PERGAMON

Neuropsychologia 41 (2003) 1583–1592

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

Brain activation patterns during measurement of sub- and supra-second intervals

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Received 31 October 2002; received in revised form 12 May 2003; accepted 12 May 2003

Abstract

The possibility that different neural systems are used to measure temporal durations at the sub-second and several second ranges has been supported by pharmacological manipulation, psychophysics, and neural network modelling. Here, we add to this literature by using fMRI to isolate differences between the brain networks which measure 0.6 and 3 s in a temporal discrimination task with visual discrimination for control. We observe activity in bilateral insula and dorsolateral prefrontal cortex, and in right hemispheric pre-supplementary motor area, frontal pole, and inferior parietal cortex during measurement of both intervals, suggesting that these regions constitute a system used in temporal discrimination at both ranges. The frontal operculum, left cerebellar hemisphere and middle and superior temporal gyri, all show significantly greater activity during measurement of the shorter interval, supporting the hypotheses that the motor system is preferentially involved in the measurement of sub-second intervals, and that auditory imagery is preferentially used during measurement of the same. Only a few voxels, falling in the left posterior cingulate and inferior parietal lobe, are more active in the 3 s condition. Overall, this study shows that although many brain regions are used for the measurement of both sub- and supra-second temporal durations, there are also differences in activation patterns, suggesting that distinct components are used for the two durations.

Keywords: Time measurement; Timing; Time perception; Neural clock; fMRI; Motor system

1. Introduction

There are a number of reasons to believe that different systems are used to measure time at the milliseconds and multisecond ranges. The measurement of tens or hundreds of milliseconds is important for coordination of muscles during movement (Hore, Wild, & Diener, 1991), while the measurement of multisecond durations is more commonly associated with learned behaviours such as social interaction or foraging (Brunner, Kacelnik, & Gibbon, 1992; Pyke, Pulliam, & Charnov, 1977). Time measurement has also been shown to have quite different properties at these two duration ranges. For instance, psychophysical characteristics differ (Gibbon, Malapani, Dale, & Gallistel, 1997), pharmacological agents (Mitriani, Shekerdijiiski, Gourevitch, & Yanev, 1977; Rammsayer, 1999) and the distraction of attention in dual task scenarios (Rammsayer & Lima, 1991) can have differential influence (but see Macar, Grondin, & Casini, 1994), while lesions to specific brain areas elicit differential impairments (Clarke, Ivry, Grinband, Roberts, & Shimizu, 1996). Based on these observations, several authors (Gibbon et al., 1997; Hazeltine, 1997; Ivry, 1996; Lewis & Miall, 2003; Rammsayer, 1999) have hypothesised that time intervals in the millisecond and multisecond ranges are measured by independent brain mechanisms. Further, we have recently suggested (Lewis & Miall, 2003) that parts of the motor system may be involved in the automatic measurement of briefer durations, while flexible cognitive modules of the prefrontal and parietal cortex are recruited for the measurement of longer periods.

Neuroimaging studies of sub- and supra-second interval measurements frequently show disparate results, although some areas appear to be consistently activated by timing at both durations (see Lewis & Miall, 2003; Macar et al., 2002 for reviews). However the task paradigms used at these two ranges are normally quite different, making it

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doi:10.1016/S0028-3932(03)00118-0

impossible to determine whether disparities in result are linked to the duration of the measured interval or to other factors. We are aware of only one neuroimaging study to date which has presented separate results from timing of sub- and supra-second intervals using the same task (Rubia et al., 1998). Subjects tapped in synchrony with a visual cue which appeared either every 0.6 or every 5 s. Production of the longer interval activated a different network of areas than production of the shorter interval, with only the right hemispheric frontal pole and anterior cingulate commonly active during both. Because the authors did not perform a direct comparison between the datasets, however, we cannot say if the observed differences in pattern are significant. Furthermore, because no control was provided for sensorimotor activities, it is impossible to be certain whether the differences were related to timing, or to other factors such as movement and sensory perception. In another study (Macar et al., 2002) subjects reproduced intervals in two different supra-second ranges (2.2–3.2 and 9–13 s), showing a similar pattern of activity for both intervals. In a third study (Rao et al., 1997) subjects produced two different sub-second intervals, 300 and 600 ms, using auditory-paced finger tapping, with almost identical results for the two.

The goal of our current investigation was to search for differences in brain activity associated with measurement of intervals longer than 2 s and briefer than 1 s, driven by the hypothesis that different neural systems would be used for each interval range. For this purpose, we chose to examine 0.6 and 3 s. We hypothesise that timing of the shorter interval would preferentially activate cortical and cerebellar motor systems whereas timing of the longer interval would draw more heavily upon prefrontal and parietal cortices. Our design ensured that the same task was used for both intervals and controlled for any non-timing related confounds associated with the difference in duration by using a cognitive subtraction.

2. Methods

2.1. Subjects

Eight right-handed subjects gave written informed consent before participating. Mean age was 26 and three were female. The experiment was approved by the Central Oxfordshire Research Ethics Committee.

2.2. Task

We used a temporal discrimination task, with visual discrimination for control and repeated the complete experimental paradigm separately for each of the two different standard durations (0.6 and 3 s) with order of presentation randomised across subjects. The behavioural conditions were: TIME, LENGTH, SIDE, and REST. These were presented in 30 s blocks with equal numbers of trials (12 for 0.6 and 7 for 3 s). The set of all four conditions was presented in random order five times during each session of fMRI data collection.

The visual stimulus, a white line (Fig. 1), was identical for TIME, LENGTH, and SIDE conditions, except that for SIDE it was shifted either to left or right of screen centre (see below). A cue word on the screen informed subjects which condition was being presented. In TIME and LENGTH, subjects were to attend either the duration of stimulus presentation or its physical size (length) and compare it to the remembered standard, indicating “less” or “more” by pressing a left or right button. All responses were made using the right hand. In SIDE, subjects were asked to simply press the button corresponding to the screen side on which the stimulus appeared, which varied randomly from trial to trial. In REST, subjects were asked to remain still and look at the fixation point; no other stimuli were presented.

In order for a temporal duration to be accurately measured, the entire interval must be attended. It is possible, however,

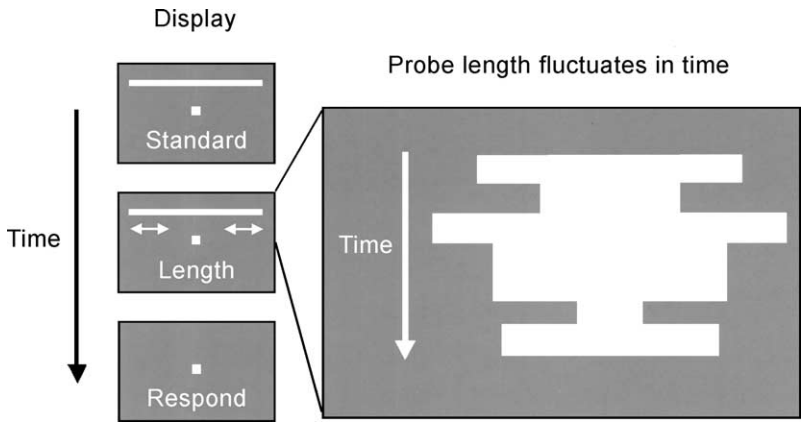

Fig. 1. Schematic diagram of stimuli. During training, each trial was initiated with presentation of the standard: a line of fixed length which appeared for a fixed duration (3 or 0.6 s). Next, a test line (probe) which varied randomly in length over time for some duration, either longer or shorter than the standard, was displayed. The word ‘Length’ or ‘Time’ reminded the subject which dimension should be compared. After the probe disappeared, subjects were cued to respond by pressing one of two buttons to indicate their decision. Later, training and testing in the magnet used the same paradigm, but without presentation of the standard.

to make a visual judgement about the length of a static line in under 300 ms (Essock, 1982). To force continued attention in the visual length judgement condition, we therefore introduced dynamic fluctuations of line length (Fig. 1). Subjects were required to attend the stimulus throughout, and make a decision based upon its mean length at the end of the presentation interval. Line length was increased or reduced by a random fraction of the target mean length ($\leq$20% of the mean, with uniform distribution), with each new length presented for a random interval chosen from a beta distribution (mean 322 ms, S.D. 207 ms), constrained to the overall duration required.

Subjects were trained on TIME and LENGTH tasks at least 1 day prior to scanning. In each training run, subjects attended either the physical length or temporal duration of the presented stimuli. At the start of training, presentation of a standard cue initiated each trial (Fig. 1). This cue was a line of fixed physical length and temporal duration (either 0.6 or 3 s). When the standard disappeared, a dynamic probe cue appeared, a white line of varying physical length within each presentation and temporal duration across presentations. When this disappeared, the word 'RESPOND' requested a response. Subjects then indicated whether the probe was shorter or longer than the remembered standard in the attended dimension (time or length).

Training sessions consisted of 12-reversal Kaernbach psychometric staircases (Kaernbach, 1991), at least four for TIME and four for LENGTH, which adjusted task difficulty by varying the disparity between standard and test stimuli until the threshold for 85% accuracy was determined. When this threshold stabilised, presentation of the standard ceased, and subjects performed further staircases in which they were forced to compare probe stimuli with a *memory* of the standard. During fMRI data collection, subjects started at the threshold established during training without presentation of the standard, and continued to perform the staircase routine throughout scanned blocks. This design aimed to maintain performance near 85% accuracy throughout. Subjects were instructed not to count mentally or subdivide the intervals using any other cognitive strategy.

2.3. Task presentation

The task was run on a PC laptop, visual stimuli were projected by an InFocus LP1000 LCD projector onto a back-projection viewed from inside the fMRI magnet bore using 90° prism glasses. A fixation point was always present at the centre of the display. Responses were recorded using a 2-button box that was sampled at 70 Hz via a 12 bit A/D converter.

2.4. fMRI data acquisition

Whole brain EPI data were acquired on a 3 T Siemens-Varian scanner, using a T2 weighted GE modulated BEST sequence (TE 30 ms, flip angle 90°), 256 mm × 256 mm FOV, 64 × 64 × 21 matrix size, and a TR of 3 s. Twenty-one contiguous 7 mm thick slices were acquired in each volume. T1 weighted structural images were also acquired, in contiguous 3.5 mm thick slices using an EPI TURBO-FLASH sequence (256 × 256 × 42 voxels).

2.5. fMRI data analysis

Data were analysed using the Oxford Functional MRI of the Brain (fMRIB)'s in-house analysis tool 'FEAT' (see http://www.fmrib.ox.ac.uk/fsl/feat4/index.html) on a MEDx platform. Pre-statistics processing included motion correction using MCFLIRT (Jenkinson & Smith, 2001) to realign images, spatial smoothing with a Gaussian kernal of FWHM = 5 mm, mean-based intensity normalisation of all volumes by the same factor; non-linear high-pass temporal filtering (Gaussian-weighted LSF straight line fitting, with sigma = 35 s), and non-linear band-pass temporal filtering to remove global changes in signal intensity above 2.8 Hz.

Statistics were computed using a general linear model convolved with a Gaussian kernel to simulate haemodynamics. Statistical images were produced for each subject by contrasting the parameters associated with each condition. Statistical maps were fit to the MNI canonical brain using fMRIB's linear image registration tool (FLIRT), and then combined across subjects using a simple fixed effects model. The resulting Z score images were thresholded at an uncorrected probability of $P < 0.001$. This threshold is commonly used in neuroimaging analysis (see e.g. Dreher & Grafman, 2002; Rowe & Passingham, 2001), and was chosen because it was deemed stringent enough to avoid false positives, whilst still allowing small activation volumes, such as those that might be differentially activated in a comparison of networks evoked by the two different stimulus intervals, to be measured.

For the [TIME–LENGTH] analysis of the 0.6 and 3 s interval experiments, activation maps were masked by multiplying each by a binary mask of significant [TIME–REST] activity to ensure that activation changes which correlated negatively with the control stimuli did not lead to false positives. A one-tailed t-test was performed to compare results from the [TIME–LENGTH] contrast from all eight subjects in the 0.6 and 3 s conditions. Overlapping activity was determined by averaging the masked, but unthresholded probability maps for 0.6 and 3 s. Probability maps were then rendered onto the MNI canonical brain and local maxima were localised using anatomical landmarks as shown in the Duvernoy atlas (Duvernoy, 1999). Dorsolateral and ventrolateral prefrontal cortices were determined as defined in (Rushworth & Owen, 1998); the frontal operculum was included in premotor cortex (Rizzolatti & Arbib, 1998).

3. Results

3.1. Behavioural performance

Because of the limited number of trials completed during fMRI data collection, the psychometric staircase was not perfectly stable. When tested at the 0.6 s interval, instead of the intended 85% correct, subjects achieved a mean accuracy of 83% correct (S.D. 4.5%) on the TIME task and 89% correct (S.D. 4.5%) on the LENGTH task, with the difference between these falling just short of significance (two-tailed paired *t*-test $P = 0.06$). When tested at the 3 s interval where fewer trials were completed in each scan session, subjects achieved a mean accuracy of 80% (S.D. 6.5%) for TIME and a significantly greater 92% (S.D. 4.5%) for LENGTH ($P = 0.008$).

3.2. Functional imaging

The [TIME–LENGTH] contrast from the 0.6 s interval experiment (Fig. 2 red areas, Table 1A) revealed peaks of activity bilaterally in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), insula, ventral premotor cortex (vPMC), pre-supplementary motor area (preSMA), and inferior parietal lobe. Lateralised peaks were observed in the right dorsal premotor cortex (dPMC) and intraparietal sulcus, and in the left cerebellar hemisphere and superior temporal gyrus (STG). For the 3 s interval experiment (Fig. 2 blue areas, Table 1B), the same contrast revealed peaks of activity bilaterally in the DLPFC, and insula, and in the right inferior parietal lobe and preSMA, and in the left hemispheric VLPFC. These two patterns of activity overlapped (Fig. 2 green areas, Table 1A), with peaks bilaterally in the insula and DLPFC, and in the right hemispheric preSMA and inferior parietal present at both 0.6 and 3 s intervals.

When direct comparisons (unpaired *t*-tests) were performed between [TIME–LENGTH] contrast data for 0.6 and 3 s experiments, peaks of activity significantly ($P < 0.001$, uncorrected) greater for the 0.6 s interval were observed bilaterally in the VLPFC and STG, in the right MTG, and in the left cerebellar hemisphere and insula (Fig. 3 and Table 3A). Only two areas were more active in the 3 s condition; these fell in the left posterior cingulate sulcus and inferior parietal lobe (Fig. 3 and Table 3B).

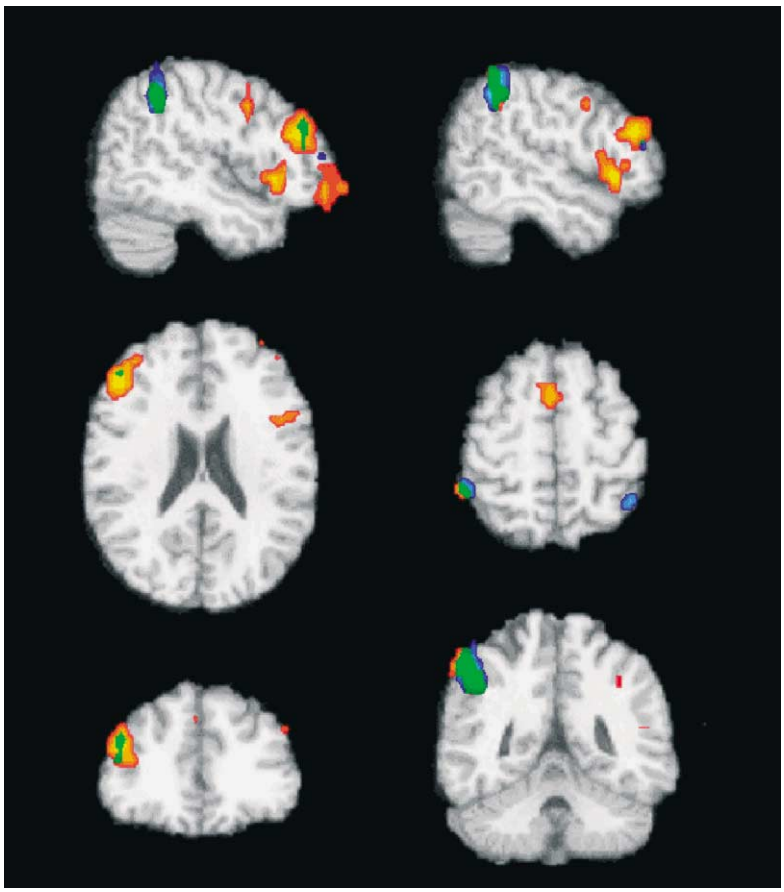

Fig. 2. Results of [TIME–LENGTH], rendered in red for 0.6 s and blue for 3 s, with areas of overlap showing in green. Slices were taken at (*x*/*y*/*z*) 48, 39, 24 mm (left column) and 54, −45, 60 mm (right column). Data are shown rendered onto the MNI canonical brain using radiological convention (right and left are inverted).

Table 1
Local maxima in activity for comparison of TIME–LENGTH at 0.6 s (A), and at 3 s (B)

x	*y*	*z*	*Z* value	Functional region	Anatomical locus
(A) TIME > LENGTH 0.6 s					
Prefrontal cortex					
50	24	0	6.0	VLPFC (R)	Pars triangularis
48	39	24	5.1	DLPFC (R)	MFG, just dorsal to IFS
62	21	0	5.1	VLPFC (R)	Ventral ramus of lateral fissure
42	53	−6	5.0	Frontal pole (R)	MFG, just anterior to IFS
−45	50	12	5.0	Frontal pole (L)	Anterior MFG, just dorsal to IFS
−36	59	24	3.2	Frontal pole (L)	MFG, inferior bank of SFS
−48	39	36	3.2	DLPFC (L)	MFG
Insula					
36	24	−6	4.7	Insula (R)	Anterior insula
−42	21	0	4.8	Insula (L)	Anterior insula
Premotor cortex					
0	15	54	5.3	preSMA (R/L)	Medial wall of SFG
3	27	48	5.4	preSMA (R)	Medial wall of SFG
48	9	42	3.8	vPMC (R)	Posterior to VPCS-level with IFS
48	9	54	3.5	dPMC (R)	Posterior bank of DVPCS
−48	15	24	4.2	Frontal operculum (L)	Frontal operculum
−56	15	42	3.3	vPMC (L)	Posterior bank of DVPCS
Parietal cortex					
53	−45	60	4.1	IPS (R)	Inferior bank IPS
45	−45	42	3.9	Inferior parietal (R)	Angular gyrus
−39	−42	48	3.6	Inferior parietal (L)	Angular gyrus
Cerebellum					
−30	−65	−42	3.3	Cerebellar hemisphere (L)	Cerebellar hemisphere, Crus I/II
Temporal cortex					
−53	−42	18	3.4	STG (L)	Posterior superior temporal gyrus
(B) TIME > LENGTH 3 s					
Prefrontal cortex					
36	53	−6	3.9	Frontal pole (R)	MFG, just lateral of SFS
45	53	12	3.1	Frontal pole (R)	MFG
42	27	48	3.7	DLPFC (R)	MFG
48	42	18	3.5	DLPFC (R)	MFG
48	39	30	3.4	DLPFC (R)	MFG
−42	48	6	3.8	DLPFC (L)	MFG, superior bank IFG
Insula					
33	24	−6	3.7	Insula (R)	Anterior insula
−45	15	0	3.4	Insula (L)	Anterior insula
−30	21	−6	3.3	Insula (L)	Anterior insula
Premotor cortex					
−53	15	0	3.4	Frontal operculum (L)	Ventral frontal operculum
3	27	42	3.5	preSMA (R)	MFG
Parietal cortex					
48	−45	48	5.0	Inferior parietal (R)	Angular gyrus
42	−50	66	3.6	Inferior parietal (R)	IPS, inferior bank

DLPFC: dorsolateral prefrontal cortex, VLPFC: ventrolateral prefrontal cortex, preSMA: pre-supplementary motor area, dPMC: dorsal premotor cortex, vPMC: ventral premotor cortex, IPS: intraparietal sulcus, STG: superior temporal gyrus, MTG: middle temporal gyrus, IFS: inferior prefrontal sulcus, IIPCS: inferior branch of the inferior precentral sulcus, MFG: middle frontal gyrus, VVPCS: ventral branch of ventral portion of precentral sulcus, DVPCS: dorsal branch of ventral portion of precentral sulcus.

4. Discussion

In this experiment, we examined the brain activity associated with measurement of 0.6 and 3 s intervals using a temporal discrimination task. We first analysed the results separately for each interval using the cognitive subtraction TIME–LENGTH to remove confounding activities due to stimulus presentation and subject responses, and next directly compared the results of this subtraction across the two intervals in order to determine the regions of activity which differed significantly between the timing systems used for sub- and supra-second durations.

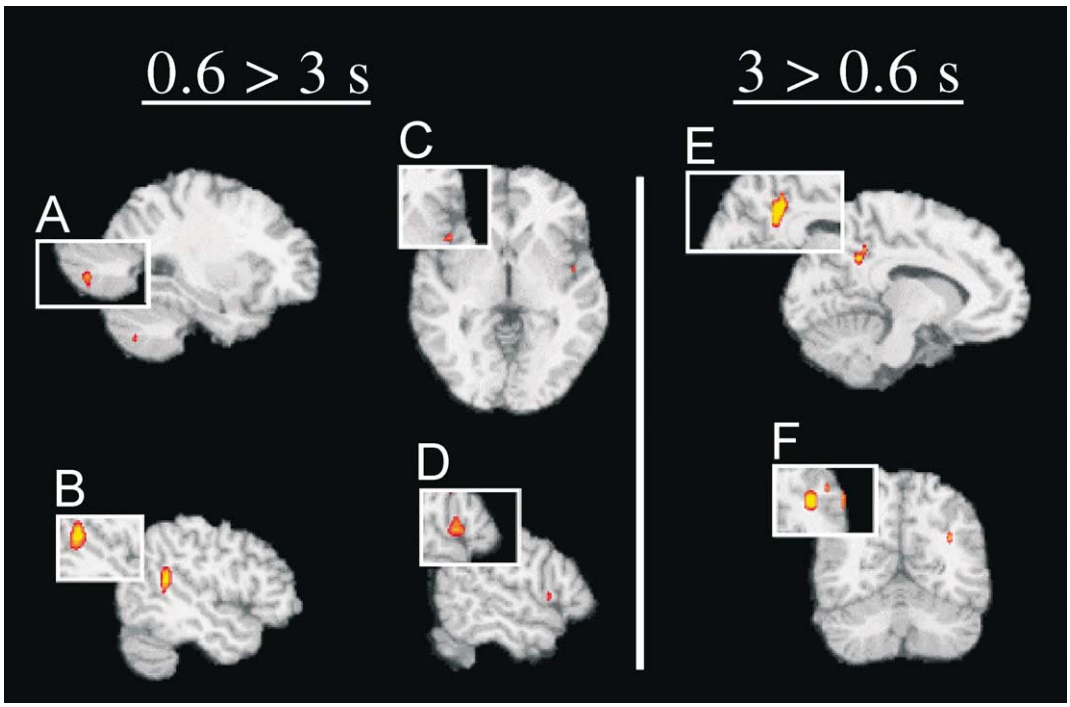

Fig. 3. Results from the *t*-test comparison of data from TIME–LENGTH at 0.6 and 3 s. Data was thresholded at $P < 0.001$ uncorrected, but insets show the active regions thresholded at $P < 0.01$ uncorrected. Data are rendered on the MNI canonical brain using radiological convention (right and left are inverted). The main areas of activity are shown. For 0.6 > 3 s: (A) cerebellar hemisphere, $x = -30$; (B) superior temporal gyrus, $x = -48$; (C) insula, $z = 0$; (D) frontal operculum, $x = 56$. For 3 > 0.6 s: (E) posterior cingulate sulcus, $x = 10$; (F) inferior parietal cortex, $y = -58$.

Our results showed that a network of areas comprising the bilateral insula and DLPFC, and the right hemispheric preSMA, frontal pole, and inferior parietal lobe (Table 2) were active during measurement of both intervals, suggesting that these areas participate in a general system for timing by temporal discrimination. A number of areas were activated more strongly during measurement of 0.6 s than during measurement of 3 s (Table 3A) showing that the networks used to measure these two durations are not identical. That some of these activities fell in the frontal operculum and cerebellum provides support for the hypothesis (Lewis & Miall, 2003) that parts of the motor system can be used for measurement of brief (sub-second) intervals. Interestingly, very few voxels were significantly more active during the measurement of 3 than 0.6 s. In addition, it should be noted that the differences between activity patterns elicited by measurement of the two intervals were subtle: although they were significant at $P < 0.001$ uncorrected, they were not significant at a Bonferroni-corrected threshold of $P < 0.01$.

4.1. Activity greater during the 0.6 s interval

Although the exact role of the cerebellum in time measurement is currently a topic of debate (Penhune & Doyon,

Table 2
Peaks of activation from areas in common at 0.6 and 3 s, comparing TIME–LENGTH

x	*y*	*z*	*Z* value	Functional region	Anatomical locus
Overlap: mean of data from TIME > LENGTH 0.6 and 3 s					
Parietal cortex					
48	−45	48	4.3	Inferior parietal (R)	Angular gyrus
Premotor cortex					
3	27	48	4.4	preSMA (R)	SFG
Prefrontal cortex					
48	42	24	4.1	DLPFC (R)	MFG, just above IFS
42	53	−6	4.1	Frontal pole (R)	MFG, just anterior to IFS
−42	50	6	4.1	DLPFC (L)	Dorsal bank IFS, MFG
Insula					
36	24	−6	4.1	Insula (R)	Anterior insula
−45	18	0	3.8	Insula (L)	Anterior insula

Table 3
Differences between activity observed for comparison of TIME–LENGTH at 0.6 and 3 s

x	*y*	*z*	*Z* value	Functional region	Anatomical locus
(A) TIME > LENGTH, 0.6 > 3 s					
Prefrontal cortex					
−42	15	24	3.1	VLPFC (L)	Anterior to junction VVPCS/IFS
Premotor cortex					
56	15	6	3.2	Frontal operculum (R)	Pars opercularis
Insular cortex					
−48	0	0	3.2	Insula (L)	Insula
Temporal cortex					
48	−33	−6	3.1	MTG (R)	MTG
45	−59	12	3.3	STS (R)	MTG/STG
−48	−42	18	5.0	STG (L)	STG
Cerebellum					
−30	−65	−42	3.3	Cerebellar hemisphere (L)	Cerebellar hemisphere, Crus I/II
(B) TIME > LENGTH, 3 > 0.6 s					
Parietal cortex					
−36	−56	30	3.3	Inferior parietal (L)	Just lateral of the IPS
Cingulate cortex					
−12	−48	36	3.3	Posterior cingulate sulcus (L)	Posterior cingulate sulcus

(A) Greater activation at 0.6 than 3 s; (B) greater activation at 3 than at 0.6 s.

2002; Ramnani & Passingham, 2001; Rao, Mayer, & Harrington, 2001; Tracy et al., 2000) many lines of enquiry have linked this structure to motor timing. Because the durations relevant for movement (for instance in muscle phasing and coordination) fall within the sub-second range (Hore et al., 1991), it has been suggested these short intervals may be measured within the motor system. Observation that cerebellar lesions can lead to deficits in movement-related timing (Ivry & Keele, 1989; Ivry, Keele, & Diener, 1988) and in non-motor timing at the milliseconds range (Casini & Ivry, 1999) have combined to implicate this structure as a candidate locus for such processes (Ivry, 1996, 1997), but see also (Gibbon et al., 1997). Supporting this idea, network models have shown that the neural architecture of the cerebellum could feasibly measure sub-second intervals in a number of different ways (de Zeeuw et al., 1998; Guigon et al., 1994; Perrett, Ruiz, & Mauk, 1993).

Regions of premotor and motor cortex may also be involved in some kinds of time measurement. The temporally predictable behaviour of build-up cells, which have been shown to increase or decrease activity during movement preparation (Matsuzaka, Aizawa, & Tanji, 1992), provides one possible mechanism for this. Our prior work has suggested that these cells may be involved in timing (Lewis & Miall, 2002). Motor or central pattern generators (CPGs), circuits producing rhythmic activity with periods ranging from under 60 ms to several seconds (Arshavsky, Deliagina, & Orlovsky, 1997), provide another possible neural mechanism for cortical measurement of brief durations. The frontal operculum is a particularly good candidate for cortical timing processes, as it is known to be involved in speech (Lawrence & Barclay, 1998), a strongly time sensitive motor activity, as well as preparation for limb movement (Rizzolatti & Arbib, 1998). As a part of the premotor cortex, the frontal operculum likely contains build-up cells (Lucchetti & Bon, 2001) and could either participate in cortical CPGs, or else modulate CPGs located elsewhere, for instance in the spinal chord (Armstrong, 1988; Arshavsky, Gelfand, Orlovsky, & Pavlova, 1978).

We recently reviewed 30 neuroimaging studies examining time measurement (Lewis & Miall, 2003) and found that 15 of the 17 papers (including this one), which both involved measurement of sub-second intervals and scanned the cerebellum, report activity in that structure (Belin et al., 2002; Coull & Nobre, 1998; Jancke, Shah, & Peters, 2000; Jueptner, Flerich, Weiller, Mueller, & Diener, 1996; Jueptner et al., 1995; Larasson, Gulayas, & Roland, 1996; Lutz, Specht, Shah, & Jancke, 2000; Maquet et al., 1996; Onoe et al., 2001; Parsons, 2001; Rao et al., 1997; Sakai et al., 1999; Schubotz, Friederici, & Von Cramon, 2000; Schubotz & Von Cramon, 2001), while only four (Kawashima et al., 2000; Lejeune et al., 1997; Lewis & Miall, 2002; Tracy et al., 2000) of the seven which scanned the cerebellum and examined only intervals longer than 1 s reported activity there. In two of these supra-second studies (Lewis & Miall, 2002; Rao et al., 2001) cerebellar activity was removed by a more complete subtraction analysis which controlled for movement and non-timing-related cognitive processes. By contrast, cerebellar activity persisted in our [TIME–LENGTH] comparison at 0.6 s measurement and in seven other studies examining the measurement of sub-second intervals with contrasts which could be expected to remove all movement

associated activation (Belin et al., 2002; Jueptner et al., 1995; Maquet et al., 1996; Onoe et al., 2001; Sakai et al., 1999; Schubotz et al., 2000; Schubotz & Von Cramon, 2001). Overall this literature supports a greater role for the cerebellum in measurement of sub- than supra-second intervals.

The frontal operculum has been operationally defined as a part of the motor system (Rizzolatti & Arbib, 1998) and was therefore included as part of the PMC in our review (Lewis & Miall, 2003). Although more data is needed to clarify the issue, this region appears to be more commonly activated by tasks involving the measurement of sub-second intervals than by those involving the measurement of supra-second intervals alone. Supporting this, nine (Coull, Frith, Buchel, & Nobre, 2000; Coull & Nobre, 1998; Gruber et al., 2000; Penhune, Zattore, & Evans, 1998; Rao et al., 1997; Roland, Skinhoj, & Lassen, 1981; Schubotz et al., 2000; Schubotz & Von Cramon, 2001) of the 21 reviewed papers involving measurement of sub-second intervals report peaks of activity in the frontal operculum, while only three of the nine examining supra-second intervals alone (Larasson et al., 1996; Lewis & Miall, 2002; Rao et al., 2001) report activity there. Because frontal opercular activity is seen in studies which either control for movement using subtractions (Gruber et al., 2000; Schubotz et al., 2000), or require no movement or preparation for movement during the test condition (Schubotz & Von Cramon, 2001), it seems unlikely that activity there is entirely due to motor confound.

Two regions of the auditory cortex, the right hemispheric middle temporal gyrus and left hemispheric superior temporal gyrus, were also more active during measurement of the 0.6 than the 3 s interval. This finding is especially interesting as all stimuli used in this experiment were visual. Two prior studies have described activity in the temporal cortex during time measurement tasks involving no auditory cues (Coull et al., 2000; Larasson et al., 1996). Others have shown auditory cortex activity during task phases which come after the cessation of auditory cues, such as continuation tapping after auditory synchronisation (Rao et al., 1997), or memory encoding after presentation (Sakai et al., 1999). It has therefore been suggested (Rao et al., 1997) that this activity may be associated with auditory imagery used for the task. Because all such studies involve the measurement of sub-second intervals (Coull et al., 2000; Larasson et al., 1996; Rao et al., 1997; Sakai et al., 1999) it is possible that this imagery is more commonly used for sub- than supra-second intervals.

The VLPFC and insula also showed greater activity in the 0.6 s condition than in the 3 s condition. The VLPFC is known to be involved in memory, and has been specifically implicated for involvement in retrieval functions (Petrides, 1994) which might be important for time measurement. It is not, clear, however why this region should be more active during the measurement of sub- than supra-second intervals. In fact the framework outlined in our review (Lewis & Miall, 2003) predicts that this region should be more involved in the latter. The role of the insula is equally unclear.

4.2. Activity greater during the 3 s interval

Two areas were more active during the 3 s than during the 0.6 s interval (Table 3B). One was the left hemispheric inferior parietal cortex, a region in which we have predicted (Lewis & Miall, 2003) greater activity during measurement of a longer intervals due to greater involvement of explicit attention. Under this interpretation, activity here suggests that LENGTH did not provide a perfect control for attention related activity. This result should be regarded with caution, however, as examination of the TIME–LENGTH contrast shows that most regions of inferior parietal were more strongly activated by measurement of 0.6 s than by 3 s. The small region in which activity associated with 3 s was significantly ($P < 0.001$) stronger than that associated with 0.6 s when the two were compared directly is therefore surrounded by areas in which the 0.6 s associated activity was stronger, but not significantly so (activity appears only at $P < 0.01$). It would thus seem unreasonable to draw any conclusions based upon the observation of stronger activity here during measurement of the longer interval.

The second area showing significantly stronger activity in association with the longer interval falls in the posterior cingulate, a region thought to be involved in spatial orientation and memory (Vogt, Finch, & Olson, 2003), and not commonly activated during time measurement (Lewis & Miall, 2003). It is not clear why this area is more active during measurement of the longer interval.

4.3. In summary

We present the first direct comparison of sub- and supra-second timing in the human brain using functional imaging. Our observation that a network of areas comprising the bilateral insula and DLPFC, and the right hemispheric preSMA and inferior parietal lobe are active during measurement of both 0.6 and 3 s using a discrimination task suggests that these regions participate in a general network for this type of timing task regardless of the exact duration measured. The observed greater parietal activity during the 3 s interval could be associated with heightened attentional requirements of this measurement, but might also result from comparison of two subtly different sub-threshold activity patterns. Our observation that the cerebellum and frontal operculum are more active during measurement 0.6 than 3 s suggests greater involvement of these motor regions in the measurement of brief intervals even during non-motor timing. The greater temporal lobe activity observed during measurement of the briefer interval suggests the preferential use of auditory imagery for measurement of these durations. Thus our data suggest a shared timing system for sub- and supra-second time measurements, with additional components specific to timing short and long intervals.

Acknowledgements

We thank Alex Kacelnik for his input in this work, and Richard Ivry for useful comments. RCM and PAL were supported by the Wellcome Trust and PAL by an Overseas Research Studentship. Additional support was provided by the MRC funded Oxford fMRIB Centre. We thank fMRIB staff for generous technical support and advice.

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