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Persistent neural activity: prevalence and mechanisms

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Persistent neural activity refers to a sustained change in action potential discharge that long outlasts a stimulus. It is found in a diverse set of brain regions and organisms and several *in vitro* systems, suggesting that it can be considered a universal form of circuit dynamics that can be used as a mechanism for short-term storage and accumulation of sensory or motor information. Both single cell and network mechanisms are likely to co-operate in generating persistent activity in many brain areas.

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Abbreviations

CAN	calcium-activated non-specific cation
mGluR	metabotropic glutamate receptor
NMDA	*N*-methyl-D-aspartate

Introduction

The importance of persistent activity for proper motor function is immediately evident from oculomotor fixation behavior. As shown in Figure 1ai, holding the eyes at an eccentric angle after a brief saccadic command is accompanied by a sustained discharge of pre-motor neurons in the oculomotor neural integrator, with different fixation angles produced by different sustained levels. The fact that this can be produced without visual or proprioceptive feedback [1] demonstrates that the persistent activity must be generated by the internal cellular and/or network dynamics of a neural circuit. This example illustrates a more general postural motor control problem that must be solved when, for example, holding your arm extended at different positions.

In fact, the behavioral importance of persistent neural activity appears to be even more general. For example, sustained action potential firing in response to a brief sensory stimulus is observed in many areas of cerebral cortex during working memory behaviors requiring short-term retention of a sensory stimulus, such as delayed match tasks [2]. Qualitatively similar sustained discharges have also been observed in subcortical brain areas, such as the basal ganglia [3], thalamus [4], superior colliculus [5], brainstem [6] and spinal cord [7]. The qualitative similarities of persistent activity in such a diversity of brain areas and species suggest the possibility that it represents a very general and fundamental form of brain dynamics.

The past few years have been a very active period in persistent firing research. This review attempts to bring together references on experimental observations of persistent neural activity across species and brain areas. First, we summarize important characteristic features of different forms of persistent activity and provide a table of references (see Supplementary table) to examples of each in different brain areas. Second, we review experiments aimed at uncovering the mechanisms of persistent neural activity. Two hypothesized general mechanisms frame the discussion: recurrent networks and intrinsic biophysical cellular properties, for example plateau potentials. (We define a plateau potential as a relatively rapid onset and offset long-lasting change in stable membrane potential dependent on intrinsic membrane conductances and/or intracellular messengers.)

Classification and prevalence of persistent neural activity

It is useful to compare and contrast persistent activity across the widely different brain areas and preparations in which it is found (see Supplementary table, previous reviews [2,3,8–14,15•,16]). Several questions can be asked in each case.

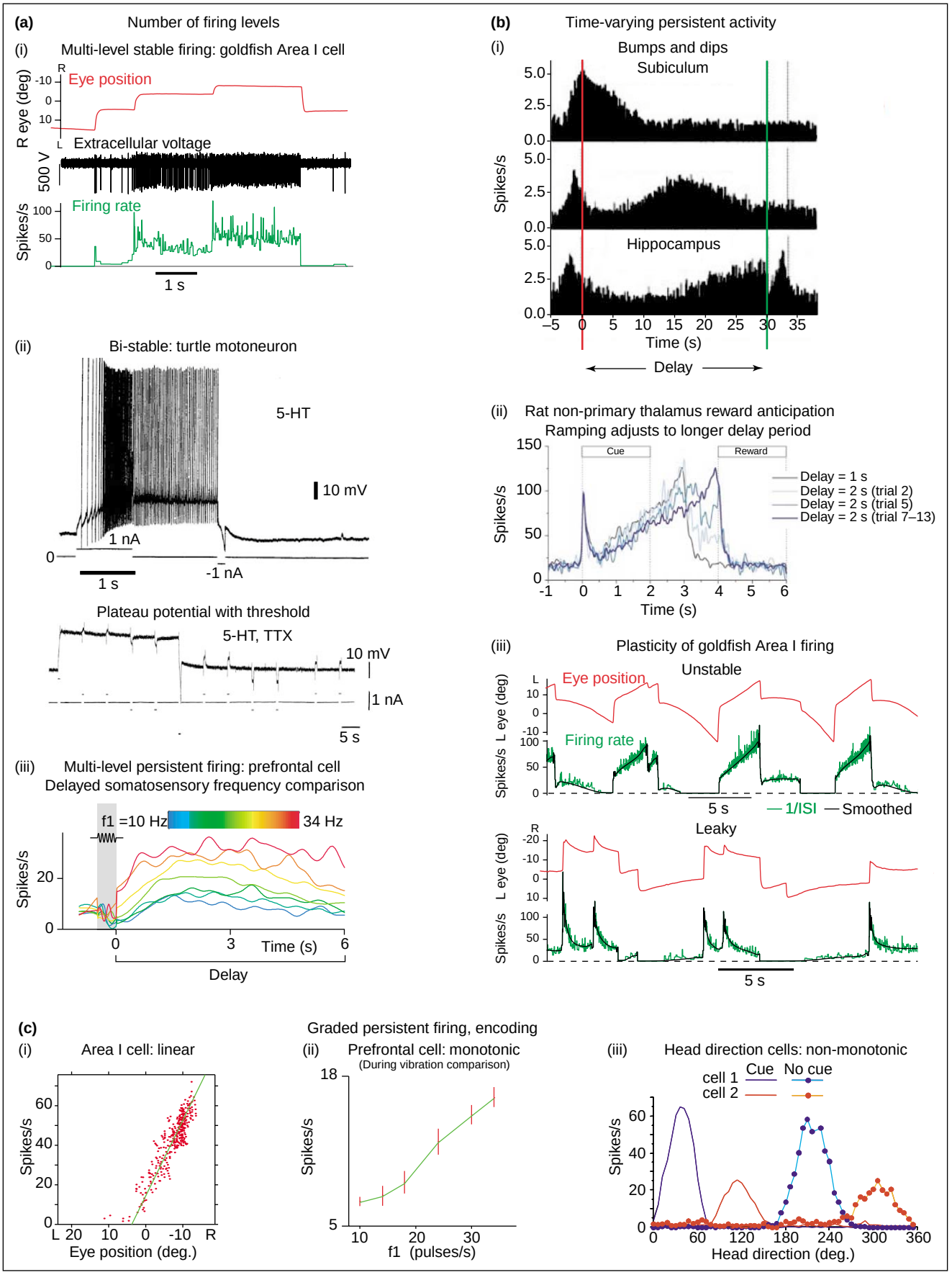
How long does the persistent activity last?

Firing that is not driven by ongoing external inputs must be explained by the internal dynamics of the cell or circuit. Typical durations range from hundreds of milliseconds to tens of seconds.

How quickly can firing be turned on and off, or changed, and is it self-terminating?

These questions are important for teasing apart mechanisms. For example, saccadic burst inputs can drive oculomotor neural integrator cells to new stable firing levels within a few hundred milliseconds. Similarly rapid transitions are found in cortical delay activity. Plateau potentials are generally self-terminating, but can also be switched off by inhibitory inputs.

Figure 1


(a)
Number of firing levels
(i)
Multi-level stable firing: goldfish Area I cell
R
L
R eye (deg)
Eye position
Extracellular voltage
500 V
Firing rate
Spikes/s
1 s
(ii)
Bi-stable: turtle motoneuron
5-HT
10 mV
1 nA
-1 nA
1 s
Plateau potential with threshold
5-HT, TTX
10 mV
1 nA
5 s
(iii)
Multi-level persistent firing: prefrontal cell
Delayed somatosensory frequency comparison
f1 =10 Hz
34 Hz
Spikes/s
Time (s)
Delay
(b)
Time-varying persistent activity
(i)
Bumps and dips
Subiculum
Hippocampus
Spikes/s
Time (s)
Delay
(ii)
Rat non-primary thalamus reward anticipation
Ramping adjusts to longer delay period
Cue
Reward
Delay = 1 s
Delay = 2 s (trial 2)
Delay = 2 s (trial 5)
Delay = 2 s (trial 7–13)
Spikes/s
Time (s)
(iii)
Plasticity of goldfish Area I firing
Unstable
Eye position
Firing rate
L eye (deg)
Spikes/s
5 s
1/ISI
Smoothed
Leaky
(c)
Graded persistent firing, encoding
(i)
Area I cell: linear
Spikes/s
Eye position (deg.)
(ii)
Prefrontal cell: monotonic
(During vibration comparison)
Spikes/s
f1 (pulses/s)
(iii)
Head direction cells: non-monotonic
cell 1
cell 2
Cue
No cue
Spikes/s
Head direction (deg.)

How many firing levels are there?

The example of oculomotor activity during eye fixation in Figure 1ai also illustrates the concept of multi-stability, that is, there are multiple levels of sustained firing. Bistability (Figure 1aii) has been described extensively in the literature on motoneurons [9,12,17,18] and might be an appropriate description of delay activity in certain short-term memory tasks. More commonly, however, neurons in higher areas show multi-stability (Figure 1aiii) during persistent activity. Persistent firing of oculomotor neural integrator cells seems graded; any firing rate over some range can be stable (Figure 1ci).

Is there an input threshold?

Plateau potentials often have thresholds (Figure 1aii). Conversely, some of the simplest recurrent network models show persistent changes in response to arbitrarily small or brief inputs. When the change in the sustained rate is proportional to the time integral of the input, the system acts as a neural temporal integrator, in the sense of calculus. This description has been applied to several kinds of persistent activity (oculomotor premotor neurons, head direction cells, sensory based decisions at low signal to noise ratios, and time estimation) [6,15•,19•].

Is firing stable or time-varying?

The firing rate of an oculomotor neural integrator cell during eye fixation in the dark is normally relatively constant between one saccade and the next [20,21•,22•]. During working memory tasks, neurons in cortex and hippocampus show both stable (Figure 1aiii) and time-varying firing (Figure 1bi; [16,23•–25•]). Delay activity that decays following a stimulus (sometimes termed retrospective coding) and activity that builds up before a decision, reward, or motor response (prospective coding) are common (Figure 1bii; [3,4,16]). Persistent firing in the goldfish oculomotor neural integrator ('Area 1', in the caudal brainstem) can be behaviorally modified to be unstable (exponentially diverging) or leaky (exponentially decaying to a steady state level or levels, Figure 1biii; [22•]).

What type of encoding occurs during persistent activity?

The sustained firing of oculomotor neural integrator cells is linearly related to eye position (Figure 1ci; [20]). A similar monotonic encoding is observed during delay activity in somatosensory cortex, representing the frequency of vibration during a vibrotactile delayed match to sample task (Figures 1aiii, 1cii; [24•]). By contrast, head direction cells (Figure 1ciii) [15•], memory fields in the multi-target delayed saccade task [14] and number encoding cells [26] show non-monotonic encoding.

How co-ordinated are the activities of different neurons?

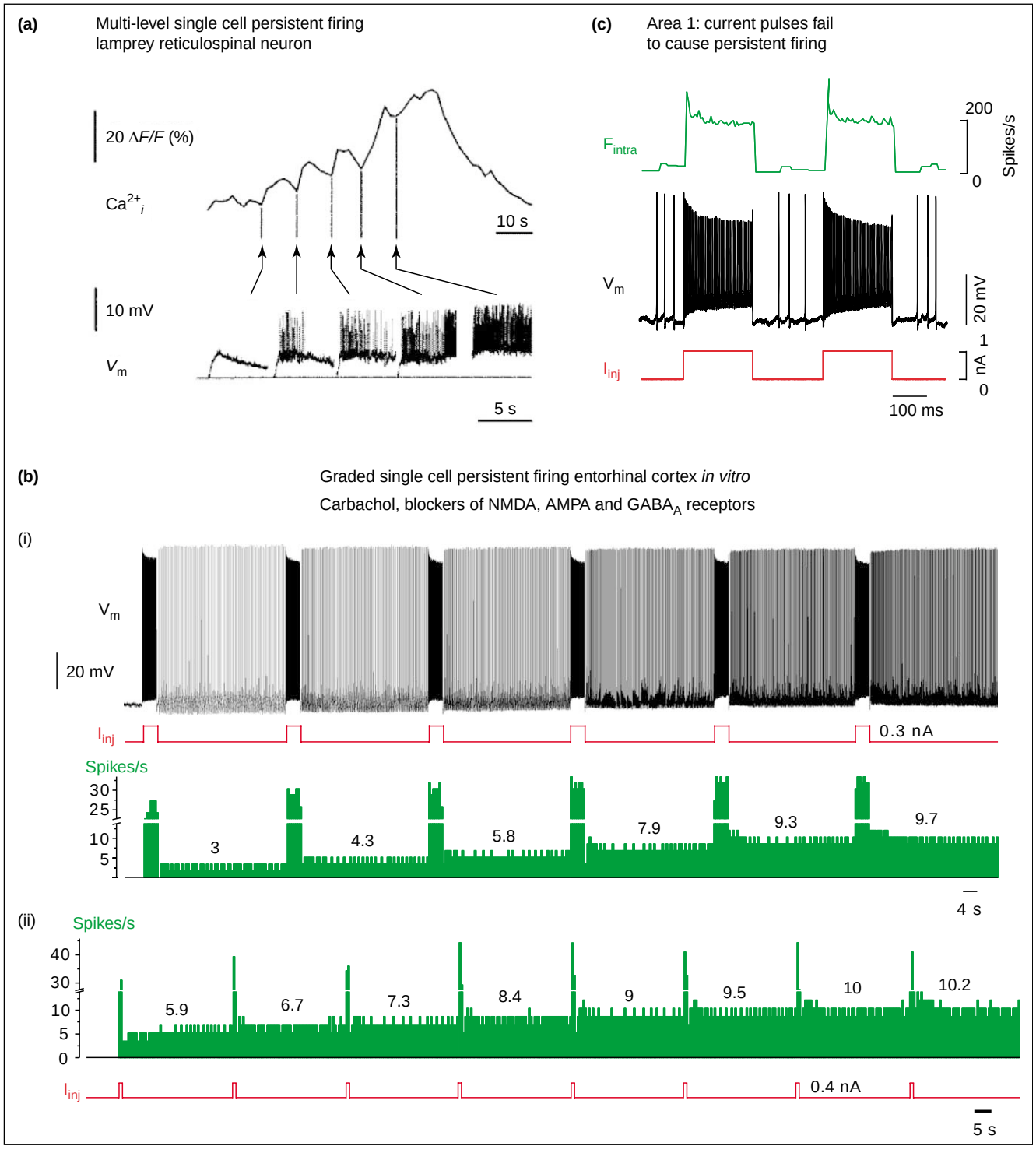
Network mechanisms are expected to produce highly coordinated and correlated activity across subsets of neurons, whereas single cell mechanisms could produce more independence in firing.

Does the persistent activity occur without training and does it show plasticity?

Spontaneous persistent activity in untrained animals is typically found in lower brain areas [20] and the head direction system [27], but has also been observed in cortex [28]. Persistent firing in higher areas generally changes during behavioral training [25•,29]. Indeed, time-varying persistent firing in cortex, hippocampus and thalamus can adjust within a few trials to a new delay period (Figure 1bii) [4,24•] or altered contingencies. In the rat head direction cell system (Figure 1ciii) and the

(Figure 1 Legend) Characteristics of different kinds of persistent neural activity. **(a)** A number of different stable firing levels. **(i)** Multi-level stable persistent firing in an oculomotor neural integrator cell in an awake behaving goldfish. Top (red): horizontal eye position, measured in the dark. Rapid saccades alternate with stable fixations. Middle: extracellularly recorded action potentials. Bottom (green): instantaneous firing rate (adapted with permission from [21•]). **(ii)** Bistable turtle motoneurons in a slice with 5-HT added. Top: a depolarizing current pulse is followed by a sustained after-discharge (UP state). The cell can be switched back into the non-firing DOWN state by a brief hyperpolarizing current. Bottom: addition of TTX reveals underlying plateau potential (different cell). Pulses greater than a threshold size can flip the cell from one stable state to the other, but smaller pulses cannot (adapted with permission from Blackwells Publishing [79]; figure kindly supplied by J Hounsgaard). **(iii)** Multi-level roughly stable firing from a monkey prefrontal cortical cell during a somatosensory vibration delayed match task. Firing rate increases with the frequency of f1, the stimulus being remembered, indicated by different colors (adapted with permission from Oxford University Press [24•]). **(b)** Different time courses of persistent firing. **(i)** Non-monotonic over time. Selected examples of rat subicular and hippocampal cell persistent firing during a delayed response task with a randomly-varied delay; data from trials with 30 s delay, marked by red and green lines. Different cells show different temporal profiles of persistent activity, including a range of bumps and dips spanning various portions of the delay (adapted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc. [23•]). **(ii)** Non-primary thalamic neurons (adapted with permission from Nature Publishing Group [http://www.nature.com/] from [4]). Cells show delay period firing that ramps up in anticipation of a reward. When the delay is changed, the ramping adapts to the new delay within a few trials. The original peak decreases as the new peak increases. **(iii)** Plasticity of goldfish Area 1firing. Top: unstable integrator. Eye position and Area 1 cell firing rate after several hours' exposure to visual surround moving with velocity proportional to eye position. Green: instantaneous firing rate, 1/(inter-spike interval). Black: smoothed with gaussian window increasing in width away from saccades. Bottom: leaky integrator. Eye position and Area 1 cell firing after several hours of visual surround moving with velocity proportional to minus eye position (adapted with permission from [22•]). **(c)** Graded persistent firing and encoding. **(i)** Linear encoding: multi-level persistent firing is often 'graded', namely any rate over some range can be stable. The same Area 1 cell is depicted here as in panel ai. Firing rate is approximately a threshold-linear function of eye position (see Aksay *et al*. [20]). **(ii)** Monotonic non-linear encoding: average delay period firing rate versus f1 stimulus frequency for another prefrontal cell. Same task as depicted in panel aiii (adapted with permission from Oxford University Press [24•]). **(iii)** Non-monotonic 'bump' encoding: different head direction cells fire maximally at different preferred directions. These cells show co-ordinated shifts by the same amount when visual cues are removed (adapted with permission from the American Psychological Association, Copyright © 1995. Data kindly supplied by JS Taube) [70].

Figure 2



Intrinsic cellular versus network mechanisms of persistent activity. **(a)** Lamprey reticulospinal neurons (adapted with permission from [34]). Intracellular calcium and firing rate show cumulative step-like sustained changes in response to successive skin or nerve stimuli (arrows). **(b)** Entorhinal cortex layer 5 pyramidal neurons *in vitro*. Slice bathed in 10 μM carbachol and neurotransmitter blockers (adapted with permission from [47] [http://www.nature.com/]). Cell could fire at multiple different stable rates (indicated above firing rate histograms). Brief depolarizing intracellular current pulses of sufficient amplitude and duration could increase the steady rate. **(i)** Intracellular voltage, current and firing rate histogram, 4 s pulses. **(ii)** Same cell, firing rate histogram and intracellular current, 1 s pulses. **(c)** Oculomotor neural integrator cells recorded intracellularly in awake behaving goldfish (adapted with permission from [1]). During single fixations, intracellular current pulses failed to cause persistent changes in firing outlasting the pulses. Abbreviations: ΔF/F, relative fluorescence change; F_{intra}, intracellular firing rate; V_m, membrane potential; I_{inj}, injected current.

goldfish oculomotor system [15•,27,30–32], sensory input seems to be important in maintaining tuning of the persistent activity. If goldfish are left in the dark, their eye fixations (and firing rates; G Major, DW Tank, unpublished) become progressively leakier [21•,22•,33]. Persistent firing can gradually be driven unstable or leaky by rotating the visual surround with velocity proportional to + or − eye position, which mimics the retinal slip from a leaky or unstable integrator, respectively (Figure 1biii; [21•,22•]).

Cellular versus network mechanisms of persistent activity

Dominance of intrinsic cellular mechanisms?

There is increasing evidence that intrinsic cellular mechanisms [12,17] are both widespread and can produce multi-stability. In many cases, persistent firing is driven by an underlying plateau potential [9]. A soma-dendritic tree can have more than one possible stable spatial pattern of membrane potential at any given time. The number of stable voltage patterns, their spatial structure and the soma voltage can change with time because of channel and intracellular signaling dynamics, and can also be altered by neuromodulators or other inputs.

Multi-level persistent firing in lamprey reticulospinal system

In the lamprey, tapping the snout sufficiently hard causes an escape response initiated by a sustained train of action potentials in a set of brainstem reticulospinal neurons. As shown in Figure 2a, a fictive form of this behavior has been reproduced *in vitro* in the semi-intact lamprey. Successive afferent stimuli cause cumulative increases in persistent firing and intracellular calcium in reticulospinal neurons, through *N*-methyl-D-aspartate receptor (NMDAR)-dependent calcium entry then activation of a calcium-activated non-specific cation (CAN) current-driven plateau potential [34,35].

Bistable and multi-level persistent firing in spinal cord and cranial nerve nuclei

Deep dorsal horn neurons *in vitro*, in anaesthetized animals, or in animals with cut spinal cords [36] show a form of multi-level persistent activity known as 'wind-up' [17,37]. In response to successive brief nociceptive afferent stimuli or intracellular current pulses, the firing rate steps up to progressively higher levels that can persist for many seconds [38]. The persistent firing is driven by an L-type calcium channel plateau potential (prolonged by a CAN conductance in rodents). Wind-up might result from voltage or calcium-dependent facilitation of these channels, although multiple interacting dendritic plateaus are another possibility. The plateau potential is also subject to neuromodulation [39].

Motoneurons exhibit bistability *in vitro* [9] in the presence of serotonergic or noradrenergic agonists [12], and in decerebrate animals [40]. Underlying the bistability is a plateau potential, mediated largely by low threshold soma–dendritic L-type Ca(v)1.3 channels [41•]. Persistent sodium currents might also contribute in mammals [40,42]. Wind-up of firing in response to successive brief stimuli also occurs [12,43], possibly through calcium and calmodulin-dependent facilitation of L-type calcium channels [44]. The plateau potentials are further up-modulated by metabotropic glutamate receptors (mGluRs) and muscarinic cholinergic agonists, and are down-modulated by γ-amino butyric acid-B receptor ($GABA_BR$) activation [12,45].

Spinal cord plateau potentials have not been conclusively demonstrated in normal awake behaving animals, although persistent delay period firing has been found in spinal interneurons [7]. Several studies show sudden persistent changes in motor unit firing after transient stimuli, and discrepancies between on and off thresholds [9,13,46] consistent with motoneuron plateaus, but circuit-based mechanisms have not been ruled out.

Multi-level persistent firing in cortical slices with cholinergic activation

Muscarinic modulation is important for working memory. Following muscarinic activation, layer 5 pyramidal cells in entorhinal cortical slices become capable of graded persistent firing, even with fast neurotransmission blocked (Figure 2b; [47•]). Transitions from one stable firing level to another can be affected by current pulses or synaptic stimulation. Stimuli below a certain threshold size or duration do not change tonic firing. Brief (≥300 ms) depolarizing pulses lead to persistent increases, but to achieve persistent decreases longer hyperpolarizations (≥5 s) are required. Up to around 12 levels have been documented per cell (Figure 2b), but an arbitrary number of stable rates seems possible (A Alonso, pers comm). The depolarizing drive comes largely from a CAN current. Firing is far more regular than that seen during working memory [48•,49], although noisy synaptic inputs would add jitter *in vivo*. It is unclear whether the CAN current switches off fast enough to explain abrupt decreases in firing often seen *in vivo*.

CAN current-driven persistent firing in single cells might be widespread in the brain. For example, muscarinic activation enables subicular [50] and hippocampal CA1 pyramidal cells to generate plateau potentials (bistability), based largely on CAN or cyclic nucleotide gated cation channels [51,52] but also involving calcium channels in CA1. Muscarinic modulation of oculomotor neural integrator circuitry has also recently been studied [53].

NMDA-dependent dendritic plateau potentials

In somatosensory cortex [54,55], prefrontal cortex [56•] and CA1 [57,58], the thin dendrites of pyramidal cells, which receive the majority of their synaptic inputs, are

capable of exhibiting voltage- and glutamate-dependent broad spikes or plateau potentials local to an individual branch in response to sufficient NMDA-receptor stimulation. It is tempting to speculate that these events might have a role in persistent neural activation *in vivo*. The waveforms of the longer plateaus also look remarkably similar to those seen in lamprey spinal cord during NMDA-activated tetrodotoxin (TTX)-resistant rhythmic bistable activity, important in fictive locomotion [59]. In CA1 terminal apical dendrites [58] and lamprey, calcium-activated potassium channels are involved in switching off the plateau potential. NMDA conductance-based plateau-potentials are actually hybrid network/cellular mechanisms of persistent activity, because *in vivo*, recent patterns of network activation dynamically set the spatial distribution of openable (glutamate-bound) voltage-dependent NMDA channels over the dendritic tree of a particular neuron. Because deactivation of NMDA channels is much slower than voltage gating, dendrites might show voltage multi-stability similar to that of intrinsic-conductance plateau potentials.

Problems with explanations based on dominant intrinsic mechanisms

Lack of persistent changes in firing in oculomotor integrator cells following intracellular current pulses

If goldfish Area 1 cells have an intrinsic plateau potential conductance near the cell body, it should be possible to switch it on and off by intracellular current injections. When this experiment was done *in vivo* [1], current pulses failed to cause persistent changes in firing (Figure 2c), suggesting network mechanisms dominate this system. However, distal dendritic or NMDA plateau potentials have not been ruled out. Other intrinsic mechanisms such as calcium wavefronts might not depend strongly on perisomatic voltage [60].

Heterogeneous time courses and plasticity of persistent firing

Intrinsic cellular mechanisms might have some difficulty reproducing some of the more complex features of persistent activity in higher areas, in which different neurons often exhibit very different time profiles of persistent firing. Several studies show a continuum of cells spanning stable, ramping, decaying and non-monotonic temporal profiles with one or more humps or dips (Figure 1b, Supplementary table; [23•,24•,25•,61]). In addition, time courses can vary from trial to trial depending on the stimulus and reward, and also at random [62]. This level of diversity, stimulus–response specificity and variability of time courses, together with their adaptability [4,24•] and plasticity [29], has not been demonstrated with purely intrinsic cellular mechanisms.

Visual feedback can be used to detune goldfish Area 1 persistent firing towards instability or leak (Figure 1biii) or to tune it back towards stability. Although this could be consistent with cellular mechanisms, it fits naturally with recurrent feedback network models, which require a fine tuning mechanism for robustness [21•,22•].

Dominance of recurrent synaptic feedback?

Recurrent synaptic feedback has long been a popular hypothesized mechanism of persistent activity, especially in the forebrain and oculomotor system. Observed ensemble patterns of persistent activity can be reproduced relatively easily as stable attractors in recurrent network models [11,16]. In addition, strong feed-forward and feedback connections exist within and between cortical areas, and there are abundant reciprocal corticothalamic connections, and corticostriato–thalamocortical and cortico-pontocerebellar–thalamocortical loops, all of which could serve as the anatomical substrate of recurrent feedback.

Despite its appeal, there is little concrete evidence that recurrent synaptic feedback dominates persistent activity in intact functioning nervous systems. This might reflect the enormous difficulty of simultaneously recording and precisely manipulating the intracellular voltage, calcium and other key signals within large numbers of neurons and dendrites *in vivo* in awake, behaving animals. Most of the relevant data are indirect or from *in vitro* systems.

A prediction of recurrent network models is that an increase in persistent firing is associated with an increase in excitatory synaptic currents. Indeed, in about a third of intracellularly recorded goldfish Area 1 cells, the rate of post synaptic potentials (PSPs) or the background noise increased clearly during more depolarized plateau-like steps in membrane potential that were shown to produce increased firing rates with network activation [1]. However, this could be explained equally well by feed-forward or recurrent architectures. In any case, the increase in PSPs might not be the dominant mechanism generating the membrane depolarizations.

A similar kind of experiment has been performed on a slice model of cortical persistent activity. In 'natural' ionic conditions (~1.2 mM Ca^{2+}), neurons in cortical slices show spontaneous and evoked transitions between UP and DOWN states lasting several seconds, similar to those seen *in vivo* during anesthesia and slow-wave sleep [63]. It has been argued [49,63,64,65•,66•] that these states might share mechanisms with *in vivo* persistent activity. Intracellular recording clearly demonstrates that the UP state is associated with time-varying sustained barrages of nearly balanced excitatory and inhibitory conductances that produce a net depolarization, increased noise and increased firing [64,66•]. The average duration of states is not affected by de- or hyperpolarization by 10–30 mV. States in nearby cells are largely synchronized. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) or NMDA receptor blockers abolish the UP states

[63,65•]. These findings suggest that UP and DOWN states are produced by recurrent network mechanisms, although a contribution from plateau potentials has not been excluded. The variability of spike firing in the UP state matches that observed during working memory persistent activity [48•].

Cross-correlograms

Simultaneously recorded goldfish Area 1 cells [67] as well as persistently firing cells in cerebral cortex [68,69] show spike-time cross-correlogram peaks, often at zero lag, consistent with common input, including recurrent feedback. Area 1 cells on opposite sides of the brain tend to have negative dips in their correlograms, consistent with mutual inhibition via their crossing axon collaterals [20]. Area 1 cells on the same side have positive correlogram peaks that are greatly reduced at high rates [67]. In both cortex and Area 1, correlograms suggest but do not prove cells are connected. They do demonstrate, however, that spikes are at least partially driven by synaptic input during persistent activity.

Co-ordinated firing

The direction preferences of simultaneously recorded head direction cells tend to shift by similar amounts when visual or other external cues are changed or removed [15•,70] — the cells appear coupled (Figure 1ciii). Similarly, in the oculomotor system, neurons on the same side of the brain generally show step increases and decreases that are largely (but not perfectly) correlated [71]. Simultaneously recorded Area 1 cells with leaky fixations in goldfish often show co-ordinated firing rate drift (E Aksay, G Major, DW Tank, unpublished), as predicted by recurrent network models.

Problems with explanations based on dominant synaptic feedback

There are several other intriguing experimental observations from both the cerebral cortex and the oculomotor neural integrator that suggest that recurrent synaptic feedback is not the whole story in these systems.

When NMDA blockers are infused or iontophoresed into cortex, it appears that persistent firing rates are depressed (or raised), but the dramatic change in time course predicted by simple recurrent feedback models is not seen (G Williams, unpublished [preliminary observations]) [72]. Dopaminergic and serotonergic agents can also change firing rates while having comparatively little effect on time courses [73,74]. Perhaps this reflects balanced effects on excitation and inhibition, but it is also suggestive of some kind of intrinsic robustness mechanism.

Simple recurrent network models predict that the firing rates of oculomotor integrator neurons should always be linearly related to one another. However, the firing rate–firing rate relation of two simultaneously recorded goldfish Area 1 cells often shifts systematically during the course of the spontaneous scanning saccadic cycle [71]. Many cells exhibit non-monotonic persistent firing that changes in the 'wrong' direction during part of the cycle [22•]. Following training to fixation instability or leak (Figure 1biii), there is also considerable unexplained diversity of firing rate drift patterns [22•]. These observations could be signs of dendritic plateaus [75], although there are also network explanations.

The need for hybrid mechanisms?

Aside from timing and co-ordination, the persistence of firing in lower areas such as spinal cord and the reticulospinal system seems to be explicable largely in terms of intrinsic cellular mechanisms. Nevertheless, with the possible exception of lamprey reticulospinal cells, supporting network mechanisms have not been excluded, and the occurrence of plateau potentials in behaving animals has not been unequivocally demonstrated.

Although it is hard to make rigorous arguments given the limits of our knowledge and experimental techniques, it seems reasonable to suggest that in the oculomotor system and many higher brain areas, network mechanisms of persistent activity might co-operate with intrinsic cellular mechanisms. The argument is threefold. First, purely network and purely cellular mechanisms both have difficulty accounting for all the observed phenomena. Second, the machinery for both kinds of mechanism has been demonstrated in abundance in many areas of cortex. And third, pure recurrent feedback networks have a robustness problem, being exquisitely sensitive to the exact amount of net positive feedback — too much leading to run-away excitation, too little to rapid decay of activity. Intrinsic cellular mechanisms of persistent activity provide a natural way to increase robustness [75].

Future directions

What would be definitive tests for recurrent network mechanisms? One approach is to remove precisely one cell or a subset of the network and to examine the effect on the remaining neurons. Many network models predict that even a small reduction in overall positive feedback will lead to a profound loss of persistence. These experiments have already been done at a crude level. In primates, localized cortical cooling changes the level of persistent firing of particular neurons, but generally the time course is fairly robust ([2,76], but see [77]). Similar inactivation experiments at a finer spatial scale should now be performed in cortex. In goldfish, local inactivation of part of Area 1 causes some deterioration of persistence times in the remaining neurons, but, again, there is surprising robustness [78]. A second approach is to examine whether precise stimulation of a defined subset of the network affects firing in the remaining neurons, as predicted by recurrent network models.

How about definitive tests for intrinsic cellular mechanisms? Different firing levels could correspond to different combinations of bistable dendrites in UP states or there might be an activated zone in each dendrite, the 'wavefront' of which moves as the firing rate changes [60]. These models could be tested by imaging dendrites *in vivo* during persistent activity. Other intrinsic mechanisms should be tested pharmacologically, preferably using selective blockers that can be applied intracellularly (such as D-890 against L-type calcium channels), to prevent network side-effects.

Conclusions

The diversity of CNS areas demonstrating persistent activity is immense (see Supplementary table), suggesting its importance and the possibility that a small set of common mechanisms will be found. The biophysical machinery for intrinsic cellular mechanisms has been found in many of these same areas, and might help to explain the robustness of persistent firing. Nevertheless, there are serious challenges to intrinsic cellular persistent activity being the dominant mechanism in higher brain areas. The observed co-variation, complex time dynamics and plasticity of persistent neural activity together with *in vitro* findings point towards network mechanisms being important. Experiments testing the relative contributions of network and cellular mechanisms in higher areas in awake behaving animals are at a very early stage.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.conb.2004.10.017.

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- • of special interest
- •• of outstanding interest

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