6. Simon, M.A., Xu, A., Ishikawa, H.O., and Irvine, K.D. (2010). Modulation of fat:dachsous binding by the cadherin domain kinase four-jointed. Curr. Biol. *20*, 811–817.

7. Lawrence, P.A., Struhl, G., and Casal, J. (2008). Do the protocadherins Fat and Dachsous link up to determine both planar cell polarity and the dimensions of organs? Nat. Cell Biol. *10*, 1379–1382.

8. Ambegaonkar, A.A., Pan, G., Mani, M., Feng, Y., and Irvine, K.D. (2012). Propagation of Dachsous-Fat planar cell polarity. Curr. Biol. *22*, 1302–1308.

9. Brittle, A., Thomas, C., and Strutt, D. (2012). Planar polarity specification through asymmetric subcellular localization of Fat and Dachsous. Curr. Biol. *22*, 907–914.

10. Zeidler, M.P., Perrimon, N., and Strutt, D.I. (1999). The four-jointed gene is required in the Drosophila eye for ommatidial polarity specification. Curr. Biol. *9*, 1363–1372.

11. Matakatsu, H., and Blair, S.S. (2004). Interactions between Fat and Dachsous and the regulation of planar cell polarity in the Drosophila wing. Development *131*, 3785–3794.

12. Simon, M.A. (2004). Planar cell polarity in the Drosophila eye is directed by graded Four-jointed and Dachsous expression. Development *131*, 6175–6184.

13. Bosch, J.A., Sumabat, T.M., Hafezi, Y., Pellock, B.J., Gandhi, K.D., and Hariharan, I.K. (2014). The Drosophila F-box protein Fbxl7 binds to the protocadherin fat and regulates Dachs localization and Hippo signaling. eLife *3*, e03383.

14. Rodrigues-Campos, M., and Thompson, B.J. (2014). The ubiquitin ligase FbxL7 regulates the Dachsous-Fat-Dachs system in Drosophila. Development *141*, 4098–4103.

15. Wu, J., Roman, A.C., Carvajal-Gonzalez, J.M., and Mlodzik, M. (2013). Wg and Wnt4 provide long-range directional input to planar cell polarity orientation in Drosophila. Nat. Cell Biol. *15*, 1045–1055.

16. Jenny, A., Reynolds-Kenneally, J., Das, G., Burnett, M., and Mlodzik, M. (2005). Diego and Prickle regulate Frizzled planar cell polarity signalling by competing for Dishevelled binding. Nat. Cell Biol. *7*, 691–697.

17. Matis, M., Russler-Germain, D.A., Hu, Q., Tomlin, C.J., and Axelrod, J.D. (2014). Microtubules provide directional information for core PCP function. eLife *3*, e02893.

18. Shimada, Y., Yonemura, S., Ohkura, H., Strutt, D., and Uemura, T. (2006). Polarized transport of Frizzled along the planar microtubule arrays in Drosophila wing epithelium. Dev. Cell *10*, 209–222.

19. Ayukawa, T., Akiyama, M., Mummery-Widmer, J.L., Stoeger, T., Sasaki, J., Knoblich, J.A., Senoo, H., Sasaki, T., and Yamazaki, M. (2014). Dachsous-dependent asymmetric localization of spiny-legs determines planar cell polarity orientation in Drosophila. Cell Rep. *8*, 610–621.

20. Olofsson, J., Sharp, K.A., Matis, M., Cho, B., and Axelrod, J.D. (2014). Prickle/spiny-legs isoforms control the polarity of the apical microtubule network in planar cell polarity. Development *141*, 2866–2874.

Neural Coding: Time Contraction and Dilation in the Striatum

Helen Motanis and Dean V. Buonomano*
Departments of Neurobiology and Psychology, Integrative Center for Learning and Memory, Brain Research Institute, University of California, Los Angeles, CA 90095, USA
*Correspondence: dbuono@ucla.edu
http://dx.doi.org/10.1016/j.cub.2015.02.057

How the brain encodes time is poorly understood. New research on rats provides evidence that striatal neurons encode time, and that the code can dilate or contract to time different intervals.

The brain is a time machine, of sorts. It is always attempting to predict the future. At this moment you are automatically predicting the next word in this ……. And given the dynamic nature of the world, the ability to tell time and process temporal information is critical for motor coordination, sensory processing, and the ability to anticipate environmental events.

Despite the fundamental importance of timing to brain function, relatively little is known about how the brain tells time on the scale of milliseconds to seconds [1,2]. In this issue of *Current Biology*, Mello *et al.* [3] examine how the brain encodes time on the scale of seconds to a minute. This is the scale, sometimes referred to as interval timing, on which animals time their actions to prepare for expected events. Rats, for example, learn to press a lever at times that reflect timing of reward availability [4]. Bees keep track of the amount of time since they last extracted pollen from a flower in order to optimize foraging [5]. And humans automatically anticipate when a traffic light will switch from red to green.

Mello *et al.* [3] used a variant of the fixed interval task, in which a reward becomes available *T* seconds after the onset of a trial, provided that the rat presses a lever. The beginning of the trial was defined as the time of the previous reward. *T* was varied in a block fashion over intervals of 12 to 60 seconds. On a given trial, a rat would generally start pressing the lever, and continue to do so at a more or less constant rate until given the reward. Analysis of the mean press start times within a block showed a progressive increase from approximately 8 to 20 seconds, over the 12 to 60 second fixed interval range. Thus, consistent with previous results, rats adjusted the timing of their actions according to the fixed interval *T*.

Based on results of electrophysiological, pharmacological, lesion and imaging studies, the basal ganglia is perhaps the structure that has most strongly been implicated in timing in the range of seconds [1,6]. For this reason, Mello *et al.* [3] recorded from the striatum during their serial fixed interval task. Unlike in previous studies, the behavioral design was devised to answer a fundamental question about the nature of the temporal code: is time encoded in an *absolute* or *relative* fashion (Figure 1).

Under an absolute strategy, the temporal code would remain exactly the same, independent of the interval being timed; thus, more and more neurons would be recruited as longer and longer intervals are timed (Figure 1A). In contrast, under the relative strategy, the same cells will participate in encoding the different intervals, but each cell will temporally rescale its activity according to the duration being timed (Figure 1B).

The results were clear: when neurons were sorted according to when they fired during the 12 second block, two-thirds of them maintained their ordinal position in the other four blocks (24, 36, 48 and 60 seconds), and their temporal tuning was dilated to match the current block's interval. These results suggest that the neurons are encoding relative time. Importantly, during a trial it was possible to decode the time based on the population of active neurons within a given time bin — that is, one could use the pattern of activity within a trial as a 'clock', and determine how long ago the trial started. As expected, this 'clock' should run slow or fast during block transitions. During a transition from a 60 second to a 12 second block, one would expect a relative clock to run slow; indeed during the first trial of a 12 second block, the decoder generally read out 6 seconds at the 10 second time point.

A recurring concern in studies demonstrating the presence of neural codes for time is whether the activity reflects ongoing motor patterns, as opposed to time *per se*. That is, if an animal is reproducibly engaging in a specific behavior, it is possible that the observed neural code could be driven by (or driving) motor activity. To address this issue, Mello *et al.* [3] focused on one of the most salient motor responses during a trial: the first lever press. The firing rate of 40% of the units that exhibited relative timing was significantly modulated by the first lever press. The firing rate of many of these neurons was further dependent on the relative time of the first lever press — for example, a neuron might fire robustly on a trial in which the first lever press occurs late in relative time (that is, in relation to *T*), but not early in relative time. Such neurons, in a sense, contained multiplexed information about time and a motor action (and thus were not encoding 'pure' relative time).

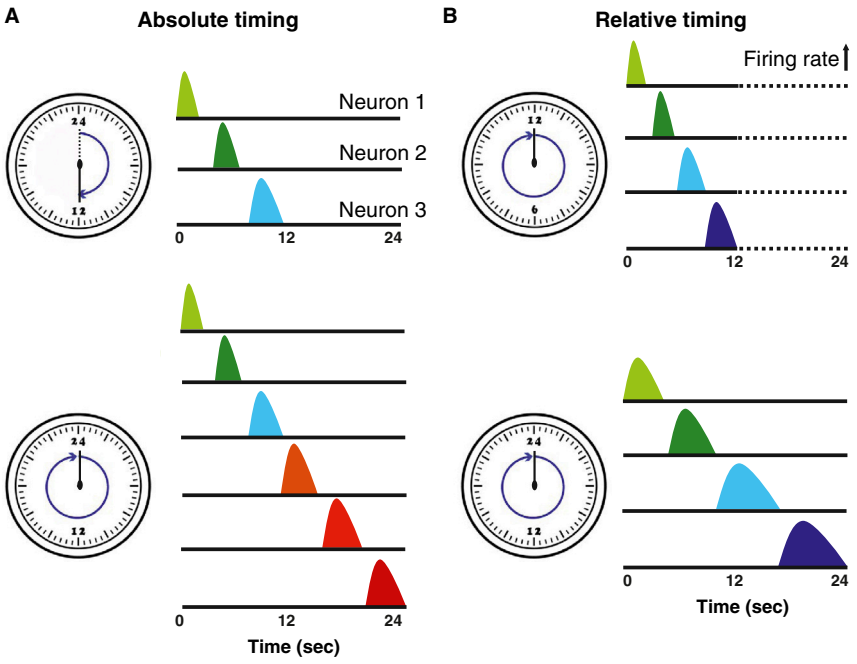

Figure 1. Relative versus absolute encoding of time.
The brain could encode time using an absolute or relative strategy. (A) Man-made clocks encode time in an absolute fashion. A full revolution of a dial around the face of a clock always takes the same amount of time, independent of the interval being timed. In the case of a neural 'population clock' — in which time is encoded in the population of currently active neurons — an absolute code would mean that, independent of the interval being timed, the same neuron is always active at the same time. (B) Under relative timing, the dial of a man-made clock would complete a full revolution in 12 seconds when timing a 12 second interval, or 24 seconds when timing 24 seconds. In the context of a neural code, relative timing would mean the temporal response profile of neurons would dilate or contract according to the interval being timed.

Given the known role of the striatum in motor actions, and the increasing evidence that neurons encode multiple dimensions in a nonlinear fashion [7–9], such 'multiplexing' is to be expected. Furthermore, it is important to emphasize that, even if the responses were well predicted by motor state, it does not necessarily follow that these neurons are not timing neurons, because generating well timed motor sequences is itself a timing task that ultimately must be controlled by central neural circuits. Mello *et al.* [3] provide additional evidence that the striatum is not simply involved in the motor aspects of the task, by showing that pharmacological inhibition of striatal activity impaired the correlation between press start time and the interval of the block (but the animals still continued to lever press). This suggests that the striatum may be causally involved in timing of this fixed interval procedure.

Theoretical and experimental studies have proposed a number of different neural mechanisms that could underlie timing, including: monotonically ramping neurons that integrate activity from a pacemaker or tonic input [10,11]; neurons that detect the beats of a population of oscillators that fire at different frequencies [12,13]; or a dynamically changing population of active neurons — sometimes referred to as a population clock [14,15]. The new results of Mello *et al.* [3] appear to be most consistent with the notion of a simple population clock in which a sequential chain of active neurons encodes time. One key question is what are the mechanisms driving this pattern. On much shorter time scales, such patterns have been proposed to arise from the dynamics with local recurrent circuits [16,17]. It seems improbable that the dynamics necessary to elicit such a temporal code is a product of local computations occurring within the striatum; striatal neurons are GABAergic, and thus unlikely to sequentially drive each other. Nevertheless, it is possible

that feedback inhibition within the striatum could generate a population clock in response to tonic input from the cortex — this scenario would parallel the model of timing in the cerebellum in which the negative feedback of the Golgi cells generates a time-varying neural trajectory in response to tonic input [18] — this cerebellar model, however, focuses primarily on subsecond timing.

Independent of the mechanisms, the neural responses would appear to be well represented as a population of sequentially activated neurons — forming, in essence, a series of temporal basis functions. It is not yet clear, however, if the population response is indeed best explained as a sequence of active neurons, each with a single temporal response field. First, on closer analyses it may prove to be the case that some neurons exhibit multi-peaked 'time fields'. Second, 32% of the neurons did not maintain their ordinal position over the different intervals, leaving open the possibility that relative and absolute temporal codes could be multiplexed. Additionally, it remains unclear whether the 'relative' neurons would encode time in the same manner during a different task or context.

Nevertheless, the new study by Mello *et al.* [3] is the first to provide clear evidence for a relative code for timing on the seconds to minute scale. The most fascinating question raised is how this is accomplished. How does a population of neurons temporally contract or dilate their responses? At the population level we can think of the firing pattern as a trajectory in N-dimensional space — where N corresponds to the number of recorded neurons. Thus, a relative temporal code corresponds to traveling along the same (or similar) trajectory at different speeds. In principle the simplest way to achieve such a rescaling is to scale the time constant of the neurons in circuits [19]. There is, however, little evidence that such a mechanism is physiologically plausible. Another possibility is that tonic inputs or neuromodulators effectively control the dynamics of the circuits in a manner that scales the speed of the neural trajectory.

Because rats can robustly rescale their motor behaviors, and humans can easily rescale the speed with which they speak or play a musical piece, future studies will have to determine not only how the brain encodes time, but how it does so in a flexible manner that allows for time dilation and contraction.

REFERENCES

1. Merchant, H., Harrington, D.L., and Meck, W.H. (2013). Neural basis of the perception and estimation of time. Annu. Rev. Neurosci. *36*, 313–336.
2. Goel, A., and Buonomano, D.V. (2014). Timing as an intrinsic property of neural networks: evidence from in vivo and in vitro experiments. Phil. Trans. R. Soc. Lond. B *369*, 20120460.
3. Mello, G.B.M., Soares, S., and Paton, J.J. (2015). A scalable population code for time in the striatum. Curr. Biol. *25*, 1113–1122.
4. Buhusi, C.V., and Meck, W.H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. Nat. Rev. Neurosci. *6*, 755–765.
5. Boisvert, M.J., and Sherry, D.F. (2006). Interval timing by an invertebrate, the bumble bee Bombus impatiens. Curr. Biol. *16*, 1636–1640.
6. Coull, J.T., Cheng, R.-K., and Meck, W.H. (2011). Neuroanatomical and neurochemical substrates of timing. Neuropsychopharmacology *36*, 3–25.
7. Buonomano, D.V., and Maass, W. (2009). State-dependent computations: spatiotemporal processing in cortical networks. Nat. Rev. Neurosci. *10*, 113–125.
8. Mante, V., Sussillo, D., Shenoy, K.V., and Newsome, W.T. (2013). Context-dependent computation by recurrent dynamics in prefrontal cortex. Nature *503*, 78–84.
9. Rigotti, M., Barak, O., Warden, M.R., Wang, X.-J., Daw, N.D., Miller, E.K., and Fusi, S. (2013). The importance of mixed selectivity in complex cognitive tasks. Nature *497*, 585–590.
10. Durstewitz, D. (2003). Self-organizing neural integrator predicts interval times through climbing activity. J. Neurosci. *23*, 5342–5353.
11. Simen, P., Balci, F., de Souza, L., Cohen, J.D., and Holmes, P. (2011). A model of interval timing by neural integration. J. Neurosci. *31*, 9238–9253.
12. Miall, C. (1989). The storage of time intervals using oscillating neurons. Neural Comput. *1*, 359–371.
13. Matell, M.S., and Meck, W.H. (2004). Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes. Cogn. Brain Res. *21*, 139–170.
14. Mauk, M.D., and Buonomano, D.V. (2004). The neural basis of temporal processing. Annu. Rev. Neurosci. *27*, 307–340.
15. Buonomano, D.V., and Laje, R. (2010). Population clocks: motor timing with neural dynamics. Trends Cogn. Sci. *14*, 520–527.
16. Long, M.A., Jin, D.Z., and Fee, M.S. (2010). Support for a synaptic chain model of neuronal sequence generation. Nature *468*, 394–399.
17. Liu, J.K., and Buonomano, D.V. (2009). Embedding multiple trajectories in simulated recurrent neural networks in a self-organizing manner. J. Neurosci. *29*, 13172–13181.
18. Mauk, M.D., and Donegan, N.H. (1997). A model of Pavlovian eyelid conditioning based on the synaptic organization of the cerebellum. Learn. Mem. *3*, 130–158.
19. Gutig, R., and Sompolinsky, H. (2009). Time-warp — invariant neuronal processing. PLoS Biol. *7*, e1000141.

Cell Division: Stem Cells Take the Stage

Sarah M. Wignall
Department of Molecular Biosciences, Northwestern University, Evanston, IL, USA
Correspondence: s-wignall@northwestern.edu
http://dx.doi.org/10.1016/j.cub.2015.03.006

A pool of proliferating germline stem cells is essential for gamete production in *Caenorhabditis elegans*. A new study applies sophisticated live imaging to assess mitotic progression and cell cycle control in these cells, yielding new insights into stem cell division.

Stem cells have the remarkable ability to both self-renew and to differentiate into specialized cell types. In adults, pools of stem cells are crucial for maintaining certain tissues, providing a means to replenish cells when needed. Sustaining a balance between self-renewal and differentiation is critical for tissue

