Finding the timer

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In a recent paper, Constantinidis *et al.* have shown that inhibitory relationships between pairs of dorsolateral prefrontal neurons can produce delays in cell activity of 200 to 1400 milliseconds. This is an important finding because it suggests that a simple form of timer might exist in the prefrontal cortex. This provides an alternative to the view that temporal processing occurs mainly in the basal ganglia.

Despite the experiences of the narrator in Proust's *À la Recherche du Temps Perdu* most of us will agree that once lost, time is something which can never be regained. It is thus essential that we keep careful track of our moments as they pass: evolution appears to have provided a system for doing just that. A network of cortical areas that includes the dorsolateral prefrontal cortex (dlPFC) and right hemispheric parietal cortex has been consistently associated with time measurement in neuroimaging and lesion studies (reviewed in [1,2]). Because the data showing involvement of these areas does not provide much information about the kind of activity occurring in them, their precise roles in time measurement, and how they work together to make up a putative 'clock' system, are not yet understood. Consequently we can only conjecture about the kind of neural activity and interaction involved and must therefore fall back upon models outlining possible scenarios.

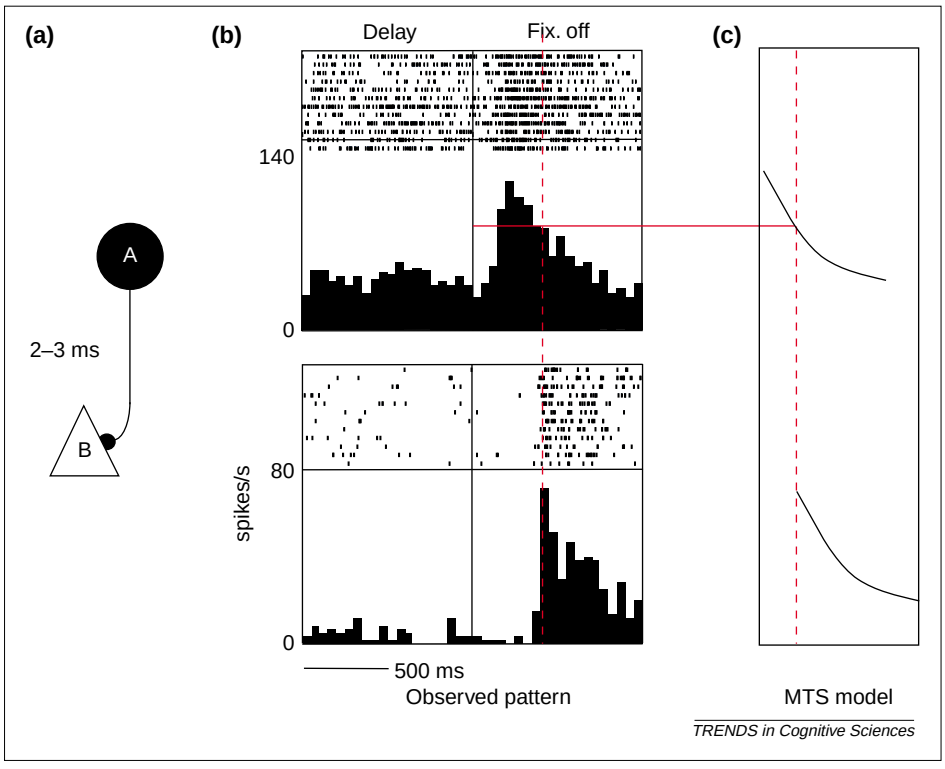

Fig. 1. (a) A feed-forward inhibitory relationship exists between cells A and B such that firing by A leads to a small decrease in activity of B after 2–3 ms. (b) The response function of cells in the dorsolateral prefrontal cortex. The cell at the top (equivalent to A) appears to inhibit the cell at the bottom (equivalent to B) when firing at above a critical frequency threshold of 80–90 spikes per second. Modified from Constantinidis *et al.* [3]. (c) Schematic, using the multiple time scales (MTS) model [5], illustrating how a decay process can be used to measure time if it consistently reaches a threshold height after the same delay.

Inhibitory relationships in the dlPFC

A recent paper by Constantinidis *et al.* has described a phenomenon that provides new avenues for these models [3]; it suggests a novel framework for how and where the measurement of time might occur. The authors recorded from pairs of neurons in the monkey dlPFC, and found an inhibitory relationship between cell pairs such that activity of one neuron was delayed by a time lag of 200 to 1400 milliseconds with respect to activity of the other. Their data suggest that this is likely to be an inhibitory effect because firing in the first neuron led to a brief decrease in activity of the second neuron after a lag of 2–3 milliseconds (Fig. 1a). The shape of the observed response functions (Fig. 1b) implies that activity in the inhibited cell only commenced when decaying activity in the inhibiting cell fell below a specific threshold level. This finding is important because it shows that inhibitory relationships between cells in the dlPFC can lead to sequencing of neural activities, which would provide a mechanism for temporal structure. It also shows that the delays induced by this type of inhibition can be as long as 1 s or more.

An earlier study showed that some cells in the dlPFC increase or decrease their firing rate along a temporally predictable curve during the delay period of a time-measurement task [4]. This curve bears more than a passing resemblance to the decay curves of the 'multiple time scales' (MTS) model of timing [5]. This model explains how time can be measured using increasing or decaying functions to mark off intervals if they consistently take a predictable amount of time to reach a specific threshold level of activity. It makes no attempt to suggest where in the brain such functions might be found. However, Constantinidis *et al.*'s finding that inhibitory interactions can delay the activity patterns of some cells for as long as 1 s, and that this inhibition appears to end when the firing frequency of the inhibiting cell has decayed beyond a certain threshold level, suggests that the predictable decay process observed in the dlPFC could be used, in combination with inhibition, to mark out a specific time interval. If linked into circuits, it would seem reasonable to suppose that temporally predictable inhibitory decay curves such as these might easily be used to measure intervals up to tens of seconds in duration.

Brain models of time measurement

To explain the full significance of this possibility for models of time measurement, it is necessary to outline existing frameworks. Some of the most dramatic data that has emerged in this context is that showing a link between dopamine levels and the rate of subjective time. In a classic paper, Warren Meck showed that rats pretrained to estimate a specific interval

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by pressing a button tended to produce a duration that was too long if their systemic dopamine levels were lowered, and too short if the levels were raised [6]. This effect has been replicated in a range of species. Meck explained the data neatly using a model in which time is tracked by a ticking internal clock, and changes in the speed of ticking relative to real time influence subjective estimates of the duration that has passed. Because this explanation specifies that the *rate* of ticking itself is altered, it is frequently interpreted as showing that the core process of the clock (equivalent to the swinging pendulum or piezo-electric crystal in a man-made mechanical clock) is controlled by dopamine levels. Approximately 80% of the dopaminergic receptors in the brain are localized to the striatum, and therefore this interpretation makes that structure a strong candidate for the locus of the 'central clock'.

This striatal hypothesis has been supported both by data from Parkinsonian patients, who have deterioration of the dopaminergic cells of the substantia nigra and show concomitant deficits in temporal processing tasks [7,8], and by neuroimaging studies that have documented activity in the striatum during time-measurement tasks (reviewed in [1,2]). Some proponents of this framework have suggested that the prefrontal cortex might be involved in memory and or attention functions, keeping track of the core clock process and helping to modulate it rather than being directly responsible for counting the passage of time [2,9].

An alternative framework, proposed in a well-argued article by Matell and Meck, shows how an array of cortical oscillators (periodic timers that repetitively measure the same duration) with different periods, could be used to feed into a striatal coincidence detector [10]. This coincidence detector could learn to use the coincidence of activity in an appropriate subset of oscillators to measure specified intervals. This framework has the advantage of providing an explanation at the cellular level, showing how the specific connectivity between cortex and spiny neurons of the striatum could be used to produce a timekeeper. Until now, however, it lacked a clear mechanism for the proposed cortical oscillators. The findings of Constantinidis *et al*. suggest a potential solution to this problem because the inhibition-induced delays they report could form the basis for an array of putative oscillators. One way in which this might work is by reciprocal inhibition between cell pairs in the dlPFC. Each cell could inhibit the other for a predictable duration, until its firing decreased enough for it to be inhibited in turn, thereby forming a classical oscillator system.

A third, more parsimonious, solution is the possibility that the central clock process occurs in the prefrontal cortex, relying on circuits using the types of delays described by Constantinidis *et al*., and the striatum is not involved at all. Although the striatum is heavily dopaminergic, it holds no monopoly on that transmitter, which is also found in many other regions of the brain including the dlPFC. It is entirely plausible that modulation of the dopaminergic dlPFC inputs might alter the observed delay relationships between cell pairs in a way that could lead to the classic dopaminergic effect seen by Meck and others. This third possibility is attractive for its simplicity, and is very much in line with current knowledge. Although striatal activity is seen during time-measurement tasks in some neuroimaging papers (for example [9,11,12]), it is absent from the results in at least as many others (for example [1,13–15]). Likewise, although patients with advanced Parkinson's disease and its associated deterioration of dopaminergic projections to the striatum show impaired temporal processing, these patients also have deterioration of the ventral tegmental area [7,8], a region that sends modulatory dopaminergic projections directly to the prefrontal cortex [16].

A framework for progress?

It will be difficult to determine which of these three frameworks is closer to the truth using lesioning and neuroimaging techniques, as these techniques cannot provide information about the behaviour of individual cells or local cellular circuits. Single-unit recording studies along the lines of Constantinidis *et al*.'s method might prove more useful, especially if combined with manipulation of dopamine, either systemically or in the dlPFC specifically. This kind of investigation could search for changes in the slope of increase (or decrease) in cell firing in the dlPFC, which might turn out to match the observed pattern of dopaminergic effect on time measurement.

Although developing models for how time measurement could be accomplished, and running experiments to test and differentiate between these models, is a fascinating pastime, it is important to keep the redundancy of biological systems in mind. Time measurement is such a basic function, which could be accomplished by any number of neural processes, and is so essential to many behaviours, that the existence of redundant mechanisms seems almost inevitable. Thus, work in this field may eventually show that evolution has done its best to help us 'regain' time by equipping us to measure it not just once, but many times using multiple clock mechanisms.

References

1 Macar, F. *et al*. (2002) Activation of the supplementary motor area and of attentional networks during temporal processing. *Exp. Brain Res.* 142, 475–485

2 Harrington, D.L. and Haaland, K.Y. (1999) Neural underpinnings of temporal processing. *Rev. Neurosci.* 10, 91–116

3 Constantinidis, C. *et al*. (2002) A role for inhibition in shaping the temporal flow of information in prefrontal cortex. *Nat. Neurosci.* 5, 175–180

4 Niki, H. and Masataka, W. (1979) Prefrontal and cingulate unit activity during timing behaviour in the monkey. *Brain Res.* 171, 213–224

5 Staddon, J.E.R. and Higa, J.J. (1999) Time and memory: towards a pacemaker-free theory of interval timing. *J. Exp. Anal. Behav.* 71, 215–251

6 Meck, W.H. (1983) Selective adjustment of the speed of internal clock and memory processes. *J. Exp. Psychol. Anim. Behav. Process.* 9, 171–201

7 Artieda, J. *et al*. (1992) Temporal discrimination is abnormal in Parkinson's disease. *Brain* 115, 199–210

8 Harrington, D.L. *et al*. (1998) Temporal processing in the basal ganglia. *Neuropsychology* 12, 3–12

9 Rao, S.M. *et al*. (2001) The evolution of brain activation during temporal processing. *Nat. Neurosci.* 4, 317–323

10 Matell, M.S. and Meck, W.H. (2000) Neuropsychological mechanisms of interval timing behavior. *BioEssays* 22, 93–103

11 Lejeune, H. *et al*. (1997) The basic pattern of activation in motor and sensory temporal tasks: positron emission tomography data. *Neurosci. Lett.* 235, 21–24

12 Jueptner, M. *et al*. (1995) Localization of a cerebellar timing process using PET. *Neurology* 45, 1540–1545

13 Maquet, P. *et al*. (1996) Brain activation induced by estimation of duration: a PET study. *NeuroImage* 3, 119–126

14 Brunia, C.H.M. *et al*. (2000) Visual feedback about time estimation is related to a right hemisphere activation measured by PET. *Exp. Brain Res.* 130, 328–337

15 Tracy, J.I. *et al*. (2000) Functional localization of a 'Time Keeper' function separate from attentional resources and task strategy. *NeuroImage* 11, 228–242

16 Porrino, L.J. and Goldman-Rakic, P.S. (1982) Brainstem innervation of prefrontal and anterior cingulate cortex in the rhesus monkey revealed by retrograde transport of HRP. *J. Comp. Neurol.* 205, 63–76

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