Getting the Timing Right: Experimental Protocols for Investigating Time with Functional Neuroimaging and Psychopharmacology

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Abstract

Functional Magnetic Resonance Imaging (fMRI) is an effective tool for identifying brain areas and networks implicated in human timing. But fMRI is not just a phrenological tool: by careful design, fMRI can be used to disentangle discrete components of a timing task and control for the underlying cognitive processes (e.g. sustained attention and WM updating) that are critical for estimating stimulus duration in the range of hundreds of milliseconds to seconds. Moreover, the use of parametric designs and correlational analyses allows us to better understand not just where, but also how, the brain processes temporal information. In addition, by combining fMRI with psychopharmacological manipulation, we can begin to uncover the complex relationship between cognition, neurochemistry and anatomy in the healthy human brain. This chapter provides an overview of some of the key findings in the functional imaging literature of both duration estimation and temporal prediction, and outlines techniques that can be used to allow timing-related activations to be interpreted more unambiguously. In our own studies, we have found that estimating event duration, whether that estimate is provided by a motor response or a perceptual discrimination, typically recruits basal ganglia, SMA and right inferior frontal cortex, and can be modulated by dopaminergic activity in these areas. By contrast, orienting attention to predictable moments in time in order to optimize behaviour, whether that is to speed motor responding or improve perceptual accuracy, recruits left inferior parietal cortex.

Keywords

fMRI • Functional neuroimaging • Motor timing • Perceptual timing • Temporal prediction • Temporal orienting • Temporal preparation • Temporal expectation • Dopamine

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Timing is integral to a great number of cognitive processes, such as language, sensorimotor control or decision-making. Closing one's fingers at just the right moment to catch a ball, for

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example, requires an exquisite sense of time in the range of tens of milliseconds. Deciding whether or not you have time to race safely through the amber traffic light before it turns red requires a sense of time in the range of hundreds of milliseconds to seconds. In these examples timing is automatic and covert. Yet we can also access a more conscious or overt representation of time. For instance, you could probably give a fair estimate of how long it has taken to read the first few sentences of this chapter; and whether this duration is shorter or longer than the time it would take for an amber traffic light to turn red. But despite this 'sense' of time, there is no dedicated neural machinery for perceiving the *duration* of a stimulus in the way that there are dedicated areas of the brain for perceiving other features of a stimulus, such as colour, form, or motion.

This lack of functional localization may be due, in part, to the complexity of estimating duration, which depends upon a number of accessory cognitive processes, such as sustained attention and working memory, in addition to the timing process itself [1–5]. To perceive a stimulus feature like colour or spatial location, external sensory input simply needs be high enough to pass the threshold for conscious perception. To perceive stimulus duration, on the other hand, we not only need external sensory input (to mark the beginning and end of the duration to be timed) but also an *internal*, memorized representation of elapsed time. These phenomenological differences were eloquently articulated more than a hundred years ago by James [6]: "*To 'realize' a quarter of a mile we need only look out of the window and feel its length by an act which… seems immediately performed. To realize an hour, we must count 'now! – now! – now! – now!' – indefinitely…and the exact sum of the bits never makes a very clear impression on our mind*." In a monograph by the French philosopher Guyau [7], published post-humously in the same year, he stated that *"time can only be perceived … as representations rather than immediate sensations*" [8].

Today, these philosophical observations can be investigated in the laboratory. Imagine a coloured circle presented in the centre of a computer screen for 2 s. An estimation of its colour or spatial location can be accomplished within the first couple of hundred milliseconds making the remainder of its presentation time redundant. On the other hand, an estimation of its duration can be accomplished only once the entire two second presentation time has elapsed. Moreover, in contrast to colour or spatial processing, duration estimation requires that the initial moment of stimulus onset be held in working memory (WM), for attention to then be maintained on the stimulus throughout its entire presentation, and for the contents of WM to be continually updated as a function of elapsing time. The difference between the 200 ms or so required to perceive colour or location and the 2,000 ms necessarily required to perceive duration explains each process' differential reliance on sustained attention and WM. That timing (at least in the range of hundreds of milliseconds and beyond) requires attention to be sustained and WM to be updated very likely contributes to the extensive network of regions typically observed in neuroimaging studies of duration estimation (e.g. [9–11]). A crucial challenge for experimental investigations of timing is how to disentangle the attentional and mnemonic processes required for estimating duration from the temporal ones. For timing of stimuli in the hundreds of milliseconds to seconds range, the need to sustain attention and to update WM cannot be eliminated. They can, however, be controlled for.

Controlling Time: Minimizing Sensorimotor and Cognitive Confounds

A well-designed fMRI study in any cognitive domain should control for basic sensorimotor processes of non-interest. Imagine a perceptual timing task in which the duration of two consecutively presented visual stimuli are compared, with a same/different response being registered with a choice button-press. That this task will activate visual cortex (due to the sensory

stimulation) and motor cortex (due to the button-press) is obvious and trivial. Ideally, we would like to remove these activations of non-interest from our map of timing-related brain areas to clarify interpretation. To do so, we need simply include a control task that presents two consecutive stimuli, of the same form, shape and location as those used in the timing task, and which requires the same button-press response. Subtracting the control task activation map from that of the timing task should remove any activity related to low-level visual and motor processing. Ideally, if the study is event-related, the contribution of motor execution processes can be further minimised by incorporating a variable temporal jitter between the stimulus to be estimated and the moment of the motor response, and then synchronising the event-related haemodynamic fMRI response to the moment of stimulus presentation. By temporally dissociating the stimulus and response stages of the task in this manner, activations induced by the later motor response can be distinguished from the stimulus-evoked signal.

However, while these procedures may control for basic sensorimotor aspects of the timing task, they do not address its higher *cognitive* demand. The perceptual timing task described above requires the first stimulus to be held in WM, compared on-line to the second stimulus, and for a decision to be made and translated into a motor response. So we need to complexity our control task to match the cognitive demands of this temporal discrimination task. For instance, we may ask participants to compare some other feature of the two stimuli, making a same/different decision on this feature (e.g. colour discrimination) rather than its temporal features. In this way, we can minimize activations induced by general higher-level cognitive processes, such as WM maintenance, on-line comparison and decision-making, as well as the low-level sensorimotor aspects of the task.

Some of the early neuroimaging studies of timing failed to control for accessory cognitive processes, comparing timing tasks to basic sensory stimulation [12], simple button-pressing [13] or rest [14]. Generally, these studies identified an extremely widespread timing-related network of activation, which, given the low-level nature of the control task to which the timing task was compared, it was impossible to unambiguously attribute to temporal processing: instead activations may have reflected the attentional, mnemonic or decisional processes necessary that were for the timing task, but not the control. Fortunately, most investigators have now adopted a more rigorous approach. For example, perceptual timing tasks are routinely compared to cognitively challenging control tasks, such as pitch discrimination in the auditory domain (e.g. [15–18]), or to colour (e.g. [15, 19–23]), intensity [24] or length [25] discrimination in the visual domain.

Many of the earliest neuroimaging studies of timing investigated motor, rather than perceptual, timing (e.g. [14, 26, 27]). Typically, these studies employed finger tapping tasks, in which participants first tapped along to a sensory pacing rhythm (synchronisation phase) then continued to tap at the same rate once the pacing rhythm had been removed (continuation phase). To isolate activity related to internally generated timing whilst controlling for accessory cognitive processes, brain activity recorded during the synchronization phase can be subtracted from that recorded during the continuation phase (e.g. [28, 29]) or to activity induced by syncopated, rather than synchronized, tapping [30–32]. More recent motor timing studies have often used temporal reproduction tasks in which participants produce a single, discrete motor response after a timed interval, and compare timing-related brain activity to that induced by control reaction–time tasks [33–35], force reproduction tasks [36, 37] or self-paced, randomly timed button presses [38]. A recent meta-analysis by Wiener et al. [11] has shown that the areas most consistently activated by motor timing (both synchronisation and reproduction paradigms) are bilateral SMA, bilateral prefrontal cortices, left insula and right inferior parietal cortex whereas perceptual timing (mostly temporal discrimination paradigms) consistently activates bilateral SMA, right prefrontal cortex and insula, and left putamen, This meta-analysis further pinpointed SMA and right

inferior frontal cortex as being the only two regions common to both perceptual and motor timing, as well as to timing in both the subsecond and suprasecond range.

Motor Preparation

Although these studies highlight a key role for SMA in timing processes, SMA has more traditionally been implicated in motor preparation (e.g. [39, 40]). Yet motor preparation itself includes temporal, as well as motor, components: when preparing a motor response, the specific motor effector with which the response will be given is selected (motor component), then prepared in advance and maintained (temporal component) until response execution. Unfortunately, the temporal component of motor preparation has sometimes been inadvertently confounded with duration estimation in neuroimaging studies of timing. For example, if reproduction of long intervals are compared directly to that of short intervals (e.g. [27, 33, 41]) the longer intervals not only make greater demands on timing but also afford greater opportunity for motor preparation: the longer the participant waits to make their response the longer they have to prepare it. Indeed, behavioural data showing faster [41] and more accurate [33] responses for long, versus short, intervals confirmed the greater degree of motor preparation in long intervals trials. Activation of SMA in these studies may have therefore reflected increased motor preparation, rather than (or as well as) increased temporal processing.

One straightforward way of minimising motor preparation confounds is to use a non-timing control task that is matched not only for the motor effector with which the response will be given (motor component of motor preparation) but also for the length of the preparatory interval (temporal component of motor preparation). In addition, it is generally easier to control for motor preparation in perceptual timing tasks than motor ones, although motor preparation confounds may still intervene. Consider again the temporal discrimination task in which the duration of a stimulus must be judged as being the same or different to that of a previous stimulus, with the decision being registered with an index or middle finger button-press. As soon as the temporal decision has been made (e.g. different), the appropriate motor response (e.g. middle finger) can be prepared. If the decision can be made before the stimulus presentation time has completely elapsed, then activity recorded during this period will confound motor preparation processes with timing ones. To avoid this, Coull et al. [20] varied the motor effector (index/middle/ring finger) associated with a particular temporal decision (shorter/equal/longer) on a trial-by-trial basis (Fig. 1a). The stimulus–response contingencies were not known until the response screen was presented at the end of each trial. In this way, even though participants could make their decision on a *temporal* level (e.g. shorter) during presentation of the stimulus, they could not begin to prepare the appropriate response effector at the *motor* level (e.g. index finger) until the response screen appeared. Processes of timing and motor preparation were thereby unconfounded.

Sustained Attention and WM Updating

These measures help control for the sensorimotor and cognitive demands of the timing *task*, whether it's motor temporal reproduction or perceptual temporal discrimination. However, these measures are not sufficient for controlling for the cognitive demands of the stimulus itself. As outlined earlier, estimating the duration of a stimulus depends upon processes of sustained attention and WM updating, processes that are not required when estimating, for example, its colour or location. Sustained attention and WM updating are dynamic, constantly evolving cognitive processes. One solution to the problem therefore is for the control task to make similarly dynamic demands. Lewis and Miall [25] pioneered just such an approach, developing a stimulus whose length fluctuated constantly throughout stimulus presentation. Their timing task required participants to estimate the duration for which this stimulus was presented, whereas

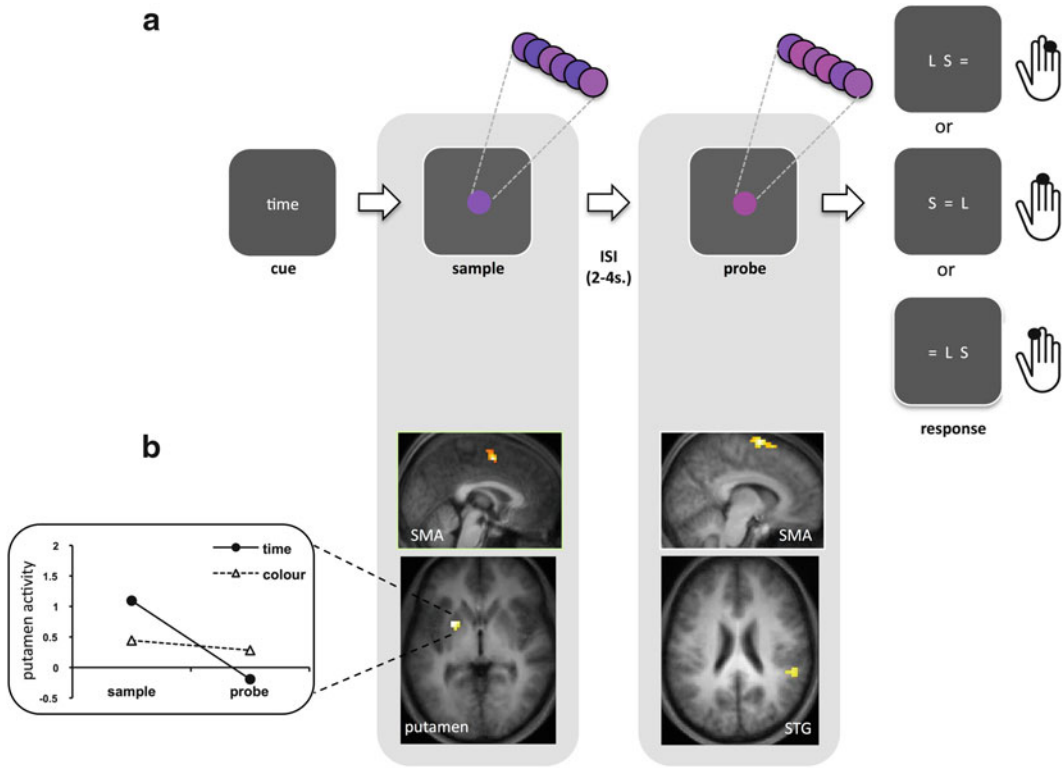

Fig. 1 (**a**) A cue (the word "time" or "colour") instructed participants to estimate either the duration or colour of two forthcoming consecutive stimuli. The first (sample) and second (probe) stimuli were presented for one of three durations (540, 1,080, 1,620 ms) and had an overall percept of one of three shades of purple (maroon, violet, or indigo). According to the cue instruction, participants estimated whether the probe was shorter (S), longer (L), or the same (=) duration as the sample (time condition) or redder (R), bluer (B), or the same (=) shade of purple as the sample (colour condition). The stimuli to be estimated were not a uniform color. Instead, five different shades of purple were presented rapidly (90 ms) and in pseudo-random order to give an overall percept of either maroon, purple, or indigo (see *insets* at top of figure). In the colour task, the subject estimated the average shade of purple by amalgamating all shades presented during the flickering percept. At the onset of the response signal, participants indicated their duration or color estimate with a three-choice button press. To minimize the possibility for motor preparation, stimulus–response contingencies varied on a trial-by-trial basis. One of three possible response screens (see right-hand side of figure) could be presented on any given trial. The left, middle, and right-sided spatial locations of the response choices (S/=/L for the time task; R/=/B for the colour task) on the computer screen mapped respectively onto a button located under the index, middle, or ring finger of the right hand. If the character corresponding to the subject's estimate appeared in e.g. the leftmost position on the screen the subject pressed on the leftmost button (i.e. with the index finger). By way of illustration, the black circles on each of the hand symbols indicate which button would have to be pressed for each of the response screens if the subject's estimate were "equal to" (represented by the symbol "="). This figure shows a trial from the time condition. The colour condition was identical apart from the substitution of the word "colour" at the cue stage, and the characters R/=/B at the response stage. (**b**) In comparison to the colour control condition, the time condition activated Supplementary Motor Area (SMA) at both sample and probe stages of the task. By contrast, the time condition activated putamen selectively at the sample stage but not at the probe, whereas right superior temporal gyrus (STG) was activated by the time condition selectively at the probe stage, not at the sample. The accompanying plot shows the mean level of putamen activity during the time and colour conditions, separately for the sample and probe stages of the task

the control task required participants to estimate its average length. In both conditions therefore, participants had to maintain attention throughout stimulus presentation and constantly update their representation of stimulus duration or length, in order to accurately perform either the timing or control tasks. Unfortunately, despite Lewis and Miall's clever use of dynamic stimuli, the timing

task was significantly more difficult than the control task, compromising clear interpretation of their results. Inspired by their ingenious solution to the problem of sustained attention and WM updating, we devised our own control stimuli, though we chose to manipulate stimulus colour, rather than length, in order to avoid illusions of movement that may have inadvertently provided temporal cues [19, 20].

We developed temporal and colour discrimination tasks, in which participants saw two consecutively presented stimuli and had to compare either their duration (timing task) or colour (control task). However, the stimuli were not of a uniform colour but instead changed shade rapidly (every 90 ms) and constantly throughout stimulus presentation (coloured insets Fig. 1a). Participants estimated the *average* colour of the stimulus by amalgamating all shades presented during the flickering percept. Therefore, for colour, as well as timing, tasks, participants had to maintain attention for the entire stimulus presentation time, integrating in WM information presented throughout this period. Importantly, there were no significant differences in accuracy of temporal and colour discrimination, suggesting these tasks were well-matched for difficulty [19, 20]. Areas activated by the timing task were compared to those activated by the colour task, revealing timing-specific activations in SMA, right prefrontal and temporal cortices, and basal ganglia [19, 20]. Given the deliberate matching of sustained attention, WM updating and task difficulty across tasks, these activations were unlikely to reflect differential recruitment of attentional or mnemonic processes, allowing us to conclude more confidently that they reflected more temporal components of stimulus processing. Investigators from several different research groups have since adopted similarly dynamic colour control stimuli [21–23].

Task Difficulty

As mentioned briefly above, an important parameter to be controlled for in any well-designed fMRI study of timing (indeed, in fMRI studies of almost any sort of cognitive processing) is task difficulty. If the timing task is more difficult than the control task it will place greater demands on attentional or effortful processing, which could contribute to timing-related activations in attention-related areas such as parietal and frontal cortices. To minimize this potential confound, it is crucial to demonstrate that the levels of performance of timing and control tasks are matched (e.g. [16–18]). Using a control task that necessitates similar levels of sustained attention and WM updating as the timing task is one way of matching difficulty across tasks [19, 20, 22]. Unfortunately, this approach is not always successful: despite Lewis and Miall's [25] pioneering use of dynamic stimuli, coupled with a sophisticated psychometric staircase procedure designed to maintain task difficulty at constant levels for both timing and control tasks, performance in their timing task was significantly worse than that for their control task. An alternative experimental approach is to deliberately manipulate task difficulty, rather than trying to match it. Tregallas et al. [42] compared easy and difficult versions of an auditory timing task, while Livesey et al. [21] took this a step further, by comparing patterns of timing-induced activity when the control task was either easier or more difficult than the timing task. They reasoned that areas differentially activated by whichever task was more difficult, whether that was the timing or the control task, were not specifically concerned with timing, whereas areas activated by the timing task, whether it was relatively easier or more difficult, reflected true timing-induced activations. Interestingly, although these two groups adopted similar approaches, the results of the two studies were quite different. Using visual stimuli in the range of 1,000–1,500 ms (similar to the dynamic colour stimuli used by ourselves), Livesey et al. [21] observed timing-selective activation of putamen, inferior frontal gyrus and a small region of left inferior parietal cortex. Conversely, Tregallas et al. [42] observed timing-selective activation of cerebellum and superior temporal gyrus with their auditory stimuli in the range of 200 ms. The anatomical differences between these two studies

most likely reflect differential activation of a stimulus-specific "automatic" timing system [9] by the brief 200 ms stimuli in the Tregallas et al. [42] study, and of a "cognitive" timing system by the seconds-range stimuli used in the Livesey et al. [21] study. The brief auditory stimuli in the Tregallas et al. study [42] were most likely processed by modality-specific systems in temporal cortex, as well as cerebellum, which has previously been associated with timing of short millisecond, rather than longer seconds-range, stimulus durations [43].

Parametric Experimental Designs

It should, by now, be clear that many parameters must be controlled for when investigating timing with fMRI. Most obviously, these include basic components of task performance, such as sensorimotor processing, selective attention, maintenance in long-term or working memory, decision-making and task difficulty. However, processes related to the dynamic nature of time itself must also be considered: motor preparation, sustained attention and WM updating. The choice of an appropriate control task is therefore critical for the success of the timing experiment. One way of circumventing the search for the perfect control task however, is instead to parametrically vary a specifically temporal component of the task. For example, by identifying areas of the brain whose activity increases as a function of increasing stimulus duration (e.g. [44]). Parametric designs are particularly powerful in isolating cognitive processes of interest as they test for systematic relationships between cognitive and neural activity: incremental changes in the cognitive process of interest (e.g. stimulus duration) are associated with corresponding changes in brain areas responsible for implementing that cognitive change. However, as mentioned earlier, long stimulus durations are confounded with high levels of motor preparation, as well as greater sustained attention and WM demands. Therefore, to minimize the influence of these dynamic cognitive confounds, the experimental paradigm should incorporate a control task whose stimuli are processed for the same parametrically varying lengths of time (e.g. [22, 23]).

We sidestepped this potential problem in one of our own experiments by parametrically modulating the amount of attention paid to stimulus duration, rather than the length of the duration itself [19]. This approach was inspired by one of the earliest, and most robust, findings in the functional neuroimaging literature: attending to a perceptual stimulus feature, such as shape, colour, speed [45] or spatial location [46], increases neural activity in sensory brain regions specialised for processing that feature, even though the comparison stimuli are perceptually identical. By analogy, we hypothesised that attending to stimulus duration would increase neural activity in brain regions specialized for processing time. We manipulated attention to duration by parametrically varying the degree of attentional selectivity to temporal or colour stimulus features (Fig. 2a). Attention-sharing instructions indicated how attention should be allocated within a particular trial: selectively to stimulus duration, more to duration than colour, to duration and colour equally, to colour more than duration, or selectively to colour. Appropriate attentional allocation was encouraged by varying the relative likelihood that the trial would require a temporal or colour discrimination (Fig. 2a). For example, half of the "attend duration and colour equally" trials required a temporal discrimination and the other half required a colour discrimination, but the participant didn't know until the trial-end which would be required, meaning both parameters had to be attended equally. By contrast, every single one of the "attend duration only" trials required a temporal discrimination, meaning the participant could ignore colour and focus exclusively on duration. In "attend duration more than colour", most of the trials required a temporal discrimination with only a few requiring a colour discrimination, meaning that participants should pay attention mostly to duration but should "keep an eye" on colour.

Behavioural and neural data confirmed that attention was allocated appropriately across the

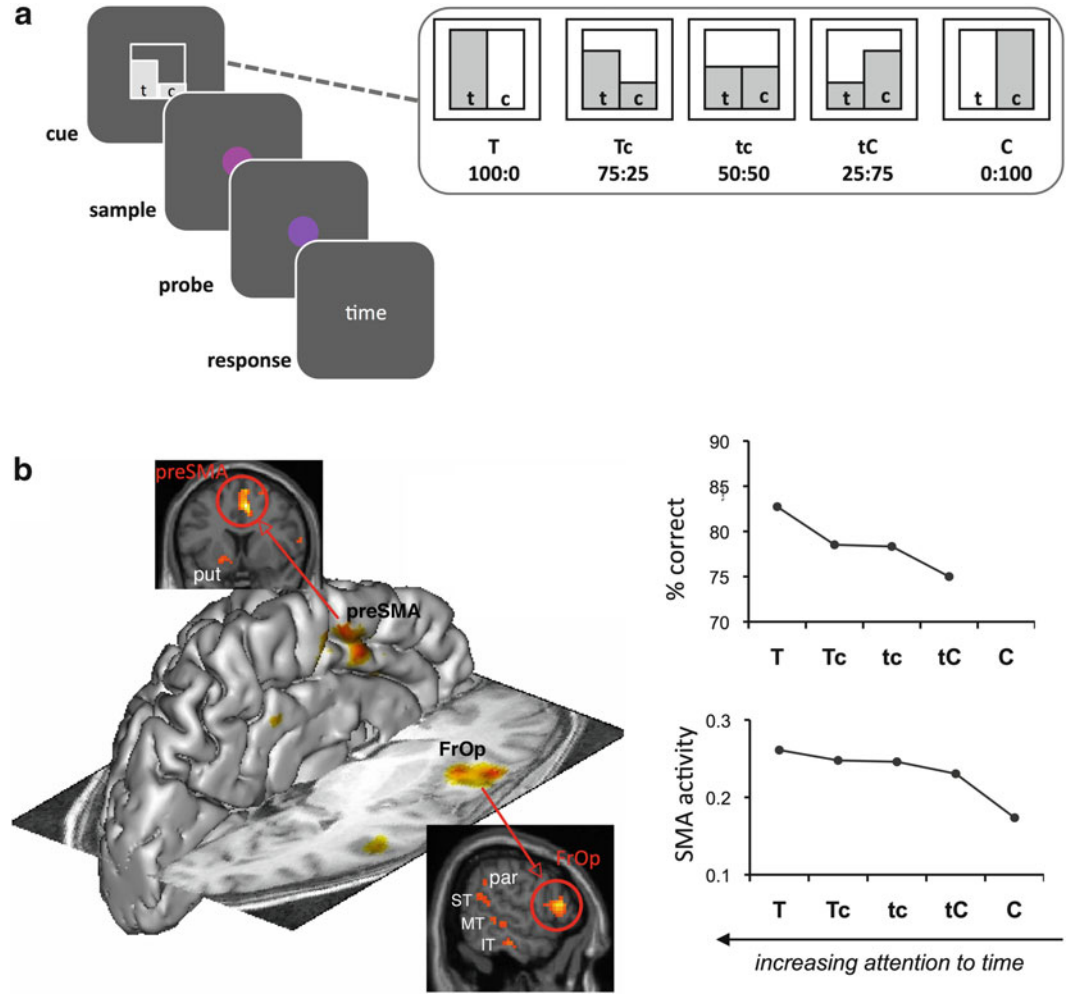

Fig. 2 (**a**) One of five attentional cues (see *inset* on the right) instructed participants to attend either selectively to stimulus time (T), to time more than color (Tc), to both parameters equally (tc), to color more than time (tC), or selectively to color (C). As a function of the cue, participants then estimated whether the duration of the probe was shorter, equal to, or longer than the sample (time condition) *and/or* whether the probe was redder, equal to, or bluer than the sample (colour condition). So, for instance, if the trial began with the 'T' cue participants had to estimate duration only, whereas if it began with the 'tc' cue they had to estimate duration and colour equally. Participants then gave a discriminatory response according to the instruction presented on the response screen, either "time" or "colour", giving a single estimate of duration *or* of colour even though they may have been instructed to estimate both. Each attentional cue condition comprised a specific ratio of temporal:colour discrimination trials (see *inset*). All trials in the T condition required a temporal discrimination (a ratio of 100:0 temporal:colour discrimination trials) whereas all trials in the C condition required a colour discrimination (a ratio of 0:100); half of the trials in the tc condition required a temporal discrimination while the other half required a colour discrimination (50:50); most (75 %) of the trials in the Tc condition required a temporal discrimination but only a few (25 %) required a colour discrimination (75:25); and most of the trials in the tC condition required a colour discrimination with only a few requiring a temporal discrimination (25:75). In this way, knowing that a temporal discrimination would be required on every single T trial should encourage participants to focus on duration and ignore colour. On the other hand, knowing there was 50:50 chance that the response required in tc trials would be either a temporal or a colour discrimination should encourage participants to divide attention equally between duration and colour characteristics. Varying the response ratios in this way encouraged attention to be allocated parametrically to either duration and/or colour across the five cue conditions. (**b**) As participants paid progressively more attention to stimulus duration across the five cue conditions, brain activity increased most notably in preSMA and right inferior frontal cortex, around the frontal operculum (FrOp). The *upper plot*

five attentional conditions: the more participants were instructed to attend to colour, the more colour discrimination gradually improved and the more activity in visual area V4, the colour processing area of occipital cortex, monotonically increased [19]. We reasoned that if parametric modulation of attention to colour modulated activity in the brain area fundamental for colour perception, then parametric modulation of attention to duration should modulate activity in brain areas fundamental for time perception. We found that the more participants were instructed to attend to duration, the more temporal discrimination gradually improved and the more activity increased primarily in preSMA and right inferior frontal cortex (Fig. 2b). Interestingly, these were precisely the two regions later identified by Wiener et al.'s [11] meta-analysis as being critical for timing.

Deconstructing Time: Distinguishing Temporal Task Components

In a version of the temporal discrimination task commonly used in fMRI studies of timing, the participant times the duration of a first (standard or sample) stimulus, storing it in memory for later retrieval. They then time the duration of a second (comparison or probe) stimulus, comparing it in WM to that of the first. With careful use of event timing and randomization, the temporal resolution of event-related fMRI allows activity associated with these two discrete stimuli to be dissociated. This, in turn, allows identification of brain areas that respond more to initial storage of temporal information (sample) than its subsequent retrieval and comparison (probe). Rao et al. [16] were the first to dissociate the initial storage component of temporal discrimination from the later comparison stage using event-related fMRI. As compared to a performance-matched cognitive control task, early timing processes were linked to activation of the basal ganglia (right caudate and putamen), whereas later processes recruited right prefrontal cortex (PFC). However, the designation of "early" and "late" processing stages lacked temporal precision, making it difficult to conclude whether brain activations represented stimulus-evoked activity related to the presentation of the first (encoding and storage) or second (retrieval and comparison) stimulus, or some mixture of the two.

We circumvented these problems by precisely time-locking the fMRI signal to presentation of the sample and probe stimuli independently [20], to achieve a more direct measure of brain activity at each stage of the task. We used the same coloured stimulus pairs as described previously, except that the sample and probe stimuli were now separated by a longer and variable inter-stimulus interval (Fig. 1a), allowing their stimulus-evoked activity to be distinguished. As before, we compared activations evoked by the timing task to those evoked by the colour task, but this was conducted separately at the sample and probe stages of the task. Notably, Harrington et al. [18] and Wencil et al. [44] later used the same approach (time-locking the fMRI signal to events separated by a variable jitter) to dissociate events in perceptual timing paradigms (auditory or visual temporal discrimination respectively), as did Wittman et al. [35] and Bueti and Macaluso [23] for motor timing (temporal reproduction). We hypothesised that timing of stimulus duration is necessary for both sample and probe stimuli, that the encoding and storage of stimulus duration into WM would occur during presentation of the sample stimulus only, whereas retrieval and comparison of stimulus duration would occur during presentation of the probe only. Whole-brain analyses revealed that putamen was selectively activated by the sample, but not probe, stimulus while right superior temporal gyrus was activated by the probe, but not

Fig. 2 (continued) demonstrates that participants were allocating attention as required: as they paid more attention to stimulus duration, their temporal discriminations were increasingly accurate. The *lower plot* shows how activity in the SMA cluster increases progressively as a function of increasing attention to duration

sample, stimulus (Fig. 1b). SMA was the only region to be equally engaged by temporal processing of *both* sample and probe (Fig. 1b). Since the only process common to these two stimuli is the timing of elapsing duration, we suggested SMA plays a fundamental role in the perceptual timing of a duration that is currently unfolding in time [20]. Collectively, these results indicated a role for SMA in timing stimulus duration, for putamen in storing duration for later recollection, and for superior temporal gyrus in retrieving and comparing stored representations of duration.

Notably, the finding that timing-induced basal ganglia activity was restricted to the initial encoding and storage of stimulus duration confirms the earlier results of Rao et al. [16], who compared temporal to pitch discrimination of auditory intervals. It was also, in turn, confirmed by a later study from the same group using the same auditory task [18] and also by Wencil et al. [44] using temporal discrimination of visual durations. Similarly, Bueti and Macaluso [23] found basal ganglia activity during the encoding, but not reproduction, phase of a motor timing task, as did Wittmann et al. [35], although this was true only for the shortest (3 s) durations, not the longer (9 and 18 s) ones. Although timing-specific putamen activation during both initial storage *and* later comparison stages of the task has been reported [16, 18], this was observed only when the temporal discrimination task was compared to a low-level sensorimotor control task that did not control for the attentional, mnemonic and executive processes necessary for stimulus comparison and decision-making. In conclusion, whether the stimuli whose duration to be estimated are auditory empty intervals [16, 18, 35] or visual filled durations [20, 23, 44], or whether the temporal decision is measured with a perceptual discrimination [16, 18, 20, 44] or a timed motor response [23, 35], the fMRI results are broadly consistent, demonstrating that timing-related basal ganglia activation is restricted to the initial encoding and storage phase of the task. Collectively, these data cast doubt on Matell and Meck's [47, 48] model of interval timing, in which basal ganglia are proposed to perform the comparison function ("coincidence detection") that would, presumably, be taking place at the probe stage of the task.

Differential activation of putamen during storage versus comparison phases of the timing task may also go some way to explaining the inconsistent nature of timing-induced basal ganglia activation reported in the fMRI literature. Figure 1b illustrates the pattern of activity in putamen during our temporal and colour discrimination tasks [20]. It shows that the putamen was preferentially activated by the timing versus colour task during presentation of the initial sample, but was *less* activated by the timing than the colour task during presentation of the subsequent probe. When data were averaged across both stages of the task, timing-specific putamen activity was effectively cancelled out. If we had not utilized the temporal resolution of event-related fMRI to separate out the individual trial components, we would have deduced that basal ganglia were not involved in the timing task.

The functional selectivity of the putamen for storing stimulus duration into WM was further corroborated by correlational analyses showing significant links between brain activity and behaviour. Specifically, the more putamen was activated by the initial sample stimulus of the timing task, the more accurately participants eventually performed the task [20]. Conversely, there was no significant correlation between timing performance and the putamen activity recorded during the subsequent probe. Nor was there any correlation between activity in the putamen and performance on the colour discrimination task, further demonstrating the temporal selectivity of the putamen activation. The link between increased timing performance and neural activity at the storage phase of the task may reflect enhanced encoding of the sample stimulus into WM (mediated by the putamen), which results in a more accurate representation of stimulus duration. Our results confirmed those of Harrington et al. [49], who had already reported a significant correlation between a performance measure of temporal sensitivity in auditory

perceptual timing, the co-efficient of variation, with activity in basal ganglia (caudate) during initial encoding of stimulus duration. More recently, Bueti and Macaluso [23] found that performance measures of the subjective perception of time (degree of overestimation) correlated significantly with putamen activity during the encoding phase of their motor timing task.

Generally, these results illustrate the utility of correlational analyses in interpreting fMRI data. First, this approach helps tease apart which aspects of performance (e.g. accuracy, variability, clock-speed) correlate with activity in which brain regions and during which phase of the task (e.g. storage/retrieval). Second, showing that activation of a particular area varies as a function of performance provides a more convincing demonstration that the activation observed is truly reflective of the cognitive process of interest, rather than an incidental, co-occurring process that has not been adequately controlled for. The cognitive selectivity of the effect can be further confirmed if it is shown that no such correlation exists between activity in the region of interest and performance on a suitable *control* task.

Altering Time: Neurochemically Modulating the Perception of Time

I hope to have highlighted the importance of controlling for incidental cognitive processes, such as sustained attention or WM, when investigating the neuroanatomical substrates of timing with fMRI. This is also good practice when investigating the neuro*chemical* substrates of timing. Ideally, psychopharmacological experiments should aim to demonstrate both psychological and pharmacological specificity of the drug effect. Pharmacological specificity can be achieved by showing that a particular drug affects performance on a task, but that a different drug (or at least a placebo) does not. Psychological specificity can be achieved by showing that a drug affects performance on one kind of task or process, but not on a different kind. A lack of pharmacological or psychological specificity would suggest that observed drug effects derive from more general consequences of drug administration, such as the anxiogenic nature of the experimental protocol or the generally sedative/excitatory properties of the drug. Therefore, to be able to confidently interpret the deleterious effects of a drug on a timing task as a truly temporal effect, it must be demonstrated that the effect is (a) significantly different from the effects of a placebo or comparison drug and (b) independent from any collateral effects of the drug on attentional and mnemonic processes.

Warren Meck and colleagues have contributed enormously to our understanding of the neurochemical bases of timing, consistently showing in rats that dopaminergic (DA) agonists and antagonists have complementary effects on timing: agonists speed up the internal clock while antagonists slow it down (e.g. [50–55]). Similarly, Thomas Rammsayer has conducted a large number of psychopharmacological timing studies in healthy volunteers, demonstrating that while DA drugs impair timing in both the tens of milliseconds and seconds time-range, drugs acting on other neurotransmitter systems have either no effect or impair only seconds-range timing. For example, the D2 receptor antagonist haloperidol impairs accuracy of perceptual timing for durations in either the tens of milliseconds range (50 ms) or the seconds (1,000 ms) range [56–60]. By contrast, the benzodiazepine midazolam [60, 61], the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine [62], or the selective noradrenaline reuptake inhibitor, reboxitine [63] significantly affect timing in the seconds range but have no effect on timing in the tens of milliseconds range. Since timing in the seconds-range requires support from accessory processes, such as WM or sustained attention, processes known to be affected by benzodiazepines [64], noradrenergic drugs [65, 66] and NMDA antagonists [67], Rammsayer [60, 63] concluded that drug effects on seconds-range timing were secondary to their effects on attention and WM. Wittmann et al. [68] drew similar conclusions after observing deleterious effects of the 5-HT2A agonist psilocybin on motor timing of long (4–5 s) but not

short (~2 s) durations. Rammsayer [60, 63] further argued that the fact that haloperidol was the only drug tested to impair timing of in the tens of milliseconds range, which does not depend upon additional processes of sustained attention or WM, suggests a more selective effect on timing *per se*.

Rammsayer's studies tackled the potentially confounding effects of drugs on attentional and mnemonic processes by comparing effects on timing in the seconds versus tens of milliseconds range, which differentially engage sustained attention and WM. However, just because a drug affects timing in the seconds, but not tens of milliseconds, range does not necessarily mean that its effects reflect modulation only of WM or attentional processes. Timing of longer, seconds-range durations depends not only upon sustained attention and WM but also, of course, upon an index of elapsed time itself, for example accumulation of temporal pulses [69, 70] or temporal integration of steadily climbing neuronal activity [71]. Therefore, it's possible that drug-effects in this time-range could reflect impairment of a specifically seconds-range timing mechanism (e.g. accumulation), which is distinct from that used to time durations in the tens of milliseconds range. Mounting evidence suggests that timing in these two different duration ranges are underpinned by distinct mechanisms [9, 72–74]. Thus it is possible that a drug-induced deficit in the seconds but not tens of milliseconds, range could reflect a specifically temporal, rather than just WM or attentional, deficit.

Controlling for Cognitive Confounds

By asking participants to time durations only tens of milliseconds long, Rammsayer was able to discount the attentional and WM contributions to drug-induced timing effects. However, for timing in the longer hundreds of milliseconds to seconds range sustained attention and WM are fundamentally necessary and cannot be disentangled from the process of timing. We therefore approached this problem from a different angle. Since it's impossible to time longer durations without sustained attention and WM, we decided instead to control for them. Specifically, we sought to dissociate drug effects on seconds-range timing from their collateral effects on attentional and/or mnemonic processes by directly comparing effects on performance of timing and control tasks that were matched for attentional and WM demand. Specifically, we used the temporal and colour discrimination tasks [19, 20], described earlier (Fig. 1a). Drug-induced impairment of the timing, but not colour, task would provide evidence for neurochemical modulation of seconds-range timing independent from any mnemonic or attentional effects.

We first examined the effects of the NMDA receptor antagonist ketamine on timing [75]. Ketamine induces perceptual and cognitive changes similar to those found during prodromal stages of schizophrenia [76–78], thus providing a useful pharmacological model of the illness [79]. Numerous studies have shown that patients with schizophrenia have difficulties in timing durations in the hundreds of milliseconds to seconds range [80–85]. Since schizophrenia is often accompanied by WM deficits, and WM is critical for timing, some of these studies controlled for possible effects of the illness on WM by examining performance on digit span, a task that requires patients to repeat a list of numbers forwards and backwards. Digit span was either uncorrelated with timing performance [82, 84] or was correlated only with clock-speed, not temporal sensitivity [86], leading authors to conclude that patients' timing impairments could not be entirely explained by WM deficits. However, the kind of verbal WM required to maintain a list of numbers in WM is quite distinct from the kind of WM required to continually update information as a function of elapsing time. We therefore controlled for WM by using the colour discrimination task described earlier (Fig. 1) that employed exactly the same stimuli as the timing task, the only difference between tasks being whether participants had to attend to the stimulus' temporal or colour characteristics.

As compared to placebo, administration of an acute dose of ketamine to healthy volunteers selectively impaired temporal, but not colour,

discrimination of visual stimuli in the hundreds of milliseconds to seconds time-range [75]. Since both temporal and colour tasks placed similar demands on sustained attention and WM updating, the lack of effect of ketamine on colour discrimination suggests ketamine-induced impairments of timing of seconds-range durations did not simply reflect a side-effect of the drug on attention and WM. Rammsayer et al. [62] had concluded that the deleterious effects of the NMDA receptor antagonist memantine in the seconds duration-range were secondary to its mnemonic effects, yet the results of our ketamine study suggest that they could in fact have reflected effects on a distinct, seconds-range, timing mechanism independent from any incidental effects on sustained attention and WM updating. However, one difference in the WM requirements of the timing and colour tasks was the way in which information was manipulated in WM. For the timing task, information was incrementally accumulated, whereas for the colour task it was averaged. Accumulation implies a unidirectionality, a fundamental feature of the flow of time itself ("time's arrow" [87]). Averaging does not imply this unidirectionality. It is possible therefore, that ketamine influenced timing behaviour more specifically by selectively impairing the ability to increment information in WM in a particular direction or order.

Identifying Anatomical Substrates of Neurochemical Modulation

The patients included in investigations of timing in schizophrenia are generally medicated with neuroleptics. This could seriously confound the timing effects observed. In one study, for example, timing deficits were found in medicated patients whereas non-medicated patients were no different to healthy controls [88]. This suggests that the timing deficits typically observed in schizophrenic patients could, in fact, be a side-effect of their neuroleptic medication. This hypothesis is strengthened by consistent demonstrations of the deleterious effects of neuroleptics on timing in rats [51, 53, 54, 89] and healthy human volunteers [56–60]. We therefore decided to investigate the effects of a DA manipulation on seconds-range timing, using our temporal and colour discrimination paradigm to carefully control for potential effects on attentional and mnemonic processes. Moreover, we conducted the study with fMRI in order to identify the regions of the timing network that were modulated by DA [90].

Functional neuroimaging adds a useful third dimension to psychopharmacology research, allowing the complex relationship between cognition, neurochemistry and anatomy to be explored in the healthy human brain [91]. In particular, it allows the anatomical bases for neurochemical modulation of human cognition to be localised. Ideally, a psychopharmacological fMRI study should control for psychological, as well as pharmacological, mechanisms by including both a control cognitive task and a placebo treatment condition within a factorial design that comprises task (timing vs. control) and treatment (drug vs. placebo) as the factors of interest. By examining differential effects of the drug on the timing task compared to the control, any effects on non-timing factors (e.g. inhibitory effects on the vasculature) are subtracted out since these would be equally present during both the timing and control tasks. The factorial design therefore provides an index of the modulatory effects of drugs on timing-related networks, not their ability to directly excite or inhibit neural tissue. Or, in other words, the drug effect manifests itself as an attenuation or enhancement of activity in brain areas that are preferentially activated by the timing task. By contrast, simply comparing the effects of drug versus placebo on the pattern of activity induced by a timing task, *without* including a control task, would confound physiological effects of non-interest with neuromodulatory effects on timing-related areas.

In our study, we manipulated DA non-pharmaceutically, using Acute Phenylalanine/Tyrosine Depletion (APTD). This is an amino acid drink deficient in the DA precursors phenylalanine and tyrosine and has been shown to reduce striatal DA release [92, 93]. Behaviourally, as compared to a balanced amino-acid drink, APTD

selectively impaired performance of the temporal, but not the colour, discrimination task. APTD effects on timing were therefore unlikely to simply reflect DA modulation of sustained attention and WM processes. Neurally, in order to identify which regions of the timing network were modulated by APTD, we directly compared time-specific activations maps (i.e. areas activated more by temporal than colour discrimination) across the APTD and balanced drink sessions. APTD affected just two of the regions of the time-specific network, attenuating activity in the left putamen of the basal ganglia and SMA [90]. These results demonstrate the anatomical, as well as cognitive, specificity of the APTD effect.

These anatomical data also allowed us to dissect the cognitive effects of APTD even more finely by examining the effects of APTD on neural activity separately at the sample and probe stages of the task (see also Fig. 1). The APTD effects on activity in putamen and SMA occurred selectively at the initial sample stage of the timing task [90]. By contrast, there were no effects of APTD on activity in *any* of the regions associated with the probe stage of the timing task (a distributed network comprising prefrontal and temporal cortices, caudate and cerebellum). Furthermore, the APTD-induced neural changes at the sample stage correlated significantly with its behavioural changes: the more APTD attenuated activity in putamen or SMA, the more it impaired accuracy of temporal discrimination. In other words, APTD's effects on activity at the initial sample stage of the task predicted participant's subsequent timing performance. This suggests that the mechanism by which APTD impairs timing is to reduce activity in those areas of the brain responsible for the initial storage of temporal information into WM. Since putamen and SMA are functionally [94] and anatomically [95] connected components of the nigrostriatal "motor" pathway [96], our fMRI approach provided direct confirmation of Rammsayer's [59] speculation that DA modulates timing via the nigrostriatal, rather than mesocortical, pathway. Moreover, the spatial and temporal resolution of event-related fMRI allowed us to pinpoint not only the neuroanatomical (putamen and SMA) substrates of the APTD modulation of timing, but also its functional ones (initial storage into WM). In addition, the matched control task allowed us to exclude the possibility that results merely reflected modulation of confounding cognitive processes, such as WM or sustained attention.

Yet our results are at odds with prior fMRI studies reporting a predominantly frontal, rather than striatal, pattern of DA modulation during timing [97, 98]. This discrepancy could be explained, however, by the fact that participants in these previous studies were patients with Parkinson's Disease, whose underlying basal ganglia dysfunction may have influenced the pattern of effect. Alternatively (though not mutually exclusively), the discrepancy might be due to the fact that APTD preferentially targets striatal, rather than frontal, activity [99]. Future studies in healthy volunteers using DA agents that preferentially modulate mesocortical, rather than nigrostriatal, pathways may yet reveal modulation of timing-induced activity in prefrontal cortex.

Choosing the Right Time: Temporal Orienting of Attention

In the laboratory, as in the real-world, the term "timing" can be used to refer either to *how long* an event lasts or *when* an event occurs. The online Merriam-Webster English dictionary (www.merriam-webster.com/dictionary/timing) gives two distinct definitions for the word "timing". One is the "observation and recording of the elapsed time of an act, action or process". Here, the critical parameter is *how long* an event lasts. Estimating the duration of an event is the form of timing that has been discussed so far in this chapter. The other definition is "the ability to select the precise moment for doing something for optimum effect (e.g. a boxer with impeccable timing)". Here, the critical parameter is *when* best to act. Selecting a moment in time in order to optimise behaviour is the focus of the final section of this chapter.

The semantic distinction between these two definitions of timing is reminiscent of the distinction between explicit and implicit timing that can be found in the scientific literature [10, 100–104]. Explicit timing tasks have a temporal task goal, which is usually to measure and register the duration of a motor act or sensory stimulus [74, 105]. In other words, an overt estimation of stimulus duration is required. Conversely, implicit timing tasks have a non-temporal, often sensorimotor task goal, that nevertheless makes use of inherent temporal regularities in either movement dynamics [101, 102] or sensory stimuli (e.g. [10, 106, 107]). Temporal regularities may simply emerge as an intrinsic property of ongoing behaviour, e.g. tapping one's foot while waiting. Alternatively, temporal regularities in the environment may be used to enhance information processing for events occurring at predictable moments in time e.g. accelerating away more quickly after a 3-2-1 countdown. Of course, elapsed time must be tracked covertly to enable timely responding, but this temporal percept is never registered in explicitly temporal terms as, for example, a verbal estimate ("2 seconds") or a perceptual discrimination (shorter/longer than a memorised standard). Rather, it is indexed implicitly by the relatively improved speed (or accuracy) of stimulus processing.

The use of the phrase "select the precise moment" in the second of the two dictionary definitions of timing illustrates the attentional nature of this process: "select" implies that only certain aspects of the environment will be attended to and processed. The phrase "doing something for optimum effect" highlights the purpose of selective attention generally, which is to process certain elements of the environment whilst ignoring others so as to optimise behaviour. In this case, attention operates to select precise moments in time but, equally, it may also select particular locations in space or specific features of objects. Yet while the cognitive neuroscience of feature or spatial attention is a vast and well-established field, the cognitive neuroscience of temporal attention is in its infancy. This is despite the fact that the behavioural benefits of temporal preparation have now been known for almost a century [108].

Temporal Orienting of Attention

The neuroscientific investigation of spatial attention is frequently conducted with variants of the spatial orienting of attention task, first devised by Posner et al. [109]. In the classic version of this task, pre-cues provide information regarding the likely location of an upcoming target. Attentional resources can then be directed ("oriented") to that location, enabling faster detection of targets appearing there. Valid cues accurately predict where the target will appear, whereas invalid cues incorrectly predict the target's location. Neutral cues provide no spatially predictive information. Typically, RTs are faster for targets appearing in validly cued, rather than invalidly or neutrally cued, locations due to a process of spatial attentional orienting. My colleague Kia Nobre and I hypothesised that target detection would also be faster for stimuli appearing at validly cued temporal intervals, due to a putative process of temporal attentional orienting [110]. We therefore devised a temporal analogue of the Posner task, in which visual cues provided valid, invalid or neutral information concerning the likely interval before an imminent target was presented. Speed of target detection was measured in a paradigm in which pre-cues provided either spatial or temporal information independently, both spatial and temporal information together, or neither spatial nor temporal information (Fig. 3a). Sensorimotor demands were matched across conditions, with the only difference being whether attention was oriented within the spatial and/or temporal domain.

As predicted, target detection was faster following valid, rather than neutral or invalid, cues in the temporal, as well as the spatial, domain [10]. This result demonstrates that it is behaviourally advantageous not only to know where a target is likely to appear but also *when* it is likely to appear. The benefits of spatial attentional orienting had already been well documented, but this was the first time such

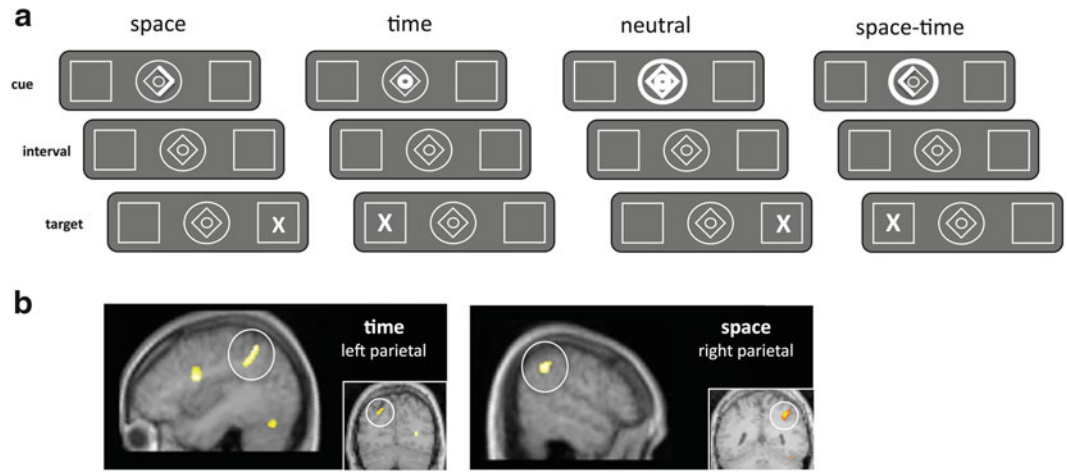

Fig. 3 (**a**) A central endogenous cue predicted the likely location (left/right box) and/or onset-time (short/long interval) of a forthcoming target (X). Cues directed attention either to the left or right location ("space"), to a short (300 ms) or long (1,500 ms) onset-time ("time"), to both location and onset-time ("space–time") or to neither location nor onset-time ("neutral"). Brightening of the left or right side of the diamond within the central cue predicted that the target would appear in the left or right peripheral box respectively. Brightening of the *inner* or *outer circle* predicted that the target would appear after a short or long interval respectively. Brightening of the entire cue in the neutral condition effectively provided no spatially or temporally predictive information. In the time condition illustrated here, the cue predicts that the target will appear after a short interval (*bright inner circle*) but provides no information concerning its location. (**b**) Spatial (versus temporal) cueing preferentially activated right-lateralised inferior parietal cortex, confirming previous reports. By contrast, temporal (versus spatial) cueing preferentially activated left-lateralised inferior parietal cortex

benefits had been shown to manifest themselves in the temporal domain. We speculated that similar attentional mechanisms operated in both spatial and temporal domains, with resources being directed in an anticipatory way to the location in space or the moment in time at which the event was predicted to happen, thus enhancing selectivity of processing at that point. Yet although spatial and temporal orienting appeared functionally similar, the brain regions underpinning these attentional processes were anatomically distinct. We directly compared the pattern of brain activity induced by spatially valid trials to that induced by temporally valid trials, which cancelled out any activations common to both tasks (e.g. those linked to processes of attentional orienting generally), leaving only areas that were differentially activated by orienting within the spatial versus temporal domain. Notably, we found hemispheric lateralization in parietal cortex for spatial versus temporal orienting of attention [110]. Spatial orienting activated right inferior parietal cortex, confirming numerous previous studies [46, 111, 112], whereas temporal orienting preferentially activated left inferior parietal cortex, specifically around the intraparietal sulcus (Fig. 3b). This result was replicated in two different groups of participants, first using PET then fMRI technologies [110], underlining the robustness of the result.

Optimising Behaviour or Estimating Duration?

At this point, it is crucial to remember that what these neuroimaging data primarily reflect are *attentional* processes: resources being oriented towards a particular moment in space or time in order to optimize behaviour. In the temporal orienting task, even though the participant has to accurately estimate duration in order to respond at the right moment, they were not required to provide an overt estimate of that duration. Their primary goal was a motor one: to respond to the target as quickly as possible.

Activation of left inferior parietal cortex by temporal orienting is therefore not incompatible with activation of SMA and right inferior frontal cortex by duration estimation (as described in preceding sections). These distinct anatomical substrates merely reflect the distinct functional characteristics of these two forms of timing: estimating duration so that attentional resources can be oriented towards the measured time in order to optimise behaviour (left inferior parietal) as opposed to estimating duration in order to register a temporal measure of elapsed time (SMA and right inferior frontal). In agreement with this, SMA and right-sided frontoparietal cortices were found to be activated in a temporal orienting task [113] when the participant was required to convert the predicted time of target appearance into an explicit judgement ("did the target appear earlier or later than expected?") rather than using the predicted time of its appearance to enhance stimulus processing.

In a recent fMRI study, we directly compared the neural substrates of these two forms of timing within the same experimental paradigm [38]. Timing was measured either explicitly, by a timed motor response (temporal reproduction task), or implicitly, by speeded detection of a temporally predictable target (temporal orienting task). In both tasks, a previously learnt visual cue preceded the interval to-be-timed, and either indicated (temporal cues) or not (neutral cues) the duration of the ensuing interval (Fig. 4a). These four conditions constituted a 2×2 factorial design, with task (reproduction/orienting) and cue (temporal/neutral) as the experimental factors. In the reproduction task, participants internally generated the cued interval, making a brief response when they estimated it had elapsed. In the orienting task, participants responded as quickly as possible to the appearance of an externally specified event that appeared at the cued interval. Neutral cue conditions, in which participants either generated a random interval (reproduction task) or detected a target appearing after a random interval (orienting task), controlled for the contribution of internally versus externally guided movement generally.

Behavioural data confirmed that participants acquired accurate representations of the cued durations in both tasks [38]. In the temporal reproduction task, duration estimates were very close to cued intervals, with variability being greater for long intervals than for short ones (i.e. timing behaviour was scalar). In the temporal orienting task, responses were faster for temporally valid targets than for neutrally cued ones. Yet although participants were using the same temporal representation in both reproduction and orienting tasks, distinct patterns of neural activity were evoked as a function of the way in which this temporal representation was used. When the temporal cue was translated into an overt estimate of elapsing time in the temporal reproduction task, SMA, basal ganglia and right-lateralised frontal and parietal cortices were preferentially recruited. Conversely, when the temporal cue was used to optimise sensorimotor processing at precise moments in time in the temporal orienting task, left inferior parietal cortex, left premotor cortex and cerebellum were preferentially engaged (Fig. 4b). By matching sensorimotor requirements across tasks, we were able to directly compare the temporal reproduction to temporal orienting tasks, confirming the fundamental role of SMA and right inferior frontal cortex in explicit duration estimation, and of left inferior parietal cortex in temporal orienting [38].

Independence from Motor Responding

Two further fMRI studies were designed to confirm the ubiquity of left inferior parietal cortex in temporal orienting. First, we aimed to show that activation of this area was independent of the type of motor response (left/right; manual/ocular) used to register stimulus detection. Second, we hoped to show that its activation was not only independent of the *type* of motor response but was, in fact, independent of the need to make a motor response of any kind. Specifically, we aimed to show that it was independent of the type of stimulus processing (motor/sensory) being optimised.

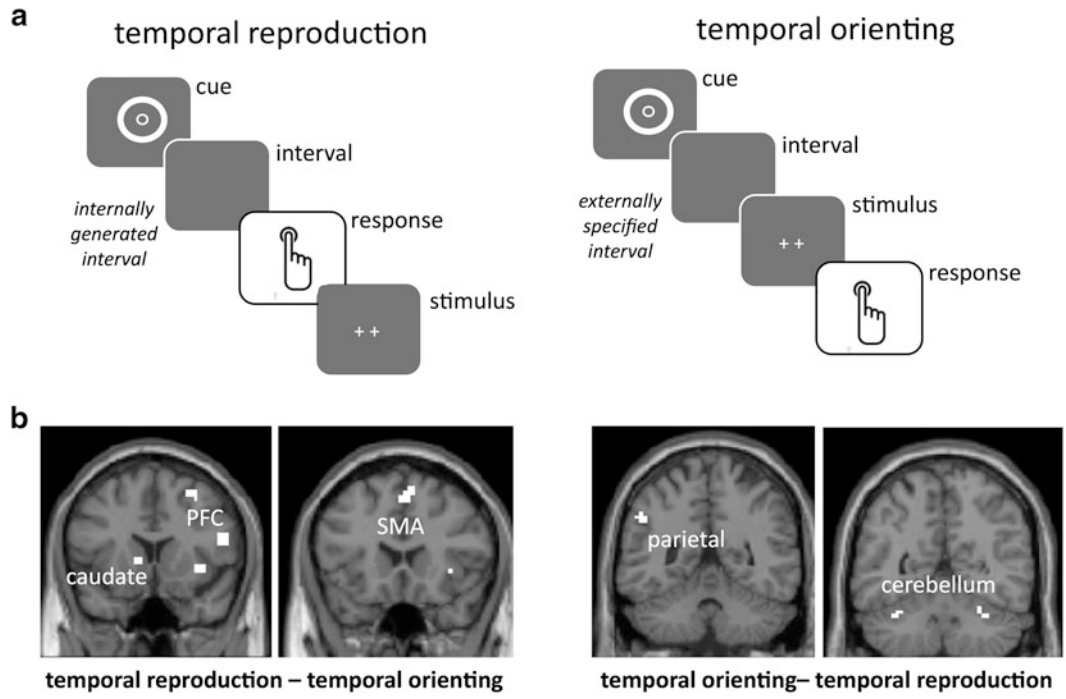

Fig. 4 (**a**) All cues comprised two concentric circles. For temporal cues, the *inner* or *outer circle* was brightened, indicating a short (600 ms) or long (1,400 ms) cue-stimulus interval respectively. For neutral cues, both *inner* and *outer circles* were brightened, indicating a random cue-stimulus interval. In the examples illustrated here, both tasks begin with a long temporal cue. In the temporal reproduction task, participants internally generated the duration indicated by the cue (short or long) then pressed a button when they estimated that that duration had elapsed. Pressing the button immediately elicited presentation of the visual response stimulus (++). In the temporal orienting task, the duration of the cue-stimulus interval was externally specified and determined by the onset-time of the response stimulus. Participants pressed a button as soon as the response stimulus was presented. The neutral cue version of each task had the same task structure except that the trial began with a neutral cue rather than a temporal one. The neutral cue version of the temporal reproduction task was a self-paced movement task in which participants pressed a button after a random interval of their choosing, thereby eliciting presentation of the response stimulus. The neutral cue version of the temporal orienting task was a simple reaction-time task in which participants pressed a button in response to a response stimulus that was presented after a random interval. (**b**) Direct comparison of the temporal reproduction and temporal orienting tasks revealed preferential activation of right prefrontal cortex, preSMA, right inferior parietal cortex and left caudate by the temporal reproduction task, but of left inferior parietal cortex and cerebellum by the temporal orienting task. Importantly, these activations do not simply reflect the neural substrates of internally versus externally guided movement. The activation maps illustrated here were first masked by the comparison of each task to its respective neutral cue condition. For example, the temporal reproduction minus temporal orienting comparison was masked by the temporal reproduction minus self-paced movement comparison. Since the neutral cue conditions engaged internally or externally guided movement to the same degree as the relevant temporal condition, but for random, rather than precisely timed, intervals, any activations related to internally or externally guided movements would be subtracted out

The impetus for these studies was the observation that a very similar area of left inferior parietal cortex had been implicated in another variant of the Posner paradigm, in which cues predicted the motor effector (e.g. index/middle finger) with which the speeded response should be made [114, 115]. It was therefore possible that activation of left inferior parietal cortex by temporal orienting may have simply reflected selective motor preparation of a speeded response. This is unlikely since motor preparation requirements were always matched across temporal orienting and comparison tasks. However, to explore this possibility more thoroughly, we

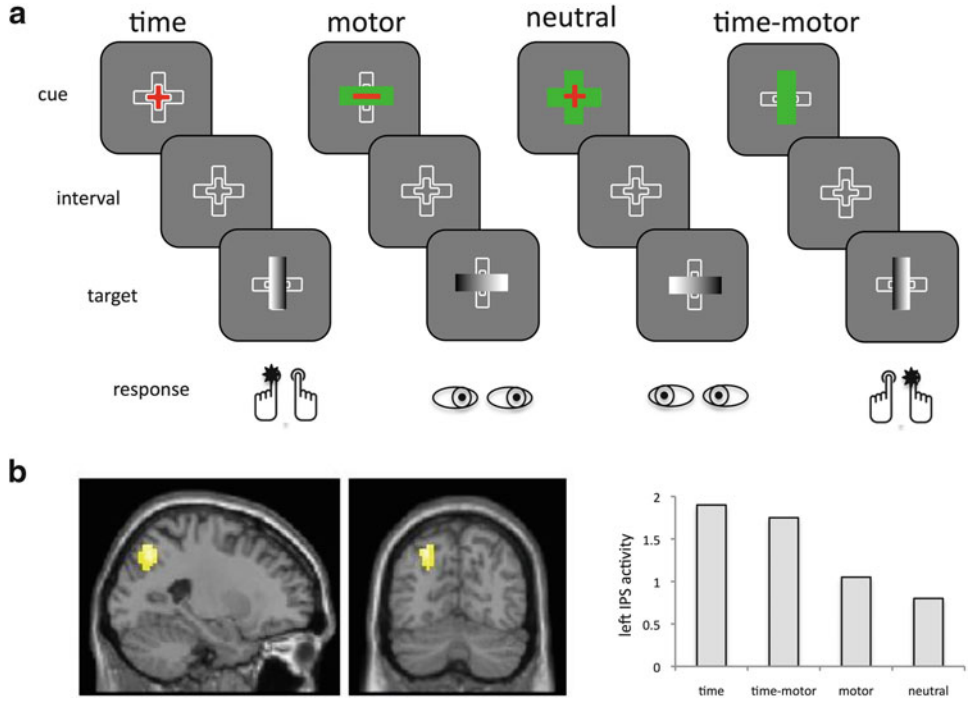

Fig. 5 (**a**) A crosshair cue predicted the onset-time (short/long interval) and/or the motor effector (manual button-press/ocular saccade) with which a response to a forthcoming target would be made. Cues directed attention either to onset-time ("time"), to motor effector ("motor"), to neither onset-time nor motor effector ("neutral"), or to both onset-time and motor effector ("time-motor"). Colouring of the inner or outer components of the crosshair cue indicated that the target would appear after a short (750 ms) or long (1,500 ms) interval respectively. Colouring of the horizontal or vertical components of the crosshair cue indicated that the target would call for an ocular saccade or a manual button-press respectively. Correspondingly, the orientation of the *target* specified the motor effector with which the motor response should be made, with vertical targets specifying manual button-presses and horizontal targets specifying saccades. The shading of the target specified the laterality of the response, with left/right responses being made towards the lighter side of the target. In the time-motor condition illustrated here, the cue predicts that the target will appear after a long interval (outer component) and will call for a manual button-press response (vertical component). When the target appears, it specifies a button-press response (vertical target) to be made with the right hand (lighter shading to the right of the target). (**b**) Temporal (versus neutral) cueing activated left intraparietal sulcus whether participants responded with manual button-presses or ocular saccades, either to the left or to the right. The accompanying plot shows that left intraparietal sulcus was activated more whenever temporal information was available, whether the effector used to register the response could also be prepared in advance (the time-motor condition) or not (the time condition)

designed a variation of the Posner task in which motor and temporal components of response preparation were independently cued within the same experimental paradigm [116]. Specifically, temporal or motor pre-cues informed participants as to when (short/long interval), and/or with which motor effector (oculomotor saccade/index finger button-press), a speeded response to an upcoming target should be made (Fig. 5a). By comparison, neutral cues provided neither temporal nor motor information. Behaviourally, temporal cues speeded responding as compared to neutral cues. This was true even when the motor effector used to register the response could not be prepared in advance, confirming that temporal preparation could benefit performance independently from motor preparation [116]. Similarly, temporal orienting activated left inferior parietal cortex, specifically within the intraparietal sulcus, whether the motor effector used to respond to the target could be prepared in advance or not (Fig. 5b). The robustness of this activation was further demonstrated by the fact that temporal orienting activated left

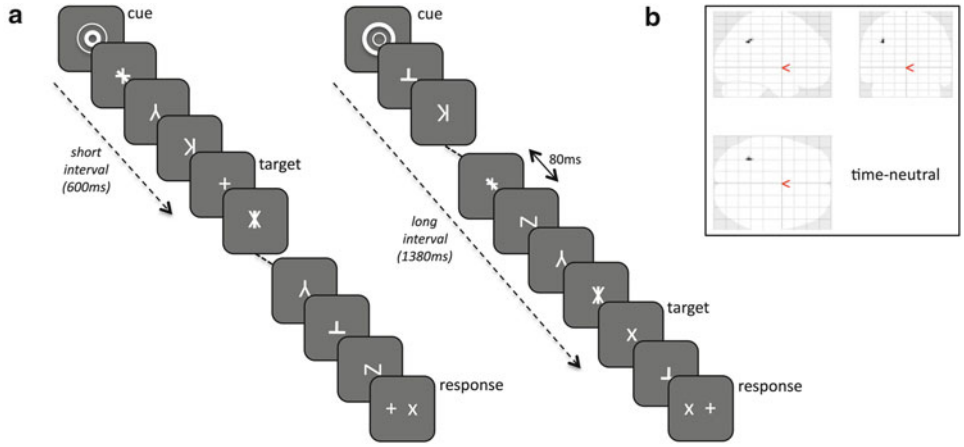

Fig. 6 (**a**) A temporal cue predicted the onset-time (short/long) of a target (either + or ×) that was embedded within a rapid serial visual presentation stream of visually similar distractors. The trial on the left shows a short temporal cue (*brightened inner circle*) and the trial on the right a long temporal cue (*brightened outer circle*), with targets appearing after a short (600 ms) or a long (1,380 ms) interval respectively. For the neutral cue (not illustrated here), both *inner* and *outer circles* were brightened, providing no temporal information. Participants indicated whether they had seen a + or x target by providing a delayed discriminatory response at trial end. To minimize the possibility for motor preparation, stimulus–response contingencies varied on a trial-by-trial basis. There were two possible response screens, and the relative positions (*left*/*right*) of the + and × symbols on the screen specified either a left or right button press, located under the index and middle fingers of the right hand. In the examples given here, the correct response would be a left button press in each case. (**b**) The only area preferentially activated by temporal versus neutral cueing in this perceptual version of the temporal orienting task was left intraparietal sulcus

intraparietal sulcus whether the laterality of the movement was left or right-sided, and whether the response was registered with a manual button-press or an oculomotor saccade [116]. We therefore concluded that left intraparietal sulcus represented an effector-independent substrate for temporal orienting and did not simply represent a motor preparation confound during the temporal orienting task. We further proposed that temporal orienting is an attentional mechanism that operates with similar principles on either the manual or ocular motor systems, in a manner analogous to that already proposed for spatial orienting [117, 118].

In a follow-up experiment, we aimed to show that temporal orienting would activate left inferior parietal cortex even when a speeded motor response was not required. Prior behavioral studies had demonstrated that temporal orienting not only confers faster motor response times [110, 119] but also enables faster and more accurate stimulus perception [120–122]. If left inferior parietal cortex is a core substrate for temporal orienting, it should also be activated when the task requires a perceptual discrimination, rather than a motor response. We therefore designed a perceptual version of the temporal orienting task [123], based on the paradigm used previously by Correa et al. [121], and compared its neural correlates directly to those of the motor version described previously. In the perceptual discrimination version of the task, participants were asked to discriminate which of two targets had been presented within a rapid serial presentation of visually similar distractors (Fig. 6a). In the motor detection version of the task, no visual distractors were presented and the participant had simply to detect the presence of the target as soon as possible after its appearance. In order to minimise the motor component of the perceptual version as much as possible, participants did not respond as soon as they had seen the target, but instead had to wait until the offset of the visual stream, at which point a choice response screen was displayed. To

minimise motor processing further still, and similar to the manipulation described earlier in the *Controlling Time* section, the stimulus–response mapping changed from trial to trial so that participants could not begin to prepare a motor response as soon as the target had been detected.

Analysis of behavioural data confirmed that temporal cues significantly enhanced both speed of motor detection and accuracy of perceptual discrimination. Crucially, fMRI results revealed that, as compared to neutral-cue control conditions, temporal orienting activated left inferior parietal cortex, deep in the intraparietal sulcus, whether temporally informative cues were used to react more quickly or, critically, to enhance perceptual sensitivity (Fig. 6b), thereby identifying this region as a core neural substrate for temporal orienting (see also [124]). Intriguingly, the level of activity in this region co-varied differentially with sensory or motor brain regions as a function of the task being performed: its activity correlated with activity in bilateral premotor/motor cortex during the motor detection task, but with activity in bilateral visual cortex during the (visual) perceptual discrimination task [123]. We suggested that, analogous to the biased competition model of spatial attention [125, 126], left intraparietal sulcus may generate a top-down biasing signal for activity in task-specific sensorimotor areas (i.e. areas recruited for processing of specific stimulus features or motor task goals) so as to bias information processing for stimuli appearing at the cued time.

Endogenous and Exogenous Temporal Cues

In the temporal orienting studies discussed so far, timing was measured implicitly by speed of motor responding or accuracy of perceptual discriminations. The way in which attention was oriented to discrete moments in time by the temporal cues, however, was explicit and voluntary. In a very recent study [127], it was not only the way in which timing was measured that was implicit but also the way in which attention was oriented in time. Specifically, we used metrically structured isochronous rhythms to manipulate temporal orienting implicitly. By analogy with the spatial attention literature, isochronous rhythms direct attention in an automatic, stimulus-driven "exogenous" manner whereas symbolic temporal cues direct attention in a more voluntary, goal-directed "endogenous" way [128]. We examined whether the temporal predictability of metrically structured rhythms would share functional and neural properties with that of symbolic temporal cues.

Prior fMRI studies of rhythm have compared temporally regular (isochronous or beat-based) to temporally irregular sequences, finding SMA and basal ganglia to be preferentially activated by temporal regularity (e.g. [15, 129–132]). Very recently, Marchant and Driver [133] found that targets were better detected when presented amidst temporally regular, rather than irregular, visual stimulus streams, and was accompanied by activity in bilateral PFC, insula, basal ganglia and, notably, inferior parietal cortex lateralized to the left hemisphere. They concluded the left parietal activation was most likely due to the temporally predictable nature of the isochronous sequence, which helped optimize target detection. In our experiment, we also examined brain activity associated with rhythmically induced improvements in target detection, but instead of comparing rhythmic to non-rhythmic sequences, we compared activity induced by strong versus weak beats of a metrically structured rhythm. Critically, all experimental conditions were equally rhythmic, in order to equate (or cancel out) processes related to rhythm perception *per se*. Behavioural responses were faster for targets presented on strong, rather than weak, beats, indicating increased allocation of attention to strong beats (see also [106, 107]). This behavioural benefit was accompanied by selective activation of left inferior parietal cortex [127]. Therefore, although basal ganglia and SMA may be activated by the perception of rhythm in the first place (e.g. [131]), left inferior parietal cortex is activated whenever temporally salient elements of that rhythm capture attention, thereby optimising processing of stimuli occurring at that time. This neuroanatomical distinction once again

reflects the functional difference between timing in order to estimate duration (perceiving rhythmicity or not) and timing in order to optimize sensorimotor processing (using rhythmicity to improve target detection).

Using Action Circuits for Time

To summarise, estimating event duration, whether the estimate is provided with a motor response or a perceptual discrimination, typically recruits basal ganglia, SMA and right inferior frontal cortex, and can be modulated by dopaminergic activity in these areas. By contrast, orienting attention to predictable moments in time in order to optimize behaviour, whether that is to speed motor responding or improve perceptual accuracy, recruits left inferior parietal cortex. Strikingly, these are areas that have all previously been implicated in motor preparation, with Goldberg [134] proposing that distinct motor areas would be recruited depending on whether the movement being prepared was internally or externally guided. Indeed, numerous neuroimaging studies of motor preparation have shown that SMA and prefrontal cortex are activated particularly by preparation of internally generated (i.e. self-willed) movements [39, 40, 135–139] and the voluntary intention to act [140], whereas left parietal and premotor cortices are activated by preparation of externally cued movements [141, 142]. This neuroanatomical distinction between internally and externally guided movement neatly parallels that between duration estimation and temporal orienting respectively, perhaps reflecting a corresponding functional parallel: responses in a temporal reproduction task are guided by internal estimates of elapsed duration whereas responses in a temporal orienting task are triggered by the onset of externally timed imperative sensory stimuli.

Highlighting the neural and functional overlap between timing and motor control is one thing. A more intriguing question is to ask what this overlap might signify? One possibility, taking us right back to the beginning of this chapter, is that this overlap simply reflects the presence of confounding cognitive processes. For example, in studies of internally generated motor preparation (e.g. [135, 138]), activation of SMA and prefrontal cortex may actually represent the timing of the intended response rather than selection of a particular motor effector: indeed, Wencke et al. [143] have noted that such studies typically examine the voluntary intention of *when* to move, not *which* motor effector to move (see also 144). Conversely, in studies of duration estimation, activation of SMA and prefrontal cortex may simply reflect confounding processes of motor preparation. This is unlikely however, since SMA and prefrontal cortex are selectively activated even when duration estimates are registered with a perceptual discrimination [11], or after motor preparation and/or execution processes have been rigorously controlled for (e.g. [20]).

A more appealing possibility is that timing shares neural circuitry with motor function because our sense of time is acquired early in development through action ([145, 146]; see also [147]). This proposal is similar in principle to other embodied theories of time perception although, given the neuroanatomical overlap between timing and motor areas, I suggest time is grounded more fundamentally in action, rather than interoception (e.g. [148, 149]) or motion perception [150, 151]. These propositions are not incompatible, of course, since action implies both motion and interoception. To begin on a personal note, I noticed that when my children were younger I often gave them motor reference frames when they asked how long a particular period of time was: for example, 15 min was the time it took to walk to school, or an hour was the time their judo/ballet class lasted. This anecdotal account is supported empirically by the results of developmental studies demonstrating that young children appear to represent time in motor terms. Their duration estimates are more accurate when the duration is filled with an action than when it is empty [152] and they find it difficult to dissociate an estimate of duration from the motor act itself. For example, 3 year-olds' could not reproduce the duration of one action with a different

action (e.g. "press the button. . .now, squeeze the bulb for the same amount of time"), although by the age of 5 such temporal transfer was possible [153]. Moreover, Droit-Volet [154] found that when 3 year-olds' were asked to press a button "longer than before" the duration of their responses did not differ, but when asked to press "harder than before" their responses lengthened. In these young children, duration actually appears to have been coded as a force parameter rather than a temporal one. A tantalizing possibility therefore is that action circuits are engaged early in development to build up and acquire representations of time, resulting in shared neural representations for action and the perception of time. Even in adults, there is evidence that when motor skills are learned incidentally temporal information is bound to the specific action in which it was learnt rather than being represented at an effector-independent level [113]. Many neuroscientific theories of different aspects of cognitive function propose shared neural representations for action and perception (e.g. [155–158]). Applied to the temporal domain, learned associations between particular actions and their durations might ultimately lead to shared neural representations for motor acts and their perceptual (i.e. temporal) correlates.

The association between action and perception is bidirectional: an internally generated action may become associated with its perceptual consequences (action-effect pairing) and an external stimulus may become associated with the motor response it evokes (stimulus–response pairing). It is tempting to consider that this functional distinction maps onto the neuroanatomical dissociation between duration estimation (basal ganglia, SMA, prefrontal cortex) and temporal orienting (left inferior parietal cortex). Therefore, for action-effect pairings, when an internally generated action results in a particular temporal percept (e.g. the child who learns that the amount of time it takes to walk to school represents a duration of 10 min), the representation for time perception is instantiated within the fronto-striatal motor circuits underlying voluntary action. By contrast, for stimulus–response pairings, when the timing of a sensory stimulus evokes a particular motor response (e.g. learning to clap in time to the music), the representation for timing may instead become instantiated in the parietal circuits necessary for sensorimotor learning. Data derived from modern neuroimaging techniques are beginning to converge with developmental evidence in children to suggest that the ontogenetic roots of our notion of time might be embedded within action circuits, an idea that was first advanced by Guyau [7, 8] over a hundred years ago.

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References

1. Michon JA. The complete time experiencer. In: Michon JA, Jackson JLJ, editors. Time, mind and behavior. Berlin: Springer; 1985.
2. Zakay D, Block RA. The role of attention in time estimation processes. In: Pastor MA, editor. Time, internal clocks and movement. New York: Elsevier Sciences; 1996. p. 143–64.
3. Fortin C, Rousseau R. Interference from short-term memory processing on encoding and reproducing brief durations. Psychol Res. 1998;61:269–76.
4. Lustig C, Matell MS, Meck WH. Not "just" a coincidence: frontal-striatal interactions in working memory and interval timing. Memory. 2005;13:441–8.
5. Brown SW. Time and attention: review of the literature. In: Grondin S, editor. Time perception. Bingley: Emerald; 2008.
6. James W. The principles of psychology. New York: Henry Holt; 1890 (reprinted Bristol: Thoemmes Press, 1999).
7. Guyau J-M. La genèse de l'idée du temps. Paris: Félix Alcan; 1890.
8. Michon JA, Pouthas V, Jackson JL. Guyau and the idea of time. Amsterdam: Elsevier; 1989
9. Lewis PA, Miall RC. Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. Curr Opin Neurobiol. 2003;13(2):250–5.
10. Coull J, Nobre A. Dissociating explicit timing from temporal expectation with fMRI. Curr Opin Neurobiol. 2008;18:137–44.
11. Wiener M, Turkeltaub P, Coslett HB. The image of time: a voxel-wise meta analysis. Neuroimage. 2010;49:1728–40.
12. Jueptner M, Flerich L, Weiller C, Mueller SP, Diener HC. The human cerebellum and temporal information processing — results from a PET experiment. Neuroreport. 1996;7:2761–5.

13. Maquet P, Lejeune H, Pouthas V, Bonnet M, Casini L, Macar F, Timsit-Berthier M, Vidal F, Ferrara A, Degueldre C, Quaglia L, Delfiore G, Luxen A, Woods R, Mazziotta JC, Comar D. Brain activation induced by estimation of duration: a PET study. Neuroimage. 1996;3:119–26.
14. Rao SM, Harrington DL, Haaland KY, Bobholz JA, Cox RW, Binder JR. Distributed neural systems underlying the timing of movements. J Neurosci. 1997;17:5528–35.
15. Schubotz RI, Friederichi AD, von Cramon DT. Time perception and motor timing: a common cortical and subcortical basis revealed by fMRI. Neuroimage. 2000;11:1–12.
16. Rao SM, Mayer AR, Harrington DL. The evolution of brain activation during temporal processing. Nat Neurosci. 2001;4:317–23.
17. Nenadic I, Gaser C, Volz HP, Rammsayer T, Hager F, Sauer H. Processing of temporal information and the basal ganglia: new evidence from fMRI. Exp Brain Res. 2003;148(2):238–46.
18. Harrington DL, Zimbelman JL, Hinton SC, Rao SM. Neural modulation of temporal encoding, maintenance, and decision processes. Cereb Cortex. 2010;20:1274–85.
19. Coull JT, Vidal F, Nazarian B, Macar F. Functional anatomy of the attentional modulation of time estimation. Science. 2004;303(5663):1506–8.
20. Coull JT, Nazarian B, Vidal F. Timing, storage, and comparison of stimulus duration engage discrete anatomical components of a perceptual timing network. J Cogn Neurosci. 2008;20:2185–97.
21. Livesey AC, Wall MB, Smith AT. Time perception: manipulation of task difficulty dissociates clock functions from other cognitive demands. Neuropsychologia. 2007;45(2):321–31.
22. Morillon B, Kell CA, Giraud AL. Three stages and four neural systems in time estimation. J Neurosci. 2009;29(47):14803–11.
23. Bueti D, Macaluso E. Physiological correlates of subjective time: evidence for the temporal accumulator hypothesis. Neuroimage. 2011;57:1251–63.
24. Ferrandez AM, Hugueville L, Lehericy S, Poline JB, Marsault C, Pouthas V. Basal ganglia and supplementary motor area subtend duration perception: an fMRI study. Neuroimage. 2003;19(4):1532–44.
25. Lewis PA, Miall RC. Brain activation patterns during measurement of sub- and supra-second intervals. Neuropsychologia. 2003;41(12):1583–92.
26. Penhune VB, Zattore RJ, Evans AC. Cerebellar contributions to motor timing: a PET study of auditory and visual rhythm reproduction. J Cogn Neurosci. 1998;10:752–65.
27. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams S, Simmons A, Andrew C, Bullmore E. Prefrontal involvement in "temporal bridging" and timing movement. Neuropsychologia. 1998;36:1283–93.
28. Jäncke L, Loose R, Lutz K, Specht K, Shah NJ. Cortical activations during paced finger-tapping applying visual and auditory pacing stimuli. Cogn Brain Res. 2000;10:51–66.
29. Lewis PA, Wing AM, Pope PA, Praamstra P, Miall RC. Brain activity correlates differentially with increasing temporal complexity of rhythms during initialisation, synchronisation, and continuation phases of paced finger tapping. Neuropsychologia. 2004;42:1301–12.
30. Mayville JM, Jantzen KJ, Fuchs A, Steinberg FL, Kelso JAS. Cortical and subcortical networks underlying syncopated and synchronized coordination revealed using fMRI. Hum Brain Mapp. 2002;17:214–29.
31. Jantzen KJ, Steinberg FL, Kelso JAS. Brain networks underlying human timing behavior are influenced by prior context. Proc Natl Acad Sci U S A. 2004;101:6815–20.
32. Jantzen KJ, Steinberg FL, Kelso JAS. Functional MRI reveals the existence of modality and coordination-dependent timing networks. Neuroimage. 2005;25:1031–42.
33. Jahanshahi M, Jones CR, Dirnberger G, Frith CD. The substantia nigra pars compacta and temporal processing. J Neurosci. 2006;26:12266–73.
34. Bueti D, Walsh V, Frith C, Rees G. Different brain circuits underlie motor and perceptual representations of temporal intervals. J Cogn Neurosci. 2008;20 (2):204–14.
35. Wittmann M, Simmons AN, Aron JL, Paulus MP. Accumulation of neural activity in the posterior insula encodes the passage of time. Neuropsychologia. 2010;48:3110–20.
36. Lewis PA, Miall RC. Brain activity during non-automatic motor production of discrete multi-second intervals. Neuroreport. 2002;13:1731–5.
37. Macar F, Anton J-L, Bonnet M, Vidal F. Timing functions of the supplementary motor area: an event-related fMRI study. Cogn Brain Res. 2004;21:206–15.
38. Coull JT, Davranche K, Nazarian B, Vidal F. Functional anatomy of timing differs for production versus prediction of time intervals. Neuropsychologia. 2013;51:309–19.
39. Deiber MP, Honda M, Ibanez V, Sadato N, Hallett M. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: effect of movement type and rate. J Neurophysiol. 1999;81:3065–77.
40. Cunnington R, Windischberger C, Deecke L, Moser E. The preparation and execution of self-initiated and externally-triggered movement: a study of event-related fMRI. Neuroimage. 2002;15(2):373–85.
41. Pouthas V, George N, Poline JB, Pfeuty M, Vandemoorteele PF, Hugueville L, et al. Neural network involved in time perception: an fMRI study comparing long and short interval estimation. Hum Brain Mapp. 2005;25(4):433–41.
42. Tregellas JR, Davalos DB, Rojas DC. Effect of task difficulty on the functional anatomy of temporal processing. Neuroimage. 2006;32(1):307–15.

43. Lee KH, Egleston PN, Brown WH, Gregory AN, Barker AT, Woodruff PW. The role of the cerebellum in subsecond time perception: evidence from repetitive transcranial magnetic stimulation. J Cogn Neurosci. 2007;19:147–57.
44. Wencil EB, Coslett HB, Aguirre GK, Chatterjee A. Carving the clock at its component joints: neural bases for interval timing. J Neurophysiol. 2010;104:160–8.
45. Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Attentional modulation of neural processing of shape, color, and velocity in humans. Science. 1990;248:1556–9.
46. Corbetta M, Miezin FM, Shulman GL, Petersen SE. A PET study of visuospatial attention. J Neurosci. 1993;13:1202–26.
47. Matell MS, Meck WH. Neuropsychological mechanisms of interval timing behaviour. Bioessays. 2000;22(1):94–103.
48. Matell MS, Meck WH. Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes. Cogn Brain Res. 2004;21(2):139–70.
49. Harrington DL, Boyd LA, Mayer AR, Sheltraw DM, Lee RR, Huang M, et al. Neural representation of interval encoding and decision making. Cogn Brain Res. 2004;21:193–205.
50. Buhusi CV, Meck WH. Differential effects of methamphetamine and haloperidol on the control of an internal clock. Behav Neurosci. 2002;116:291–7.
51. MacDonald CJ, Meck WH. Differential effects of clozapine and haloperidol on interval timing in the supraseconds range. Psychopharmacology (Berl). 2005;182:232–44.
52. Matell MS, King GR, Meck WH. Differential modulation of clock speed by the administration of intermittent versus continuous cocaine. Behav Neurosci. 2004;118:150–6.
53. Meck WH. Selective adjustment of the speed of internal clock and memory processes. J Exp Psychol Anim Behav Process. 1983;9:171–201.
54. Meck WH. Affinity for the dopamine D2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock. Pharmacol Biochem Behav. 1986;25:1185–9.
55. Meck WH. Neuroanatomical localization of an internal clock: a functional link between mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. Brain Res. 2006;1109:93–107.
56. Rammsayer T. Dopaminergic and serotoninergic influence on duration discrimination and vigilance. Pharmacopsychiatry. 1989;22 Suppl 1:39–43.
57. Rammsayer T. Is there a common dopaminergic basis of time perception and reaction time? Neuropsychobiology. 1989;21(1):37–42.
58. Rammsayer TH. On dopaminergic modulation of temporal information processing. Biol Psychol. 1993;36:209–22.
59. Rammsayer TH. Are there dissociable roles of the mesostriatal and mesolimbocortical dopamine systems on temporal information processing in humans? Neuropsychobiology. 1997;35:36–45.
60. Rammsayer TH. Neuropharmacological evidence for different timing mechanisms in humans. Q J Exp Psychol B. 1999;52:273–86.
61. Rammsayer T. Effects of benzodiazepine-induced sedation on temporal processing. Human Psychopharmacol. 1992;7(5):311–8.
62. Rammsayer TH. Effects of pharmacologically induced changes in NMDA receptor activity on human timing and sensorimotor performance. Brain Res. 2006;1073–1074:407–16.
63. Rammsayer TH, Hennig J, Haag A, Lange N. Effects of noradrenergic activity on temporal information processing in humans. Q J Exp Psychol B. 2001;54:247–58.
64. Curran HV. Benzodiazepines, memory and mood: a review. Psychopharmacology (Berl). 1991;105 (1):1–8.
65. Coull JT, Middleton HC, Robbins TW, Sahakian BJ. Clonidine and diazepam have differential effects on tests of attention and learning. Psychopharmacology (Berl). 1995;120:322–32.
66. Coull JT, Middleton HC, Robbins TW, Sahakian BJ. Contrasting effects of clonidine and diazepam on tests of working memory and planning. Psychopharmacology (Berl). 1995;120:311–21.
67. Morgan CJ, Curran HV. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology (Berl). 2006;188(4):408–24.
68. Wittmann M, Carter O, Hasler F, Cahn BR, Grimberg U, Spring P, et al. Effects of psilocybin on time perception and temporal control of behaviour in humans. J Psychopharmacol. 2007;21 (1):50–64.
69. Gibbon J, Church RM, Meck WH. Scalar timing in memory. Ann N Y Acad Sci. 1984;423:52–77.
70. Treisman M. Temporal discrimination and the indifference interval: implications for a model of the "internal clock". Psychol Monogr. 1963;77 (13):1–31.
71. Reutimann J, Yakovlev V, Fusi S, Senn W. Climbing neuronal activity as an event-based cortical representation of time. J Neurosci. 2004;24:3295–303.
72. Gibbon J, Malapani C, Dale CL, Gallistel CR. Toward a neurobiology of temporal cognition: advances and challenges. Curr Opin Neurobiol. 1997;7:170–84.
73. Buonomano DV, Bramen J, Khodadadifar M. Influence of the interstimulus interval on temporal processing and learning: testing the state-dependent network model. Philos Trans R Soc Lond B Biol Sci. 2009;364:1865–73.
74. Ivry RB, Schlerf JE. Dedicated and intrinsic models of time perception. Trends Cogn Sci. 2008;12 (7):273–80.
75. Coull JT, Morgan H, Cambridge VC, Moore JW, Giorlando F, Adapa R, Corlett PR, Fletcher PC. Ketamine perturbs perception of the flow of time in

healthy volunteers. Psychopharmacology (Berl). 2011;218:543–56.
76. Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, et al. Psychological effects of ketamine in healthy volunteers. Phenomenological study. Br J Psychiatry. 2006;189:173–9.
77. Fletcher PC, Honey GD. Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. Trends Cogn Sci. 2006;10:167–74.
78. Corlett PR, Honey GD, Krystal JH, Fletcher PC. Glutamatergic model psychoses: prediction error, learning, and inference. Neuropsychopharmacology. 2011;36:294–315.
79. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 1994;51:199–214.
80. Lhamon WT, Goldstone S. The time sense: estimation of one second durations by schizophrenic patients. AMA Arch Neurol Psychiatry. 1956;76:625–9.
81. Tysk L. Time estimation by healthy subjects and schizophrenic patients: a methodological study. Percept Mot Skills. 1983;56:983–8.
82. Elvevåg B, McCormack T, Gilbert A, Brown GD, Weinberger DR, Goldberg TE. Duration judgements in patients with schizophrenia. Psychol Med. 2003;33:1249–61.
83. Davalos DB, Kisley MA, Ross RG. Effects of interval duration on temporal processing in schizophrenia. Brain Cogn. 2003;52:295–301.
84. Carroll CA, Boggs J, O'Donnell BF, Shekhar A, Hetrick WP. Temporal processing dysfunction in schizophrenia. Brain Cogn. 2008;67:150–61.
85. Carroll CA, O'Donnell BF, Shekhar A, Hetrick WP. Timing dysfunctions in schizophrenia as measured by a repetitive finger tapping task. Brain Cogn. 2009;71:345–53.
86. Lee KH, Bhaker RS, Mysore A, Parks RW, Birkett PB, Woodruff PW. Time perception and its neuropsychological correlates in patients with schizophrenia and in healthy volunteers. Psychiatry Res. 2009;166:174–83.
87. Eddington AS. The nature of the physical world. Cambridge: Cambridge University Press; 1928.
88. Goldstone S, Nurnberg HG, Lhamon WT. Effects of trifluoperazine, chlorpromazine, and haloperidol upon temporal information processing by schizophrenic patients. Psychopharmacology (Berl). 1979;65 (2):119–24.
89. Maricq AV, Church RM. The differential effects of haloperidol and methamphetamine on time estimation in the rat. Psychopharmacology (Berl). 1983;79:10–5.
90. Coull JT, Hwang HJ, Leyton M, Dagher A. Dopamine precursor depletion impairs timing in healthy volunteers by attenuating activity in putamen and supplementary motor area. J Neurosci. 2012;32:16704–15.
91. Coull JT, Thiele C. Functional imaging of cognitive psychopharmacology. In: Frackowiak RSJ et al., editors. Human brain function. 2nd ed. New York: Academic; 2004.
92. Montgomery AJ, McTavish SF, Cowen PJ, Grasby PM. Reduction of brain dopamine concentration with dietary tyrosine plus phenylalanine depletion: an [11C] raclopride PET study. Am J Psychiatry. 2003;160:1887–9.
93. Leyton M, Dagher A, Boileau I, Casey K, Baker GB, Diksic M, Gunn R, Young SN, Benkelfat C. Decreasing amphetamine-induced dopamine release by acute phenylalanine/tyrosine depletion: A PET/[11C]raclopride study in healthy men. Neuropsychopharmacology. 2004;29:427–32.
94. Postuma RB, Dagher A. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. Cereb Cortex. 2006;16:1508–21.
95. Lehericy S, Ducros M, Krainik A, Francois C, Van de Moortele P, Ugurbil K, Kim D. 3-D diffusion tensor axonal tracking shows distinct SMA and pre-SMA projections to the human striatum. Cereb Cortex. 2004;14:1302–9.
96. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–81.
97. Harrington DL, Castillo GN, Greenberg PA, Song DD, Lessig S, Lee RR, Rao SM. Neurobehavioral mechanisms of temporal processing deficits in Parkinson's disease. PLoS One. 2011;6(2):e17461.
98. Jahanshahi M, Jones CR, Zijlmans J, Katzenschlager R, Lee L, Quinn N, Frith CD, Lees AJ. Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease. Brain. 2010;133:727–45.
99. Le Masurier M, Cowen PJ, Sharp T. Fos immunocytochemical studies on the neuroanatomical sites of action of acute tyrosine depletion in the rat brain. Psychopharmacology (Berl). 2004;171:435–40.
100. Michon JA. Implicit and explicit representations of time. In: Block RA, editor. Cognitive models of psychological time. Hillsdale: Lawrence Erlbaum Associates; 1980. p. 37–58.
101. Grondin S. From physical time to the first and second moments of psychological time. Psychol Bull. 2001;127:22–44.
102. Zelaznik HN, Spencer RMC, Ivry RB. Dissociation of explicit and implicit timing in repetitive tapping and drawing movements. J Exp Psychol Hum Percept Perform. 2002;28:575–88.
103. Jones CR, Malone TJ, Dirnberger J, Edwards M, Jahanshahi M. Basal ganglia, dopamine and temporal processing: performance on three timing tasks on and off medication in Parkinson's disease. Brain Cogn. 2008;68:30–41.
104. Merchant H, Zarco W, Bartolo R, Prado L. The context of temporal processing is represented in the multidimensional relationships between timing tasks. PLoS One. 2008;3(9):e3169.

105. Grondin S. Timing and time perception: a review of recent behavioural and neuroscience findings and theoretical directions. Atten Percept Psychophys. 2010;72:561–82.
106. Jones MR. The patterning of time and its effects on perceiving. Ann N Y Acad Sci. 1984;423:158–67.
107. Jones MR. Attending to sound patterns and the role of entrainment. In: Nobre AC, Coull JT, editors. Attention and time. Oxford: Oxford University Press; 2010. p. 137–330.
108. Woodrow H. The measurement of attention. Psychol Monogr. 1914;17.
109. Posner MI, Snyder C, Davidson BJ. Attention and the detection of signals. J Exp Psychol. 1980;109:160–74.
110. Coull JT, Nobre AC. Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. J Neurosci. 1998;18:7426–35.
111. Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat Neurosci. 2000;3(3):292–7.
112. Nobre AC. The attentive homunculus: now you see it, now you don't. Neurosci Biobehav Rev. 2001;25 (6):477–96.
113. O'Reilly JX, Mesulam MM, Nobre AC. The cerebellum predicts the timing of perceptual events. J Neurosci. 2008;28(9):2252–60.
114. Rushworth MFS, Nixon PD, Renowden S, Wade DT, Passingham RE. The left parietal cortex and motor attention. Neuropsychologia. 1997;35:1261–73.
115. Rushworth MF, Johansen-Berg H, Gobel SM, Devlin JT. The left parietal and premotor cortices: motor attention and selection. Neuroimage. 2003;20(S1): S89–100.
116. Cotti J, Rohenkohl G, Stokes M, Nobre AC, Coull JT. Functionally dissociating temporal and motor components of response preparation in left intraparietal sulcus. Neuroimage. 2011;54:1221–30.
117. Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van Essen DC, Corbetta M. Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. J Neurosci. 2003;23:4689–99.
118. Eimer M, Forster B, Velzen JV, Prabhu G. Covert manual response preparation triggers attentional shifts: ERP evidence for the premotor theory of attention. Neuropsychologia. 2005;43:957–66.
119. Griffin IC, Miniussi C, Nobre AC. Orienting attention in time. Front Biosci. 2001;6:D660–71.
120. Correa Á, Lupiáñez J, Milliken B, Tudela P. Endogenous temporal orienting of attention in detection and discrimination tasks. Percept Psychophys. 2004;66(2):264–78.
121. Correa Á, Lupiáñez J, Tudela P. Attentional preparation based on temporal expectancy modulates processing at the perceptual level. Psychon Bull Rev. 2005;12(2):328–34.
122. Martens S, Johnson A. Timing attention: cuing target onset interval attenuates the attentional blink. Mem Cognit. 2005;33(2):234–40.
123. Davranche K, Nazarian B, Vidal F, Coull JT. Orienting attention in time activates left intraparietal sulcus for perceptual and motor task goals. J Cogn Neurosci. 2011;23:3318–30.
124. Wiener M, Turkeltaub P, Coslett HB. Implicit timing activates the left inferior parietal cortex. Neuropsychologia. 2010;48:3967–71.
125. Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci. 1995;18:193–222.
126. Kastner S, Ungerleider LG. The neural basis of biased competition in human visual cortex. Neuropsychologia. 2001;39(12):1263–76.
127. Bolger D, Coull JT, Schon D. Metrical rhythm implicitly orients attention in time as indexed by improved target detection and left inferior parietal activation. J Cogn Neurosci. 2014;26:593–605.
128. Rohenkohl G, Coull JT, Nobre AC. Behavioural dissociation between exogenous and endogenous temporal orienting of attention. PLoS One. 2011;6: e14620.
129. Bengtsson SL, Ehrsson HH, Forssberg H, Ullen F. Effector-independent voluntary timing: behavioural and neuroimaging evidence. Eur J Neurosci. 2005;22 (12):3255–65.
130. Chen JL, Zatorre RJ, Penhune VB. Interactions between auditory and dorsal premotor cortex during synchronization to musical rhythms. Neuroimage. 2006;32:1771–81.
131. Grahn JA, Brett M. Rhythm and beat perception in motor areas of the brain. J Cogn Neurosci. 2007;19:893–906.
132. Grahn JA, McAuley JD. Neural bases of individual difference in beat perception. Neuroimage. 2009;47:1894–903.
133. Marchant JL, Driver J. Visual and audiovisual effects of isochronous timing on visual perception and brain activity. Cereb Cortex. 2013;23:1290–8.
134. Goldberg G. Supplementary motor area structure and function: review and hypotheses. Behav Brain Sci. 1985;8:567–88.
135. Deiber MP, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RSJ. Cortical areas and the selection of movement: a study with positron emission tomography. Exp Brain Res. 1991;84:393–402.
136. Frith CD, Friston KJ, Liddle PF, Frackowiak RSJ. Willed action and the prefrontal cortex in man: a study with PET. Proc Biol Soc. 1991;244:241–6.
137. Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements: I. An investigation using measurement of regional cerebral blood flow with PET and movement related potentials in normal and Parkinson's disease subjects. Brain. 1995;118:913–33.
138. Jenkins IH, Jahanshahi M, Jueptner M, Passingham RE, Brooks DJ. Self initiated versus externally triggered movements: II. The effect of movement predictability on regional cerebral blood flow. Brain. 2000;123:1216–28.

139. Krieghoff V, Brass M, Prinz W, Waszak F. Dissociating what and when of intentional actions. Front Hum Neurosci. 2009;3:3.
140. Lau HC, Rogers RD, Haggard P, Passingham RE. Attention to intention. Science. 2004;303:1208–10.
141. Rushworth MF, Ellison A, Walsh V. Complementary localization and lateralization of orienting and motor attention. Nat Neurosci. 2001;4(6):656–61.
142. Hesse MD, Thiel CM, Stephan KE, Fink GR. The left parietal cortex and motor intention: an event-related functional magnetic resonance imaging study. Neuroscience. 2006;140(4):1209–21.
143. Wenke D, Waszak F, Haggard P. Action selection and action awareness. Psychol Res. 2009;73:602–12.
144. Brass M, Haggard P. The what, when, whether model of intentional action. Neuroscientist. 2008;14:319–25.
145. Fraisse P. The adaptation of the child to time. In: Friedman WJ, editor. The developmental psychology of time. New York: Academic; 1982. p. 113–40.
146. Levin I. The development of the concept of time in children: an integrative model. In: Macar F, Pouthas V, Friedman WJ, editors. Time, action and cognition: towards bridging the gap. Dordrecht: Kluwer Academic; 1992. p. 13–33.
147. Walsh V. A theory of magnitude: common cortical metrics of time, space and quantity. Trends Cogn Sci. 2003;7:483–8.
148. Craig AD. Emotional moments across time: a possible neural basis for time perception in the anterior insula. Philos Trans R Soc Lond B Biol Sci. 2009;364:1933–42.
149. Wittmann M. The inner experience of time. Philos Trans R Soc Lond B Biol Sci. 2009;364:1955–67.
150. Chambon M, Droit-Volet S, Niedenthal PM. The effect of embodying the elderly on time perception. J Exp Soc Psychol. 2008;44:672–8.
151. Nather FC, Bueno JL, Bigand E, Droit-Volet S. Time changes with the embodiment of another's body posture. PLoS One. 2011;6(5):e19818.
152. Fraisse P. Etude comparée de la perception et de l'estimation de la durée chez les enfants et chez les adultes. Enfance. 1948;1:199–211.
153. Droit-Volet S, Rattat A-C. Are time and action dissociated in young children's time estimation? Cogn Dev. 1999;14:573–95.
154. Droit-Volet S. Time estimation in young children: an initial force rule governing time production. J Exp Child Psychol. 1998;68:236–49.
155. Rizzolatti G, Riggio L, Dascola I, Umiltá C. Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. Neuropsychologia. 1987;25:31–40.
156. Gallese V, Fodiga L, Fogassi L, Rizzolatti G. Action recognition in the premotor cortex. Brain. 1996;119:593–609.
157. Hommel B, Müsseler J, Aschersleben G, Prinz W. The theory of event coding (TEC): a framework for perception and action planning. Behav Brain Sci. 2001;24:849–78.
158. Schubotz RI. Prediction of external events with our motor system: towards a new framework. Trends Cogn Sci. 2007;11:211–8.