# highlighted topics

*Plasticity in Respiratory Motor Control*
## Invited Review: Neural network plasticity in respiratory control

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and B. G. Lindsey.** Invited Review: Neural network plasticity in
respiratory control. *J Appl Physiol* 94: 1242–1252, 2003; 10.1152/jappl-
physiol.00715.2002.—Respiratory network plasticity is a modification in
respiratory control that persists longer than the stimuli that evoke it or
that changes the behavior produced by the network. Different durations
and patterns of hypoxia can induce different types of respiratory mem-
ories. Lateral pontine neurons are required for decreases in respiratory
frequency that follow brief hypoxia. Changes in synchrony and firing
rates of ventrolateral and midline medullary neurons may contribute to
the long-term facilitation of breathing after brief intermittent hypoxia.
Long-term changes in central respiratory motor control may occur after
spinal cord injury, and the brain stem network implicated in the produc-
tion of the respiratory rhythm could be reconfigured to produce the cough
motor pattern. Preliminary analysis suggests that elements of brain
stem respiratory neural networks respond differently to hypoxia and
hypercapnia and interact with areas involved in cardiovascular control.
Plasticity or alterations in these networks may contribute to the chronic
upregulation of sympathetic nerve activity and hypertension in sleep
apnea syndrome and may also be involved in sudden infant death
syndrome.

raphe; ventral respiratory group; hypoxia; memory; cough

NEURAL PLASTICITY ALLOWS THE brain to adapt. The brain
stem neural network that produces the respiratory
rhythm and motor pattern must possess a multidimen-
sional adaptability. Breathing is coordinated with mul-
tiple behaviors that use the same muscles and struc-
tures (swallowing, locomotion, posture, micturition,
defecation, vocalization, vomiting, and coughing). Ven-
tilation and blood flow are also coordinated to meet
variable metabolic demands.

For the purposes of this review, modulation refers to
modifications of the respiratory motor output during

acute or extended changes in metabolic demand. Mod-
ifications that persist longer than the experimental
manipulations or injury that evoked them (i.e., a mem-
ory) is termed plasticity. Modifications that cause the
network to produce a different behavior, such as cough-
ing, also represent a type of plasticity. Recently, it has
been shown that the network implicated in the produc-
tion of eupnea in the ventrolateral medulla, the Böt-
zinger-ventral respiratory group (Böt-VRG), reconfig-
ures to produce the airway protective behavior cough (5, 86, 87).
Coughing differs from breathing in kind and purpose.

Numerous reports suggest that brain stem respira-
tory networks contribute to the maintenance of modi-
fications of output of greater duration than the stimu-
lus that evoked them, i.e., express short- and long-term
memories (e.g., Refs. 11, 52, 53, 54, 77; also see Ref. 20,

review). The expression of these memories can be induced by exposure to hypoxia (15, 17, 35, 76, 77). Other studies raise the conjecture that at least part of the plasticity expressed by respiratory neural networks is coded in altered patterns of firing synchrony as well as changes in firing rate (46, 63).

## RESPIRATORY MEMORY: CHANGES IN THE BREATHING MOTOR PATTERN THAT PERSIST BEYOND THE INDUCING HYPOXIA

Responses to sustained as well as single and repetitive brief bouts or episodes of hypoxia have been extensively reviewed in this series (56) and elsewhere (55). Briefly, there is a transient plasticity associated with both the onset and offset of a respiratory response to a stimulus (hypoxia, hypercapnia, or many other stimuli with an excitatory effect on breathing). This transient is termed short-term potentiation (STP) (77, 100). STP refers to the progressive increase in respiratory activity in the first few cycles in response to a stimulus and to the slow decay back to baseline in a seemingly exponential manner after hypoxia (77).

Development of STP of respiration was studied in anesthetized, paralyzed, vagotomized, and glomectomized cats and rats. Peak integrated phrenic nerve activity was used as an index of respiratory output. Respiratory output was increased, and the potentiating mechanism was activated by electrical stimulation of a carotid sinus nerve. Development of STP was determined from the magnitude of potentiation of respiratory output after various durations (0–60 s) of stimulation at a fixed rate. The development of STP is relatively slow but much faster than the decay or afterdischarge. The average time constant for the development of the potentiation was 9 s, whereas the time constant for its decay was 46.1 ± 3.9 s (100). The magnitude of potentiation depends on the number of pulses in the stimulus train; 15 s at 16 Hz produced approximately the same magnitude of STP as 30 s at 8-Hz stimulation. It has been suggested that the slow increase of respiration during stimulation and the decay afterward are due to a common mechanism. Wagner and Eldridge (100) suggested that increased intracellular free $Ca^{2+}$ facilitates neurotransmitter release in respiratory control pathways. Poon et al. (76) noted that $N$-methyl-D-aspartate may mediate a slow excitatory response through neuronal nitric oxide synthase excitation, but the mechanism, although neural, remains undefined.

In many rodent strains, there is a short-term decline in respiratory cycle frequency that coincides with the STP of motoneuron firing rates. Both the short-term decline in respiratory cycle frequency and STP have a similar time course; the mean time constant for frequency to return to baseline is 45 ± 25 s (15, 17). Posthypoxic frequency decline results entirely from prolongation of time in expiration. The change in expiratory time is in the opposite direction of that evoked by hypoxia. This phenomenon, the poststimulus behavior in the opposite direction of the evoked response, has
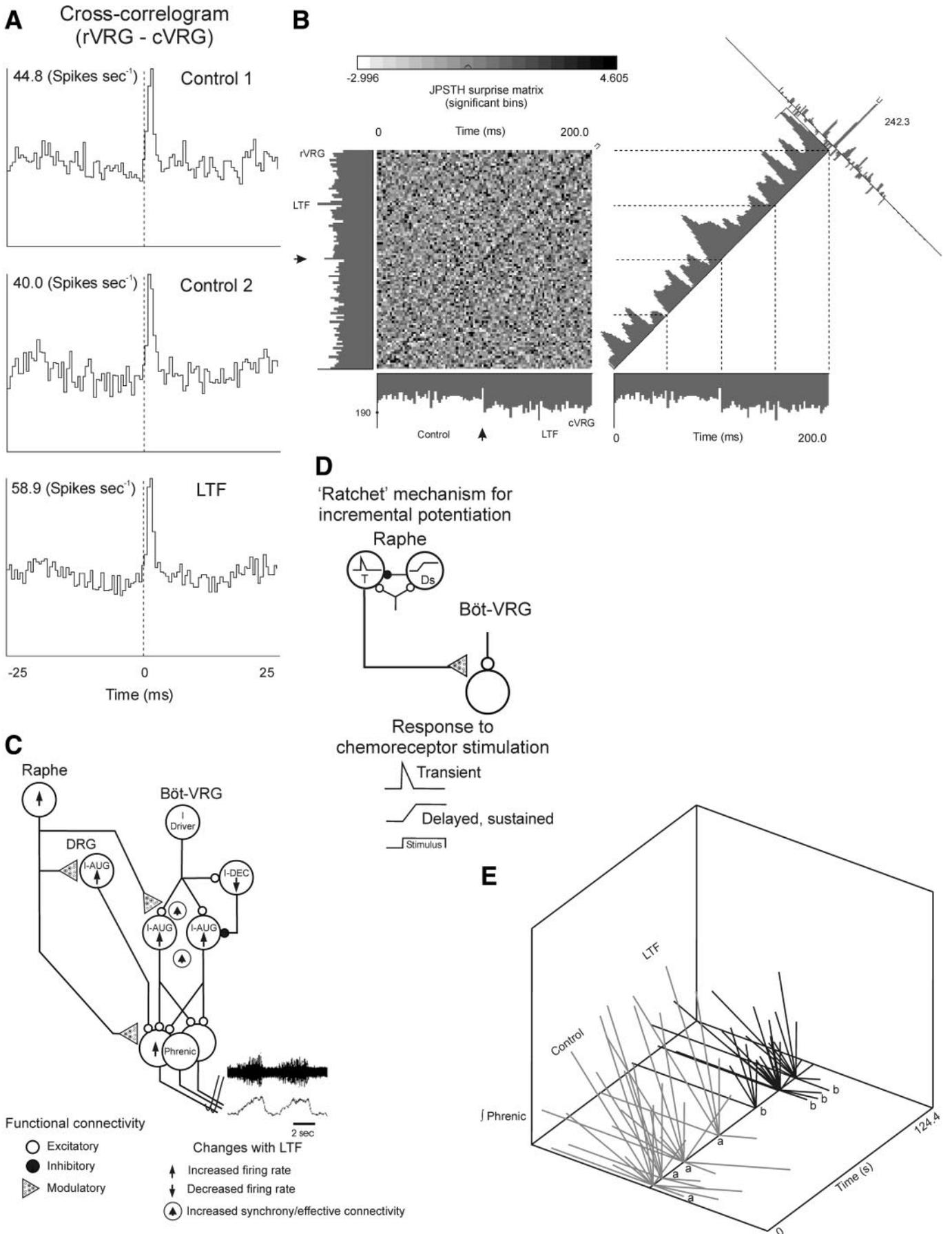
also been observed after vagal stimulation, in which case expiration lengthens during stimulation and shortens to less than control baseline values after stimulation. These changes in pattern have been referred to as "activity-dependent" plasticity by Poon and co-workers (75, 89, 102).

In rats, during 2 min of electrical stimulation of the carotid sinus nerve, there is a decrease in the breathing frequency and the product of frequency and integrated phrenic activity that still remains above baseline. This response is short-term depression (35). The relationship of short-term depression to posthypoxic frequency decline has yet to be determined.

Chemical blockade of ventrolateral pontine activity prevents prolongation of time in expiration and the short-term decline in respiratory frequency after hypoxia, with no effect to the response to hypoxia (15, 17). Chemical stimulation of the ventrolateral pons prolongs time in expiration without affecting inspiratory time. Expiratory-modulated ventrolateral pontine activity increases after hypoxia (17). Thus plasticity expressed transiently in the respiratory pattern as a decrease in frequency after hypoxia may be mediated by changes in network influences of connections between the medullary respiratory pattern generator and lateral pontine nuclei.

Functional pontomedullary interconnectivity is not understood despite anatomic data suggesting reciprocal projections among nuclei (24, 37, 40, 69, 90, 103). Although anatomic studies have revealed dense projection between the pontine respiratory group (PRG) and Böt-VRG, physiological studies have described the projections from (and to) respiratory-modulated neurons in the PRG to (and from) Böt-VRG as diffuse and scant (8, 41, 92). A study on the functional connectivity between neurons in PRG and Böt-VRG (85) found evidence for connectivity in only 7% of 255 pairs of simultaneously recorded pontine-medullary respiratory neurons. In this study of vagotomized animals, inspiratory, inspiratory-expiratory phase spanning, and decrementing expiratory activities were recorded in the pons. Neurons with these firing patterns could contribute to inspiratory phase termination if they inhibited Böt-VRG inspiratory neurons. Although pairs with pontine references with these firing patterns and Böt-VRG inspiratory target neurons accounted for nearly 50% of the cross-correlation histograms tested, they were components of only 5 of the 15 cross-correlation histograms with significant features. In only one case was monosynaptic connectivity likely.

Long-term facilitation (LTF), an increase in respiratory motor output that persists more than 1 h, is another type of plasticity and a robust type of memory. LTF is induced by repeated hypoxia, chemical stimulation of carotid chemoreceptors, or electrical stimulation of the carotid sinus nerve or brain stem midline but not by hypercapnia (4, 35, 52, 54, 58, 62, 63, 97). In vagotomized cats, LTF can increase integrated phrenic nerve amplitude to approximately twice that of baseline. Induction of respiratory LTF requires repeated brief, intermittent, but not extended, stimulation (62,

**A** Cross-correlogram (rVRG - cVRG)

44.8 (Spikes sec⁻¹)  Control 1

40.0 (Spikes sec⁻¹)  Control 2

58.9 (Spikes sec⁻¹)  LTF

Time (ms)

**B** JPSTH surprise matrix (significant bins)

-2.996    4.605

Time (ms)  0    200.0

rVRG

LTF

Control    LTF  cVRG

190

242.3

Time (ms)  0    200.0

**D** 'Ratchet' mechanism for incremental potentiation

Raphe

Böt-VRG

Response to chemoreceptor stimulation

Transient

Delayed, sustained

Stimulus

**C**

Raphe

Böt-VRG

DRG

I Driver

I-AUG

I-DEC

I-AUG

I-AUG

Phrenic

2 sec

Functional connectivity

○ Excitatory
● Inhibitory
◢ Modulatory

Changes with LTF

↑ Increased firing rate
↓ Decreased firing rate
⬤ Increased synchrony/effective connectivity

**E**

LTF

Control

∫ Phrenic

Time (s)

124.4

97) analogous to the stimulus protocols necessary for the induction of the late phase of long-term potentiation (47).

Current theories propose that memory storage, retrieval, and expression are reflected in patterns of coincident neural network activity, i.e., distributed synchrony (3). Measures of spike train firing rates and correlations in respiratory-related medullary sites following induction of LTF have revealed changes in neuron activity and synchrony (63). Unlike studies of hippocampal long-term potentiation (47), the analysis of the brain stem respiratory network before and after the induction of LTF offers the advantage of having direct physiological linkages between detected changes in effective connectivity and the expressed memory, i.e., specific changes in the motor pattern generated by the network under observation. Altered connectivity among Böt-VRG and medullary raphe neurons was identified in spike train data sets that met the following criteria (63): *1*) the constituent neurons had respiratory-modulated firing patterns, *2*) significant changes in firing rate during carotid chemoreceptor stimulation were correlated with altered respiratory efferent activity, *3*) persistent firing rate changes were expressed during LTF, *4*) there was evidence of effective connectivity at circuit sites appropriate to contribute to LTF, and *5*) changes in effective connectivity as measured by cross-correlation histograms after induction of LTF were greater than those during different control periods.

The results supported the hypothesis that changes in firing rates and synchrony of Böt-VRG premotoneurons and altered effective connectivity among other functionally antecedent elements of the brain stem respiratory network (Fig. 1, *A–C*), including raphe neurons, contribute to the expression of LTF. Subsequent research has shown similar changes in synchrony with training in other motor systems (84). The changes in effective connectivity and firing rate with LTF and the inferred relationships are consistent with the hypothesis that serotonergic neurons are necessary for the expression of LTF (36, 54, 62). Modulatory transmitters, such as serotonin, could act on synaptic mechanisms or alter the excitability of the premotoneurons directly (63, 99), possibly through changes in the amplitude of spike after hyperpolarization mediated by small-conductance $Ca^{2+}$-activated $K^+$ channels (82, 98, 99).

The suggestion that LTF is a consequence of both pre- and postsynaptic changes in I-Driver-to-premotoneuron connectivity (Fig. 1; see Fig. 2 for detailed network description) is consistent with emerging principles of network plasticity and reconfiguration. During the reconfiguration process, neurons switch roles to serve different operations and contribute to adaptive behaviors. These changes in behavior may be automatic or learned and, in either case, may outlast the inducing stimuli or training paradigm. Invertebrate systems (49) have provided insights into mechanisms of plasticity that underlie network reconfiguration (48, 50). In the lobster, stimulation of foregut mechanoreceptors suppresses participation of the ventral dilator neuron in the pyloric network while promoting a role for the same neuron in the cardiac sac network (38). This transformation requires cooperative modification

Fig. 1. *A* and *B*: altered firing synchrony of I-Driver-ventral respiratory group (VRG) inspiratory neuron pair after induction of long-term facilitation (LTF). *A*: a narrow offset peak with a positive 0.5-ms time lag documents the increased firing probability of a caudal (c) Bötzinger (Böt)-VRG inspiratory neuron following spikes in a more rostral (r) Böt-VRG neuron. *Top* two cross-correlograms were calculated from 2 samples of spike data recorded before induction of LTF (*top*: DI = 10.7, 8,267 reference and 4,892 target spikes; *middle*: DI = 10.6, 8,216 reference and 4,569 target spikes). *Bottom* correlogram was calculated from a 300-s sample recorded after LTF induction (DI = 12.4, 8,170 reference and 5,892 target spikes). *B*, *left*: surprise matrix derived from a normalized joint peristimulus time histogram (JPSTH, *right*) calculated from interleaved samples of spike data from the neurons represented in *left*. The data consisted of 1,760 concatenated control and LTF data segments, each 200 ms in duration. Arrows indicate pre- to postinduction border. Note that the *top left* and *bottom right* quadrants represent correlations of spike trains that are actually disjoint many minutes in time. The increased number of significant bins along the diagonal in the *top right* quadrant indicates an increase in effective connectivity after LTF. *B*, *right*: smoothed (gaussian of 2 bins) histogram that is a tally of corresponding paradiagonal bins in the surprise matrix; the pairs of neurons discharged more synchronously after induction of the respiratory memory. Calculation was based on 12,960 rostral Böt-VRG neuron spikes and 10,546 caudal Böt-VRG cell spikes. *C*: graphical summary of changes in brain stem neuron firing rate and effective connectivity with LTF and related hypotheses. Support for the hypothesis that distributed brain stem processes contribute to the expression of the respiratory memory includes *1*) observed increases in the firing rates of putative dorsal respiratory group (DRG) and Böt-VRG premotoneurons and modulatory raphe neurons (up arrows in representative "cell bodies") and *2*) increased synchrony or effective connectivity (circled arrows). I-AUG, inspiratory neurons with augmenting firing rates; I-DEC, inspiratory neurons with decrmenting firing rates. *D*: graphical representation of a possible mechanism for the "ratcheting" of LTF with transient repeated episodes of peripheral chemoreceptor stimulation. Some potential sites of modulation are shown in *C*. *E*: gravitational representation of concatenated spike data with repeated patterns of synchrony before and after induction of LTF. Correlations were evaluated with the gravity method (25, 26). Each of the neurons was represented as a particle in *N* space with a time varying charge that was a filtered version of its spike activity. Near-coincident spiking caused particles to aggregate. Next, the spike trains were screened for evidence of recurring transient assembly configurations, which are patterns of activity matching within defined parameters that repeated more often than predicted by chance (46). Two recurring patterns of synchrony are shown (designated *a* and *b*), displayed as 2 sets of aggregation velocity vectors with common origins at their times of occurrence. Pattern *a* (gray) occurred only before LTF; pattern *b* (black) occurred only after LTF. [From Ref. 63, with permission from The Physiological Society.]

of both pre- and postsynaptic sites in the induction of a persistent switching of neuronal function (65).

In a striking parallel to the induction of LTF, albeit in the direction of disfacilitation, operant conditioning has been demonstrated in the freshwater snail, *Lymnaea stagnalis*. Brief repetitive aversive stimuli produced persistent decreases in cyclic breathing behavior and in the activity of central pattern generator neurons (91).

Respiratory neurons are commonly described by the phase of the respiratory cycle in which they are most active and are further categorized as augmenting, decrementing, early, late, and so forth, depending on their patterns of discharge. Another useful classification scheme is based on the strength and consistency of the respiratory signals of neurons, using the $\eta^2$ measure derived from an analysis of variance (71). High-$\eta^2$-valued cells are tightly locked to the respiratory cycle by regular temporal sequences of excitatory and inhibitory postsynaptic potentials, whereas low-$\eta^2$-valued cells may have mixtures of respiratory and nonrespiratory inputs. Orem and co-workers (70, 72) have proposed that low-$\eta^2$-valued cells are the interface between nonrespiratory inputs, such as those used in learned behavioral control. A study of cats trained to stop inspiration behaviorally suggests that phase termination is not mediated by cells with proposed inspiratory-inhibitory actions during eupnea (70). Augmenting expiratory cells with inhibitory actions on inspiratory cells are not activated during behavioral inhibition of inspiration. Indeed, these cells, like most high-$\eta^2$-valued cells of all classes, are inactivated during the behavioral response. However, other inspiratory, expiratory, and phase-spanning neurons with low $\eta^2$ values are activated intensely during behavioral inspiratory inhibition (70). This result is consistent with the hypothesis that these neurons can integrate nonrespiratory inputs and influence pattern generation when necessary but otherwise do not interfere with breathing (72).

The response profiles of concurrently monitored raphe neurons to carotid chemoreceptor stimulation vary; the firing rates of some increase transiently at the onset of carotid chemoreceptor stimulation and decline as a delayed increase in others develops (58). These distinct response properties and related short-time scale correlations indicative of recurrent inhibitory connections led to the proposal of a "ratchet" model in which *1*) neurons with the transient response contribute to the generation of the facilitated state during states of high firing rate and *2*) inhibitory actions of the delayed responders could play a role in limiting the amount of potentiation induced with each stimulus (Fig. 1*D*).

A fundamental unanswered question in neuroscience is whether temporal patterns of neuronal activity encode information in the central nervous system (22). An adaptation of the "gravity" method of spike train analysis was used to detect pair-wise patterns of synchrony of spikes in five samples from the set of raphe neurons that met the above criteria (46, 63).

Patterns that had more matches in the real data set than in 100 randomized control data sets were reported as significant. The average number of matching patterns in the five samples before LTF was $18.8 \pm 3.6$ (SD). There were $56.8 \pm 10.0$ (SD) significant patterns that repeated both during control and LTF, whereas $11.8 \pm 3.9$ (SD) patterns were found only during LTF. An example of recurring patterns of spikes in concatenated samples of the recording of five spike trains from before and after LTF is shown in Fig. 1*E*. Each set of vectors with a common origin represents a particular pattern of coordinated firings. Direction of the vectors denotes a specific pair, whereas length corresponds to synchrony. Reflex-induced transient and long-term configurations of pontomedullary networks generate spatiotemporal patterns of synchrony, which are not apparent in conventional measures of firing rate. Such nonrandom patterns of coincident spikes in parallel channels may play a role in the internal operations of the respiratory network (2) and act on the Böt-VRG network, contributing to the expression of LTF.

Available data suggest that LTF involves multiple brain stem and spinal sites in the sensory-motor pathway. Persistent motoneuron membrane changes are important for the maintenance of LTF (23, 42). "Recruitment" of increasing numbers of participating loci may represent an "escalation" as the organism experiences persistent or prolonged patterns of hypoxia (30). This hypothesis is consistent with emerging views of motor learning in other systems. The vestibuloocular reflex is an eye movement driven by vestibular signals; it maintains visual targets during movements of the head by producing eye movements in the opposite direction. The gain of this reflex (the ratio of eye velocity to head speed) can be modified by a cerebellum-dependent type of oculomotor learning that compensates for conditions where this ratio departs from unity. The neural circuits mediating the different types of eye movement behavior have been studied extensively (79) and include parallel pathways from the vestibular afferents to the oculomotor neurons. Plasticity in both the vestibular nuclei and in a pathway through the cerebellar cortex mediates the adaptive gain control.

Responses of many respiratory neurons during and after induction of LTF have only been measured for a time span on the order of several minutes (62, 63). It is probable that the contributions to LTF of these adaptive neural networks continue to change during the expression of a memory that persists for hours.

## NETWORK RECONFIGURATION

*Injury.* Respiratory patterning and plasticity are altered after cervical spinal cord injury ($C_2$ hemisection). The crossed phrenic phenomenon refers to the fact that respiratory activity can be evoked ipsilateral to the injury. Activity can be evoked by asphyxia shortly (1–2 h) after the injury (29), and spontaneous inspiratory activity is apparent after 1–2 mo. This activity is due to bifurcation of the bulbospinal respiratory premotoneurons (28). In as little as 4 h and for as much as 17

mo after hemisection, serotonergic, glutamatergic, and GABAergic terminals on phrenic motoneurons are larger on the hemisected side than on the intact side (12, 94, 95). Blockade of serotonergic metabolism before transection prevents these changes, and addition of a serotonergic agonist after the injury increases the evoked activity.

After $C_2$ hemisection, plasticity not only occurs segmentally but also supraspinally (27). Respiratory rate was shown to increase after hemisection (29). The increased rate remained in spontaneously breathing, vagally intact anesthetized animals at 1 and 2 mo. After vagotomy, the respiratory rates were not statistically different between sham-operated and hemisectioned rats. With vagotomy in the 2-mo survivors, respiratory rate was 25% slower than in vagotomized sham-operated controls during normocapnia (27). During hypercapnia, the respiratory rates were not significantly different; during hypoxia, the hemisected animals had significantly greater respiratory rates than controls. Furthermore, the motor amplitude response decreased coincident with the increased respiratory rate response (27). At 2-mo posthemisection, the evoked increase in the amplitude of both phrenic and hypoglossal neurograms was attenuated during hypercapnia. These data indicate plasticity occurring in the pontomedullary respiratory pattern generator.

Similar to that shown in the acute studies, the changes 2 mo after hemisection depended on serotonin. Pretreatment with the serotonin neurotoxin 5,7-dihydroxytryptamine prevented the effects of $C_2$ hemisection on contralateral phrenic neurogram amplitude and normalized the change in respiratory rate during hypoxia. These results suggest that there are neuroplastic changes in segmental and brain stem respiratory motor output after $C_2$ hemisection that coincide with the spontaneous recovery of some ipsilateral phrenic function. Some of these effects may be modulated by serotonin-containing neurons.

*Cough.* Current understanding of cough can be summarized as follows. A cough is elicited by stimulation of central airway receptors that project via vagal afferents to second-order neurons in the nucleus tractus solitarii (9, 45). These second-order neurons project to areas of the brain stem known to contain populations of neurons involved in respiratory control (21). Recent data support the hypothesis that ventrolateral medullary respiratory neurons generate the cough motor patterns of respiratory pump and laryngeal muscles (5, 86, 87).

The act of coughing is produced by concurrent and sequential changes in the activation pattern of laryngeal and thoracoabdominal respiratory muscles. A cough usually begins with an enhanced inspiration due to contraction of the diaphragm and other inspiratory muscles acting in concert with the muscles that enlarge the upper airways (abductors). Next, the compressive phase is brief and is differentiated by continued activity in the diaphragm and nearly simultaneous activation of expiratory thoracic and abdominal muscles as well as upper airway muscles that close the

laryngeal folds (adductors). In the subsequent expulsive phase, the diaphragm ceases activity and the glottis opens as the adducting muscles relax and the abductors contract; the continued strong expiratory muscle activity results in high airflow velocities (44, 83, 87, 101).

Data that support a model (Fig. 2*A*) for the participation of ventrolateral medullary respiratory neurons in the generation of the cough motor pattern of respiratory muscles have been published (5, 86, 87). The differential responses of the same simultaneously recorded respiratory neurons to peripheral chemoreceptor and airway stimulation illustrate the distinction between modulation during a response to a change in chemical drive and plasticity of the network in the production of cough (Fig. 2*B*). Neurons with decrementing expiratory firing patterns during eupnea reveal the same pattern and order of activity during peripheral chemoreceptor stimulation, reflecting activation of corresponding respiratory muscle activity (Fig. 2*B*, *right*). During cough, the activity of one cell diminished (Fig. 2*B*, *top left*), while that of the other, an expiratory laryngeal motoneuron (Fig. 2*B*, *bottom left*), had a shifted onset time and peak firing frequency that was associated with the simultaneous activation of inspiratory and expiratory muscle activity during the compressive phase of cough.

## FUTURE DIRECTIONS AND POTENTIAL CLINICAL IMPLICATIONS

LTF is induced by intermittent hypoxia but not by hypercapnia (62, 97). Transient stimulation of either peripheral or central ($CO_2$ and pH sensitive) chemoreceptors increases ventilation; however, the two systems differentially influence rate, tidal volume, and the duration of changes in the respiratory motor pattern. A preliminary inquiry to address these disparities examined the responses of PRG, raphe, and Böt-VRG neuronal activity to selective stimulation of both peripheral and central chemoreceptors (68). Neurons were recorded simultaneously with the use of multielectrode array technology; phrenic neurograms were monitored concurrently. Peripheral and central chemoreceptors were stimulated selectively by 30- to 40-s injections of $CO_2$-saturated saline via the external carotid artery (0.2–1.0 ml) or the vertebral artery (1.0 ml), respectively. In an initial evaluation of the direction of firing rate, changes suggest that central and peripheral chemoreceptor inputs are processed differently; however, some pontine and medullary network resources are shared.

Sleep disorders that disrupt breathing are associated with a multitude of disorders and risks such as the development of learning disabilities (7, 31), sudden infant death (33), pulmonary and systemic hypertension (81), Parkinson's disease, and autonomic dysfunction and other disorders and risks (1, 10, 13, 14, 32, 51, 64, 88, 96). Sudden infant death syndrome (SIDS) is the unexpected death of a seemingly healthy infant. SIDS is the most common cause of death in infants

Fig. 2. *A*: network model for control of cough and response to peripheral chemoreceptor stimulation. "Ball-and-stick" model is shown of ventrolateral medullary respiratory neuronal network connections together with inputs from nucleus tractus solitarius (NTS) 2nd-order neurons that receive "cough" receptor, pulmonary stretch receptor (PSR; PUMP cells), and carotid chemoreceptor (chemo) afferents. The network includes I-Driver neurons, inspiratory neurons that are also active before the expiratory-inspiratory phase transition; they have a relatively constant discharge rate throughout the inspiratory phase. This category is specifically limited to rostral Böt-VRG neurons with evidence of excitatory connections to other I neurons (6). I-AUG neurons include bulbospinal neurons with axonal projections to the spinal cord [does not exclude collateral axons in the brain stem and propriobulbar neurons with axons confined to the brain stem (not shown)]. Expiratory neurons with decrementing firing rates (E-DEC) are most active during the early-expiratory (postinspiratory) interval. Expiratory neurons with augmenting discharge patterns (E-AUG) also include bulbospinal (BS) cells. Early E-AUG neurons begin to discharge early in the phase and are active throughout. The activity of late E-AUG neurons is limited primarily to the late part of the expiratory interval (stage 2 expiration). Input from carotid chemoreceptors is relayed via NTS 2nd-order neurons to I-AUG premotoneurons producing increased inspiratory ramp. E-DEC and E-AUG neurons are also excited, limiting inspiratory and expiratory phase duration, producing an increase in respiratory frequency. For detailed descriptions of the model, see Refs. 57, 58, 63, 86, and 87. PHR MN, phrenic motoneurons; Exp, expiratory. *B*: firing rate histograms of 2 types of decrementing expiratory neurons during eupnea: cough (*left*) and stimulation of carotid chemoreceptors by close arterial injection of $CO_2$-saturated saline solution (*right*). See text for detailed description. ∫PHR, integrated phrenic nerve; ∫IL10, integrated lumbar iliohypogastric nerve. The c in circle is 2nd-order chemoexcitatory in synapse key. [Reprinted from Ref. 62, with permission from Elsevier Science.]
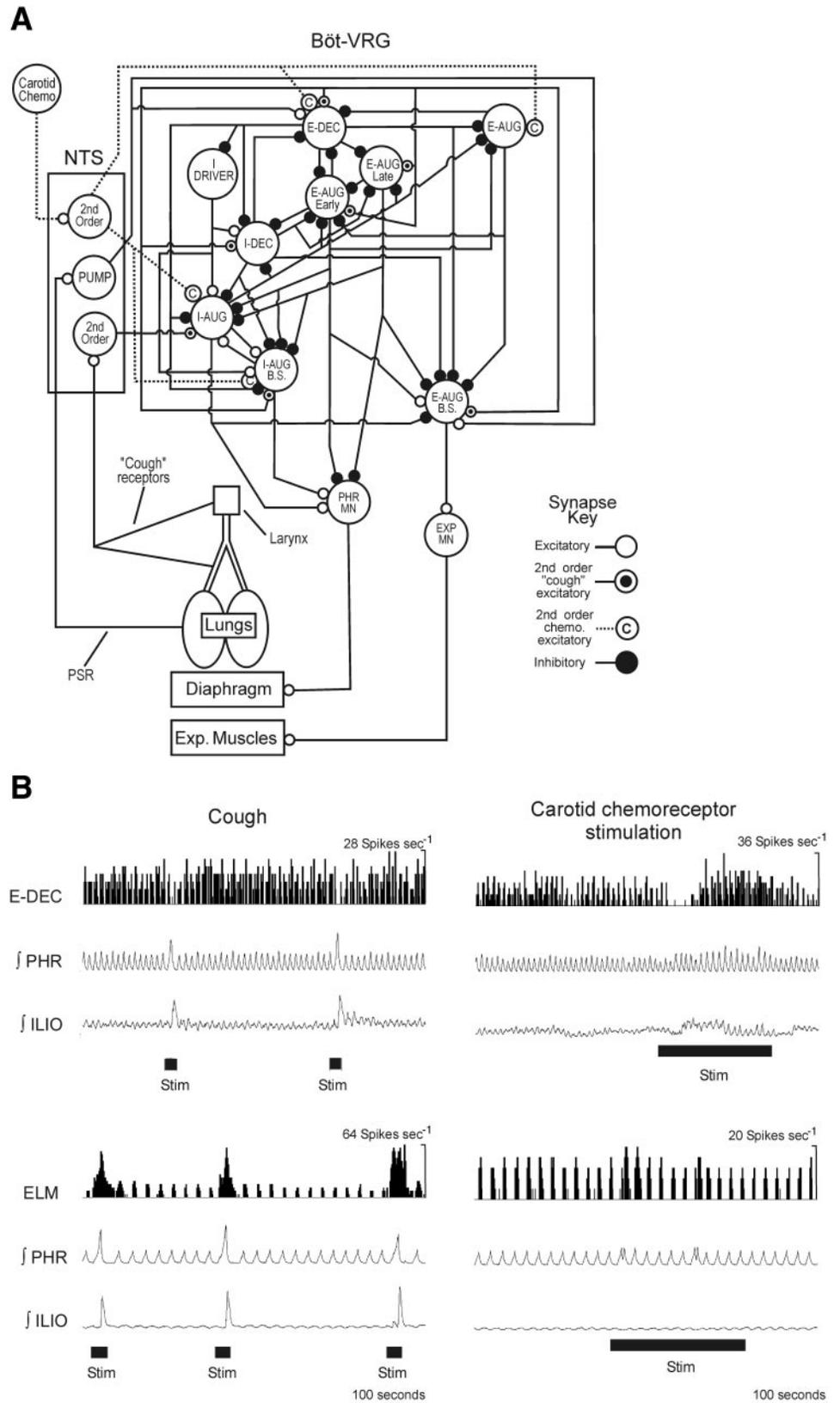


between 2 wk and 1 yr of age. The mechanisms underlying a portion of the SIDS cases appear to have origins in the fetal environment resulting in neural damage that later compromises responses to breathing or blood pressure challenges during sleep. The deficits appear to involve alterations in neural network function within regions involved in oxygen-sensing and cardiovascular control (33, 34). Kinney and co-workers (43)

proposed "the medullary serotonergic network deficiency hypothesis" in which a developmental abnormality in serotonergic neurons in the caudal raphe results in a failure of protective responses to life-threatening stressors during sleep.

Approximately 18 million Americans suffer from sleep apneas (67). Sleep apneic patients are at risk for developing hypertension (16, 39, 66). Although hypoxemia is intermittent during the sleep apneic periods, hypertension is constant. Sustained hypertension must be caused by something in addition to the transient hypoxemia (80). This risk for morbidity is associated with an "upregulation" of sympathetic nerve activity, similar to LTF, associated with intermittent and repetitive hypoxic events during sleep (18, 19, 39). Furthermore, these effects are reversed when apnea is eliminated with treatment (66). The neural mechanisms for this upregulation of sympathetic nerve activity are unknown. One mechanism may be coupling between the respiratory and cardiovascular control systems.

Not only is sympathetic activity modulated with the respiratory cycle but also this modulation is dynamic, i.e., it increases during and after hypoxia. The neural substrate for this interaction is undefined. Recent studies have focused on neuronal interaction between medullary respiratory-modulated and premotor sympathetic neurons of the rostral ventrolateral medulla and the depressor and pressor regions of the caudal ventrolateral medulla (59–61, 73, 74, 93). As previously noted, persistent changes in activity and effective connectivity of neurons in the caudal raphe nuclei and VRG have been implicated in expression and maintenance of respiratory LTF (4, 35, 52, 57, 58, 63). Recent preliminary results suggest that putative pressor neurons in the caudal-most caudal ventrolateral medulla (cCVLM) respond to hypoxic episodes with increased activity. Recordings of hypoxia-responsive raphe nuclei neurons have transient firing rate modulations correlated with those caudal ventrolateral neurons (60, 61).

In an attempt to further delineate the sources of respiratory modulation of sympathetic activity, another study measured discharge patterns and functional connectivity of neurons in the Böt-VRG, caudal ventrolateral medulla, and midline raphe along with respiratory motor and sympathetic nerve activity during hypoxic stimulation (60). In four multi-array recordings made in two cats, extracellular activity of single neurons and phrenic and splanchnic or cervical sympathetic neurograms were monitored during hypoxia and baroreceptor stimulation. Cells were recorded simultaneously in the Böt-VRG, raphe, and cCVLM. Neurons monitored in all three regions had firing rate modulations correlated to the cardiac and/or respiratory cycles and rate changes during hypoxia. Putative pressor neurons in the cCVLM showed increases in activity during both hypoxia and lowered blood pressure. These results suggest that neurons in that pressor region of the brain receive inputs from respiratory neurons.

The aim of a related study (59) was to measure discharge patterns and functional connectivity of neurons in the pons, Böt-VRG, and caudal raphe during hypoxic stimulation. Recordings were made in two decerebrated, vagotomized, thoracotomized, paralyzed adult cats. Discharge patterns of many single neurons in the pons, Böt-VRG, and caudal raphe were recorded together with phrenic nerve, heart rate, and blood pressure during stimulation of carotid chemoreceptors, the main sensors of blood oxygen tension. Neurons in all three regions had firing rate modulations correlated to the cardiac and/or respiratory cycles and showed rate changes during stimulation. Short time scale correlations between responsive pontine and medullary neurons provided evidence of effective connectivity among neurons in the monitored sites, supporting a model of a distributed pontomedullary cardiorespiratory control network. The effective connectivity was appropriate to contribute to sympathetic efferent responses (59).

The plasticity of the respiratory brain stem underlies numerous adaptive and reactive transformations in both normal and pathophysiological conditions, from overcoming the resistive load of sleep apneas to the autoresuscitation function of gasping (78). Some responses, such as coughing, which protects the airways, are triggered quickly; other changes may require perturbations that are extended (STP) or repeated (LTF) for their full expression. Improved methods of diagnosis and treatment of cardiorespiratory diseases such as sleep apnea and SIDS require an understanding of the brain mechanisms that control and coordinate the respiratory and cardiovascular control systems in the maintenance of homeostasis.

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