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Bursting Neural Networks: A Reexamination

Abstract. *Many of the motor neurons in the lobster (*Panulirus interruptus*) stomatogastric ganglion exhibit plateau potentials; that is, prolonged regenerative depolarizations resulting from active membrane properties, that drive the neurons to fire impulses during bursts. Plateaus are latent in isolated ganglia but are unmasked by central input. These findings emphasize the role of cellular properties as compared to synaptic wiring in the production of cyclic motor patterns by ensembles of neurons.*

The bursting motor patterns underlying cyclic behaviors such as walking, chewing, and breathing have been attributed to two major types of mechanisms. (i) Bursting might arise as an emergent property of synaptic interactions among passive neurons having only simple capabilities such as repetitive firing of impulses. (ii) Alternatively, it might arise from the special active regenerative membrane properties of individual neurons, as in endogenously bursting neurons. The stomatogastric ganglion (STG) of lobsters can be used for studying rhythm generation. Its approximately 30 neurons can be individually identified; synaptic connections among them have been extensively described (Figs. 1B and 2A). The neurons produce two different rhythms underlying cyclic behaviors of the stomach during food digestion (*1*). The slow gastric rhythm has been considered as emerging from the network of synapses among 12 passive neurons (*2, 3*). For the faster pyloric rhythm, the 11 follower neurons have been considered to be passive and to be synaptically controlled by a separate group of three endogenous bursters (*1, 3, 4*). We have reexamined the properties of all the "passive" neurons, and have found that many have active regenerative membrane properties contributing to their bursting. Further, we have found that these special properties become evident when a neuron is under the influence of inputs from the central nervous system (CNS) (*5*).

We dissected the stomatogastric nervous system of the spiny lobster (*Panulirus interruptus*) and transferred it to a saline-filled dish (*6, 7*). A diagram of the preparation is shown in Fig. 1A; this preparation was used unless otherwise stated because, compared with the weak output of the isolated STG, both the gastric and pyloric rhythms remained quite active if the commissural ganglia from the CNS were left connected to the STG (*8*). In some experiments, the STG was isolated by cutting the "input" (stomatogastric) nerve (Fig. 1A), and the whole nerve was stimulated to drive command-fiber inputs to the STG (*9*). Identified neuron somata in the STG were impaled with double-barrel microelectrodes, or with two single electrodes, for conventional intracellular recording and current injection. It was essential to show that the evoked responses described here were due to the intrinsic properties of a neuron under study, rather than to synaptic network interactions. Given the known synaptic circuitry of the STG (see Figs. 1B and 2A), this was done by checking that responses were not associated with significant changes in the firing of any presynaptic neurons, monitored in extracellular nerve records. Also, presynaptic neurons were sometimes impaled and their firing directly controlled with intracellularly injected current to eliminate network interactions.

Our main finding is that many STG neurons have the capability of generating "plateau potentials": prolonged regenerative depolarizations resulting from intrinsic membrane properties and contributing to the production of bursts. Other examples of plateaus include the prolonged action potentials in heart muscle of vertebrates, and the spontaneous depolarizations in endogenously bursting neurons of crustaceans and mollusks (*10*). Such plateaus derive from a sustained negative-resistance characteristic of a cell's membrane. Several criteria were adapted from previous studies (*10*) to identify plateau-potential characteristics in STG neurons: (i) the occurrence of relatively large (for example, 5 to 20 mV) oscillations in membrane potential; (ii) the ability, when brief pulses of current are used (about 20 to 50 msec, 1 to 5 nA), to cause all-or-none transitions between a resting region of membrane potential and a more depolarized relatively stable (plateau) region of potential (*11*), at which a neuron typically fired impulses; (iii) the requirement for currents above a threshold intensity to cause transitions; and (iv) in certain cases, the production of bursts by a neuron when all the patterned synaptic input to it was abolished (*7, 12*).

Plateau characteristics are illustrated in Fig. 1 with the CP neuron (*13, 14*). During spontaneous gastric rhythms, the cell showed large oscillations of membrane potential with bursts of spikes occurring on the depolarized phases (Fig. 1C). Bursts were suppressed by a steady hyperpolarizing current, leaving smaller oscillations of membrane potential presumably due to synaptic input (Fig. 1D, left). A brief depolarizing current pulse then could trigger a response (burst) that outlasted and grew after the stimulus [that is, was regenerative; Fig. 1, D (right) and E]; a passive neuron would at most have fired only while the stimulus current was on. Once initiated, a response could be terminated by a brief hyperpolarizing pulse (Fig. 1F). Both the

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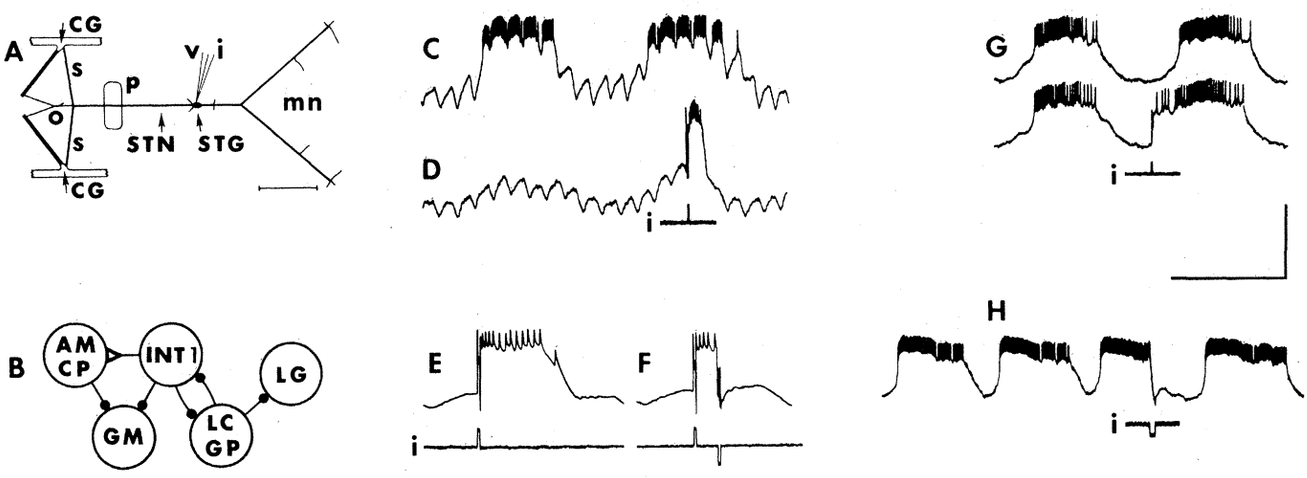

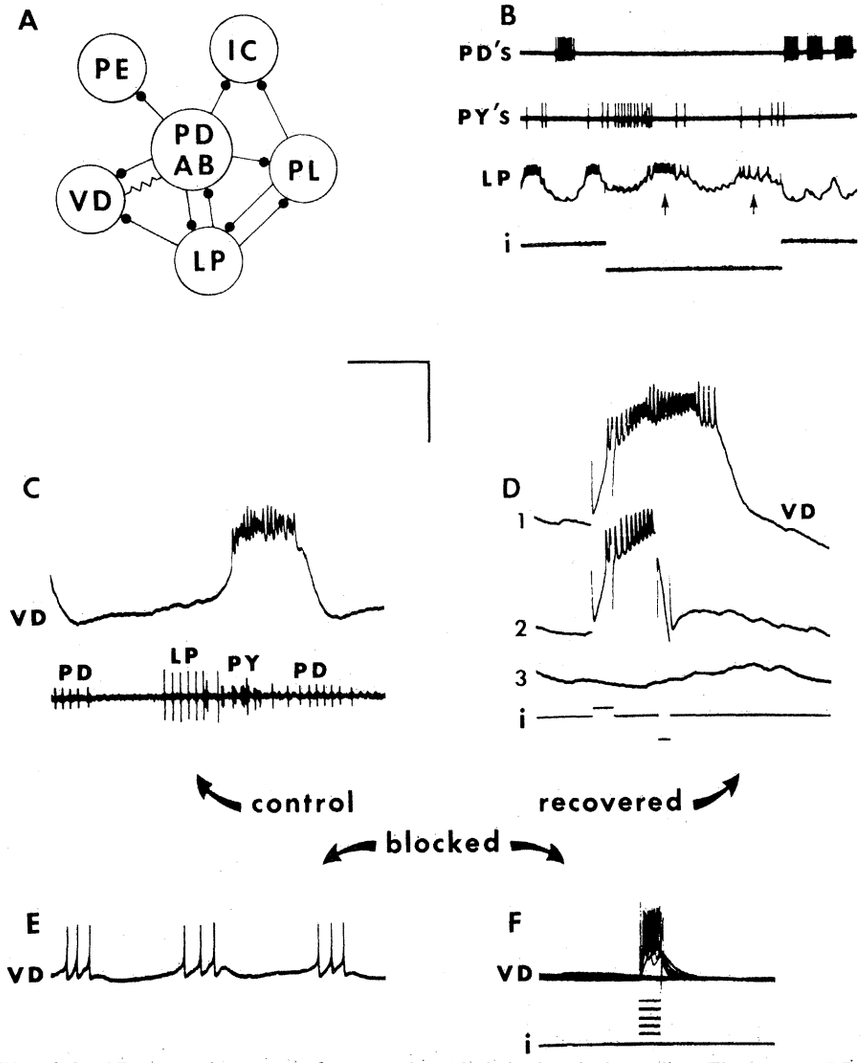

Fig. 1 (above). (A) Scale diagram of the preparation used. Abbreviations: *CG*, commissural ganglion; *i*, current-injecting electrode; *mn*, motor nerves to stomach muscles; *o*, esophageal ganglion; *p*, Vaseline pool for sucrose nerve blockade; *s*, superior esophageal nerve; *STG*, stomatogastric ganglion; *STN*, stomatogastric nerve; *v*, recording electrode. Calibration: 1 cm. (B) Simplified diagram of gastric neuron interconnections. Solid circles indicate IPSP's; the triangle indicates a functional excitatory connection. See (*13*) for cell names. (C) Intracellular record from CP neuron during two spontaneous bursts of ongoing gastric rhythm; see (*14*). (D) Same CP neuron as (C), two cycles of CP subthreshold activity when hyperpolarized by 2.0 nA. During the second cycle (right), a plateau potential was triggered by a 50-msec 4.5-nA depolarizing current pulse (*i*). (E) In another CP hyperpolarized by 1.6 nA, a plateau was triggered by a 20-msec 4.7-nA depolarizing pulse, and (F) was later terminated by a similar hyperpolarizing pulse. (G) Another CP, without any polarization. The superior esophageal nerves were cut to eliminate "fast" modulation (*14*). Upper trace: control interval between ongoing bursts. Lower trace: premature initiation of a burst by a 50-msec 1.5-nA pulse; note the gastric rhythm was not reset. (H) Another nonpolarized CP; a spontaneous burst was terminated by a 230-msec 1.5-nA pulse; a large gap occurred afterward. Time calibration: (C, D, G, and H) 5 seconds; (E and F) 1 second. Voltage: (C, D, E, F, and G) 20 mV; (H) 40 mV. Current: (D, E, and F) 20 nA; (G and H) 10 nA. Data slightly retouched. Fig. 2 (right). (A) Simplified diagram of pyloric neuron interconnections. Resistor symbol: electrotonic connection. The pyloric rhythm is basically driven by the three electrically coupled, endogenously bursting PD/AB neurons. (B) Intracellular record from LP neuron (third trace) during intracellular application of hyperpolarizing current (*i*) to a PD neuron to shut off both PD neurons [monitored on first trace, a nerve record of "pdn" (*13*)] and the AB neuron by spread of current through their electrical coupling. The last two LP bursts (arrows) could not be attributed to modulation from PL neurons [monitored on second trace, a nerve record of "pyn" (*13*); PY's include PL and PE units]. (C to F) Reversible blockade of the input nerve. (C) Central inputs intact; one cycle of ongoing pyloric rhythm with intracellular record from VD neuron and a nerve record ["v–lvn" (*13*)] of other motor neurons, with names labeled. (E) Central inputs were blocked by filling the pool in Fig. 1A with isotonic sucrose solution; weak VD bursting was due to synaptic modulation from the PD/AB bursters (*4*); compare with (C). (F) Central inputs blocked; VD showed impulses but not plateaus in response to 50-msec depolarizing pulses of 1 to 5.5 nA (*i*); individual impulses are obscured as traces are superimposed; VD was steadily hyperpolarized by 0.5 nA to stop ongoing firing. (D) Demonstration of plateau potentials in VD after reversal of nerve blockade by refilling pool with saline; VD was steadily hyperpolarized by 3.6 nA to reveal subthreshold activity (trace D3); a plateau could then be triggered by a depolarizing pulse (D1; upward deflection *i* trace; 50 msec, 2 nA) and later terminated by a hyperpolarizing pulse (D2; downward deflection *i* trace; 35 msec, 5.8 nA); compare with (F). (D and F) Oscilloscope and stimulator were synchronized to the pyloric rhythm; depolarizing pulses were given just after the end of PD burst. Time calibrations: (B and E) 1 second; (C, D, and F) 0.2 second. Voltage: LP, 40 mV; VD, all 20 mV. Current: (B) 100 nA; (D) 20 nA; (F) 10 nA. Data slightly retouched.

initiation and termination of a response required currents above certain threshold sizes (that is, the responses appeared to be voltage-dependent). This behavior was not due to network interactions because it persisted when firing of interneuron 1 was suppressed by intracellularly injected hyperpolarizing current; interneuron 1 is the main source of synaptic input to the CP from the gastric network (*2*) (Fig. 1B). Responses were most readily demonstrated with the CP hyperpolarized, but could also be shown during normal bursting; in Fig. 1G a burst was prematurely started by a brief depolarizing stimulus, and in Fig. 1H a spontaneous burst was prematurely terminated by a hyperpolarizing pulse. The CP therefore can generate plateau potentials, and its bursts during gastric rhythms behaved in many ways like plateaus superimposed on the periodic synaptic input.

The capability for plateaus was observed in four of the six types of gastric system motor neurons, including the AM, CP, GP, and perhaps the LC motor neurons (*15*). It is possible that these neurons operate as endogenous bursters under some conditions (*10, 16, 17*); if, for example, this occurred in the LC or GP, or both, they could drive the gastric rhythm and control the whole gastric network through their synaptic connections (Fig. 1B).

All five types of the pyloric-follower motor neurons also exhibited a capability for plateau potentials, both during spontaneous pyloric rhythms (with central ganglia intact), and in the isolated STG following stimulation of the input nerve (*15, 17*). Plateaus in the LP and VD were particularly strong. In the IC, early PY, and late PY, they were relatively weak during spontaneous rhythms, but were of larger amplitude and duration after input-nerve stimulation. Other cellular properties contribute to LP bursting (*10*). We found that LP bursts terminated spontaneously even when inhibition from the PL neurons was removed by hyperpolarizing them. Also, the LP would fire at least a few bursts, acting like an endogenous burster, when patterned synaptic input to it was abolished by strongly hyperpolarizing the three PD and AB neurons, which otherwise drive the pyloric rhythm (Fig. 2B).

The dependence of plateaus on central input led us to hypothesize that specific transmitter substances, released by certain inputs to the STG from the CNS, unmask or enhance a latent ability of these neurons to generate plateau potentials. Plateaus were observed if central ganglia were attached, or after input-nerve stimulation, but were usually abolished by cutting the input nerve, or by reversibly blocking the conduction of impulses in the input nerve by means of a pool of isotonic sucrose solution (*8*) (Fig. 1A). In general, during input nerve blockade, plateau responses usually could not be elicited in gastric and pyloric-follower neurons when varied test pulses and polarization levels were used; the neurons were typically silent or less active also. For example, the VD neuron showed intense plateaus as long as the input nerve was working (Fig. 2, C and D), but these disappeared completely under nerve blockade (Fig. 2, E and F). This neurally mediated unmasking effect appears similar to the enhancement of endogenous bursting in some crustacean and molluscan neurons after input stimulation or after the application of peptide hormones (*8, 18*).

The presence of plateaus during brisk motor rhythms indicates that plateau potentials are a major mechanism in the operation of both the gastric and pyloric generators. Plateaus have several implications for the properties of bursting networks. (i) The gastric and pyloric-follower networks (and perhaps others) may have a type of pattern-generating mechanism intermediate between the extremes of emergent property and endogenous burster. Plateaus would serve as a driving force for bursting; the start and end of bursts could tend to occur spontaneously but also could be controlled by a synaptic network which creates the pattern of coordination among neurons (*10*). We have observed that a barrage of excitatory postsynaptic potentials can trigger plateaus (for example, in the AM, CP, and VD) while a barrage of inhibitory postsynaptic potentials (IPSP's) can terminate plateaus (for example, IPSP's from the PB/AB neurons can terminate evoked plateaus in the pyloric-follower neurons). (ii) Alternatively, any of the neurons discussed might under some conditions act as an endogenous burster and help to drive the rhythm of its network. (iii) The regenerative character of plateaus may increase the gain of a neuron, so that a minimum of synaptic input can control transitions between an "off" state and an "on" state of strong repetitive firing. (iv) Plateaus may enhance temporal contrast, so that the firing of a neuron and its synaptic output effects (on other neurons or on muscle tension) build up and decay rapidly. (v) Plateaus may affect synaptic transmission. It is known for many STG synapses that sustained depolarization in a presynaptic neuron can modulate spike-mediated release of transmitter, or produce direct sustained release through nonspiking mechanisms (*19*). (vi) The unmasking of plateaus by CNS inputs (for example, command fibers) may have a major role in the regulation of pattern generators: how they are turned on and maintained in operation.

Up to now, synaptic connectivity has received the most attention from investigators in explaining the activity patterns of neural networks. Our results instead emphasize the significance of cellular properties (*1*), and we suggest that the tests for plateaus used here could be applied in examining the generation of rhythms in other systems (*20*).

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11. During a plateau, a relatively constant potential level (exclusive of impulses) was observed, but this constancy may have been because the firing of impulses prevented further depolarization.
12. The same tests for plateaus were applied to the PD neurons (considered to be endogenous bursters) in the isolated STG, with similar results (*7*). Direct measurement by voltage clamp of negative resistance characteristics is difficult because of the apparent inexcitability of the somata of STG cells.
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taken (with updates) from Maynard and Dando's review of stomach anatomy. Their CP (cardiopyloric), GP (gastro-pyloric), LC (lateral cardiac), and LG (lateral gastric) neurons are equivalent to the DG, MG, LG, and LPG neurons, respectively of (2). The names of other STG neurons are AM (anterior median), GM (gastric mill), Int 1 (interneuron 1), PD (pyloric dilator), AB (anterior burster), LP (lateral pyloric), VD (ventricular dilator), IC (inferior cardiac), and PY (pyloric) of which there are two subgroups, PE (early PY) and PL (late PY); D. K. Hartline and D. V. Gassie, Jr., in preparation.
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15. Although plateaus were most clearly demonstrated while a cell's firing was suppressed by steady hyperpolarization, plateau properties are present in nonpolarized cells, as we have shown for most cell types by prematurely triggering and terminating ongoing bursts with current pulses (as in Fig. 1, G and H).
16. Some of the rare spontaneous gastric rhythms in the isolated STG (2) may have been due to the occurrence of plateau potentials in gastric neurons even though central inputs were severed. We have observed the CP to burst endogenously in one such isolated STG to date.
17. Plateau behavior in the isolated STG, either spontaneous or following stimulation of the input nerve, rules out the possibility of its being due to network interactions involving neurons in central ganglia.
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20. We also tried replacement of Ca^{2+} with 1 to 5 m*M* Ba^{2+} in isolated STG's, which resulted in the occurrence of prominent plateaus in the same gastric neurons as exhibited plateaus under central input. We hesitate to use Ba^{2+} plateaus as a criterion for identifying "bursty" neurons since neurons which do not normally generate plateaus will do so with Ba^{2+} [for example, the crayfish and lobster stretch receptors; Y. Washizu, *Comp. Biochem. Physiol.* **15**, 535 (1965)].
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Norepinephrine in Chronic Paranoid Schizophrenia: Above-Normal Levels in Limbic Forebrain

Abstract. *In postmortem examination of brains of four patients with chronic paranoid schizophrenia, above-normal norepinephrine levels were measured in the ventral septum, the bed nucleus of the stria terminalis, the nucleus accumbens, and the mammillary bodies. No changes were detected in other limbic forebrain regions, including the hypothalamus and the medial olfactory (preoptic) area. The results point to the possibility of a malfunction of limbic noradrenergic mechanisms in schizophrenia, especially the paranoid variety.*

Brain catecholamines (CA), both dopamine (DA) and norepinephrine (NE), have been implicated in the pathophysiology of schizophrenia (*1*). In this respect, the evidence includes (i) the psychotogenic activity of drugs (such as *d*-amphetamine and *l*-dopa) that increase the synaptic availability of brain CA (*2*); (ii) the ability of neuroleptics with antipsychotic activity to block peripheral (*3*) and central (*4*) CA receptors; and (iii) the reduced activity of DA β-hydroxylase in the brain of schizophrenic subjects (*5*); this latter finding, however, has been disputed (*6*). [Studies on the CA-related enzymes monoamine oxidase (*7*) and DA-stimulated adenylate cyclase (*8*), as well as a preliminary study on DA and homovanillic acid (*9*), have failed to provide a uniform picture.] The limbic forebrain has been suggested as a possible seat of the behavioral abnormalities seen in schizophrenic subjects (*10*). The limbic forebrain in the rat contains not only a rich dopaminergic innervation and a DA-sensitive adenylate cyclase (*11*), but also an NE-sensitive adenosine 3′,5′-monophosphate generating system which is blocked in a dose-dependent manner by neuroleptics with antipsychotic activity (*12*). Thus, although the apparent correlation between the antipsychotic potency of neuroleptics and their action on dopaminergic systems (*13*) in general favors the view that brain DA is implicated in schizophrenia (*14*), there also is evidence suggesting a malfunction of noradrenergic mechanisms (*5, 15, 16*).

Our studies on the distribution of NE (*17*), DA (*9*), and serotonin (*18*) in the human brain have shown that NE has the strongest limbic representation of the three major brain amines in this species. Thus, the highest levels of NE in the forebrain (means of 1 to 2 μg per gram of wet tissue) occur in the hypothalamus, nucleus accumbens, medial olfactory (preoptic) area, bed nucleus of the stria terminalis, and the central amygdaloid nucleus; the nuclei of the ventral septum as well as the mammillary body and the paramedian thalamic region also contain appreciable concentrations of NE (means of about 0.5 μg/g).

We present data here on the distribution of NE in limbic forebrain regions of four patients with chronic paranoid schizophrenia. In this study postmortem brain material was used; it included the following groupings (*19*): (i) four patients diagnosed by Bleuler's criteria as chronic paranoid schizophrenics, (ii) three individuals with no diagnosed disease who committed suicide, and (iii) 12 controls with no evidence of psychiatric or neurologic disease. In an earlier study of neu-

Table 1. Norepinephrine in limbic brain areas of four schizophrenic subjects compared with controls specifically matched as to age and postmortem interval. Of a given control brain, not all of the listed regions were available for analyses. The statistical significance of differences was determined with a two-tailed *t*-test; *N*, number of controls; S.E.M., standard error of mean.

Brain region	Norepinephrine (micrograms per gram of wet tissue)				
	Controls			Schizophrenics	
	N	Mean ± S.E.M.	Range	Mean ± S.E.M.	Percentage of control
Hypothalamus, total	12	1.83 ± 0.18	0.91–2.71	1.86 ± 0.22	102
Hypothalamus, anterior	4	2.29 ± 0.31	1.48–2.29	2.07 ± 0.30	90
Hypothalamus, posterior	4	1.64 ± 0.36	0.75–2.41	1.88 ± 0.18	115
Hypothalamus, lateral	12	1.49 ± 0.12	0.89–2.20	1.63 ± 0.17	109
Nucleus accumbens	8	1.58 ± 0.16	1.21–2.36	2.40 ± 0.27*	152
Medial olfactory (preoptic) area	8	1.49 ± 0.27	0.56–2.51	1.69 ± 0.19	113
Bed nucleus of stria terminalis	4	1.23 ± 0.17	0.84–1.69	2.72 ± 0.26†	221
Ventral septum	4	0.53 ± 0.11	0.33–0.82	1.59 ± 0.24‡	300
Mammillary body	12	0.45 ± 0.02	0.33–0.58	0.69 ± 0.16§	153
Paramedian thalamic nuclei	4	0.48 ± 0.02	0.44–0.51	0.53 ± 0.06	110

*$P < .02$. †$P < .005$. ‡$P < .01$. §$P < .05$.

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