Opinion TRENDS in Cognitive Sciences Vol.10 No.9

Remembering the time: a continuous clock

Penelope A. Lewis[1,2] and R. Chris Miall[3]

[1] School of Psychology, University of Liverpool, Liverpool L69 7ZA, UK
[2] Institute of Cognitive Neuroscience, UCL, 17 Queen Square, London WC1N 3AR, UK
[3] School of Psychology, University of Birmingham, Birmingham B15 2TT, UK

The neural mechanisms for time measurement are currently a subject of much debate. This article argues that our brains can measure time using the same dorsolateral prefrontal cells that are known to be involved in working memory. Evidence for this is: (1) the dorsolateral prefrontal cortex is integral to both cognitive timing and working memory; (2) both behavioural processes are modulated by dopamine and disrupted by manipulation of dopaminergic projections to the dorsolateral prefrontal cortex; (3) the neurons in question ramp their activity in a temporally predictable way during both types of processing; and (4) this ramping activity is modulated by dopamine. The dual involvement of these prefrontal neurons in working memory and cognitive timing supports a view of the prefrontal cortex as a multipurpose processor recruited by a wide variety of tasks.

Introduction

Awareness of the passage of time is inextricably intermingled with memory. This is not only true for the remembrance of things past. Sometimes we must remember the beginning of an event to judge its duration but often we must also remember the time as it passes, and if distracted we can 'lose track of time' and burn the muffins or miss the train. In this article, we propose that the same neurons which are used for working memory can also be used to index the passage of time.

Most models of how the brain measures time acknowledge the link between time and memory. In scalar expectancy theory [1], a framework which has dominated the field for almost 30 years, working memory takes the form of an accumulator process which collects quantized ticks from a hypothetical neural pacemaker. A more recent model [2], the multiple time scales (MTS) framework, dispenses with the pacemaker entirely and proposes that time can be measured using the decaying strength of memory traces. In this article, we expand upon this idea by suggesting that continuous, temporally predictable changes in firing rate could be used to measure time, and observe that some of the prefrontal 'delay' cells which are known for their role in working memory actually behave in this manner during timed intervals.

We propose that this temporally predictable ramping activity might serve as the timekeeping process during cognitively controlled time perception. Our hypothesis is supported by four crucial points. First, the dorsolateral prefrontal cortex, where these cells are located, is necessary for cognitively controlled time measurement tasks. Second, both working memory and cognitively controlled timing are modulated by dopamine and disrupted by manipulation of the mesolimbocortical dopamine pathway, which projects to the dorsolateral prefrontal cortex. Third, prefrontal neurons have been shown to ramp their activity in a temporally predictable way during timed intervals, and fourth, this ramping activity appears to be modulated by dopamine. We begin with an explicit definition of the form of time perception under discussion.

What is cognitively controlled timing?

Some timing processes help us to synchronize with our environment, including circadian and ultradian rhythms, for which the mechanisms are relatively well understood [3]. Other forms of time measurement, such as that needed for the coordination of complex movements, estimation of how long it takes to perform specific tasks, or prediction of when the train is about to depart, remain more mysterious. Because these tasks vary widely, it would be surprising if they all drew upon the same brain system.

Many researchers have suggested that distinct mechanisms exist for the measurement of different temporal durations [4–8], for motor versus nonmotor timing [9] and, more recently, for the timing of continuous cyclical versus discrete broken movements [8,10]. Several authors [8,11,12] have also suggested the existence of distinct mechanisms for automatic and cognitive forms of timing.

In a recent article [13], we built upon these findings by proposing that it is not any single characteristic, but rather a constellation of several characteristics which determines which timing system is recruited in any particular task. We tested this proposal using a meta-analysis of the neuroimaging literature on time measurement. Although other task characteristics might also be important, our analysis was constrained to consider just three: the duration measured, whether or not the timed intervals were defined by movement and, whether timing was continuous (e.g. an unbroken series of predictable intervals) or intermittent (e.g. broken into discrete measurements by the presence of unpredictable irregular intervals). Our findings indicated that tasks involving continuous measurement of a series of predictable subsecond intervals defined by movement (e.g. rapid paced finger tapping) tend to recruit primary

Corresponding author: Lewis, P.A. (p.a.lewis@liverpool.ac.uk).
Available online 8 August 2006.

 1364-6613/$ – see front matter doi:10.1016/j.tics.2006.07.006

sensorimotor and premotor areas, whereas tasks with the opposing characteristics tend to recruit right hemispheric prefrontal and parietal cortices (Figure 1). These results suggest that tasks recruiting only the sensorimotor system can be performed relatively automatically, whereas tasks which draw upon multipurpose prefrontal and parietal modules known for their involvement in working memory and attention might require more cognitive involvement.

Importantly, our analysis showed that having any two out of the three characteristics associated with a task type (cognitive or automatic) dramatically increased the probability that the areas associated with that timing system would be recruited. Accordingly, we can think of any task having two or more cognitive attributes (e.g. measuring more than a second, discontinuously, and without relying upon movement) as a 'cognitively controlled timing task', and any task with two or more of the opposing characteristics as an 'automatic timing task'. These definitions can be applied *post hoc* to any study of time measurement, a strategy which is useful in determining whether or not the existing literature supports the cognitive–automatic framework.

Cognitively controlled timing, right dorsolateral prefrontal cortex, and memory

Cognitively controlled timing activates the right hemispheric dorsolateral prefrontal cortex (DLPFC) more frequently than any other brain area [13]. The remainder of this article will focus specifically upon this region and its role in tracking the passage of time.

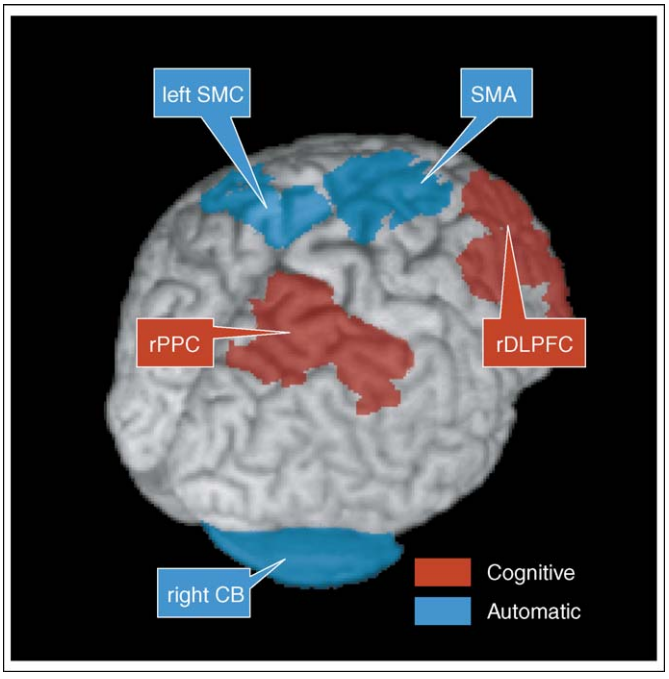

Figure 1. 3D depiction of the human brain regions associated with cognitively controlled (red) and automatic (blue) timing systems. These areas, identified in a meta-analysis of imaging studies [13], were defined for illustration using voxel-labelled templates in the automatic anatomical labelling atlas [50] and the mri3dX Brodmann atlas, rendered onto the SPM canonical brain (http://www.fil.ion.ucl.ac.uk/spm). Abbreviations: CB, cerebellum; SMA, supplementary motor area; SMC, sensorymotor cortex; rPPC, right posterior parietal cortex; rDLPFC, right dorsolateral prefrontal cortex.

The right DLPFC corresponds to the middle portion of middle and superior frontal gyri (e.g. Brodmann areas 9, 9/46 and 46) in humans, and to the region adjacent to the superior frontal sulcus in macaques [14]. That this part of the prefrontal cortex is strongly associated with working memory is evident from numerous studies using targeted lesions and single unit recording in monkeys, as well as from patient work and a vast collection of neuroimaging data [15]. Given the consensus that some form of working memory is important for timing, it is unsurprising that the DLPFC is essential to some timing tasks and that cells in this area exhibit a variety of time-sensitive behaviours [16]. Support for the right hemispheric lateralization of the involvement of this region in timing comes from neuropsychological work [17,18], examination of parkinsonian patients with unilateral deficits influencing the prefrontal cortex [19], and neuroimaging studies showing activity here during timing tasks (see Macar *et al*. [20] and Rubia and Smith [21] for reviews).

Importantly, right dorsolateral prefrontal activity is much more common in cognitively controlled timing tasks than in those classified as automatic [13]. Lesions to this area have been shown to disrupt cognitive timing [17], and the differential involvement of the right DLPFC in cognitive and automatic timing has been supported by a recent transcranial magnetic stimulation study showing impaired reproduction of suprasecond (more cognitive) but not subsecond (more automatic) intervals [22]. A parallel study showed that repetitive transcranial magnetic stimulation to the right but not left DLPFC disrupts the timing of suprasecond durations [23].

Overall, these data suggest that the region of the DLPFC that is known to be important for working memory is also essential for cognitively controlled time measurement but with an apparent bias to the right hemisphere. This area does not appear to be important for more automatic forms of timing.

Working memory and cognitive time measurement draw upon the same mental resources

Behavioural evidence that working memory and time measurement draw upon the same cognitive resources stems from dual-task studies showing interference between these two types of processing. Both visuospatial and phonological working memory tasks disrupt timing, and the extent of such disruption has been shown to correlate with the extent of working memory load (e.g. number of items to be remembered, number of syllables to be rehearsed or degrees of mental rotation) [24]. It is important to note that these experiments used timing tasks that would be classified as cognitively controlled.

Turning to pharmacology, manipulations targeting working memory can also disrupt cognitive timing. For example, benzodiazepines that influence working memory impair the processing of suprasecond intervals [6,8,11,25], whereas timing at the range of milliseconds appears to be unaffected by these drugs [26]. Similar dissociations have been shown for drugs thought to influence attentional processing such as the selective noradrenaline reuptake inhibitor reboxetene [25]. Rammsayer and co-workers [8,11,25] have interpreted this as evidence for two distinct

timing mechanisms: an automatic mechanism for the measurement of durations in the millisecond range and a cognitive mechanism, mediated by attention and drawing upon working memory, for the measurement of intervals in the range of seconds. This proposal differs from our cognitive–automatic framework [13] only in that these authors regard the timed duration as the prime discriminant between systems, whereas we propose that a combination of characteristics determines which system is recruited. Also, Rammsayer and co-workers investigated extremely brief intervals (~50 ms) and placed the cut-off between timing systems at around 500 ms, whereas we suggest that the critical value is closer to 1 s. Irrespective of these minor differences, both frameworks agree that separate systems exist for different types of time measurement and that at least one of these systems draws upon cognitive processors in the prefrontal cortex, with those regions known to be involved in working memory as prime candidates.

Dopamine, DLPFC, time, and memory

Additional evidence linking time perception to working memory stems from the observation that both are modulated by dopamine, a neurotransmitter which regulates activity throughout much of the brain, including the prefrontal cortex. The influence of prefrontal dopaminergic projections upon working memory is well documented [27]. Both increases in prefrontal dopamine and application of dopamine antagonists have been shown to disrupt this process [28], suggesting that deviation from an optimal level is detrimental to performance. Additionally, prefrontal dopamine levels increase during working memory tasks [29] and recording studies have demonstrated dopaminergic modulation of the layer III pyramidal cells associated with maintenance of information in working memory [30] (e.g. 'delay' neurons [28]). The importance of dopamine for temporal processing is also well established. A comprehensive review of work in nonhumans [31] argues that increasing levels of dopamine leads to a speeding up of subjective time. By contrast, decreasing dopamine leads to a slowing of subjective time [18]. In humans, both control subjects [8] and parkinsonian patients [4,19] have demonstrated a strong dopaminergic influence upon temporal processing, although it has been difficult to replicate the precise effects seen in the animal data [32].

Because the basal ganglia are heavily innervated by dopamine, and because their function is severely disrupted in Parkinson's disease, the influence of dopamine on subjective time measurement has typically been interpreted as support for the central role of these structures in timing. However, in addition to the mesostriatal dopaminergic pathway projecting from the substantia nigra to the striatum, the dopaminergic system includes a mesocortical pathway with projections from the ventral tegmental area to the prefrontal cortex. This provides a direct route by which dopaminergic inputs might act upon the prefrontal cortex to influence time perception [8,11,33,34]. The suggestion that mesocortical dopamine might influence cognitive time perception is informed not only by the anatomical overlap between the prefrontal regions innervated by this pathway and those known to be involved in time measurement, but also by the observation that parkinsonian patients experience more severe deficits in temporal processing in the late stages of the disease, when cells in the ventral tegmental area have been destroyed [35,36]. The recent demonstration of temporal deficits in several other dopaminergic disorders involving the prefrontal cortex, such as Huntington's disease [37], schizophrenia [38], and attention deficit hyperactivity disorder [39], are also in line with this view.

Pharmacological studies provide further evidence for the involvement of mesolimbic dopamine in cognitive timing. In a series of targeted investigations, Rammsayer and co-workers capitalized upon the differential influences of various dopamine antagonists upon mesostriatal and mesocortical pathways to determine the relative importance of each for different forms of time perception. They found that remoxipride, an atypical neuroleptic agent which blocks dopamine D2 receptors in the mesocortical system but not in the mesostriatal system, disrupts comparison of durations in the seconds range, without affecting comparisons of durations in the range of milliseconds, or movement timing [11]. The same study showed that haloperidol, which blocks D2 receptors in both systems, impairs the timing of both short and long duration processing and also interferes with movement timing. In conjunction with the results from studies with benzodiazepines and noradrenergic blockers discussed above [6,8,11,25], these data support the role of mesocortical dopamine in a cognitive timing system which draws upon working memory and attention, and of mesostriatal dopamine in both this cognitive system and a more automatic timing process [8,11,25]. Recent work with deep brain stimulation in the subthalamus has also supported a role for the mesostriatal dopaminergic system in cognitively controlled timing [40], with the suggestion that the observed effects might be mediated by striatocortical projections. This raises the possibility that the mesostriatal dopaminergic pathway influences cognitive timing via striatocortical projections, whereas mesostriatal influences on automatic timing are mediated in some other fashion – a proposal which could reconcile the broad literature on dopaminergic influences on timing with the evidence that prefrontal involvement is specific to cognitive timing. This possibility is also in good keeping with our suggestion that dopaminergic influences on cognitively controlled timing stem from the influence of this transmitter on pyramidal cells of the DLPFC because this region receives numerous striatocortical projections (Figure 2).

Overall, the data on dopamine suggest a selective influence of prefrontal dopamine on more cognitive timing tasks, thus implying that this form of timing might be mediated via the same dopamine-sensitive processors as working memory.

Time measurement and memory decay traces

The proposal of time measurement as a continuous process suggests that, rather than using a discrete ticking clock, we use something akin to a continuously fading memory trace of neuronal activity to track the passage of time. This idea was initially suggested at a theoretical level in the form of the MTS model [2]. This model proposes that forgetting

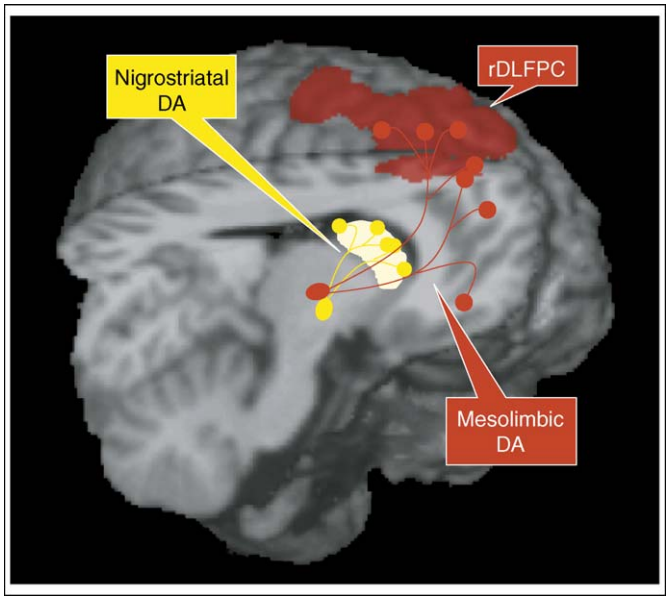

Figure 2. 3D depiction of a human brain which has been sliced to reveal the midbrain. The mesostriatal dopaminergic pathway, which projects from the substantia niagra pars compacta to the striatum, is depicted in bright yellow, with the caudate (one of the basal ganglia) shown in paler yellow. The mesocortical dopaminergic pathway, which projects from the ventral tegmental area to the cortex (particularly the frontal lobes), is represented in bright red, with the rDLPFC shown in darker red. These areas were defined using voxel-labelled templates derived from the mri3dX Brodmann atlas and rendered onto the SPM canonical brain. Abbreviations: DA, dopaminergic pathway; rDLPFC, right dorsolateral prefrontal cortex.

occurs along a predictable time course, which can be described as a sum of exponential curves [41] (Figure 3a), so the strength of a memory could be used to determine how much time has passed since it was formed. The MTS model involves several mathematical constraints that are not easily matched by individual prefrontal neurons, such as the requirement for logarithmic decay, and precise details of how the level of starting activity is stored and compared with the level of activity later in an interval. Nevertheless, a looser interpretation of the memory decay idea, in which the memory is held within a population of cells (Figure 3c), provides a compellingly parsimonious framework that can predict the fundamental psychophysical properties of interval timing (e.g. scalar timing and bisection at the geometric mean) [2,42].

The physiological feasibility of time measurement using a continuously decaying (or increasing) signal has become apparent as specific populations of cells behaving in this way during timing have been identified [34,43,44]. For instance, cells in the macaque prefrontal cortex have been shown to 'ramp' their activities in a predictable way during temporal comparison [45], and similar activities have been observed in rats during temporal production [43]. These firing patterns are highly reminiscent of the increases of firing rates ('delay activity') which occur when information is held online [46], and which are thought to serve as a basis for working memory (Figure 3b,c). Neuroimaging work in humans also supports this hypothesis; a recent study showed that functional magnetic resonance imaging signal in the DLPFC varies with the duration being measured [47]. Interestingly, some subregions of the DLPFC increased their average activity as the presented interval

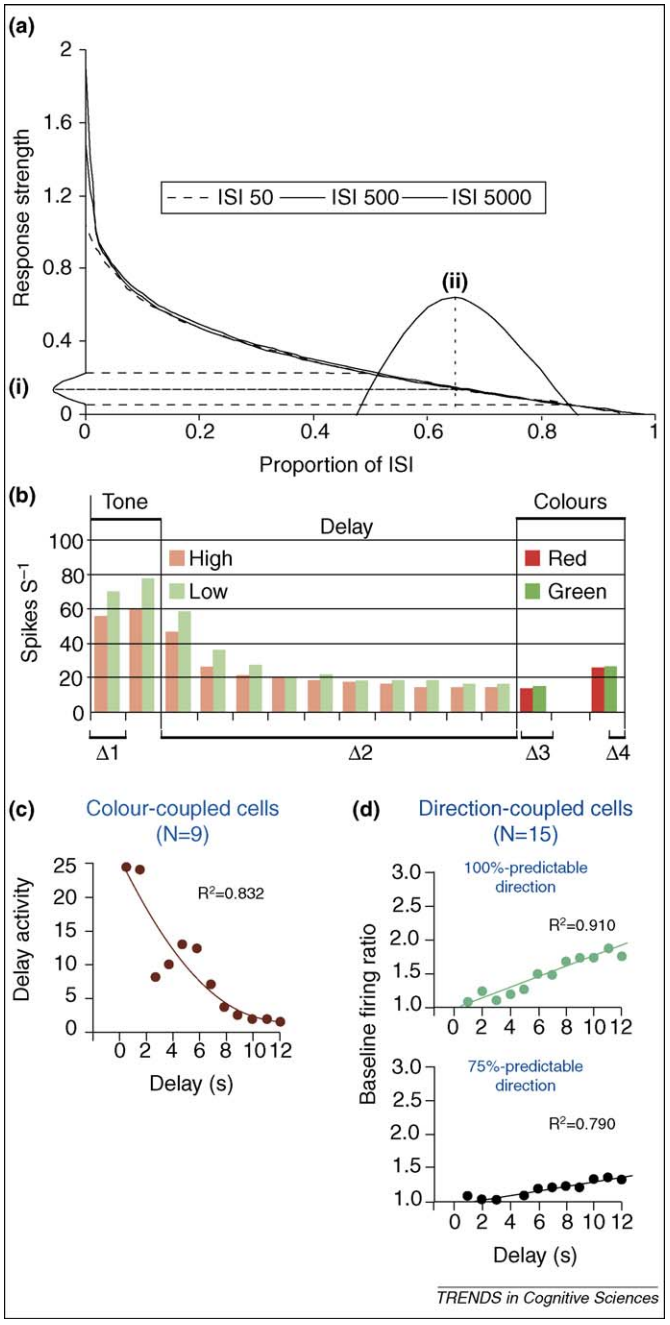

Figure 3. Memory for time. **(a)** Illustration of how 'forgetting curves' could be used to measure time under the MTS model. Three overlapping memory traces are shown for three intervals, all decaying along a predictable trajectory, such that measurements of strength at any given point can be used to determine how much time has passed. A threshold (horizontal line) with associated noise is assumed to trigger output from the system. The scalar property of timing arises naturally from this construct because a fixed uncertainty window in the memory strength (I) leads to variance in estimated duration (II), and the three curves have equal proportional variance. Modified, with permission, from Ref. [51]. **(b)** The activity of a monkey prefrontal neurone during the delay interval (Δ2) between presentation of tones and colours. The activity decays smoothly. Modified, with permission, from Ref. [46]. **(c,d)** Population data for similar prefrontal cells [46] showing decay (c) or ramping activity (d) across the 12-s delay interval.

increased, whereas other subregions decreased their activity, supporting the idea that both increasing and decaying activity could serve as a measure of time. Surprisingly, these correlations were observed in the left rather than the right hemisphere and were found in different locations during encoding and retrieval.

Concluding remarks: can time be measured using the same neural machinery as working memory?

We have outlined a substantial body of evidence suggesting that both cognitive time measurement and working memory rely upon the right hemispheric DLPFC. Dual-task interference suggests that both forms of computation place demands upon the same cognitive processing units. Both processes are influenced by dopamine, a neuromodulator known to effect function in this region, and we have argued that both types of processing might even draw upon the same cell population in this region – the dopamine-sensitive layer III pyramidal delay neurons.

The importance of memory for time perception is widely acknowledged. However, a traditional perspective has been to suppose that working memory is used in time perception – for instance, in the manner of an accumulator process keeping track of the ticks from a neural oscillator as proposed by the scalar expectancy theory model. In this article, we have drawn upon concepts from the newer MTS model to suggest that, instead of merely keeping track of the progress of a separate time keeper, these working memory processes might actually constitute the time-dependent process itself. This formulation can be taken one step further by proposing that the prefrontal time keeper function does not rely upon working memory *per se* but instead simply draws upon the same neural processors as working memory. Thus, the same regions – and potentially even the same cells – that are involved in working memory can be thought of as serving a distinct function when they are used for time measurement.

Our suggestion that the prefrontal processing units used in working memory can also be used to measure time is in keeping with the adaptive coding hypothesis [48], which proposes the prefrontal cortex as a multipurpose processor recruited for a wide variety of functions. This hypothesis explains why the same prefrontal regions are involved in so many cognitive tasks, including working memory, word generation, divided visual attention, problem solving, response suppression and cognitive time perception. A conceptually similar framework suggests that the parietal cortex might provide multipurpose calculations of magnitude [49], thus explaining its involvement in diverse tasks, including perception of size, number, and intensity, distance, as well as time. Taken together, the proposals of adaptive coding in the prefrontal cortex, and of generalized magnitude calculation in the parietal cortex, represent a move away from functional modularity and towards a more flexible and integrative view of the brain.

Although this article focuses on the right DLPFC, several other regions have consistently been shown to be important for cognitively controlled time measurement. Although the right DLPFC might serve as the time-dependent process within cognitively controlled timing tasks, this does not preclude the involvement of areas such as insula–operculum, basal ganglia, supplementary motor area and cerebellum in this and other forms of timing. These regions might work in conjunction with the right DLPFC or form alternate timing systems recruited in parallel with it. Because ramping neural activity is fairly common throughout the prefrontal cortex, it is also possible that timing activities in other parts of the prefrontal lobe might rely upon a similar mechanism. More research is needed both to test this proposed mechanism and to explore the roles of these other regions in timing (Box 1).

Box 1. Questions for further research

- Does concurrent performance of a working memory task disrupt automatic timing? How does this differ from the influence of identical tasks upon cognitively controlled timing?
- Do drugs like haloperidol and remoxipride (which antagonize the dopaminergic system), benzodiazepines (which influence working memory) and reboxetine (which influences attentional procession) show differential effects upon cognitive and automatic timing tasks?
- What is the relative importance of specific task characteristics (e.g. duration timed, continuousness of timing and involvement of movement in timing) for dissociation between cognitive and automatic timing via dual tasks and drugs (see above)?
- Are other task characteristics important for dissociating between cognitive and automatic timing?
- How does dopamine influence the pattern of ramping activity in dorsolateral layer III pyramidal cells during timing tasks? Is there a clear relationship between such influence and the observed behavioural effects?
- Can perturbation of the ramping activity in the right DLPFC (perhaps by microstimulation) influence the perceived duration of a stimulus?
- Might ramping activity in other areas [e.g. supplementary motor area (SMA) or pre-SMA and premotor cortex] underpin automatic timing?

References

1 Gibbon, J. (1977) Scalar expectancy theory and Weber's law in animal timing. *Psychol. Rev.* 84, 279–325
2 Staddon, J.E. and Higa, J.J. (1999) Time and memory: towards a pacemaker-free theory of interval timing. *J. Exp. Anal. Behav.* 71, 215–251
3 Perreau-Lenz, S. *et al.* (2004) The biological clock: the bodyguard of temporal homeostasis. *Chronobiol. Int.* 21, 1–25
4 Gibbon, J. *et al.* (1997) Toward a neurobiology of temporal cognition: advances and challenges. *Curr. Opin. Neurobiol.* 7, 170–184
5 Rammsayer, T.H. *et al.* (1993) Aging and temporal discrimination of brief auditory intervals. *Psychol. Res.* 55, 15–19
6 Rammsayer, T.H. and Vogel, W.H. (1992) Pharmacologic properties of the internal clock underlying time perception in humans. *Neuropsychobiology* 26, 71–80
7 Rammsayer, T.H. and Lima, S.D. (1991) Duration discrimination of filled and empty auditory intervals: cognitive and perceptual factors. *Percept. Psychophys.* 50, 565–574
8 Rammsayer, T.H. (1999) Neuropharmacological evidence for different timing mechanisms in humans. *Q. J. Exp. Psychol. B* 52, 273–286
9 Clarke, S. *et al.* (1996) Exploring the domain of the cerebellar timing system. In *Time, Internal Clocks, and Movement* (Pastor, M.A. and Artieda, J., eds), pp. 257–280, Elsevier
10 Spencer, R.M. *et al.* (2003) Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. *Science* 300, 1437–1439
11 Rammsayer, T.H. (1997) Are there dissociable roles of the mesostriatal and mesolimbocortical dopamine systems on temporal information processing in humans? *Neuropsychobiology* 35, 36–45
12 Rammsayer, T.H. (2006) Effects of pharmacologically induced changes in NMDA receptor activity on human timing and sensorimotor performance. *Brain Res.* 1073–1074, 407–416
13 Lewis, P.A. and Miall, R.C. (2003) Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. *Curr. Opin. Neurobiol.* 13, 250–255
14 Rushworth, M. and Owen, A. (1998) The functional organization of the lateral frontal cortex: conjecture or conjuncture in the electrophysiology literature. *Trends Cogn. Sci.* 2, 46–53

15 Wager, T.D. and Smith, E.E. (2003) Neuroimaging studies of working memory: a meta-analysis. *Cogn. Affect. Behav. Neurosci.* 3, 255–274
16 Genovesio, A. *et al.* (2006) Neuronal activity related to elapsed time in prefrontal cortex. *J. Neurophysiol.* 95, 3281–3285
17 Harrington, D.L. *et al.* (1998) Cortical networks underlying mechanisms of time perception. *J. Neurosci.* 18, 1085–1095
18 Koch, G. *et al.* (2002) Selective deficit of time perception in a patient with right prefrontal cortex lesion. *Neurology* 59, 1658–1659
19 Koch, G. *et al.* (2005) Memory for time intervals is impaired in left hemi-Parkinson patients. *Neuropsychologia* 43, 1163–1167
20 Macar, F. *et al.* (2002) Activation of the supplementary motor area and of attentional networks during temporal processing. *Exp. Brain Res.* 142, 475–485
21 Rubia, K. and Smith, A. (2004) The neural correlates of cognitive time management: a review. *Acta Neurobiol. Exp. (Wars.)* 64, 329–340
22 Jones, C.R. *et al.* (2004) The right dorsolateral prefrontal cortex is essential in time reproduction: an investigation with repetitive transcranial magnetic stimulation. *Exp. Brain Res.* 158, 366–372
23 Koch, G. *et al.* (2003) Underestimation of time perception after repetitive transcranial magnetic stimulation. *Neurology* 60, 1844–1846
24 Fortin, C. and Breton, R. (1995) Temporal interval production and processing in working memory. *Percept. Psychophys.* 57, 203–215
25 Rammsayer, T.H. *et al.* (2001) Effects of noradrenergic activity on temporal information processing in humans. *Q. J. Exp. Psychol. B* 54, 247–258
26 Rammsayer, T.H. (1994) Effects of practice and signal energy on duration discrimination of brief auditory intervals. *Percept. Psychophys.* 55, 454–464
27 Marie, R.M. and Defer, G.L. (2003) Working memory and dopamine: clinical and experimental clues. *Curr. Opin. Neurol.* 16 (Suppl. 2), S29–S35
28 Goldman-Rakic, P.S. (1995) Cellular basis of working memory. *Neuron* 14, 477–485
29 Watanabe, M. *et al.* (1997) Increase of extracellular dopamine in primate prefrontal cortex during a working memory task. *J. Neurophysiol.* 78, 2795–2798
30 Arnsten, A.F. (1997) Catecholamine regulation of the prefrontal cortex. *J. Psychopharmacol.* 11, 151–162
31 Meck, W.H. (1996) Neuropharmacology of timing and time perception. *Brain Res. Cogn. Brain Res.* 3, 227–242
32 Malapani, C. *et al.* (1998) Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction. *J. Cogn. Neurosci.* 10, 316–331
33 Rammsayer, T.H. (1993) On dopaminergic modulation of temporal information processing. *Biol. Psychol.* 36, 209–222
34 Lewis, P.A. (2002) Finding the timer. *Trends Cogn. Sci.* 6, 195–196
35 Harrington, D.L. *et al.* (1990) Procedural memory in Parkinson's disease: impaired motor but not visuoperceptual learning. *J. Clin. Exp. Neuropsychol.* 12, 323–339
36 Artieda, J. *et al.* (1992) Temporal discrimination is abnormal in Parkinson's disease. *Brain* 115, 199–210
37 Paulsen, J.S. *et al.* (2004) fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's Disease. *AJNR Am. J. Neuroradiol.* 25, 1715–1721
38 Elvevag, B. *et al.* (2004) Identification of tone duration, line length, and letter position: an experimental approach to timing and working memory deficits in schizophrenia. *J. Abnorm. Psychol.* 113, 509–521
39 Meaux, J.B. and Chelonis, J.J. (2005) The relationship between behavioral inhibition and time perception in children. *J. Child Adolesc. Psychiatr. Nurs.* 18, 148–160
40 Koch, G. *et al.* (2004) Subthalamic deep brain stimulation improves time perception in Parkinson's disease. *Neuroreport* 15, 1071–1073
41 Rubin, D.C. *et al.* (1999) The precise time course of retention. *J. Exp. Psychol. Learn. Mem. Cogn.* 25, 1161–1176
42 Staddon, J.E. *et al.* (2002) Habituation, memory and the brain: the dynamics of interval timing. *Behav. Processes* 57, 71–88
43 Matell, M.S. and Meck, W.H. (2004) Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes. *Brain Res. Cogn. Brain Res.* 21, 139–170
44 Constantinidis, C. *et al.* (2002) A role for inhibition in shaping the temporal flow of information in prefrontal cortex. *Nat. Neurosci.* 5, 175–180
45 Niki, H. and Watanabe, M. (1979) Prefrontal and cingulate unit activity during time behavior in the monkey. *Brain Res.* 171, 213–224
46 Fuster, J.M. (2001) The prefrontal cortex – an update: time is of the essence. *Neuron* 30, 319–333
47 Jech, R. *et al.* (2005) Cumulative blood oxygenation-level-dependent signal changes support the 'time accumulator' hypothesis. *Neuroreport* 16, 1467–1471
48 Duncan, J. (2001) An adaptive coding model of neural function in prefrontal cortex. *Nat. Rev. Neurosci.* 2, 820–829
49 Walsh, V. (2003) A theory of magnitude: common cortical metrics of time, space and quantity. *Trends Cogn. Sci.* 7, 483–488
50 Tzourio-Mazoyer, N. *et al.* (2002) Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289
51 Staddon, J.E. (2005) Interval timing: memory, not a clock. *Trends Cogn. Sci.* 9, 312–314