

Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging

Penelope A Lewis* and R Christopher Miall

A recent review of neuroimaging data on time measurement argued that the brain activity seen in association with timing is not influenced by specific characteristics of the task performed. In contrast, we argue that careful analysis of this literature provides evidence for separate neural timing systems associated with opposing task characteristics. The 'automatic' system draws mainly upon motor circuits and the 'cognitively controlled' system depends upon prefrontal and parietal regions.

Addresses

University Laboratory of Physiology, Parks Road, Oxford, OX1 3PT, UK
*e-mail: penny.lewis@physiol.ox.ac.uk

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Abbreviations

fMRI functional magnetic resonance imaging
PMC lateral premotor area
SMA supplementary motor area

Introduction

Every action we take and every stimulus we perceive has a temporal dimension. The neural mechanisms used to measure time are currently a topic of intensive investigation – the number of neuroimaging studies seeking to define and describe them is growing rapidly, including more than 20 studies published since the year 2000. To date, no strong consensus has been reached about which brain regions are involved in time measurement; however, a recent review [1**] argues that the specific characteristics of the performed timing task do not affect the observed pattern of brain activity. Contrary to this, we suggest that much of the current ambiguity on the topic of neural time presentation may be due to the inappropriate grouping of studies that use very different time measurement tasks, thus drawing upon distinct neural timing systems. If this is the case, it should be possible to isolate the various neural systems involved in time measurement by a careful grouping of the literature, on the basis of the different task parameters used. In this review, we use precisely that approach, dividing studies of time representation according to three general task characteristics: the duration measured, the use of movement to define a

temporal estimate, and the continuity and predictability of the task.

The importance of stimulus characteristics

Our decision to characterise studies in relation to interval duration and to use of movement builds on previous suggestions that these factors discriminate between two or more different time measurement systems. Evidence suggesting the existence of different neural systems for timing at different duration ranges includes: distinct psychophysical characteristics at different durations [2]; differential responses to pharmacological agents [2–6]; differential impairment of performance by dual task [7]; and, most recently, different patterns of brain activation during the measurement of sub-second and supra-second intervals (PA Lewis, RC Miall, unpublished data).

The timing of brief intervals is frequently linked with motor control because voluntary movements are typically of sub-second durations, and can be reproduced with extreme temporal consistency. The circuitry used to ensure this consistency is likely to be located within the motor system and may be used to measure brief intervals even in the absence of movement [8,9]. This timing could be accomplished using cortically modulated central pattern generators in the spinal cord, temporal pattern generation originating from the motor cortex [10–12], or temporally predictable changes in the activity of build-up cells: preparatory cells that gradually increase in activity prior to movement [13,14]. The cerebellum may also be involved in motor timing [15,16] and shows particularly appropriate circuitry for the measurement of brief intervals [17–20]. Our division of studies on the basis of interval length and involvement of movement therefore stems from the suggestion that motor circuitry may be involved in time measurement under some circumstances, specifically during the measurement of sub-second durations or durations defined by movement.

Our division of studies according to the predictability and continuity of the time measurement task is rooted in two proposals. First, several authors have suggested that time measurements in the sub-second range are automatic, whereas measurements in the multi-second range require attention [3,6]. Second, continually measuring intervals in a repeating cycle, or in a non-repeating but pre-learned and therefore predictable pattern, requires less direct attention than the discrete measurement of non-continuous trials. This proposal arises from studies of automatic movement showing that attention is not required for the performance of over-learned motor tasks [21]. The

consistent timing achieved in these tasks [22] must also be performed in the absence of attention, and is very likely to draw upon an over-learned motor plan or programme [22,23]. Once selected and initiated, a motor programme can be executed without requiring direct attention. The measurement of a continuous series of predictable or over-learned movements should therefore require attention only during the selection and initiation phases.

Taken together with the suggestion that motor circuitry can be used to measure temporal intervals even in the absence of movement, these two proposals suggest the preferential use of motor circuitry for continuous, predictable (as opposed to discontinuous or unpredictable) time measurement tasks.

The hypothesis: automatic versus cognitively controlled timing

On the basis of our predictions regarding how the three task characteristics discussed above draw on different neural resources, we propose that two distinct systems exist for measuring time in the types of behavioural tasks examined here. We also submit that each of the task characteristics discussed above helps to partially determine which system is active in any given task. One hypothesised system, which we will designate the ‘automatic’ timing system, is primarily involved in the continuous measurement of predictable sub-second intervals defined by movement. Automatic timing is likely to recruit circuits within the motor system that can measure time without attentional modulation. Central pattern generators would provide an ideal mechanism for this system, as they are characterised by continuous rhythmic output. The other hypothesised system, which we will designate the ‘cognitively controlled’ timing system, is more involved in the measurement of supra-second intervals not defined by movement and occurring as discrete epochs. Cognitively controlled timing is likely to draw upon multi-purpose cognitive circuits within the prefrontal and parietal cortices [24]; in particular, activity is expected in areas associated with attention and working memory [3,6,25,26].

Neuroimaging studies

Figure 1 summarises the published neuroimaging literature on primate time measurement [PA Lewis, RC Miall, unpublished data, 1^{••},9,14,27–47^{••},48–52]. It lists the areas of brain activity reported in each study in response to time measurement tasks. Tasks are categorised according to whether or not a duration greater than one second was measured, whether measured intervals were defined by movement, and whether time measurement was continuous, with predictable intervals. The take home message is shown by the pattern of highlighted boxes in the figure: there is great variability between studies, but activity clusters in the upper left and bottom right corners of the table.

Figure 2 shows the percentages of studies reporting activation in a given brain area as a proportion of all studies that imaged that area and used a particular combination of timing task characteristics. An important observation to make from Figure 2 is that the activity patterns observed when studies are divided according to combinations of task characteristics (Rows [b]–[i]) produce a more coherent picture, with a higher proportion of studies in a specific category activating the same areas, than the pattern observed when studies are combined across all categories (Row [a]). If diverse tasks all drew upon the same neural timing mechanism, we might expect a stronger consensus in Row (a). Because different networks appear to be activated by tasks with different combinations of characteristics (Rows [b]–[e] versus Rows [f]–[i]), the observed pattern strongly supports the possibility of anatomically distinct neural mechanisms in time measurement.

Looking specifically at the categories emphasising automatic-related task characteristics (Rows [f]–[g]) we see very frequent activity in the motor system — the bilateral supplementary motor area (SMA) and the left sensorimotor cortex are most commonly activated; the right cerebellum and lateral premotor area (PMC) are only slightly less frequently activated; the left thalamus and the basal ganglia are also activated. Activity in the right superior temporal gyrus is also common, whereas the prefrontal cortex and the majority of parietal cortices activate only rarely.

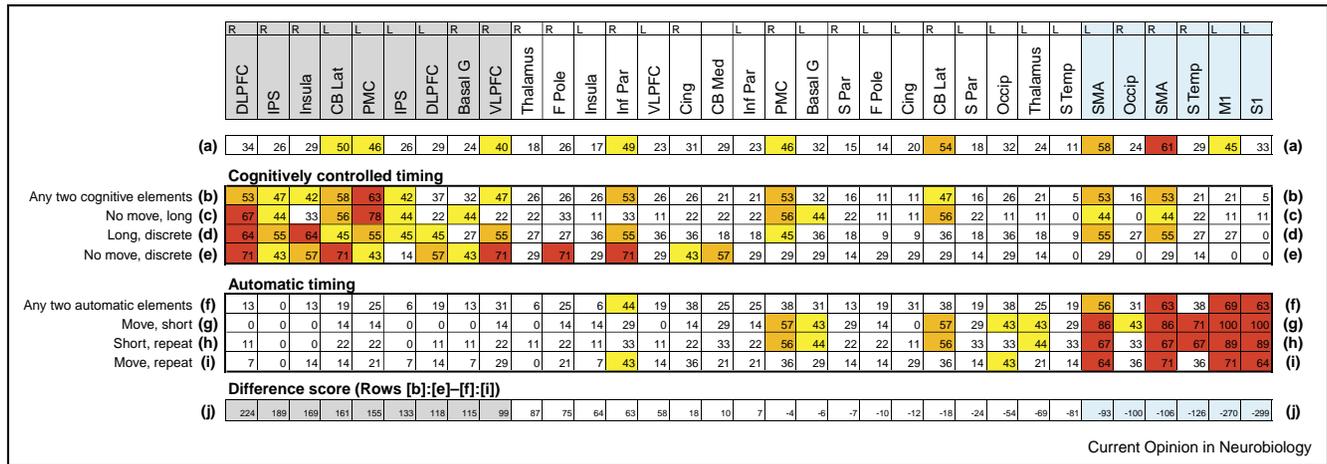
Turning to the categories emphasising cognitive-control-related task characteristics (Rows [b]–[e]), we see that although some regions frequently observed in association with automatic timing (right PMC and bilateral SMA) also activate in these conditions, considerable activity occurs in the left cerebellum and in the prefrontal and parietal cortices, with a bias to the right cortical hemisphere. This pattern suggests that, although the use of the cognitively controlled system does not preclude involvement of some parts of the automatic system, additional areas are recruited for tasks with these characteristics.

Before reading too much into the observed patterns, we should consider whether all of the activity discussed is truly associated with timing mechanisms or whether some of it might be due to confounding factors.

Challenges to the hypothesis — confounds

Because our analysis uses the most inclusive contrast from each dataset examined, much of the activity we describe may be due to task-related but non-temporal processes. Auditory, visual, and primary sensorimotor cortical activity found in association with automatic timing, for instance, might simply be due to sensory stimuli and motor responses. Some regions of the motor system, however, are active even in studies where very little

Figure 2



A summary of the activation patterns seen in Figure 1. The data from Figure 1 have been categorised by task characteristics. The percentages of studies reporting activity in specific regions in response to timing, calculated using only studies with the appropriate combinations of task characteristics, are indicated. More commonly activated regions are colour-coded from yellow (low activation) to red (high activation). For clarity, only areas that were active in at least 10% of all eligible studies are shown; many areas reported only in a minority of studies are therefore excluded from both figures. Row (a) shows the percentages of activity, calculated across all 35 datasets reviewed. Row (b) deals with studies in which any two of three task characteristics examined were associated with the cognitively controlled system. Rows (c)–(e) specify the three possible pairings of characteristics. Rows (f)–(i) follow a similar model, but for task characteristics associated with the automatic system. Columns are arranged from left to right by difference in the summed percentages in the cognitive tasks versus the automatic tasks (see Row [j]): those to the left are commonly activated in cognitive but not in automatic related tasks (grey cells in Row [j]), and vice versa for those on the right (blue cells in Row [j]); those in the centre are not strongly biased to either task type (white cells in Row [j]). Abbreviations as in Figure 1.

movement or movement preparation (and in some cases none at all) occurred during scanning. This is the case for activity in the right cerebellar hemisphere [29,36,50,51], the premotor cortex [28,33,40,51], the SMA [33,40,51], and the left basal ganglia [40,51,53], in timing tasks requiring only covert decisions, memory encoding, memory rehearsal of rhythms, or detection of oddballs. Because this activity is not due to movement (although motor imagery may occur), it may be genuinely linked to timing.

Turning to the involvement of sensory systems, several studies have described activity in the superior temporal lobe during time measurement tasks involving no auditory cues [27,30,32]. Others have shown auditory activity during task phases occurring after auditory cue cessation, such as continuation of tapping after auditory synchronisation [46], or memory encoding after presentation [50].

This activity may be associated with auditory imagery used for the task [46], and because it occurs most often in automatic timing tasks, specifically in those not involving supra-second intervals (Rows [g] and [h]), auditory imagery may be preferentially used under these circumstances. In contrast, the absence of occipital activity in tasks without visual stimuli makes it unlikely that this region is associated with temporal processing.

The areas that commonly activate during cognitively controlled tasks include regions known for their involvement in working memory (e.g. the dorsolateral prefrontal cortex), recall (e.g. the ventrolateral prefrontal cortex), and attention (e.g. the intraparietal sulcus and inferior parietal lobe), all of which processes are believed necessary for cognitively controlled time measurement [3,6,25,26]. Because tasks associated with the cognitively

(Figure 1 Legend Continued) encoding of rhythms versus the control condition, in which subjects ignored temporal information. [52] We present data from temporal measurement versus forward and backwards counting. [53] The authors report PET studies of music performance, perception, and comprehension in musicians and non-musicians. These studies suggest that the neural systems underlying music are distributed throughout the left and right cerebral and cerebellar hemispheres, with different aspects of music processed by distinct neural circuits. However, this study is excluded from Figure 1 because a comprehensive list of activated regions is not provided. Abbreviations: Basal G, basal ganglia; CB Lat, lateral cerebellum; CB Med, medial cerebellum; Cing, cingulate (anterior and posterior) DLPFC, dorsolateral prefrontal cortex (includes Brodmann’s areas 9 and 46); F Pole, frontal pole (includes Brodmann’s area 10); Inf Par, inferior parietal gyrus; IPS, intraparietal sulcus; M1, primary motor area; Occip, occipital lobe; S1, primary somatosensory area; S Par, superior parietal gyrus; S Temp, superior temporal gyrus; VLPFC, ventrolateral prefrontal cortex (includes Brodmann’s areas 45, 47, and 11). The SMA and the pre-SMA are combined as SMA; the frontal operculum is included in PMC [58], as are the frontal eye fields. The transverse temporal gyrus is included in superior temporal gyrus. Cerebellar nuclei are included in the appropriate cerebellar hemisphere. Where the laterality is not given, or is <5 mm, it is shown as bilateral. If localisations specified by authors are ambiguous (i.e. insula/operculum), they are indicated in both areas.

controlled system are quite different from those associated with the automatic system, it could be argued that the prefrontal and parietal activities observed during the former, when lenient comparisons are applied, are due to confounding task characteristics — for example, memory-related or decision-related processes — rather than to time measurement alone. That these same regions are active even when more complete cognitive subtractions are used [PA Lewis, RC Miall, unpublished data, 14,47**], however, suggests their genuine involvement in temporal processing.

Conclusions

A clear dissociation in brain activity related to timing is seen when neuroimaging studies of time measurement are divided according the interval to be measured, the use of movement to define time, and the continuity or predictability of the task. This dissociation cannot be explained by confounding task characteristics alone, and thus provides support for the existence of two distinct systems for time measurement. One, which we term the ‘automatic’ system, is closely linked to the motor and premotor circuits, with some involvement of the auditory cortex. This system does not draw much upon the prefrontal or parietal cortices. It may track time using temporal pattern generators, the temporally predictable increase or decrease of activity in build-up cells, or one of the various timing capabilities of the cerebellum. Auditory imagery may also be used. The other system, termed ‘cognitively controlled’, draws heavily upon the prefrontal and parietal cortices, which are likely to fulfil memory and attentional requirements, respectively. The prefrontal cortex is thought to be quite flexible in function, containing modules that can be recruited on demand for any one of several tasks [24]. It is possible that, although some timing functions can be performed within the less flexible neural circuits of the automatic system, direct attention to a timing task leads to the recruitment of flexible, multi-purpose modules to construct a more versatile, but temporary, clock system.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
1. Macar F, Lejeune H, Bonnet M, Ferrara A, Pouthas V, Vidal F, •• Maquet P: **Activation of the supplementary motor area and of attentional networks during temporal processing.** *Exp Brain Res* 2002, **142**:475-485.
 - This paper includes a review of recent timing studies, similar to the present one, but making the counter argument that the activation patterns seen do not support segregation of the neural systems by perceptual and motor tasks, nor by discrete and sequential timing tasks. The authors point to a core set of structures activated irrespective of particular procedural features.
 2. Gibbon J, Malapani C, Dale CL, Gallistel C: **Toward a neurobiology of temporal cognition: advances and challenges.** *Curr Opin Neurobiol* 1997, **7**:170-184.
 3. Mitriani L, Shekerdjiiski S, Gourevitch A, Yanev S: **Identification of short time intervals under LSD25 and mescaline.** *Act Nerv Super (Praha)* 1977, **19**:103-104.
 4. Rammsayer TH, Vogel WH: **Pharmacologic properties of the internal clock underlying time perception in humans.** *Neuropsychobiology* 1992, **26**:71-80.
 5. Rammsayer TH: **On dopaminergic modulation of temporal information processing.** *Biol Psychol* 1993, **36**:209-222.
 6. Rammsayer TH: **Neuropharmacological evidence for different timing mechanisms in humans.** *Q J Exp Psychol B* 1999, **52**:273-286.
 7. Rammsayer TH, Lima SD: **Duration discrimination of filled and empty auditory intervals: cognitive and perceptual factors.** *Percept Psychophys* 1991, **50**:565-574.
 8. Ivry RB: **The representation of temporal information in perception and motor control.** *Curr Opin Neurobiol* 1996, **6**:851-857.
 9. Schubotz RI, Friederici AD, Von Cramon DY: **Time perception and motor timing: a common cortical and subcortical basis revealed by fMRI.** *Neuroimage* 2000, **11**:1-12.
 10. Armstrong DM: **The supraspinal control of mammalian locomotion.** *J Physiol (Lond)* 1988, **405**:1-37.
 11. Arshavsky YI, Gelfand IM, Orlovsky GN, Pavlova GA: **Messages conveyed by spinocerebellar pathways during scratching in the cat. I. Activity of neurons of the lateral reticular nucleus.** *Brain Res* 1978, **151**:479-491.
 12. Arshavsky YI, Deliagina TG, Orlovsky GN: **Pattern generation.** *Curr Opin Neurobiol* 1997, **7**:781-789.
 13. Matsuzaka Y, Aizawa H, Tanji J: **A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task.** *J Neurophysiol* 1992, **68**:653-662.
 14. Lewis PA, Miall RC: **Brain activity during non-automatic motor production of discrete multi-second intervals.** *Neuroreport* 2002, **13**:1731-1735.
 15. Clarke S, Ivry R, Grinband J, Roberts S, Shimizu N: **Exploring the domain of the cerebellar timing system.** In *Time, Internal Clocks, and Movement*. Edited by Vroon GES, Vroon PA. New York: Elsevier Science Ltd; 1996:257-280.
 16. Ivry RB, Keele SW: **Timing functions of the cerebellum.** *J Cogn Neurosci* 1989, **1**:136-152.
 17. de Zeeuw CI, Simpson JI, Hoogenraad CC, Galjart N, Koekkoek SK, Ruijgrok TJ: **Microcircuitry and function of the inferior olive.** *Trends Neurosci* 1998, **21**:391-400.
 18. Medina JF, Garcia KS, Nores WL, Taylor NM, Mauk MD: **Timing mechanisms in the cerebellum: testing predictions of a large-scale computer simulation.** *J Neurosci* 2000, **20**:5516-5525.
 19. Guigon E, Grandguillaume P, Otto I, Boutkhil L, Burnod Y: **Neural network models of cortical functions based on the computational properties of the cerebral cortex.** *J Physiol (Paris)* 1994, **88**:291-308.
 20. Perrett SP, Ruiz BP, Mauk MD: **Cerebellar cortex lesions disrupt learning-dependent timing of conditioned eyelid responses.** *J Neurosci* 1993, **13**:1708-1718.
 21. Passingham R: **Attention to action.** *Phil Trans R Soc Lon B Biol Sci* 1996, **351**:1473-1480.
 22. Shapiro D, Zernicke RF, Gregory L, Dieterich M: **Evidence for generalized motor programs using gait pattern analysis.** *J Motor Behav* 1981, **13**:33-47.
 23. Carter MC, Shapiro DC: **Control of sequential movements: evidence for generalised motor programs.** *J Neurophysiol* 1984, **52**:787-796.
 24. Duncan J: **An adaptive coding model of neural function in prefrontal cortex.** *Nature Rev Neuroscience* 2001, **2**:820-829.

25. Wearden JH: **'Beyond the fields we know': exploring and developing scalar timing theory.** *Behav Processes* 1999, **45**:3-21.
26. Gibbon J: **Scalar expectancy theory and weber's law in animal timing.** *Psychol Rev* 1977, **84**:279-325.
27. Lutz K, Specht K, Shah NJ, Jancke L: **Tapping movements according to regular and irregular visual timing signals investigated with fMRI.** *Neuroreport* 2000, **11**:1301-1306.
28. Roland PE, Skinhoj E, Lassen NA: **Focal activations of human cerebral cortex during auditory discrimination.** *J Neurophysiol* 1981, **45**:1139-1151.
29. Belin P, McAdams S, Thivard L, Smith B, Savel S, Zilbovicius M, Samson S, Samson Y: **The neuroanatomical substrate of sound duration discrimination.** *Neuropsychol* 2002, **40**:1956-1964.
30. Brunia CH, de Jong BM, van den Berg-Lenssen MM, Paans AM: **Visual feedback about time estimation is related to a right hemisphere activation measured by PET.** *Exp Brain Res* 2000, **130**:328-337.
31. 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**:7426-7435.
32. Coull JT, Frith CD, Buchel C, Nobre AC: **Orienting attention in time: behavioural and neuroanatomical distinction between exogenous and endogenous shifts.** *Neuropsychol* 2000, **38**:808-819.
33. Gruber O, Kleinschmidt A, Binkofski F, Steinmetz H, Von Cramon DY: **Cerebral correlates of working memory for temporal information.** *Neuroreport* 2000, **11**:1689-1693.
34. Jancke L, Loose R, Lutz K, Specht K, Shah NJ: **Cortical activations during paced finger-tapping applying visual and auditory pacing stimuli.** *Brain Res Cogn Brain Res* 2000, **10**:51-66.
35. Jancke L, Peters M, Himmelbach M, Nosselt T, Shah J, Steinmetz H: **fMRI study of bimanual coordination.** *Neuropsychol* 2000, **38**:164-174.
36. 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**:2761-2765.
37. Jueptner M, Rijntjes M, Weiller C, Faiss JH, Timmann D, Mueller SP, Diener HC: **Localization of a cerebellar timing process using PET.** *Neurology* 1995, **45**:1540-1545.
38. Kawashima R, Inoue K, Sugiura M, Okada K, Ogawa A, Fukuda H: **A positron emission tomography study of self-paced finger movements at different frequencies.** *Neurosci* 1999, **92**:107-112.
39. Kawashima R, Okada J, Umetsu A, Sugiura M, Inoue K, Suzuki K, Tabuchi M, Tsukiura T, Narayan SL, Nagasaka T *et al.*: **Human cerebellum plays an important role in memory-timed finger movement: an fMRI study.** *J Neurophysiol* 2000, **83**:1079-1087.
40. Larsson J, Gulyas B, Roland PE: **Cortical representation of self-paced finger movement.** *Neuroreport* 1996, **7**:463-468.
41. Lejeune H, Maquet P, Bonnet M, Casini L, Ferrara A, Macar F, Pouthas V, Timsit-Berthier M, Vidal F: **The basic pattern of activation in motor and sensory temporal tasks: positron emission tomography data.** *Neurosci Lett* 1997, **235**:21-24.
42. Macar F, Vidal F: **Time processing reflected by EEG surface Laplacians.** *Exp Brain Res* 2002, **145**:403-406.
43. Maquet P, Lejeune H, Pouthas V, Bonnet M, Casini L, Macar F, Timsit-Berthier M, Vidal F, Ferrara A, Degueldre C *et al.*: **Brain activation induced by estimation of duration: a PET study.** *Neuroimage* 1996, **3**:119-126.
44. Onoe H, Komori M, Onoe K, Takechi H, Tsukada H, Watanabe Y: **Cortical networks recruited for time perception: a monkey positron emission tomography (PET) study.** *Neuroimage* 2001, **13**:37-45.
45. 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**:752-765.
46. Rao SM, Harrington DL, Haaland KY, Bobholz JA, Cox RW, Binder JR: **Distributed neural systems underlying the timing of movements.** *J Neurosci* 1997, **17**:5528-5535.
47. Rao SM, Mayer AR, Harrington DL: **The evolution of brain • activation during temporal processing.** *Nat Neurosci* 2001, **4**:317-323.
- In this study, the authors present fMRI results from a temporal discrimination task. Data were separated into individual 2.5 s epochs across the task interval. The authors suggest that early activity in the basal ganglia and cortex was related to encoding and maintaining time intervals, and to attention, whereas later activity in the DLPFC was related to temporal comparisons. The late cerebellar activity was not related to explicit timing functions. They argue that the basal ganglia were uniquely involved in temporal encoding.
48. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams S, Simmons A, Andrew C, Bullmore E: **Prefrontal involvement in 'temporal bridging' and timing movement.** *Neuropsychol* 1998, **36**:1283-1293.
49. Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Andrew C, Bullmore ET: **Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI.** *Neurosci Biobehav Rev* 2000, **24**:13-19.
50. Sakai K: **Neural representation of a rhythm depends on its interval ratio.** *J Neurosci* 1999, **19**:10074-10081.
51. Schubotz RI, Von Cramon DY: **Interval and ordinal properties of sequences are associated with distinct premotor areas.** *Cereb Cortex* 2001, **11**:210-222.
52. Tracy JI, Faro SH, Mohamed FB, Pinsk M, Pinus A: **Functional localization of a 'Time Keeper' function separate from attentional resources and task strategy.** *Neuroimage* 2000, **11**:228-242.
53. Parsons LM: **Exploring the functional neuroanatomy of music performance, perception, and comprehension.** *Ann NY Acad Sci* 2001, **930**:211-231.
54. Volz H, Nenadic I, Gaser C, Rammsayer T, Hager F, Sauer H: **Time • estimation in schizophrenia: an fMRI study at adjusted levels of difficulty.** *Neuroreport* 2001, **12**:313-316.
- The authors describe an fMRI study of schizophrenic patients and healthy controls in an auditory time estimation task, with pitch discrimination as a control. However, we exclude it from [Figure 1](#) because only the schizophrenic versus control group data are reported.
55. Ramnani N, Passingham RE: **Changes in the human brain during • rhythm learning.** *J Cogn Neurosci* 2001, **13**:952-966.
- The authors report a PET study of complex rhythm learning, paced by visual cues, compared to a random interval control condition. There were learning-related increases in the cerebellum, intraparietal and medial parietal cortex, pre-SMA, and lateral premotor cortex. Learning-related decreases were found in the prestriate and inferior temporal cortex. However, we exclude it from [Figure 1](#) because the reported activities are associated with learning rather than timing.
56. Penhune VB, Doyon J: **Dynamic cortical and subcortical • networks in learning and delayed recall of timed motor sequences.** *J Neurosci* 2002, **22**:1397-1406.
- The authors used PET to examine learning and retention of timed motor sequences across five days of practice. They suggest that during early learning cerebellar mechanisms are involved to produce accurate motor output; during late learning, the basal ganglia may be involved in automatization. At recall, there is distributed activity in M1, premotor, and parietal cortex. However, we exclude it from [Figure 1](#) as the results relate to learning and retention rather than to rhythm production.
57. Schubert T, Von Cramon DY, Niendorf T, Pollmann S, Buback P: **Cortical areas and the control of self-determined finger movements: an fMRI study.** *Neuroreport* 1998, **9**:3171-3176.
58. Rizzolatti G, Arbib MA: **Language within our grasp.** *Trends Neurosci* 1998, **21**:188-194.