mean (± standard error) for those highlighted words in paragraphs that were followed by 0.5-mA stimulation as compared to highlighted words not followed by stimulation during the same test session (b). No such difference was observed for higher current intensities (c). * $p < 0.025$.

at 0.40 mA, but not 0.20 or 0.80 mA, enhances retention performance in rats[15,16].

The findings reported here extend our research on vagus nerve stimulation from the modulation of emotional memory in rodents to the modulation of verbal memory in humans. Similar stimulation parameters improved the retention performance of rats (0.40 mA) and humans (0.50 mA). Furthermore, the inverted-U-shaped function for memory performance predicted by the Yerkes–Dodson law[7–9] and shown for rats[15,16] was also found in humans. That is, only moderate stimulation intensities delivered during the memory consolidation period tend to enhance memory. This finding parallels the dose-related effects of many peripherally acting neurohormones on memory storage.

Because stimulation followed the reading of paragraphs from only one of two paragraph blocks, and because stimulation was counterbalanced between blocks, the observed effects on memory are unlikely to have resulted from changes in attention. Further, it is highly unlikely that the enhanced retention performance observed following stimulation delivered at 0.50 mA was due to differences in the affective valence of any one block of paragraphs. This is because the order of paragraph presentation was counterbalanced, and there were no significant differences in blood pressure or heart rate observed after the reading of the paragraphs and before stimulation. The facilitated recognition performance following 0.50-mA stimulation probably was not due to practice effects because higher stimulation intensities (0.75–1.50 mA) did not significantly affect retention performance, even though these higher intensities were always administered at later test visits than the 0.50-mA stimulation (**Table 2**). In addition, practice effects would be expected to uniformly enhance recognition of highlighted words during a given test session, regardless of whether or not the words were followed by stimulation.

The intensity-dependent memory enhancement produced by vagal stimulation indicates that vagal afferents with low-to-moderate activation thresholds may underlie the observed memory modulation[15,16]. The vagus nerve mediates cardiopulmonary reflexes and complex visceroendocrine responses[25–27] that occur during arousal and that modulate memory storage. We have found in rats[15] and now in humans that memory is enhanced by vagal stimulation intensities that likely recruit myelinated axons that transmit mechanoreceptor signals from thoracic organs, such as the heart and lungs, to the brain[28]. The vagal nuclei receive neural messages from the periphery and deliver viscerosensory information to more rostral levels of the neuroaxis[28,29]. Further, vagus nerve stimulation produces changes in the electrophysiological and metabolic profile of forebrain[30–32] (K.B.C., D.C.S. & R.A.J. *Soc. Neurosci. Abstr.* **23**, 787, 1997) and brainstem structures[33,34] involved in learning and memory. Such findings further support the notion that neural information carried by vagal afferents about peripheral states influence the course of memory storage. Therefore, the present findings in human subjects parallel those in rodents[15], and suggest that stimulation intensities that maximally recruit vagal A and B fibers, with perhaps some low-threshold C-fiber activation[16], improve memory performance.

The clinical use of vagus nerve stimulation at 0.75 to 1.50 mA to reduce the frequency and severity of seizures in individuals with refractory epilepsy is gaining acceptance. These studies suggest that lower levels of stimulation (0.50 mA) may have the additional effect of enhancing memory storage. Furthermore, the capacity of vagal stimulation to enhance memory performance may be applied therapeutically to individuals experiencing cognitive impairments that result from traumatic injury or disease. Yet as promising as these possible therapeutic uses may be, the present findings have a broader and arguably more important impact on our understanding of the mechanisms of memory. The demonstration that vagal stimulation enhances affective memory in rodents[15] and, now, verbal memory in humans emphasizes that the processes that modulate memory formation are likely to be similar regardless of the nature of the memory itself or the particular mammalian species in which the memory develops.

Methods

PATIENTS AND STUDY TIME COURSE. This study was ancillary to a randomized, double-blind clinical trial evaluating the effectiveness of vagus nerve stimulation to suppress epileptic seizures. The protocol for the study was reviewed and approved by the Springfield Committee for Research Involving Human Subjects (SIU School of Medicine). Patients enrolled in the study met the following criteria: more than four seizures a month over three consecutive months, prescription use of no more than two antiepileptic drugs, no use of benzodiazepines and no history of epilepsy surgery. Data from one subject were excluded from analysis because of that subject's prescription use of Tenormin, a beta-receptor antagonist antihypertensive. Memory was tested during each of five separate visits over twenty-four weeks. The first visit served to familiarize subjects with the testing procedures and as a baseline test, approximately one week before the surgical implantation of the stimulation device as described[35,36]. Visits 2, 3, 4 and 5 were approximately two, eight, sixteen and twenty-four weeks after surgery (**Table 2**). Stimulation at 0.50 mA paired with reading of the paragraphs occurred in one-half the subjects (Group A) during Visit 2. Similar stimulation for the other half of the subjects (Group B) was given during Visit 4. Paired stimulation at higher intensities, between 0.75 and 1.50 mA, was administered to subjects in Group A during Visits 3, 4 and 5 and to subjects in Group B during Visit 5. Data from Group A, Visits 4 and 5 were not analyzed statistically, as there were no comparable data from Group B.

DESCRIPTION OF NARRATIVE PARAGRAPHS AND INSTRUCTIONS TO SUBJECTS. During each test visit, patients silently read paragraphs from both the *Ekwell Reading Inventory* and *Reading by Doing: An Introduction to Effective Reading*. A pool of 70 paragraphs were matched according to length (130 to 160 words) and reading difficulty (U.S. grades six through eight as calculated by the Flesch-Kincaid Grade Level and Flesch Reading Ease formulas). Each block of paragraphs began with a practice paragraph (shown as X in **Table 1**) followed by six alternating paragraphs, half of which contained seven highlighted, concrete, imageable nouns ('loaded' paragraphs). Thus, in each paragraph block there were three loaded and three 'unloaded' paragraphs, with the order of presentation counterbalanced both between and within subjects as described[6] (**Table 1**).

At the beginning of each session, subjects were informed that several questions would be asked about each paragraph once they had finished reading it. They were also instructed to place a cardboard mask over each paragraph so that only two lines of text were exposed at one time through a 'window'. The patients were instructed to read at a comfortable pace, sliding the mask down the paragraph as they read, but not to move the mask back to expose previously read lines.

STIMULATION PARAMETERS AND PROCEDURES. Each stimulation device was turned on for the first time one hour before testing at Visit 2 to allow habituation to any sensory discomfort that might occur. At that time, calibration pulses (see ref. 23 for a description of detailed stimulation parameters and current-ramping procedures) were delivered to ensure that the device was functioning properly.

Half of the patients (Group A, **Table 2**) received one 30.0-s train (30 Hz; 0.50-ms pulse width) of stimulation after reading loaded paragraphs in one of two blocks of paragraphs. Sham stimulation was paired with the reading of loaded paragraphs in the other block of paragraphs. Thus, three stimulations were associated with one block of paragraphs, and three sham stimulations were administered in the other block (see **Table 1**). Sham stimulation consisted of adjusting the location of a 'regulatory' magnet placed on the patient's skin over the stimulation device. Removal of the magnet triggers stimulation. Once testing in Visit 2 was completed, each patient in Group A was ramped to that individual's final stimulation intensity between 0.75 and 1.50 mA. The final intensity of stimulation depended on each patient's subjective responses to the stimulation. Therefore, subjects in Group A received stimulation at 0.50 mA during Visit 2 and stimulation between 0.75 and 1.50 mA during Visits 3, 4 and 5.

All other patients (Group B) received only sham stimulation during Visits 2 and 3 (see **Table 2**). Vagal stimulation (or sham stimulation) for these patients was under the control of the examiner during Visit 4 (0.50 mA; 30 Hz; 0.50-ms pulse width; 30-s trains) and Visit 5 (ramped to between 0.75 and 1.50 mA following testing on Visit 4). This stimulation or sham stimulation followed the reading of loaded paragraphs. For periods between test visits, all patients received continuous, intermittent stimulation at currents either of threshold (1 Hz; 0.13-ms pulse width; 30-s on and 180-min off) or individual tolerance (0.75 to 1.50 mA; 30 Hz; 0.50-ms pulse width; 30-s on and 5-min off).

ADMINISTRATION OF VAGUS NERVE STIMULATION AND MEMORY TESTS. After subjects read each paragraph, their blood pressure and pulse rate were measured as indices of arousal. The subjects were then asked one factual and one inferential/logical question about the paragraph that had just been read to assess reading comprehension. Then, approximately two minutes after reading each loaded paragraph in either the first or second block, patients received sham stimulation or vagal stimulation for 30.0 s at either 0.50 mA (Group A, Visit 2; Group B, Visit 4) or between 0.75 and 1.50 mA (Group A, Visits 3, 4 and 5; Group B, Visit 5). Patients were asked to recall the just-read highlighted words immediately after stimulation or sham stimulation.

After completing all 14 paragraphs and taking a short rest period, patients were given a recognition-memory test composed of the 42 target nouns previously seen in the loaded paragraphs, randomly distributed throughout a list of 206 comparable distractor nouns. The distractor words used in each test were drawn from a list of 600 concrete imageable nouns[37]. Subjects were instructed to mark those words that they recalled having seen as highlighted words in the loaded paragraphs. Subjects were allotted 5 min to finish this test and were notified by the experimenter when 2.5 and 4 min had elapsed. All subjects successfully completed the recognition test within the allotted time. Each test session lasted approximately 2.5 h.

ANALYSIS OF WORD-RECOGNITION SCORES. We controlled for stimulation-time effects in trials in which stimulation was time-locked to the reading of paragraphs by analyzing retention performance for only those visits in which patients first received stimulation at 0.50 mA and those visits when higher stimulation intensities were first used. Because total test duration was approximately 2.5 h, words read later in the test session might have been more easily recognized than words read earlier. Therefore, word-recognition scores of each subject on Visits 2 through 5 were normalized by dividing the number of highlighted words recognized from the first and second paragraph blocks, respectively, of each test session by the number of highlighted words recognized from the first and second paragraph blocks, respectively, of the baseline session, which occurred approximately one week before implantation.

Acknowledgements

The authors thank Mary Aiello for scheduling patients and organizing test visits. This research was supported by Cyberonics, Inc.

RECEIVED 10 JUNE; ACCEPTED 16 NOVEMBER 1998

1. Eysenck, M. W. *Attention and Arousal* (Springer-Verlag, Berlin, 1982).
2. McGaugh, J. L. Time-dependent processes in memory storage. *Science* **153**, 1351–1358 (1966).
3. McGaugh, J. L. Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. *Annu. Rev. Neurosci.* **12**, 255–287 (1989).
4. Cahill, L. & McGaugh, J. L. Modulation of memory storage. *Curr. Opin. Neurobiol.* **6**, 237–242 (1996).
5. Cahill, L., Prins, B., Weber, M. & McGaugh, J. L. Beta-adrenergic activation and memory for emotional events. *Nature* **371**, 702–704 (1994).
6. Nielson, K. A. & Jensen, R. A. Beta-adrenergic receptor antagonist antihypertensive medications impair arousal-induced modulation of working memory in elderly humans. *Behav. Neural Biol.* **62**, 190–200 (1994).
7. Broadhurst, P. L. Emotionality and the Yerkes-Dodson law. *J. Exp. Psychol.* **54**, 345–352 (1957).
8. Hebb, D. O. Drive and the C.N.S. (Conceptual Nervous System). *Psychol. Rev.* **62**, 243–253 (1955).
9. Yerkes, R. M. & Dodson, J. D. The relation of strength of stimulus to rapidity of habit-formation. *J. Comp. Neurol. Psychol.* **18**, 459–482 (1908).
10. Williams, C. L. & Jensen, R. A. in *Neuronal Control of Bodily Function, Basic, and Clinical Aspects: Vol. 6 Peripheral Signaling of the Brain: Role of Neural-Immune Interactions, Learning and Memory* (eds Frederickson, R. C. A., McGaugh, J. L. & Felton, D. L.) 467–472 (Hogrefe & Huber, Toronto, 1991).

11. Williams, C. L. & Jensen, R. A. Effects of vagotomy on leu-enkephalin-induced changes in memory storage processes. *Physiol. Behav.* **54**, 659–663 (1993).
12. Flood, J. F., Smith, G. E. & Morley, J. E. Modulation of memory storage processing by cholecystokinin: Dependence on the vagus nerve. *Science* **234**, 832–834 (1987).
13. Nogueira, P. J. C., Tomaz, C. & Williams, C. L. Contribution of the vagus nerve in mediating the memory-facilitating effects of substance P. *Behav. Brain Res.* **62**, 165–169 (1994).
14. Williams, C. L. & McGaugh, J. L. Reversible lesions of the nucleus of the solitary tract attenuate the memory-modulating effects of posttraining epinephrine. *Behav. Neurosci.* **107**, 955–962 (1993).
15. Clark, K. B., Krahl, S. E., Smith, D. C. & Jensen, R. A. Post-training unilateral vagal stimulation enhances retention performance in the rat. *Neurobiol. Learn. Mem.* **63**, 213–216 (1995).
16. Clark, K. B. *et al.* Post-training electrical stimulation of vagal afferents with concomitant vagal efferent inactivation enhances memory storage processes in the rat. *Neurobiol. Learn. Mem.* **70**, 364–373 (1998).
17. Nielson, K. A., Radtke, R. C. & Jensen, R. A. Arousal-induced modulation of memory storage processes in humans. *Neurobiol. Learn. Mem.* **66**, 133–142 (1996).
18. Woodbury, D. M. & Woodbury, J. W. Effects of vagal stimulation on experimentally induced seizures in rats. *Epilepsia* **31**, S7–S19 (1990).
19. Woodbury, J. W. & Woodbury, D. M. Vagal stimulation reduces the severity of maximal electroshock seizures in intact rats: Use of a cuff electrode for stimulating and recording. *Pacing Clin. Electrophysiol.* **14**, 94–107 (1991).
20. Lockard, J. S., Congdon, W. C. & DuCharme, L. L. Feasibility and safety of vagal stimulation in a monkey model. *Epilepsia* **31**, S20–S26 (1990).
21. Zabara, J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. *Epilepsia* **33**, 1005–1012 (1992).
22. Penry, J. K. & Dean, J. C. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: Preliminary results. *Epilepsia* **31**, S40–S43 (1990).
23. Ben-Menachem, E. *et al.* Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. *Epilepsia* **35**, 515–526 (1994).
24. Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology* **45**, 224–230 (1995).
25. Armour, J. A., Wurster, R. D. & Randall, W. C. in *Neural Regulation of the Heart* (ed. Randall, W. C.) 159–186 (Oxford, New York, 1977).
26. Paintal, A. S. Vagal sensory receptors and their reflex effects. *Physiol. Rev.* **53**, 159–227 (1973).
27. Curry, D. L. Reflex inhibition of insulin secretion: Vagus nerve involvement via CNS. *Am. J. Physiol.* **247**, 827–832 (1984).
28. Cechetto, D. F. Central representations of visceral function. *Fed. Proc.* **46**, 17–23 (1986).
29. Rutecki, P. Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia* **31**, S1–S6 (1990).
30. O'Brien, J. H., Pimpaneau, A. & Albe-Fessard, D. Evoked cortical responses to vagal, laryngeal, and facial afferents in monkeys under chloralose anesthesia. *Electroencephalogr. Clin. Neurophysiol.* **31**, 7–20 (1971).
31. Car, A., Jean, A. & Roman, C. A pontine primary relay for ascending projections of the superior laryngeal nerve. *Exp. Brain Res.* **22**, 197–210 (1975).
32. Ko, D. *et al.* Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET $H_2$15O blood flow imaging. *Neurosurgery* **39**, 426–431 (1996).
33. Krahl, S. E. Vagus nerve stimulation for the control of seizures: Possible modulatory role of the locus coeruleus. *Dissertation Abstr. Int.* **56**, 559 (1995). (University Microfilms No. 9516027)
34. Naritoku, D. K., Terry, W. J. & Helfert, R. H. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. *Epilepsy Res.* **22**, 53–62 (1995).
35. Terry, R. S., Tarver, W. B. & Zabara, J. The implantable neurocybernetic prosthesis system. *Pacing Clin. Electrophysiol.* **14**, 86–93 (1991).
36. Ramsey, R. E. *et al.* Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. *Epilepsia* **35**, 627–636 (1994).
37. Paivio, A., Yuille, J. C. & Madigan, S. A. Concreteness, imagery, and meaningfulness values for 925 nouns. *J. Exp. Psychol.* **76**, 1–25 (1968).