

Neural representation of interval time

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Animals can predict the time of occurrence of a forthcoming event relative to a preceding stimulus, i.e. the interval time between those two, given previous learning experience with the temporal contingency between them. Accumulating evidence suggests that a particular pattern of neural activity observed during tasks involving fixed temporal intervals might carry interval time information: the activity of some cortical and subcortical neurons ramps up slowly and linearly during the interval, like a temporal

integrator, and peaks around the time at which the event is due to occur. The slope of this climbing activity, and hence the peak time, adjusts to the length of a temporal interval during repetitive experience with it. Various neural mechanisms for producing climbing activity with variable slopes, representing the length of learned intervals, are discussed. *NeuroReport* 15:745–749 © 2004 Lippincott Williams & Wilkins.

Key words: Biophysical model; Climbing activity; Interval time; Neural integrator; Prediction; Prefrontal cortex; Timing

INTRODUCTION

One of the most important tasks of the brain is the prediction of forthcoming events to allow for behavioral preparation, anticipatory responses, and planning. Such prediction requires animals to extract and utilize the temporal structure of their worlds, that is, the temporal relations between various environmental events or between the own behavior and its effects. In many cases, extracting just the serial order of events is not sufficient since actions somehow have to be time-locked to the anticipated events to be useful: the right timing matters. Hence, it is not surprising that at least mammals and birds can also predict the precise timing of events relative to some preceding stimulus, given previous experience with the temporal contingency between those two. This has been shown in a variety of classical and operant conditioning procedures involving fixed temporal intervals, working memory, temporal discrimination, and other timing tasks [1–4]. The present review focuses on some very recent ideas and exciting developments regarding the explicit neural representation of interval times, especially on scales of seconds to minutes, in behavioral contexts such as operant conditioning or prediction (some of the older literature on the neurobiology of timing, and on (subsecond) temporal information processing within specific sensory or motor modalities, is reviewed in [5–7]).

NEURAL CORRELATES OF INTERVAL TIMING: CLIMBING ACTIVITY

A key observation with regards to the neural representation of interval time might come from studies of working memory [8–11]. In a working memory task, a cue is briefly presented followed by a delay of hundreds of milliseconds up to many seconds. After the delay period, the animal is confronted with a choice situation where the correct

response depends on the nature of the cue presented previously. Therefore, some information about the cue or the forthcoming choice has to be actively maintained in (working) memory during the delay. In most experiments, the duration of the delay period is fixed (or may vary with a Gaussian distribution around some mean), and hence the relative time of occurrence of the choice situation is predictable (the specific motor response required at choice, however, often is not). In many cortical areas, most prominently the prefrontal cortex, persistently elevated firing rates have been observed within subpopulations of neurons during the delay period [9–12]. This persistent activity often takes a particular, monotonic form: It either slowly decays or slowly climbs during the delay period up to the point where the response is required (Fig. 1) [11,13–20]. Such slowly climbing or decaying activity has also been observed in tasks where animals are required to withhold responses for fixed temporal intervals (differential reinforcement at low rates) [21,22]. While slowly falling activity is most often correlated with the nature of the preceding cue, climbing activity in many cases is selective for a particular object or event animals expect to occur after the delay: in this sense it is anticipatory [16,18]. A slowly and monotonically changing anticipatory signal above frontal areas, termed contingent negative variation (CNV), was noted earlier in human EEG studies [23].

Climbing activity can span widely different time intervals from hundreds of milliseconds [18] up to tens of seconds [16]. Moreover, it is often quite linear as one would expect for a perfect temporal integrator (Fig. 1) [13,24], but which is a nontrivial property given the highly nonlinear dynamics of the nervous system. This raises the intriguing possibility that climbing activity does not only encode information about the expected event, but also about its time of occurrence relative to the preceding cue. Niki and Watanabe [21] were among the first to link prefrontal neural activity to

timing processes. If climbing activity in fact carries interval time information, one would expect it to adapt to experienced temporal intervals, to allow optimal discrimination within the relevant interval, and since neural activity cannot grow to infinity. This was shown by Komura *et al.* [24], who found linearly climbing activity in thalamic neurons in a trace conditioning protocol where a predictive stimulus precedes a reward by a fixed interval. Climbing activity is triggered by the predictive (conditioned) stimulus and peaks around the time at which the reward is due. As the delay between offset of the predictor and the delivery of reward is either increased or decreased, the slope of climbing activity adjusts within a few trials to the new temporal interval (Fig. 1). That is, while the maximum firing rate around the expected time of occurrence and the onset time of climbing activity remain the same, the rate at which activity changes increases or decreases as the delay period is reduced or prolonged. Such adaptation of climbing activity to the length of the temporal interval has recently also been observed in prefrontal and infero-temporal cortex during working memory tasks [13,25,26].

As noted above, climbing activity might be prospective in the sense that it is correlated with the upcoming target, and might represent the duration of a learned temporal interval via its slope. Slowly decaying activity, on the other hand, which is correlated with the preceding cue [16,18], might allow an animal to judge retrospectively the time that has elapsed since presentation of the cue even if the experienced intervals are novel [27,28]. In accordance with this interpretation, cue-related persistent activity is present early on during training, or even during inter-trial intervals where not needed for task performance [29] and in untrained animals [30], while anticipatory activity related to the forthcoming choice emerges only later during acquisition of a stimulus association task [31].

Recently Leon and Shadlen [32] provided more direct evidence that climbing activity might be related to interval time measurement. They trained monkeys in an interval time discrimination task while recording from neurons in posterior parietal cortex. The animals had to judge whether a test stimulus was turned on for a longer or a shorter interval than a previously presented standard stimulus of either 314 ms or 800 ms duration. Leon and Shadlen [32] found both slowly rising and slowly decaying activity, correlated with the passage of time, whose slopes were steeper for the shorter duration standard. Moreover, during trials where the monkeys made an error, the slope of climbing activity seemed to be misadjusted, being either too steep or too flat. Finally, pooling responses from many neurons, neural activity at each point in time during the test interval predicted well the probability of a longer or a shorter response for that test cue duration as determined from psychometric response functions. That is, there was a close agreement between the behavioral and the neural data (see Fig. 6 in [32]).

READ-OUT OF TEMPORAL INTEGRATOR-LIKE ACTIVITY

How could climbing activity be read out to trigger responses at the right moment in time? Experimental findings suggest two basic possibilities: first, climbing activity when exceeding some rather constant firing rate threshold (say, 60 Hz) might cause an abrupt increase or

decrease in the firing rate of some postsynaptic response neurons around the expected time of occurrence (see [33] for the possible neural mechanisms). Neurons that exhibit such a fast increase or decrease aligned to the expected time of occurrence in working memory, operant, or trace conditioning tasks, have been observed in various cortical [34,35] and subcortical [36,37] areas. These responses seem to signal the expected time of occurrence since they also occur in the absence of the actual target stimulus. Second, transiently synchronized action potential times of different simultaneously recorded neurons have been observed to slightly precede the expected time of occurrence [38,39], thus providing a possible read-out signal (see [40,41] and [42], respectively, for how such anticipatory transient synchrony might arise from the slowly falling (or climbing) activity of presynaptic integrator-neurons, and during the course of learning based on spiking-time-dependent synaptic plasticity [43]).

BIOPHYSICAL BASIS OF TEMPORAL INTEGRATOR-LIKE ACTIVITY

What are the biophysical mechanisms underlying the generation of slowly climbing, temporal integrator-like activity? There are at least three different possible implementations that have been proposed. First, climbing activity might be due to slowly activating or inactivating membrane currents with time constants in the range of seconds (or even minutes). Cortical pyramidal cells are equipped with a variety of such currents [44–46]. Adjustment to different temporal intervals might be possible if the rate of (in-) activation of the current depends on membrane voltage or firing activity [26]. Alternatively, there could be many such currents with a range of very different time constants [47], but no biophysically plausible mechanisms of how this could produce climbing activity with adjustable slope have been suggested so far. While slow currents may provide a simple and robust timing mechanism [26], there are also several problems associated with their use for interval timing. One of the problems is that the range of temporal intervals that could be represented this way might be quite limited, bounded by the fastest and the slowest time constant that can be achieved through the activity-dependence of the current. Another potential problem is that a mechanism relying on slow intrinsic time constants might be difficult to control. For instance, it might take quite long to fully inactivate a slowly activating channel again, *i.e.*, to reset the neuron to its initial state for processing the next interval (but see [26]).

A second way to account for interval timing and climbing activity is through stochastic 'decay' processes within networks of bistable units: Assume single neurons or subpopulations of neurons can switch between two different stable firing rates, separated by a kind of threshold at which switching from one rate to the other occurs (Fig. 2a left) [8]. If there is noise in the system, it will drive neurons occasionally across the threshold, causing a sudden change in firing rate. The time it takes the noise, on average, to cause a switch from lower to higher activity (or vice versa) will depend on the location of the threshold, which is affected by factors such as the strength of synaptic inputs, and the amplitude of the noise (Fig. 2a left) [42,48]. Averaging over many trials or over a population of such neurons (as usually done with experimental data), due to

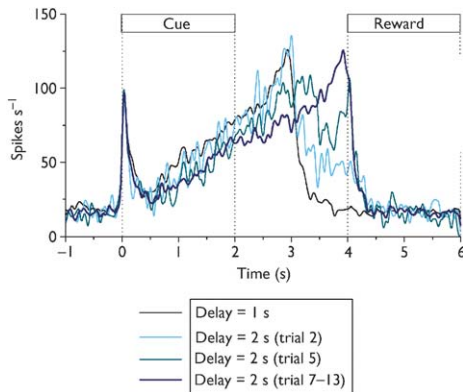


Fig. 1. Firing rate of a thalamic neuron as a function of time shows climbing activity. After presentation of a predictive cue, the firing rate of some neurons steadily climbs and reaches a peak coincident with the time at which a subsequent event, in this case a reward, is due to appear. The interval between cue and reward was initially 1 s, but was then increased to 2 s (trials 2–13). So climbing activity initially peaks one second after offset of the cue, but then quickly adjusts to the new time of occurrence by changing its slope. Reprinted from [24] with kind permission (Copyright 2001 by Nature Publishing Group).

the stochastic nature of the switching one can get monotonically rising (or falling) activity histograms with a time course depending on the average switching time [42,48]. These histograms, however, may not be linear as often observed experimentally (Fig. 1, Fig. 2a right) [13,24]. More importantly, smoothly climbing activity seems to be a phenomenon that occurs for single neurons within single trials *in vivo* (see Fig. 2b in [19]; analysis in [32]). It is, therefore, not just due to averaging across many trials or neurons [32]; only a minority of neurons seems to exhibit truly bistable activity [13,49]. This does not entirely rule out this account of interval timing, since there remains the possibility that some downstream neurons read out the activity of a population of converging bistable neurons, thereby exhibiting a slowly ramping up (or down) behavior within their own activity. Of course, this still would imply a larger population of bistable neurons somewhere in the brain, switching up and down at different times during the interval.

Finally, neurons might produce much slower effective time constants from a much faster intrinsic dynamics [33,50]. This third possibility relies on the idea of a neural

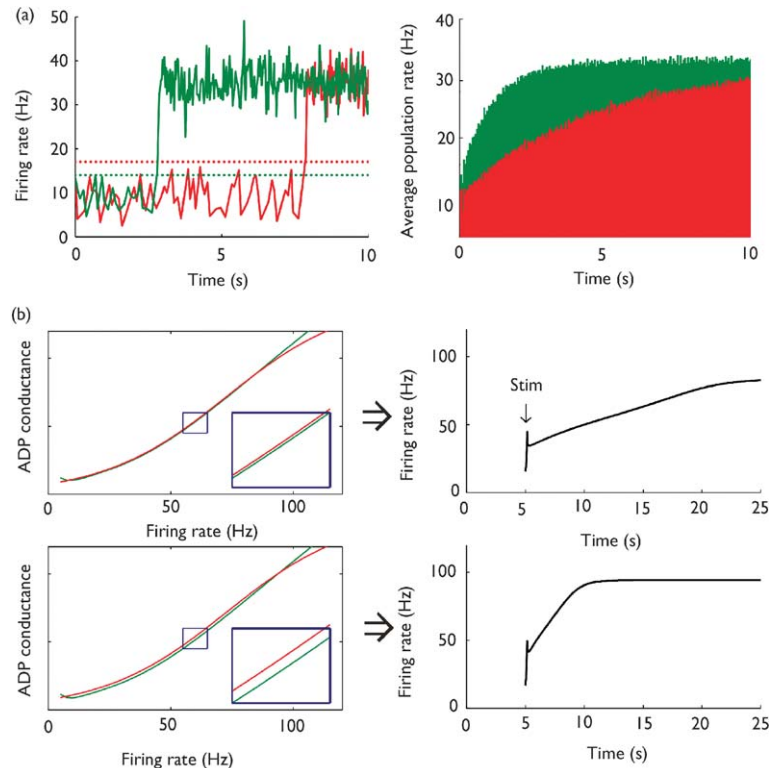


Fig. 2. Possible biophysical basis of climbing activity. (a) Climbing activity may be due to stochastic activity in bistable neurons [42,48]. On the left, two activity traces (solid lines; illustrated simply as a random process here) of a neuron are shown that can be in any one of two stable firing modes, separated by a threshold (dotted lines). Noise will eventually drive the neuron across the threshold and hence cause a switch from the lower to the higher stable firing rate. For a higher threshold (red) this will take longer, on average, than for a lower threshold (green). Right hand side: Averaging over many such neurons, one obtains a firing rate histogram with a time course depending on the location of the threshold. The time course may appear more linear, at least for relatively brief intervals, if the transition from the low to the high firing rate is slower (more gradual) than as shown on the left [48]. It may also depend on the interactions between neurons (neglected here). (b) Climbing activity may be due to fine adjustment of a cellular feedback loop. The top graph shows on the left a configuration that produces very slowly climbing activity, corresponding to a long interval, as depicted on the right (model simulations, see [33]; Stim = time of presentation of the predictive stimulus). The average amount of a Ca^{2+} -activated after-depolarizing (ADP) conductance (red curve) that is generated in a neuron at different firing rates is just slightly larger (see magnified area in inset) than the amount of this conductance that would actually be required (green curve) to maintain the neuron at any of these rates. That is, over the range ~ 10 –75 Hz there is a small excess of current driving the neuron to higher firing rates. In the bottom graph, the discrepancy between the amount of ADP conductance generated and the one required is larger, corresponding to faster climbing activity, hence a shorter temporal interval, as on the right (bottom). By reversing the vertical order of the two curves, i.e., shifting the green above the red curve, slowly decaying activity would be produced. Modified from [33], with permission (Copyright 2003 by the Society for Neuroscience).

integrator [51], and Fig. 2b shows how it works. Climbing activity might arise on the single neuron level through a positive feedback loop between neural firing, firing rate dependent Ca^{2+} influx into the cell, and Ca^{2+} -activated depolarizing currents (see [50] for a population level account utilizing a similar principle). The red curves in Fig. 2b give the amount of Ca^{2+} -activated depolarizing current [45,52] that flows if a neuron fires at a given rate (more precisely, they give the average conductance underlying the current). The green curves, in contrast, give the amount of this conductance that would be required to maintain the neuron at a particular firing rate. Hence, wherever these two curves overlap or intersect, the neuron receives exactly what it needs to maintain its current firing rate. If the red curve is only slightly above the green curve, as in Fig. 2b (top, see inset), the neuron gets slightly more depolarizing current than it would need to maintain its current firing rate, and hence firing rate increases over time. Since the mismatch between current needed and current provided is only very small, however, the firing rate will increase only very slowly, in fact orders of magnitude slower than commanded by the intrinsic time constants of the neuron [33]. By changing the distance between the two curves (bottom graph in Fig. 2b), which could be achieved through long-term plasticity mechanisms that change the strength of synaptic input to the neuron [33,53], the time course of climbing activity can theoretically be adjusted within an arbitrary range, largely independent of the intrinsic time constants of the neuron. There indeed exists some experimental evidence that Ca^{2+} -activated currents within cortical pyramidal cells could support such a mechanism [54].

While the neural integrator-arrangement could span, in principle, intervals of arbitrary length, and can be controlled in a fast and flexible manner, additional mechanisms are required for achieving and maintaining the sensitive balance of parameters that allow a neuron to work as a timer [33,55]. Such biophysical mechanisms of how neurons could self-organize into a neural integrator-configuration [33], as well as various other ideas on how robust neural integration could be achieved on the single neuron or network level without much fine-tuning [55–57], have been proposed.

CONCLUSIONS AND OPEN ISSUES

The brain might rely on a number of different mechanisms for processing temporal information within various modalities, on various time scales, and for various coding or information processing purposes [5–7]. The present review focused on climbing activity since it currently seems to be the most promising candidate for the explicit neural encoding of interval times in the context of prediction. Climbing activity enables a direct and continuous read-out of the time ahead of an anticipated event, or, alternatively, the time that has elapsed since presentation of the predictive stimulus (see also [27]).

I would like to conclude by mentioning a few of the many open issues that still remain. Besides the still largely unknown cellular and synaptic basis of climbing activity, further *in vivo* experiments are certainly needed that directly link climbing activity to interval timing. For instance, does climbing activity break down in delay tasks where the delays are drawn from a uniform random distribution lacking any temporal predictability? Another interesting

question is how climbing activity observed during motor and perception tasks [15,58,59], often interpreted as motor preparation or accumulation of evidence, relates to climbing activity observed in tasks involving fixed temporal delays. Finally, the slope of climbing activity might be affected not only by the length of the temporal interval, but also by other variables like the value of an anticipated reward or the frequency of a to-be-remembered vibrotactile (flutter) stimulus [13,19,24]. This raises the question of how exactly the nervous system disentangles these various factors (or whether it actually has to).

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Acknowledgements: This work was funded by a grant from the Deutsche Forschungsgemeinschaft (DU 354/2-2). Many thanks to Thomas Wennekers for his helpful feedback on the manuscript.

DOI: 10.1097/01.wnr.0000115486.61443.0e