WHAT MAKES US TICK? FUNCTIONAL AND NEURAL MECHANISMS OF INTERVAL TIMING

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Abstract | Time is a fundamental dimension of life. It is crucial for decisions about quantity, speed of movement and rate of return, as well as for motor control in walking, speech, playing or appreciating music, and participating in sports. Traditionally, the way in which time is perceived, represented and estimated has been explained using a pacemaker–accumulator model that is not only straightforward, but also surprisingly powerful in explaining behavioural and biological data. However, recent advances have challenged this traditional view. It is now proposed that the brain represents time in a distributed manner and tells the time by detecting the coincidental activation of different neural populations.

GLOBAL POSITIONING SYSTEM (GPS). A network of artificial satellite transmitters that provide highly accurate position fixes for Earth-based, portable receivers.

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Time and space are the fundamental dimensions of our existence. Although space is gradually losing its value in a world of computer networks, cellular phones and virtual libraries, time is becoming the essence of our times, as is reflected by ever increasing speed, rate of return and productivity — concepts that are intrinsically related to time. Time is also crucial for everyday activities, from our sleep–wake cycle to walking, speaking, playing and appreciating music, and playing sports. We can engage in these activities because, like most animals, we process and use temporal information across a wide range of intervals (FIG. 1) — in contrast to, for example, the limited range of the light spectrum that we can see.

Being able to tell the time is also advantageous for gathering spatial information. Just as a position in space can be triangulated by using distance to landmarks, the GLOBAL POSITIONING SYSTEM (GPS) provides current position by triangulating temporal information (the difference or coincidence in phase of signals) from satellites. COINCIDENCE DETECTION is also used by bats, owls and frogs to form an accurate, topographic representation of space from INTERAURAL TIME DIFFERENCES[1]. For these species, telling space is telling time. Timing and time perception are fundamental to survival and goal reaching in humans and other animals[2,3], and are possible over multiple timescales[4–6] owing to the number of biological mechanisms that have evolved to deal with time.

This article reviews the rapid progress that has been made in understanding the functional and neural mechanisms of INTERVAL TIMING. Traditionally, the manner in which durations in the seconds-to-minutes range are perceived, represented and estimated has been explained using a pacemaker–accumulator model[7–9]. This model is relatively straightforward, and provides powerful explanations of both behavioural and physiological data[10–12]. However, recent advances that challenge the traditional pacemaker–accumulator model have come from studies that use various modern techniques, which range from drug microinjection and ensemble recording in genetically modified and wild-type rodents to functional MRI (fMRI) and positron emission tomography (PET) in neurologically impaired and control humans. These data indicate that time might be represented in a distributed manner in the brain, and that telling the time is a matter of detecting the coincidental activation of different neural populations.

Multiple timers for multiple timescales

To deal with time, organisms have developed multiple systems that are active over more than 10 orders of magnitude with various degrees of precision (FIG. 1a).

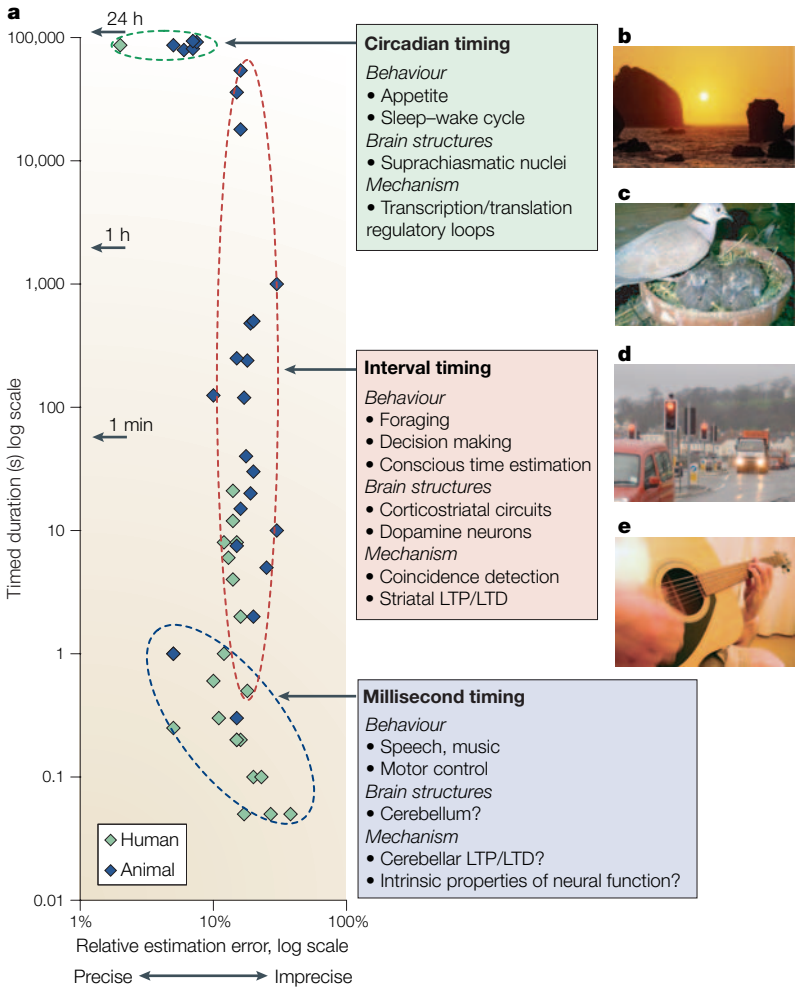

Figure 1 | **Timing across different timescales. a** | A compilation, which is by no means exhaustive, of data from various studies[29,130–141] that indicate the precision of humans and other animals in various timing tasks. Performance is precise (but less flexible) in a narrow range around 24 h (circadian timing), less precise (but more flexible) in a wide seconds-to-minutes-to-hours range (interval timing), and is of mixed precision in the sub-second range (millisecond timing) in which performance is probably linked to the intrinsic properties of the neural system involved[29]. **b–e** | Circadian rhythms[13] are most recognizable in nature (**b**), but interval and millisecond timing also guide fundamental animal behaviours. For example, although female ring doves use circadian-timing strategies to coordinate egg incubation, males use interval-timing strategies[31] (**c**). Interval timing is involved in decision making[2,3] (**d**), and millisecond timing is central to the playing of music[30] (**e**). LTD, long-term depression; LTP, long-term potentiation.

COINCIDENCE DETECTION
The activation of neurons not by single inputs, but by the simultaneous activity of several inputs. For example, coincidental activation or inactivation of specific dendritic inputs might trigger a neuron to fire, thereby transforming a time code into a rate code. Similarly, in the binaural auditory system, coincidental activation that results from hearing a sound with a specific interaural time difference is used to transform a time code into a spatial code.

CIRCADIAN RHYTHMS[13], which operate over the range of the 24-h light–dark cycle, control sleep and wakefulness as well as metabolic and reproductive fitness (FIG. 1b). Interval timing in the seconds-to-minutes range is involved in foraging[14], decision making[2,3] (FIG. 1d) and multiple-step arithmetic[15], and has been demonstrated in birds[16–18], fish[19], rodents[20–22], primates[23], and human infants[24] and adults[25,26]. MILLISECOND TIMING is crucial for motor control[27], speech generation[28] and recognition[29], playing music[30] and dancing (FIG. 1e). These different timing strategies inform decision making in both individuals and groups; for example, to coordinate egg incubation, male ring doves use interval-timing strategies whereas females use circadian-timing strategies[31] (FIG. 1c).

Circadian, interval and millisecond timing involve different neural mechanisms[32]. In mammals, the circadian clock that drives metabolic and behavioural rhythms is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. This master clock coordinates tissue-specific rhythms according to light input[33] and other cues — such as social information[34] — that it receives from the outside world. The circadian timer relies on a molecular network of transcriptional feedback loops[35]. On the other hand, interval timing depends on the intact striatum, but not on the intact SCN[36] or cerebellum[37,38]. In the interval-timing range, the striatum and the cerebellum might both be activated, possibly contributing to different aspects of performance[39,40] as a function of the sequential stages of motor memory consolidation[41].

Traditional approaches to interval timing

The scalar property. Three types of behavioural procedure have traditionally been used to investigate interval timing in humans and other animals: estimation, production and reproduction. In humans, the first two protocols tend to rely on verbal instructions or responses, requiring the participant to translate between performance and a verbal representation of duration, which can lead to confounds. A more reliable approach, which can be used equally well with a wide variety of animal species[25,42], is to use a reproduction procedure, in which the subject is presented with a given criterion duration and then required to reproduce this duration (FIG. 2). Typically, the participant's responses follow a normal distribution around the criterion duration, and the width of this response distribution is proportional to the criterion duration. The way in which the mean and standard deviation of the response distribution covary is usually referred to as the scalar property[43], and resembles WEBER'S LAW[44], which is obeyed by most sensory dimensions. The scalar property applies not only to behavioural responses, but also to neural activation as measured by ensemble recording, or by the haemodynamic response to timed events measured with fMRI[45–47] (FIG. 2).

The pacemaker–accumulator model. The established explanation for the scalar property is based on an internal clock model[9], in which pulses that are emitted regularly by a pacemaker[7,48–50] are temporarily stored in an accumulator. At the time of reward or FEEDBACK, the number of pulses that have been received from the accumulator is stored in reference memory[8] (FIG. 3a). This information-processing (IP) model implements the scalar expectancy theory[43], in that the response is controlled by the ratio comparison between the current subjective time/clock reading — stored in the accumulator — and a sample taken from the distribution of remembered criterion durations, which are represented as the number of pulses from previously reinforced clock readings stored in reference memory. In this framework, the scalar property derives from the assumption that the accumulation error is proportional to the criterion duration[8,43] (FIG. 3b). The model has some notable advantages: it is straightforward, thereby encouraging its application

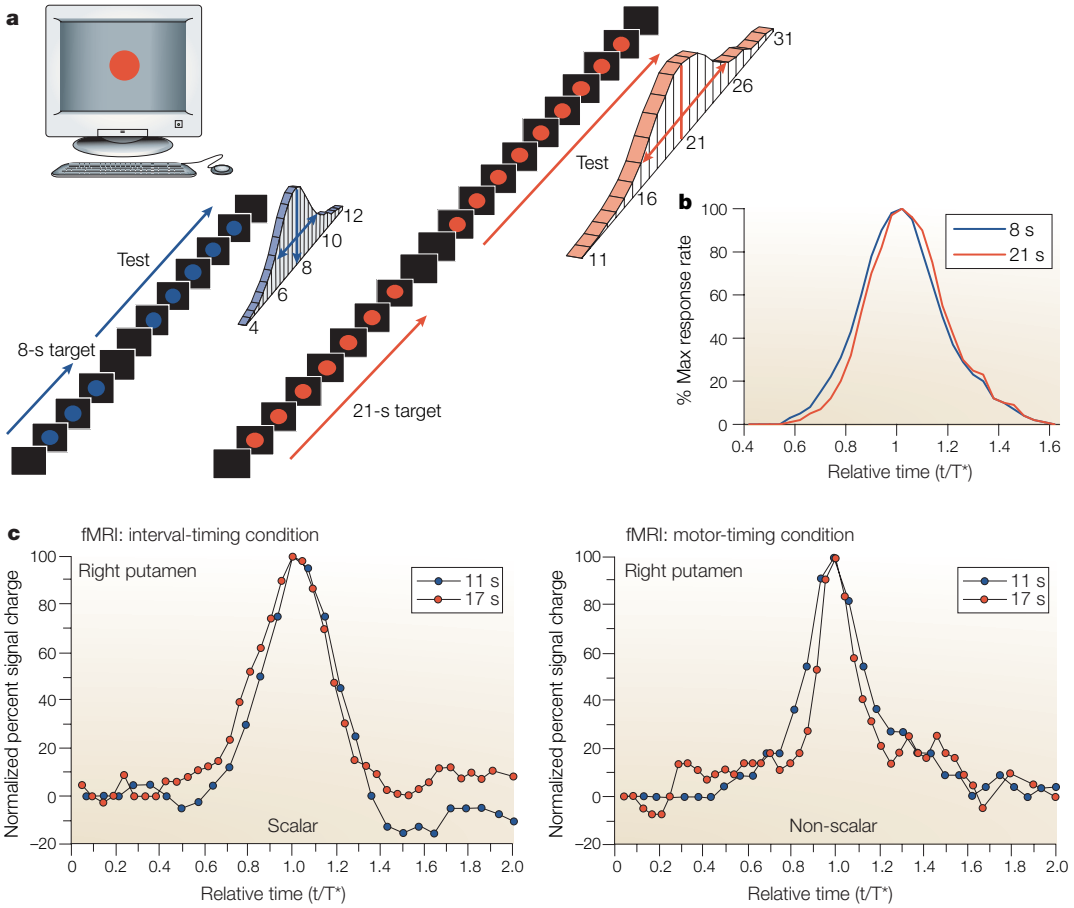

Figure 2 | **The scalar property is a hallmark of interval timing at both the behavioural and neural levels. a** | In a typical duration reproduction procedure known as the 'peak-interval procedure', participants receive training trials, during which they are presented with target stimuli of specific criterion durations (8 s or 21 s in this example), and test trials, in which participants are asked to reproduce the criterion interval. In test trials the responses typically distribute normally around the criterion interval with a width that is proportional to the temporal criterion. **b** | When the response distributions are scaled and superimposed, they demonstrate the scalar property at the behavioural level[8,43]. T*, test criterion. **c** | The scalar property also applies at the neural level for the haemodynamic response associated with a participant's 'active' reproduction of a timed criterion, but not for 'passive' responses triggered by a cue associated with an interval that is not timed. fMRI, functional MRI. Panel **b** modified, with permission, from REF. 25 © (1998) American Psychological Association. Panel **c** reproduced, with permission from REF. 45 © (2004) Elsevier Science.

INTERAURAL TIME DIFFERENCE
The difference in the time of arrival of a sound wave at an animal's two ears. It ranges from 100 µs in gerbils to about 650 µs in humans and is one of the sources of information used by various species to make a topographic representation of space.

INTERVAL TIMING
Perception, estimation and discrimination of durations in the range of seconds-to-minutes-to-hours.

CIRCADIAN RHYTHMS
Repetition of certain phenomena in living organisms at about the same time each day. The most thought of circadian rhythm is sleep, but other examples include body temperature, blood pressure, and the production of hormones and digestive secretions.

MILLISECOND TIMING
Perception, estimation and discrimination of durations in the sub-second range.

WEBER'S LAW
Formulated by Ernst Weber in 1831 to explain the relationship between the physical intensity of a stimulus and the sensory experience that it causes. Weber's Law states that the increase in a stimulus needed to produce a just-noticeable difference is constant. Later, Gustav Fechner (1801–1887) generalized Weber's law by proposing that sensation increases as the logarithm of stimulus intensity: S = k logI, where S = subjective experience, I = physical intensity, and k = constant.

FEEDBACK
To signal the end of the to-be-timed duration to the participant, a feedback signal is presented. In experiments involving animals, the feedback is usually an appetitive stimulus (for example, food) or aversive stimulus (for example, footshock). In experiments that involve human participants, the feedback may take various forms, including verbal reward, gaining 'points', and so on.

to many species and tasks[4,10]; it has clearly separated clock, memory and decision stages[8], which makes it possible to map these components onto brain structures[11] and neurotransmitter systems[12]; and it is surprisingly successful (considering its simple structure) in terms of making testable predictions[8].

The first investigations of the biological substrates of the clock and memory stages of the pacemaker–accumulator IP model used pharmacological manipulations, and provided considerable support for a dissociation between the clock stage, which is affected by dopaminergic manipulations, and the memory stage, which is affected by cholinergic manipulations[8] (FIG. 3a). For example, dopaminergic drugs selectively affect the subjective speed of an internal clock in both animals[51–54] and humans[55] (FIG. 3c), whereas cholinergic drugs alter memory storage[12,51] (FIG. 3f). More specifically, dopaminergic antagonists produce a deceleration of the subjective clock speed (FIG. 3d) in proportion to their affinity for the dopamine D2 receptor[51,52] (FIG. 3e), whereas cholinergic activity in the frontal cortex is proportional to the absolute error of a TEMPORAL MEMORY TRANSLATION CONSTANT[12,56] (FIG. 3g,h).

Despite the success of the IP model in explaining a large set of behavioural and physiological results, its relevance to the brain mechanisms that are involved in interval timing is unclear. For example, the idea that there is a direct and/or exclusive connection between the dopaminergic system and the speed of an internal clock has been challenged by studies in which patients with Parkinson's disease were asked to time two durations[57]. When learning two criterion durations, the responses tended to migrate towards each other if the patients were tested off their dopaminergic medication (FIG. 4c). The connection has also been challenged by the inconsistency between the relatively modest effects of dopaminergic drugs on behaviour[54] and the observed levels of dopamine release in the striatum *in vivo*[58], and

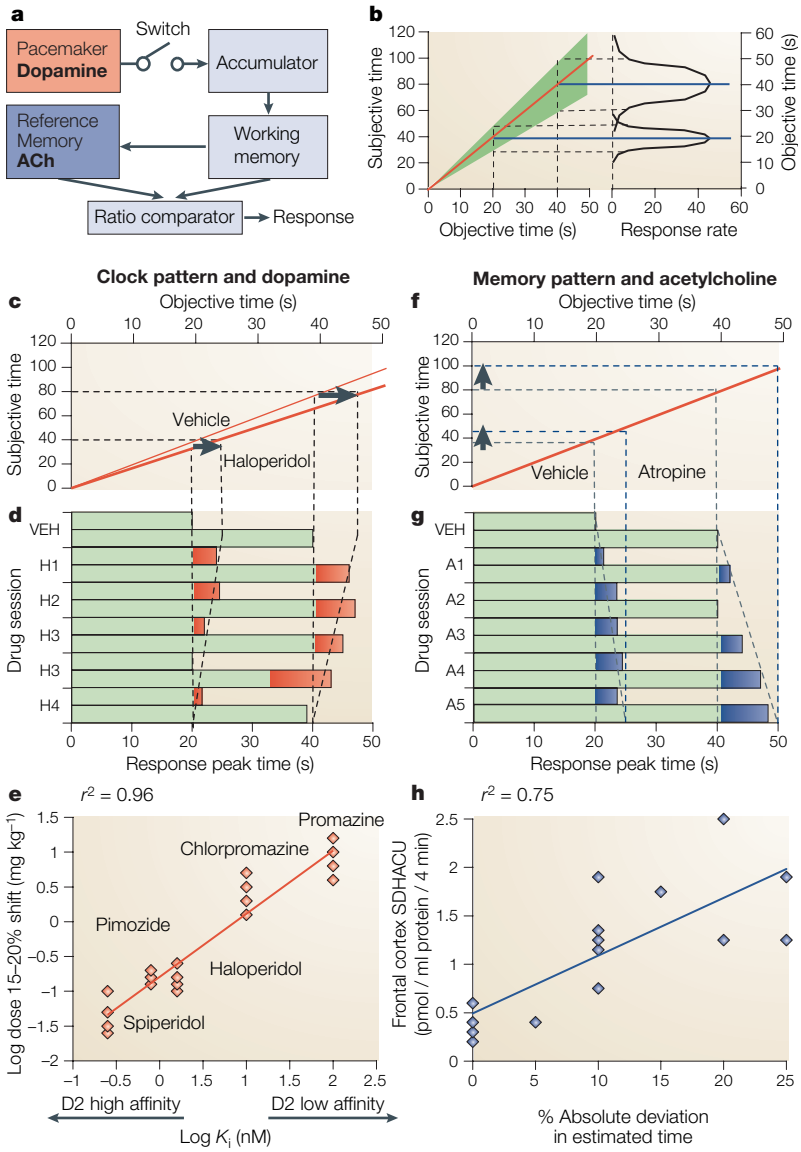

Figure 3 | **The pacemaker–accumulator model and dopaminergic and cholinergic synapses. a** | Shows an information-processing (IP) model of time perception[8] implementing the scalar expectancy theory[43]. In the model, a dopaminergic pacemaker sends 'pulses' to an accumulator during the training period, and the number of pulses is stored in reference memory (which depends on the 'effective level' of acetylcholine (ACh)). During a trial, the number of pulses in working memory (current) is compared with that in reference memory. **b** | The model explains the scalar property (FIG. 2) by assuming that the estimation error increases in proportion to the criterion duration (green area). **c**–**e** | The effects of the D2 dopamine receptor antagonist haloperidol are consistent with the slowing down of time accumulation. Acute administration of haloperidol results in a sudden scalar (proportional to the timed criterion) rightward shift of the estimated time, whereas its repeated administration (H1, H2 and so on) results in a gradual return of the estimated time to the criterion duration[12] (**d**). The rightward shift of the estimated time is proportional to the affinity of the drug for the D2 receptor[53] (**e**). K_i, affinity coefficient; VEH, vehicle. **f**–**h** | The effects of cholinergic drugs are consistent with effects on reference memory. Repeated administration of the muscarinic cholinergic receptor antagonist atropine results in a gradual scalar rightward shift of the estimated time[12] (**g**). The effect is correlated with the activity of cholinergic neurons in the frontal cortex as measured by sodium-dependent high-affinity choline uptake (SDHACU)[56] (**h**).

by pharmacological studies that found that, besides its involvement in the speed of an internal clock, dopamine also modulates the attentional processing of temporal information[59].

Despite the number of findings that support the biological plausibility of the pacemaker–accumulator mechanism[60], alternative biological mechanisms have been evaluated as possible substrates for interval timing. For example, to address the challenges outlined above, a number of alternative theoretical models of interval timing have been proposed, involving NEURAL OSCILLATORS[61,62], sustained neural activation[63–65], network dynamics[66] or switching among behavioural states[67]. Although most of these theoretical models successfully account for some aspects of the behavioural data, validation of these emerging timing models will require examination of the relevant neurobiological evidence.

Neural mechanisms of interval timing

Recent findings indicate that it might be necessary to integrate data from several approaches to reveal the neural mechanisms of interval timing. The evidence supports the idea that there are two timing circuits that can be dissociated: an automatic timing system that works in the millisecond range, which is used in discrete-event (discontinuous) timing and involves the cerebellum; and a continuous-event, cognitively controlled timing system that requires attention and involves the basal ganglia and related cortical structures. Because these two timing systems work in parallel, suitable experimental controls might be required to engage (and reveal) each system independently of the other[68,69].

Timing in sickness and in health. An impaired ability to process time in the seconds-to-minutes range is found in patients with disorders that involve dopaminergic pathways, such as Parkinson's disease[57,70], Huntington's disease (HD)[71] and schizophrenia[72–76]. By contrast, the failure of a neurological disorder — such as cerebellar injury — to affect the scalar property is taken to indicate that the affected structures are not essential for proper interval timing[37]. Instead, the cerebellum might contain an internal model of the motor–effector system[77], so cerebellar damage could increase variability in motor and perceptual timing[78].

For example, Parkinson's disease, in which the nigrostriatal dopaminergic projections degenerate, disrupts interval timing in a number of ways. Patients show the scalar property when medicated with L-dopa (FIG. 4a), but not when tested off-medication (FIG. 4b). Moreover, patients with Parkinson's disease are unable to time two (or more) durations independently: the reproduced criteria for the two criterion durations tend to migrate towards each other (FIG. 4c). This migration effect is eliminated, and accurate timing is reinstated, after stimulation of the subthalamic nucleus (FIG. 5d), which is one of the relay nuclei in thalamo-cortical-striatal circuits (see the section on electrophysiological studies, below). Finally, patients with Parkinson's disease also show poor timing of motor actions[57,70]. By contrast, the preservation of the scalar property after cerebellar lesions (FIG. 4d) supports the view that the striatum and cerebellum are involved in different aspects of timing and time perception. Although the

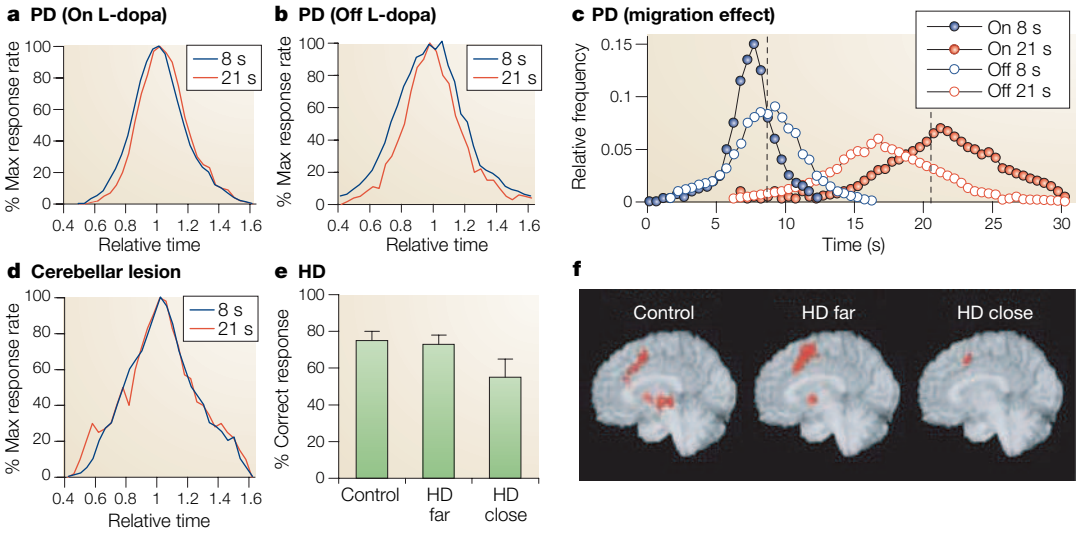

Figure 4 | **Interval timing in patients with Parkinson's disease, Huntington's disease and cerebellar lesions. a**–**c** | Two separate causes of failure to time correctly in unmedicated patients with Parkinson's disease (PD). In a peak-interval procedure during which participants time 8- and 21-s criterion durations, patients show the scalar property when medicated with L-dopa (**a**), but not when tested off-medication, owing to increased variability (larger width function; **b**). Moreover, when timing the 8- and 21-s durations, unmedicated patients also show inaccurate representation of time — the remembered durations tend to migrate towards each other (**c**). **d** | The scalar property is preserved after cerebellar lesions. **e**,**f** | As patients with Huntington's disease (HD) approach the age at which they are predicted to develop symptoms (HD close), they show a deficit in interval timing (panel **e**) and decreased activation of the basal ganglia, thalamus and pre-supplementary motor area/cingulate (panel **f**). HD far, onset of syptoms predicted to be a number of years away. Panels **a** and **b** redrawn from REF. 57. Panel **c** reproduced, with permission, from REF. 57 © (1998) MIT Press. Panel **d** redrawn from REF. 37. Panels **e** and **f** modified, with permission, from REF. 71 © (2004) American Society of Neuroradiology.

TEMPORAL MEMORY TRANSLATION CONSTANT
A parameter in the scalar expectancy theory that is responsible for producing scalar transforms of sensory input taken from an internal clock and stored in temporal memory. It is used to explain systematic discrepancies in the accuracy of temporal memory.

NEURAL OSCILLATOR
Repetitive, periodical activation of a neuron. The intrinsic mechanisms that control the period of the oscillator (the interval between two neuronal spikes) range from fast ion currents (for example, 40 Hz oscillations in sparsely spiny neurons in the frontal cortex) to slow transcriptional feedback loops (for example, 24-h oscillation in the SCN).

ATTENTIONAL SET
Set of to-be-attended features that are primed for use in a specific task, such that participants would be more likely to attend to the features in the attentional set than to other features of the task.

MOTOR SET
Sets of to-be-activated motor programs that are primed for use in a specific task, such that participants would be more likely to respond using one of the motor programs in the motor set than using other responses.

cerebellum is not essential for interval timing, it is required for correct millisecond timing[79].

Another disorder that affects dopaminergic pathways is Huntington's disease, an autosomal-dominant, neurodegenerative disorder that involves degeneration of the medium spiny neurons in the caudate nucleus and putamen. Patients who are approaching the age at which they are predicted to develop Huntington's disease ('HD close'; FIG. 4e) perform worse in tests of interval timing than either control individuals or patients whose predicted time of disease onset is more than 12 years away ('HD far'). In fMRI studies of interval timing (FIG. 4f), control participants showed activation of the caudate–putamen, thalamus, pre-supplementary motor area (pre-SMA) and cingulate cortex. Patients in the 'HD far' group showed similar activation, but with possible hyperactivation in the pre-SMA and caudate nucleus, which might explain their relatively normal timing performance[71]. By contrast, patients in the 'HD close' group showed decreased activation in all three foci. Such results complement behavioural[80], pharmacological[81] and electrophysiological[82] evidence that separate brain mechanisms underlie different components of the interval-timing system[83].

Lesion studies. Traditionally, because interval timing depends on the intact striatum[37,57,70] but not on the intact cerebellum[37,38], the cerebellum has been charged with millisecond timing[78] and the basal ganglia with interval timing[84–86]. Despite this simplistic dissociation, two recent findings have shed new light on the involvement of the basal ganglia and cerebellum in motor control and interval timing. In the first study, participants were required to shift their attention between two streams of events — one visual and one auditory — both of which contained target and distractor stimuli. Patients and control participants were tested under three conditions. The first was a double-response condition, in which they were instructed to respond to a target in one dimension, then to a target in the other dimension, and so forth. The second was a single-response condition, in which overt responses were required only to targets in one modality, while targets in the other modality served as cues for attention switching without requiring overt responses. The third condition was a focused condition, in which participants responded only to targets in one dimension and did not attend to the other dimension[87]. Relative to the focused condition, patients with both Parkinson's disease and cerebellar lesions were impaired in the double-response condition, which indicates that they might have difficulty with tasks that require rapid switching of both ATTENTION and MOTOR SETS. However, when the motor demands were reduced in the single-response task, patients with cerebellar lesions performed better than those with Parkinson's disease, which indicates that cerebellar lesions might cause deficits in switching the motor set whereas Parkinson's disease might lead to deficits in switching the attentional set[87].

In another line of research, patients with cerebellar damage showed deficits in producing discontinuous, but not continuous, movements, indicating that the cerebellum might have a specific role in event-based

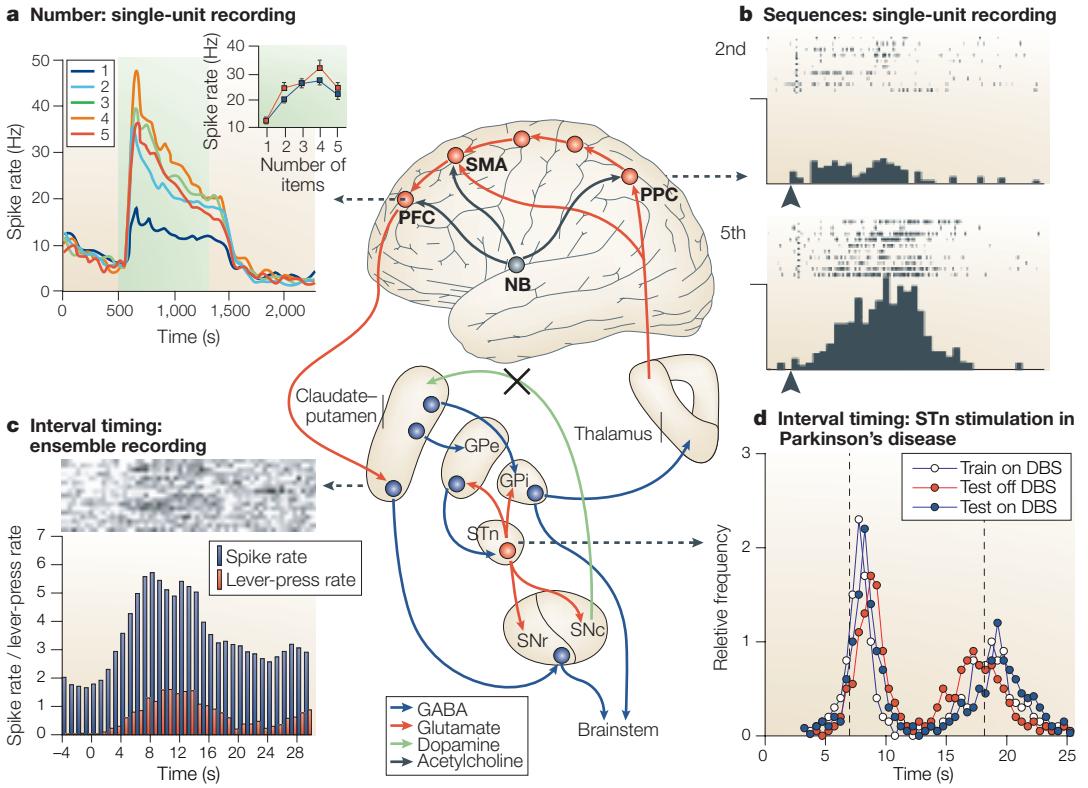

Figure 5 | **Electrophysiological evidence for the involvement of thalamo-cortico-striatal circuits in the representation of time and numerosity.** The central panel depicts the thalamo-cortico-striatal projections and their neurotransmitter systems. Curved arrows show neural pathways; dashed arrows indicate data obtained in a specific condition or from the specific brain area. **a**,**b** | The thalamus projects to cortical areas that are involved in the processing of numerosity: the frontal cortex (**a**) and parietal cortex (**b**). Panel **a** shows the representation of numerosity in the frontal cortex of primates; spike rate varies with number of items. Panel **b** shows the neural representation of the second and fifth items in a motor sequence in the primate parietal cortex. **c** | Cortical areas send glutamatergic connections to the caudate–putamen, the neural activation of which peaks at the criterion duration in interval-timing procedures. **d** | Degeneration of the dopaminergic nigrostriatal projection (as seen in Parkinson's disease) results in abnormal processing of temporal information (FIG. 4). Deep brain stimulation (DBS) of the indirect subthalamic projection eliminates the retrieval deficit but not the encoding distortion. GABA, γ-aminobutyric acid; GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; NB, nucleus basalis; PFC, prefrontal cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STn, subthalamic nucleus; X, denotes degeneration of nigrostriatal projection in Parkinson's disease. Panel **a** reproduced, with permission, from REF. 99 © (2002) American Association for the Advancement of Science. Panel **b** reproduced, with permission, from REF. 97 © (2002) Macmillan Magazines. Panel **c** drawn using data from REF. 101. Panel **d** drawn using data from REF. 142.

timing[39,78,88]. Together, these studies suggest that separate timing circuits can be dissociated when continuity, motor demands and attentional set are manipulated[41,80,89].

Electrophysiological studies. The thalamo-cortical-striatal circuits that include the basal ganglia, the prefrontal cortex (PFC) and the posterior parietal cortex (PPC) have been shown (for example, by brain imaging studies[89,90]) to be activated both in interval-timing tasks and in tasks that require integration of some stimulus dimension over a time interval, such as integration of somatosensory signals and the counting of events in numerically based behavioural tasks[91]. These data are consistent with the involvement of the basal ganglia, PFC and PPC in the representation of number, sequence or magnitude, as well as in interval timing, thereby supporting a mode-control model of counting and timing in which number and time are processed by the same neural areas[92–95].

For example, neurons in the PPC were activated not only during timing tasks[96], but also during tasks in which primates were required to perform a sequence of movements a number of times; in such tasks, PPC neurons fired selectively depending on the ordinal number (position in the sequence) in a block of trials[97] (FIG. 5b). The number–order–magnitude circuit of which the PPC is a part also includes areas of the PFC[98], which extract the quantity of visual field items[99] (FIG. 5a), although some recent reports have challenged the hypothesis that a single parietal region underlies both symbolic and nonsymbolic number representation in humans[100].

A recent study investigated the pattern of striatal firing in a reproduction task in which rats were probabilistically rewarded[101] at two durations, 10 s and 40 s. Probabilistic reward rules have been shown to have important consequences at the neural level for dopaminergic neurons in the substantia nigra pars

compacta (SNc), which project to the striatum[102]. Such a probabilistic task might, therefore, reveal the involvement of nigrostriatal pathways in interval timing. Although rats responded reliably at both durations, electrophysiological recordings revealed that two distinct subsets of striatal neurons were activated, thereby dissociating motor responses from temporal coding in the striatum. In one set of striatal neurons the firing pattern peaked at about the 10-s reward point (FIG. 5c), whereas the activity of the other set of neurons gradually increased throughout the 40-s interval[101]. Similar striatal ramp-like activity has been observed in DELAYED MATCHING-TO-SAMPLE TASKS before the anticipated cue[103,104]. This indicates that sustained activity over delay intervals is an important feature of striatal activation that might be crucial for bridging the interval between the moment when information is acquired and the moment when that information can be used in a decision.

Striatal neurons can code multiple durations, but only if the PFC is intact. Lesions of the agranular frontal cortex or the nucleus basalis magnocellularis[105] impair rats' ability to time two stimuli simultaneously, but not their ability to time each stimulus sequentially, although such lesions do cause small, but reliable, changes in the content of reference memory[106]. A recent study investigated neural activity in the agranular frontal cortex of rats that had been trained to time two stimuli of different durations[107]. After training, rats were tested with the two separate stimuli, and with the compound stimulus. Most neurons (60%) responded only to the compound stimulus; fewer neurons responded both to the compound and to the separate stimuli (10%); and very few neurons responded only to one stimulus (3%). That a large proportion of cells responded only to the compound stimulus supports the hypothesis that the agranular cortex is important for divided attention, for shifting attention between the two stimuli, and/or for the dynamic allocation of attention in time[108].

Functional imaging studies. In recent years, functional imaging of millisecond and interval timing has received considerable interest. Two informative reviews are noteworthy[89,90]. The first[90] analysed the imaging method (fMRI/PET), target duration (from 0.3 s to 24 s), timing procedure (discrimination, production, reproduction, generalization, synchronization, detection of deviants and reproduction of sequences), stimulus modality (visual or auditory) and control conditions of a number of studies. The review found that many studies report activations of areas such as the basal ganglia and cerebellum during timing tasks, but that some or all of the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex and right parietal cortex are also activated, and the authors questioned whether these brain areas are part of a dedicated timing circuit or are simply task-specific. They proposed that a brain area is part of the timing circuit if its activation is sensitive to parametric aspects of the timing procedure[109,110] or to variations in timing performance[111,112].

This definition was successfully used in a recent study from the same group of researchers, in which participants were asked to direct their attention to the duration of an event or to its colour (FIG. 6a), thereby combining parametric variations in timing performance and appropriate control conditions (time versus colour). As expected, areas in the visual cortex showed a linear increase in activation when participants paid more attention to the colour of the stimuli (FIG. 6c,d). In turn, the SMA showed a linear activation when participants paid more attention to time, thereby identifying this area as part of the timing circuit (FIG. 6b,c). Other areas, such as the putamen, were also active when participants paid more attention to time (FIG. 6b).

Another approach that has been used to try to make sense of the many brain regions that have been reported to be activated by timing procedures is the grouping of active areas by the characteristics of the timing procedure used. Areas can be grouped by, for example, the duration measured (sub-second/supra-second), the use of movement to define a temporal estimate, and the continuity or predictability of the procedure, under the assumption that repetitive actions require less attention[89]. This analysis revealed two clusters of foci. The 'automatic timing' cluster includes areas that were found to be activated by procedures that required repetitive movements and involved the timing of relatively short durations: these areas include the SMA, primary motor cortex and primary somatosensory cortex. The 'cognitively controlled timing' cluster includes areas that were found to be activated when the durations used were longer and the amount of movement required was limited: these areas include the DLPFC, intraparietal sulcus and premotor cortex. Interestingly, the brain area most consistently activated in neuroimaging studies of interval timing was the SMA, and the basal ganglia and cerebellum were not identified in either cluster, possibly because both areas might be continuously active and their differentiation might require additional control conditions. Together with the other approaches, the results of neuroimaging studies indicate that interval timing engages various neural circuits, whose roles in temporal or other aspects of tasks are still uncertain.

A coincidence-detection model

The data reviewed above fail to show that the basal ganglia have an exclusive role in temporal processing. Instead, the more general role of the basal ganglia might be to monitor activity in the thalamo-cortico-striatal circuits, and to act as a coincidence detector that signals particular patterns of activity in working memory[78,113,114]. Because such a role lends itself to temporal coding[62], a biologically plausible model of interval timing was developed to describe timing as an emergent activity in the thalamo-cortico-striatal loops[84,85]. In this striatal beat-frequency (SBF) model, timing is based on the coincidental activation of medium spiny neurons in the basal ganglia by cortical neural oscillators[115] (FIG. 7a,b). Synchronous cortical activity has been reported[116] and the mechanisms of its generation are currently being investigated[117]. For example, neurons in the motor

DELAYED MATCHING-TO-SAMPLE TASKS
Presentation of a stimulus is followed by a delay, after which a choice is offered and the originally presented stimulus must be chosen. With small stimulus sets, the stimuli are frequently repeated, and therefore become highly familiar. So, typically, such tasks are most readily solved by short-term or working memory rather than by long-term memory mechanisms.

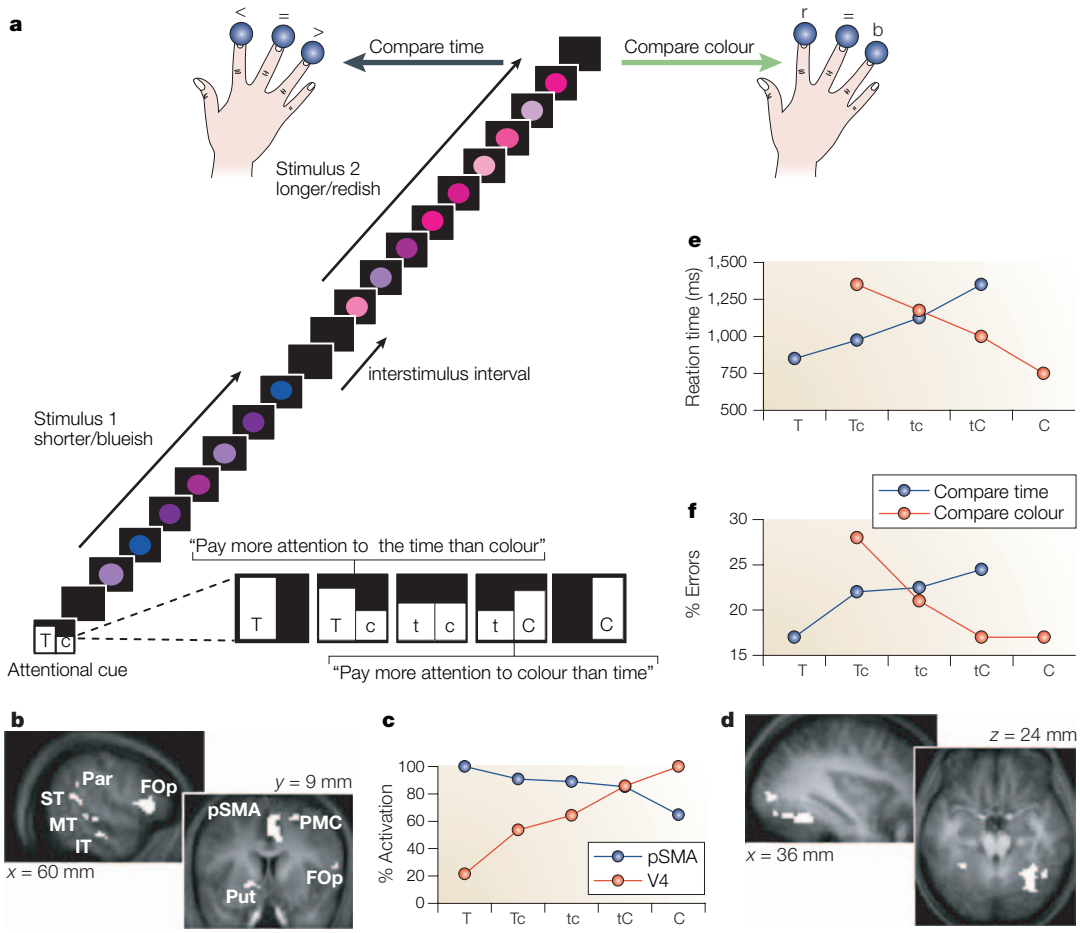

Figure 6 | **Differential activation of the circuits involved in the processing of time and colour.** An attentional cue directed participants to allocate their attention solely to time (T), solely to colour (C), equally to time and colour (tc), more to time (Tc) or more to colour (tC). Participants were presented with two circular stimuli of different durations, the colour of which flickered randomly in time, and were asked to compare either their duration or colour by responding with a different finger (**a**). **b**–**d** | When comparing time (blue curve), a circuit involving the pre-supplementary motor area (pSMA), dorsal premotor cortex (PMC), putamen (Put), and frontal operculum (Fop) was activated (**b**,**c**). When asked to compare colour (red curve), activation was observed in visual area V4 (**c**,**d**). **e**,**f** | The activation of these circuits correlated with decreases in reaction time and response errors. IT/MT/ST, inferior/middle/superior temporal cortex; PMC, dorsal premotor cortex; Par, inferior parietal cortex. Modified, with permission, from REF. 143 © (2004) American Association for the Advancement of Science.

LONG-TERM POTENTIATION (LTP). An enduring increase in the amplitude of excitatory postsynaptic potentials as a result of high-frequency (tetanic) stimulation of afferent pathways. It is measured both as the amplitude of excitatory postsynaptic potentials and as the magnitude of the postsynaptic-cell population spike. LTP is most frequently studied in the hippocampus and is often considered to be the cellular basis of learning and memory in vertebrates.

LONG-TERM DEPRESSION (LTD). An enduring weakening of synaptic strength that is thought to interact with LTP in the cellular mechanisms of learning and memory in structures such as the hippocampus and cerebellum. Unlike LTP, which is produced by brief high-frequency stimulation, LTD can be produced by long-term, low-frequency stimulation.

cortex increase their synchrony when animals are trained to expect a 'go' signal[118], and the synchrony of neurons in the somatosensory[119] and visual cortices[120] is modulated by attention. The cortical oscillators are assumed to be synchronized at the onset of a trial, and to oscillate at a fixed frequency throughout the criterion interval. Experience-dependent changes in cortico-striatal transmission are assumed to make the striatal neurons more likely to detect the specific pattern of activation of cortical oscillators at the time of reward delivery and/or feedback (FIG. 7b) through cortico-striatal LONG-TERM POTENTIATION (LTP) and LONG-TERM DEPRESSION (LTD)[121–124]. Under these assumptions, the activity of the stimulated striatal neurons increases before the expected time of reward, and peaks at the criterion interval (FIG. 7d), a result that parallels the ensemble recordings of striatal neurons in reproduction procedures[101] (FIG. 7e). Most importantly, simulations show that the SBF model demonstrates the scalar property[85] (FIG. 7f,g).

In this model, the synchronization of cortical oscillations at trial onset and the experience-dependent changes in cortico-striatal transmission are ascribed to the dopaminergic neurons in the SNc and ventral tegmental area (VTA). This assumption is supported by studies that have investigated the coding of a predictive signal by dopaminergic neurons[125] in probabilistic reward tasks[102]. For example, under conditions in which it is uncertain whether a reward will be delivered (in FIG. 7e probability of reward is $p = 0.75$), the activity of dopaminergic neurons shows a characteristic pattern with a burst at trial onset, a burst at the expected time of reward and sustained activity throughout the interval[102]. According to the SBF model, the dopaminergic burst at trial onset could trigger the synchronization of the cortical oscillators, the sustained activity could reflect attentional activation of the thalamo-cortico-striatal circuits, and the burst at the expected time of reward could reflect the updating of

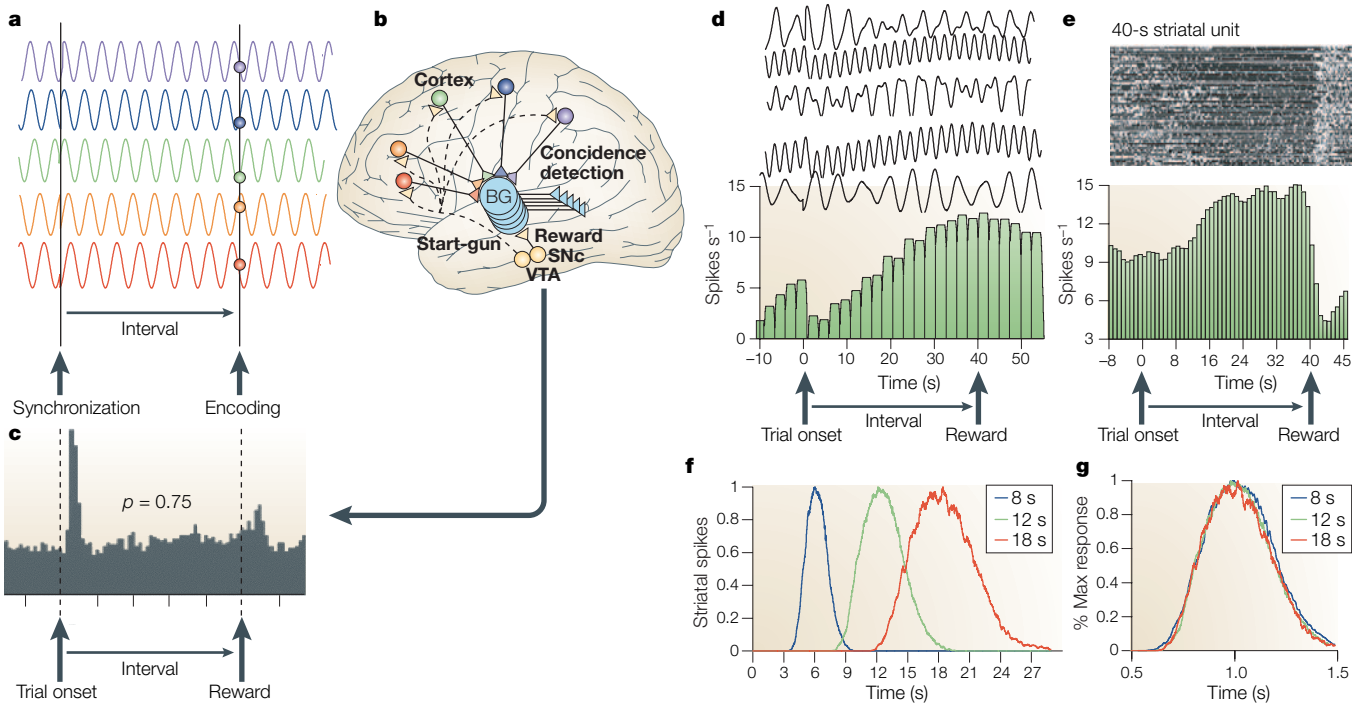

Figure 7 | **The striatal beat-frequency model.** Oscillatory cortical neurons (**a**) project onto striatal medium spiny neurons (**b**), which continuously compare the current pattern of activation of cortical cells with the pattern detected at the time of the reward (coincidence detection). Dopaminergic projections from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) are prominently active at trial onset, possibly implementing a 'start-gun' that synchronizes the cortical oscillators; throughout the interval, possibly modulating corticostriatal transmission; and at the expected time of reward, possibly coding for an error in reward prediction (**c**). BG, basal ganglia. Panel **d** shows five striatal neurons detecting the coincidence of the five cortical oscillators at the criterion duration. The histogram of activation of a simulated striatal population (**d**) matches the pattern of activation recorded in the striatum (**e**), which peaks at the criterion duration. Large scale simulations indicate that the model can represent the distribution of responses at different intervals (**f**), and that these distributions superimpose in relative time units, demonstrating the scalar property of interval timing (**g**). Panel **c** reproduced, with permission, from REF. 102 © (2003) American Association for the Advancement of Science. Data in panel **e** taken from REF. 101. Data in panels **f** and **g** taken from REF. 85.

cortico-striatal transmission[126] (FIG. 7a,c). Despite giving a comprehensive picture of the neural circuits that are involved in interval timing, the current instantiation of the SBF model[85] has yet to be developed to address the effect of cholinergic drugs on memory storage[12,51], simultaneous temporal processing[105] and the similarities between counting and timing[92–95].

Interestingly, coincidence detection and spike counting could be two sides of the same coin. Mathematical studies indicate that the problem of comparing two neural spike patterns could be solved by different strategies, depending on the acceptable discrimination error[127]. At one end of the spectrum, when the desired discriminative accuracy is high — for example, when the spike patterns code for continuous variables or quantities, such as time — the solution involves coincidence detection. At the other end of the spectrum, when the desired discriminative accuracy is low — for example, when the patterns code for a discrete variable, such as number — the solution involves simply counting the spikes in the two spike patterns. This result suggests a continuum between coincidence detection and spike counting, and supports a mode-control model of counting and timing in which number and time are processed by the same neural mechanism[92–95].

Conclusions

The ability to process temporal information accurately is crucial for goal reaching, neuroeconomics[128], and the survival of humans and other animals[2,3], and requires multiple biological mechanisms to track time over multiple timescales[4–6]. In mammals, the circadian clock that drives metabolic and behavioural rhythms is located in the SCN. Another timer, which is responsible for automatic motor control in the millisecond range, relies on the cerebellum. In contrast to these relatively localized timing mechanisms, a general-purpose, flexible, cognitively controlled timer that operates in the seconds-to-minutes range involves the activation of a network of brain areas that form part of the thalamo-cortico-striatal circuits, notably the basal ganglia, the SMA, the PFC and the PPC. The operation of this network of circuits as a timekeeper can be better understood in terms of coincidental activation of various brain areas. As these areas are involved in several cognitive phenomena, it is likely that this circuit is not limited to temporal processing, but is also involved in other processes, such as the estimation of quantity or numerosity. This neural circuit might be able to switch function between coincidence detection for estimating time, to spike counting for estimating numerosity, depending on the accuracy that is required to solve the

task[127]. As such, the coincidence-detection model and the pacemaker–accumulator model may be two sides — neural and behavioural — of the same coin.

A crucial issue is to differentiate the roles of specific thalamo-cortico-striatal circuits in temporal cognition, for example, by using ensemble recording techniques. Another important question relates to the molecular bases of interval timing; in this respect, the use of transgenic animal models has the potential to shed light on the molecular foundations of the 'stopwatch'[129]. Finally, the development of modern computational tools and techniques to enable integration of information from all these techniques will soon be crucial for elucidating the processes that are involved in controlling working memory and motor functions, processing time, quantity or numerosity, attending to significant events, making decisions and calculating speed, productivity and rate of return.

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Competing interests statement

The authors declare no competing financial interests.

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