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Single-cell persistent activity in anterodorsal thalamus

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ABSTRACT

The anterodorsal nucleus of the thalamus contains a high percentage of head-direction cells whose activities are correlated with an animal's directional heading in the horizontal plane. The firing of head-direction cells could involve self-sustaining reverberating activity in a recurrent network, but the thalamus by itself lacks strong excitatory recurrent synaptic connections to sustain tonic reverberating activity. Here we examined whether a single thalamic neuron could sustain its own activity without synaptic input by recording from individual neurons from anterodorsal thalamus in brain slices with synaptic blockers. We found that the rebound firing induced by hyperpolarizing pulses often decayed slowly so that a thalamic neuron could keep on firing for many minutes after stimulation. The hyperpolarization-induced persistent firing rate was graded under repeated current injections, and could be enhanced by serotonin. The effect of depolarizing pulses was much weaker and only slightly accelerated the decay of the hyperpolarization-induced persistent firing. Our finding provides the first direct evidence for single-cell persistent activity in the thalamus, supporting the notion that cellular mechanisms at the slow time scale of minutes might potentially contribute to the operations of the head-direction system.

Head-direction cells, which signal an animal's directional heading in the environment, have been found in several anatomical areas close to the Papez circuit, including postsubiculum, anterodorsal thalamus, lateral mammillary body, posterior cingulate cortex and other brain areas in awake, behaving animals [28,29,33]. While the precise mechanism of how head-direction cell activity is generated is still unclear, several theoretical models assume that the activity arises as a self-sustained or attractor state in a recurrent network that can support reverberating activity through suitable synaptic connections [21,25–27,35,37]. Self-sustaining activity through synaptic interactions has been attributed to persistent activities in other brain areas as well, such as the oculomotor system [1,22] and the prefrontal cortex [32].

Recent physiological studies of synaptically isolated individual neurons in entorhinal cortex [9], medial mammillary body [10], and prefrontal cortex [34] suggest that intrinsic properties of single neurons can give rise to graded persistent activity with many levels of stable firing rates. The first evidence of single cell persistent firing in the head-direction system came from the postsubiculum [36]. Given these results, it is pertinent to ask whether persistent firing also exists upstream, in the subcortical structures of the head-direction system. We chose the anterodorsal thalamic nucleus because it has the highest percentage (~60%) of head-direction cells [29] and lacks extensive collaterals to provide mutually excitatory connections among the thalamic principal cells. While it is theoretically possible to build an attractor network by connecting multiple areas without resorting to excitatory connections within the thalamus [3,23,26], it is important to determine experimentally whether single-cell persistent activity exists in the thalamus, because the slow time scales of persistent activity may potentially make the system easier to stabilize.

Coronal slices from Long Evans rats (Male, p21–p35) were cut in ice-cold dissection buffer containing (in mM): 212.7 sucrose, 5 KCl, 1.25 NaH_2PO_4, 10 $MgCl_2$, 0.5 $CaCl_2$, 26 $NaHCO_3$, 10 dextrose, bubbled with 95% O_2/5% CO_2 (pH 7.4). Slices were transferred to normal artificial cerebrospinal fluid (ACSF) for at least an hour prior to recording. Normal ACSF was similar to the dissection buffer except that sucrose was replaced by 124 mM NaCl, $MgCl_2$ was lowered to 1 mM, and $CaCl_2$ was raised to 2 mM.

Visualized whole-cell current-clamp recordings were made with glass pipettes filled with intracellular solution containing (in mM): 130 K-gluconate, 2 $MgCl_2$, 5 NaCl, 0.2 EGTA, 4 MgATP, 0.5 Na_3GTP, 10 Na-phosphocreatine and 10 HEPES (pH 7.4, 270–280 mOsm). Only cells with resting potentials <−55 mV, series resistance <25 MΩ and membrane resistance >100 MΩ were studied. 10 mM kynurenic acid and 0.1 mM picrotoxin were added to the bath to block fast glutamatergic and GABAergic transmissions.

The data were sampled at 5 kHz using Igor Pro (Wavemetrics, Inc.) and analyzed with the help of NeuroMatic v1.91b (Jason Rothman), and Matlab (Mathworks, Inc.). Only cells with a lin-

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ear current/spike frequency relationship were studied (40 out of 76 cells). The remaining cells strongly accommodate and never showed the persistent activity that we intended to study.

The instantaneous firing rate between any two consecutive spikes was taken as the inverse of the inter-spike interval (grey traces in Fig. 1A). The average firing rate was calculated using a sliding 5 s time window with a step-size of 0.5 s (black traces in Fig. 1A). As the time window approached the onset of current injection, its size was allowed to shrink, reducing gradually from 5 s to a minimum size of 1 s, so as to prevent the window from starting before the onset. The same procedure was followed to calculate the firing rate traces in Fig. 3A (bottom panel).

The basal and maximum firing rates in Fig. 1B were based on average firing rates in 5 repeated sweeps, each lasting 30 s. The average firing rate was calculated using spikes occurring in the 10 s to 20 s window after the offset of the stimulus (current injection). A delay of 10 s after stimulus offset was used to reduce potential transient artifacts associated with the post-rebound increase in the firing rate. In Fig. 1B, the mean and standard deviation of the basal firing rate were based on the last five sweeps before the application of the hyperpolarizing pulses, whereas those of the maximum firing rate were based on the responses to the last five hyperpolarizing pulses, whose total number ranged from 14 to 32.

The average firing rates in both Figs. 2B and 3B were calculated similarly, using a 10 s time window that started 10 s after stimulus offset. In Fig. 2B, the average firing rates were fitted by a decaying exponential function of the form: $f = f_0 + Ae^{-t/\tau}$, where the decay time constant τ and parameters f_0 and A were obtained by minimizing the square error.

We used whole-cell patch clamp recording on single neurons in anterodorsal thalamic slice preparations to look for possible persistent activity. We studied only thalamic neurons with stable membrane potential and no spontaneous firing in order to avoid unstable cells, and injected a constant current (20–100 pA) to induce a basal firing rate (below ~10 Hz). Then we applied 4-s long hyperpolarizing pulses every 30 s. The amplitude of the pulses was adjusted such that the lowest membrane potential during the pulses lied between −75 and −80 mV. Results from a representative neuron are shown in Fig. 1A. After the offset of each hyperpolarizing pulse, the firing rate rebounded immediately and then decayed rapidly within a few seconds to a tonic level of firing rate. The tonic component of the firing rate showed a graded increase from ~1 Hz to ~6 Hz as a result of the application of the first 7–8 hyperpolarizing pulses. Application of more hyperpolarizing pulses did not increase the firing rate further, indicating a saturation point around ~6 Hz. After the train of 32 hyperpolarizing pulses terminated, the firing rate decreased monotonically to less than 2 Hz within 30 min (Fig. 1A, bottom trace). Thus the sustained increase of firing rate induced by hyperpolarization could last tens of seconds, but not tens of minutes.

The maximum sustained firing rate achieved by the application of hyperpolarizing pulses varied from cell to cell, and tended to be higher for cells with higher basal firing rates, following approximately a sigmoidal relationship, with a plateau around 14 Hz (Fig. 1B). Here the average maximum firing rate of the 5 cells with the maximum firing rates above 10 Hz was 13.5 ± 0.7 Hz. By contrast, the maximum firing rates induced by injection of 1-s long depolarizing currents were much higher than that induced by the hyperpolarizing pulses (50.7 ± 9.4 Hz for $n = 9$ cells). For example, the cell in Fig. 1A could reach at least 38 Hz under depolarizing currents (data not shown).

The hyperpolarization-induced increase in firing rate in thalamic neurons had graded levels, and thus was different from the phenomenon of firing rate potentiation, which was essentially binary [16]. Furthermore, the increased firing rate in the thalamus would decay within tens of minutes rather than lasting over many hours. To further verify this, we applied the same stimulation condition in [16] to our thalamic preparation and hyperpolarized the membrane potential by 30 mV below the resting potential for 5 min by constant current injection. We applied the procedure to 4/11 cells with stable basal firing rate under constant depolarizing current, and found that the firing rate increased temporarily but then decayed within 15 min to a level that was not significantly different from the initial firing rate (t-test, $p = 0.69$). This behavior is completely different from the stable potentiation of firing rate, which lasted for hours [16]. The remaining 7/11 cells all showed a high degree of firing rate accommodation and none of them showed any firing rate potentiation; that is, injection of constant depolarizing current failed to elicit a stable basal firing rate in these cells, and they all stopped firing completely within 5 min after the offset of constant hyperpolarizing current injection.

The hyperpolarization-induced firing rate increase in thalamic neurons is also different from the entorhinal and postsubicular persistent activities [9] and [36] which were induced by depolarization. For comparison, we applied carbachol (CCh, 100 μM) to the bath and injected a series of 4-s long, 0.3 nA depolarizing pulses for $n = 3$ thalamic cells. Unlike the entorhinal neurons, depolarizing pulses failed to induce any persistent activity in these thalamic cells although hyperpolarizing pulses led to graded increases in firing rate for 2 of these cells.

To examine how depolarizing pulses may affect hyperpolarization-induced firing in thalamic neurons, we used a series of 14 hyperpolarizing pulses to induce sustained firing, and then applied either no stimulus (control) or a series of six depolarizing pulses (4-s long, 100 pA, once every 30 s). As shown by a representative neuron in Fig. 2A and B, depolarizing pulses led to somewhat faster initial decay of the average firing rate (see Sample 3), even though the final firing rate in the presence of depolarizing pulses was similar to that in control (Sample 7). This is quantified by a summary of $n = 4$ cells in Fig. 2C and D. As shown in Fig. 2C, with positive pulses, the time constant of exponential fitting ($\tau = 29.3 \pm 3.7$ s) was significantly reduced from that of the control ($\tau = 92.3 \pm 5.2$ s) (t-test, $p < 0.0008$). However, as Fig. 2D shows, the difference between the initial and final firing rate with the administration of depolarizing pulses remained about the same as the control (2.95 ± 0.54 Hz for control, and 2.70 ± 0.75 Hz for positive pulses; t-test, $p = 0.407$).

Serotonin (5-HT) is known to modulate neuronal activities in the thalamus [14], and in particular, the anterodorsal nucleus [4–6], which has one of the highest expression levels of 5-HT_7 receptors in the brain [12,30]. Blockade of 5-HT and cholinergic receptors in the anterodorsal thalamus disrupts head-direction activity in the anterodorsal thalamus [24]. To check whether 5-HT alters the hyperpolarization-induced firing increase, we recorded the responses of thalamic neurons to a series of hyperpolarizing pulses before and after bath-application of 5-HT (20 μM). As shown in Fig. 3A, bath-application of 5-HT enhanced the observed graded increase in firing rate, and this difference became more apparent as more pulses were applied. This enhancement effect is further illustrated in Fig. 3B which compares the average levels of induced firing rates 10 s after stimulus offset for $n = 4$ neurons, either with or without 5-HT. The difference between the final firing rates reached under the two conditions was highly significant ($p < 0.0003$ in t-test on the last five data points). The sigmoidal curves are included in Fig. 3B only to guide the eyes.

We have shown that a subset of neurons in anterodorsal thalamic nucleus exhibit graded increases in firing rate in response to repeated hyperpolarizing pulses. The increase can be sustained up to several minutes while the firing rate decays gradually. Depolarization is not as effective as hyperpolarization in controlling persistent activity. Although depolarizing pulses lead initially to a faster decay of firing rate, they have little influence on the

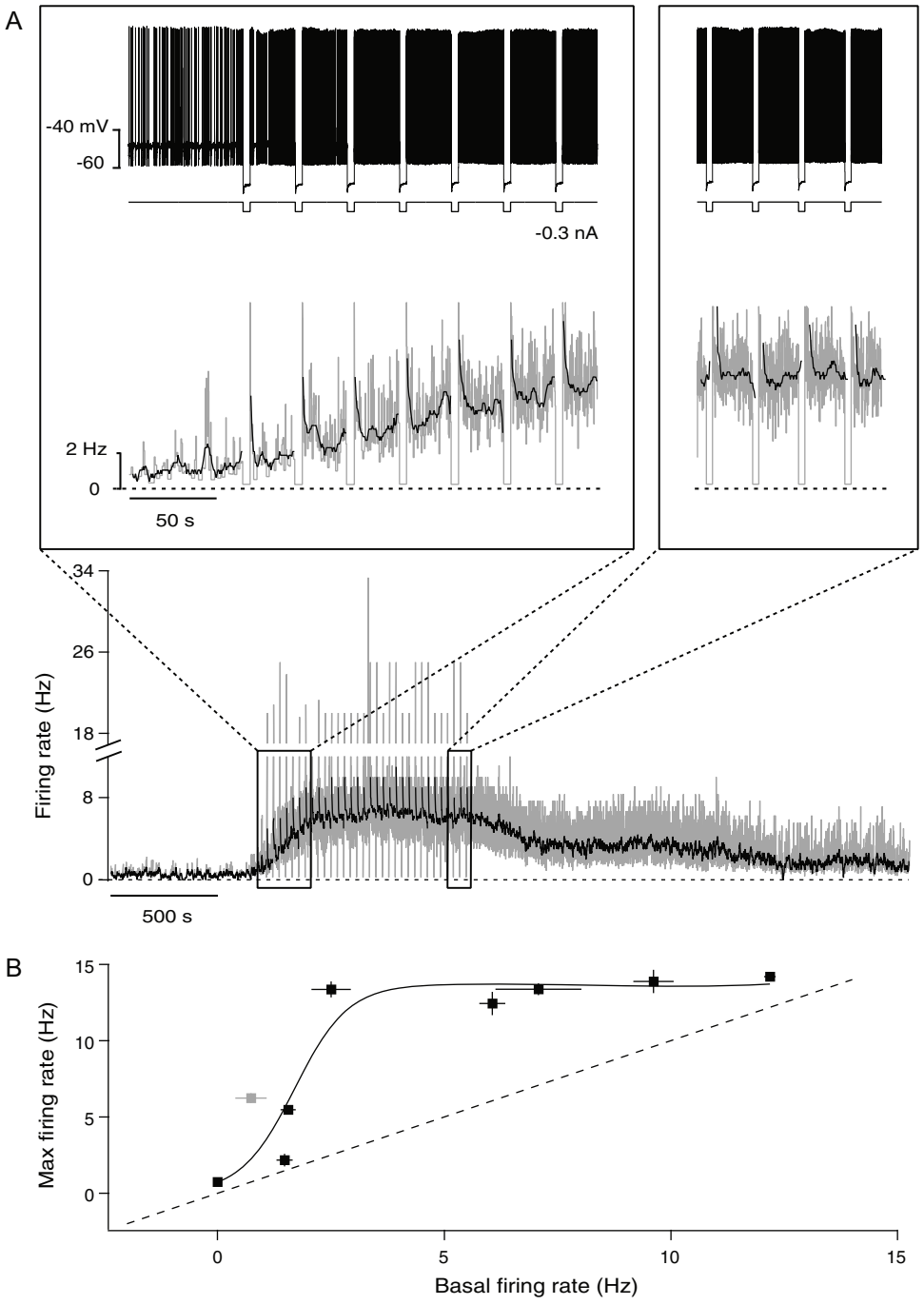

Fig. 1. Hyperpolarization-induced graded increase in firing rate in an anterodorsal thalamic neuron. (A) Inside the blowup boxes, the top panels show parts of the voltage trace of the neuron receiving a series of 32 hyperpolarizing current pulses, while the bottom panels show instantaneous firing rate (*grey traces*) and its running average with a sliding 5 s time window (*black traces*). The panel below the blowup boxes shows the overall picture of both the instantaneous and the average firing rates during the entire experiment. The firing rate increased gradually to reach a plateau, and then decayed slowly after the hyperpolarizing pulses terminated. (B) Relationship between the basal firing rate and the maximum firing rate achieved by a series of hyperpolarizing pulses for $n = 9$ cells was fit by a sigmoidal curve. The error bars indicate standard deviations of the basal and maximum firing rates. The cell shown in (A) corresponds to the grey square.

final firing rate after the pulses terminate. We have also observed a serotonin-dependent enhancement of the hyperpolarization-induced increase in firing rate.

In vivo studies in freely behaving rats show that ~60% of the cells recorded from anterodorsal thalamus are head-direction cells [29]. In our experiments, about 53% (40/76) of the cells recorded exhibited graded persistent firing, and these cells also showed little firing rate accommodation. The remaining cells did not exhibit graded persistent firing and they all showed a high degree of firing rate accommodation. Given that most neurons in the anterodorsal thalamus in the rat are principal neurons [17,31], further studies are required to correlate the morphology of the cells with the functional property of persistent firing.

The hyperpolarization-induced graded increase in firing rate reported in this study differs from the depolarization-induced persistent activity in entorhinal cortex [9], amygdala [10], and postsubiculum [36]. In the latter cases, the persistent firing was induced by depolarization instead of hyperpolarization, and it appeared much more stable, without any tendency for spontaneous decay, at least on the time scale of many minutes. Our phenomenon is

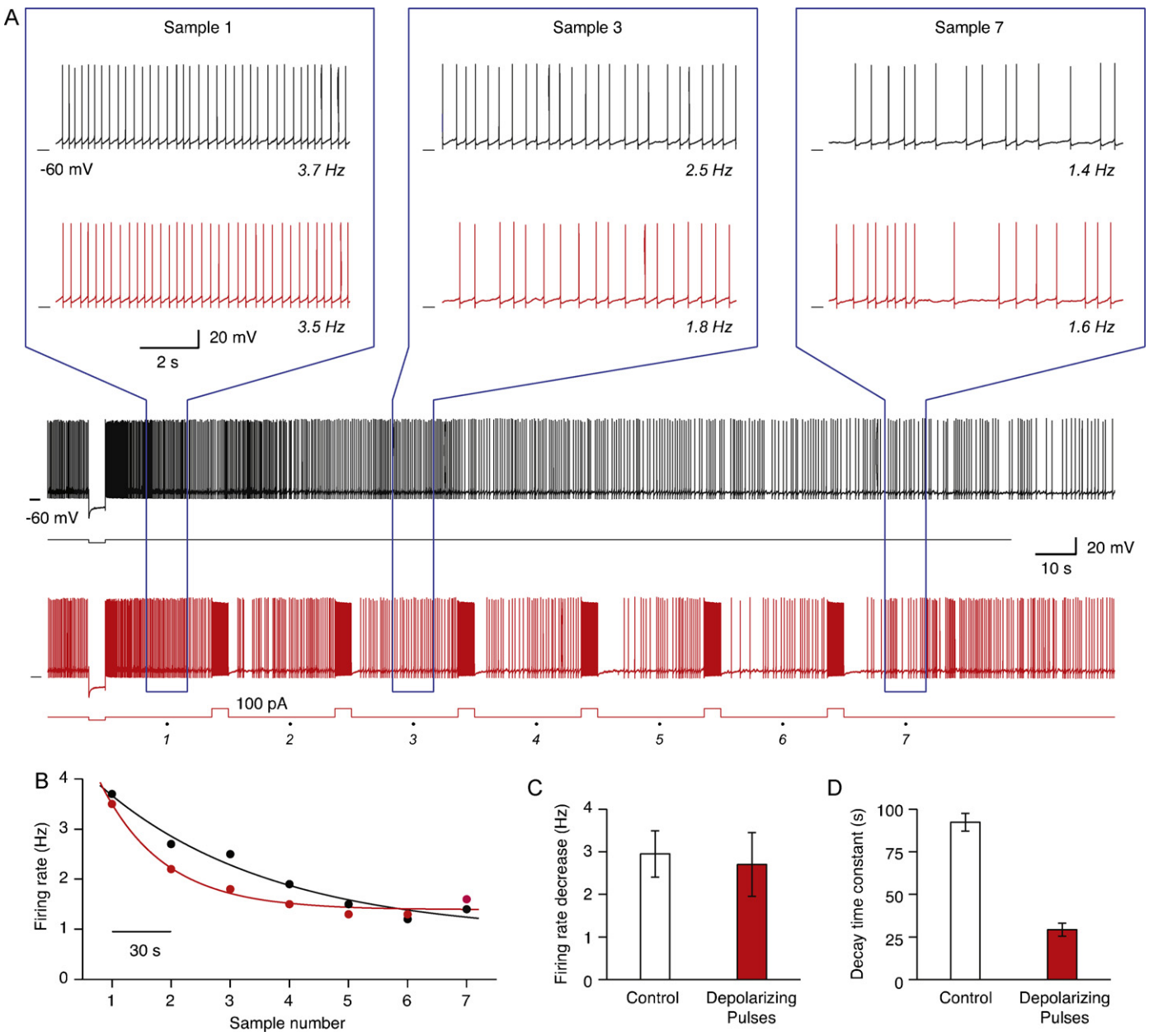

Fig. 2. (A) Depolarizing pulses had small effects on firing rate decay. The firing rate of the cell was first elevated by a series of 14, 4-s long hyperpolarizing pulses (only the last one is shown), followed by either no stimulation as control (*black traces*, *middle panel*) or six, 4-s long 100 pA depolarizing pulses (*red traces*, *bottom panel*). The blowup boxes show 10-s long sample traces whose mean firing rates are indicated at the right. (B) Exponential decay functions (*curves*) were fitted to the average firing rates (*dots*), which were calculated using the 7 sample traces as indicated by the dots in panel A. (C) Depolarizing pulses had no strong effect on the difference between the initial and the final firing rate, but (D) the time constant τ of the exponential decay was greatly reduced (mean ± SD are shown). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

also different from firing rate potentiation in the vestibular nucleus, which does not exhibit graded levels of firing rate [16]. We have confirmed directly that under conditions similar to the original reports, the thalamic neurons in our preparations do not exhibit the persistent activities described in [9] or [16].

The phenomenon we observed in the thalamus is similar but not identical to the hyperpolarization-induced graded persistent activity in the prefrontal cortex [34]. One difference is that the thalamic persistent firing tends to decay spontaneously whereas the prefrontal cortical persistent firing appears much more stable. Another difference is that depolarizing pulses can completely turn off the persistent firing in the prefrontal cortex, whereas in anterodorsal thalamus we have not observed this effect.

The goal of this paper is to demonstrate the existence of single-cell persistent activity in a component of the head-direction system: the anterodorsal thalamus. Although the exact mechanism of the thalamic graded persistent activity is unknown and beyond the scope of this paper, several general mechanisms for single-cell persistent activities have been proposed elsewhere [11,15,34]. For example, calcium-dependent nonspecific cation channels are implicated in the persistent activity in the entorhinal cortex [9,11] and the postsubiculum [36]. The persistent firing in prefrontal cortex may involve hyperpolarization-activated cation channels (I_h) and other mechanisms [34]. For comparison, the anterodorsal thalamus also has I_h current, which can be enhanced by serotonin [4,5]. Since single-cell persistent activity has been found

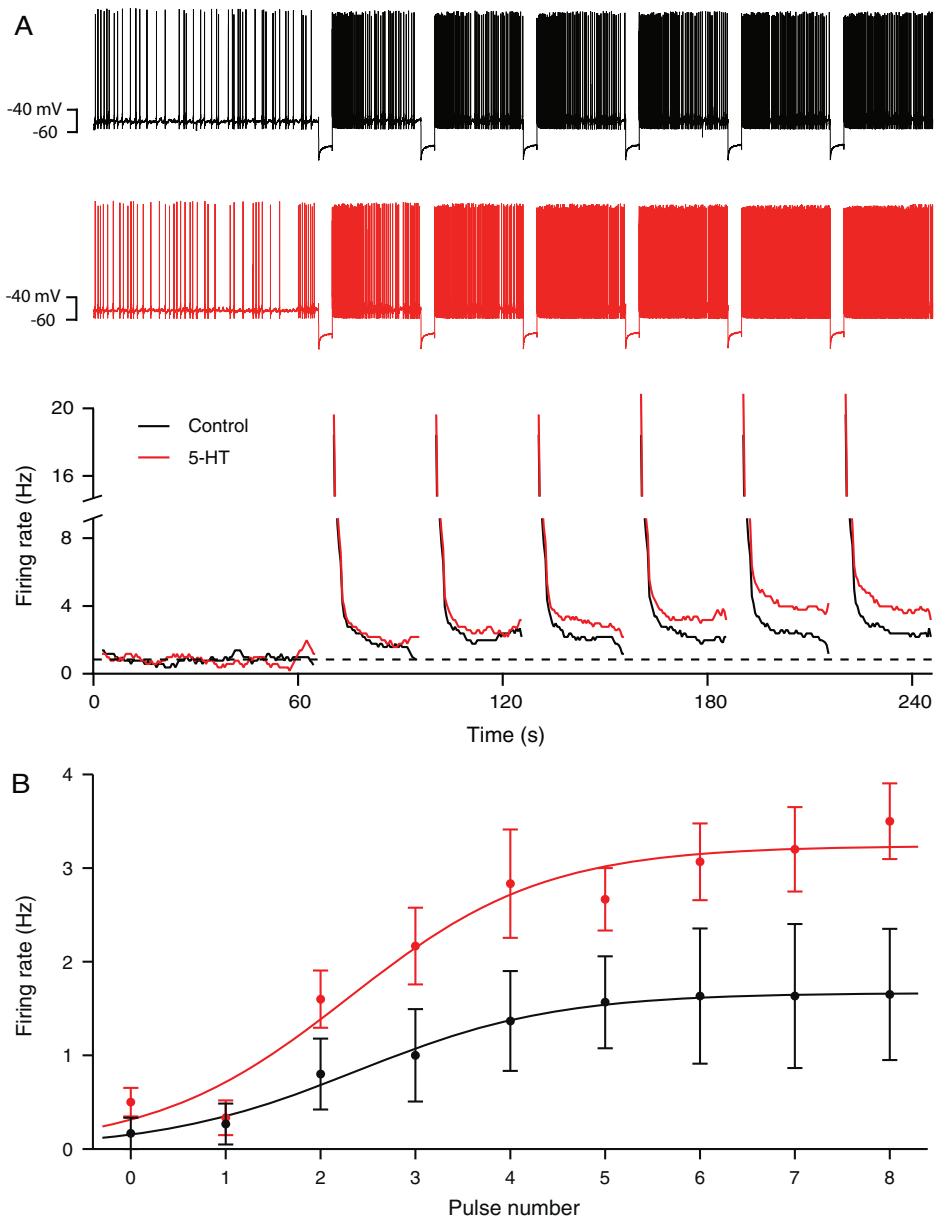

Fig. 3. Serotonin enhances hyperpolarization-induced firing. (A) Gradual increase in firing rate induced by a series of 4-s long hyperpolarizing pulses (*black traces*) was enhanced after bath application of serotonin (*red traces*). The top two panels show the membrane potential while the bottom panel shows the average firing rate. The dotted line in the bottom panel indicates the basal firing rate. (B) Population average firing rates (±SD) during a series of hyperpolarizing pulses, first under control conditions (black symbols), and then in the presence of serotonin in the bath (red symbols). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

in the anterodorsal thalamus and the postsubiculum [36] which is downstream from the thalamus, one should also look for this phenomenon upstream in the mammillary body [2]. One should also compare with other thalamic nuclei including the neighboring anteroventral nucleus [7,8,13,18,20], and test the effects of other neuromodulators besides serotonin [14,19].

How could the single-cell persistent activity observed in this and other previous studies be useful for the head-direction system? The thalamic head-direction cells observed in freely moving animals can have a peak firing rate as high as ~100 Hz, and the activity can change rapidly with the animal's head movement [29]. By contrast, the single-cell persistent activity observed in this study saturates at ~15 Hz and tends to be sluggish (Fig. 1). Similarly, the persistent activity in postsubiculum does not reach a high firing rate, although it can be triggered by a short stimulus that induces only a few spikes [36]. Because of the low firing rate, the single-cell persistent activity might not be the main mechanism responsible for the firing around the peak of the directional tuning curve of a head-direction cell, especially those with high peak firing rates. This observation, however, does not rule out the possibility that the thalamic neurons that exhibit persistent activity in slice preparations may still behave as head-direction cells *in vivo*. We found that the thalamic neurons exhibiting hyperpolarization-induced single-cell persistent activity can fire at much higher rates during rebound or when injected with depolarizing current. Therefore, a thalamic head-direction cell, driven by depolarizing synaptic current around the peak of its tuning curve, might switch to persistent activity mode at a low firing rate when the animal's head is away from the preferred direction. How suitable hyperpolarization could be generated in *in vivo* condition is unclear, but presumably it could

come from inhibitory interneurons in the thalamus and the reticular nucleus during certain sequences of head movements. We emphasize that the persistent activity at low firing rate can still be important for the peak firing of head-direction cells, because the preferred directions of different cells are known to be rigidly coupled. Stabilizing any subset of these cells should help stabilizing the whole system. The slow time scale of the persistent activity could potentially make the system more stable and more resistant to activity drift.

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