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A right hemispheric prefrontal system for cognitive time measurement

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Abstract

Despite a growing body of neuroimaging data, little consensus has been reached regarding the neural correlates of temporal processing in humans. This paper presents a reanalysis of two previously published neuroimaging experiments, which used two different cognitive timing tasks and examined both sub- and supra-second intervals. By processing these data in an identical manner, this reanalysis allows valid comparison and contrasting across studies. Conjunction of these studies using inclusive masking reveals shared activity in right hemispheric dorsolateral and ventrolateral prefrontal cortex and anterior insula, supporting a general-purpose system for cognitive time measurement in the right hemispheric prefrontal cortex. Consideration of the patterns of activity in each dataset with respect to the others, and taking task characteristics into account, provides insight into the possible role of dorsolateral prefrontal cortex in working memory and of posterior parietal cortex and anterior cingulate in attentional processing during cognitive time measurement tasks.

Keywords: Cognitively controlled time measurement; Time perception; fMRI; Attention; Working memory; Timing

Timing is crucial to both perception and action. In order to perform flexible, behaviourally relevant time measurement, several quite specific processes seem to be necessary (Staddon and Higa, 1999; Wearden, 1999; Gibbon, 1977). These include a time-varying process which changes at a regular rate, a working memory store which keeps track of this process within each interval measured, retrieval from a reference memory store containing information about prior experience, and a mechanism which can compare current working memory values to these standards. In addition, behavioural data (Casini and Ivry, 1999) strongly support the modulatory role of attention in time measurement. The presence of these five components in a neural clock system is widely accepted (Gibbon et al., 1984; Killeen and Fetterman, 1993; Staddon and Higa, 1999; Triesman, 1963), however, the anatomical loci of the various processes are much disputed.

In a recent meta-analysis (Lewis and Miall, 2003b) of 34 neuroimaging datasets examining this topic, we found that tasks involving repetitive, continuous timing such as paced finger tapping, frequently draw upon a different network of brain regions from those involving discrete trials separated by inter-trial intervals. These results imply that continuous timing can be performed more or less automatically by a subsection of the motor system, while discrete timing requires more cognitively controlled processing, especially when the intervals measured are one second or longer, and draws on the right prefrontal and parietal cortices. When studies specifically investigating discrete timing are examined as a group, a pattern characterised by right hemispheric activity in the prefrontal and parietal cortices emerges (Coull et al., 2000, 2004b; Pouthas et al., 2005a; Lewis and Miall, 2002; Brunia et al., 2000; Coull and Nobre, 1998; Jueptner et al., 1996; Maquet et al., 1996; Rao et al., 2001; Roland et al., 1981; Tracy et al., 2000). Recent work with transcranial magnetic stimulation (TMS) has further supported the involvement of right dorsolateral prefrontal cortex in this type of task (Jones et al., 2004; Koch et al., 2003). One ambitious neuroimaging study (Rao et al., 2001) even attempted to partition the observed network of activity into the subfunctions expected for time measurement, suggesting that the prefrontal cortex may be involved in working memory and comparison functions used during time measurement, while inferior parietal cortex is involved in modulatory attention, and the basal ganglia serve a ‘timekeeper’ function equivalent to the time-varying process.

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In two recent studies (Lewis and Miall, 2002, 2003b), we used functional magnetic resonance imaging (fMRI) to examine the neural correlates of cognitively controlled timing at sub- and supra-second intervals. The first experiment used a temporal production task, with force production as a control. The second experiment balanced attention and motor preparation more carefully using a temporal comparison task and was repeated for both sub- and supra-second durations. Our results supported the possibility of a right hemispheric prefrontal network for time measurement, but because these data were analyzed using quite different procedures we were not able to formally combine these datasets or validly compare one set of results to the other. In this paper, we reanalyse data from the second experiment using methods identical to those applied to the first thus allowing a formal conjunction by masking which reveals those areas of activity, which are common to all three datasets. Our reanalysis also makes it possible to discuss the relative activity patterns observed in each dataset with respect to the various timing tasks.

1. Materials and methods

1.1. Task experiment 1

We modified a temporal production task (Fig. 1A) to increase difficulty in an attempt to make subjects attend carefully, and thus to elicit maximal activity in the timing network. In the time condition, the word 'Time', cued the start of temporal production intervals which subjects terminated by pressing a force-sensitive button when they believed the target duration had elapsed. The target duration of the first trial in each block was 3 s, but the target durations of subsequent trials were either just noticeably longer (JND+) or just noticeably shorter (JND−) than the duration of the interval produced in the trial just completed, as specified by randomly selected 'Time+' or 'Time−' cues. The pressure condition was structured similarly: the word 'Press' cued subjects to press the button with attention to the force applied. Accuracy of performance was assessed in terms of modulations of Time or Force in the cued directions, see Lewis and Miall (2002, 2003b) for further details of the task.

1.2. Task experiment 2

This experiment aimed first to confirm that the network of areas isolated in experiment 1 was not specific to the temporal production task, second to find out which of these areas remained when motor and attentional demands were more carefully controlled, and third to examine the network involved in timing both short (0.6 s) and long (3 s) intervals. The task was a temporal discrimination with a visual discrimination control. Three conditions were used: time, length, and side. These were presented in 30 s blocks of trials, and cues were identical for time and length except that the word 'Time' or 'Length', as appropriate, was presented throughout each block. In each trial, subjects were shown a white line displayed against a blue background (Fig. 1B). This stayed on the screen for a set duration and subjects responded with left or right button presses to indicate judgments about whether it was shorter or longer than a standard in an attended dimension (time or length). The experiment was performed separately by each subject with standard time intervals of 0.6 and 3 s.

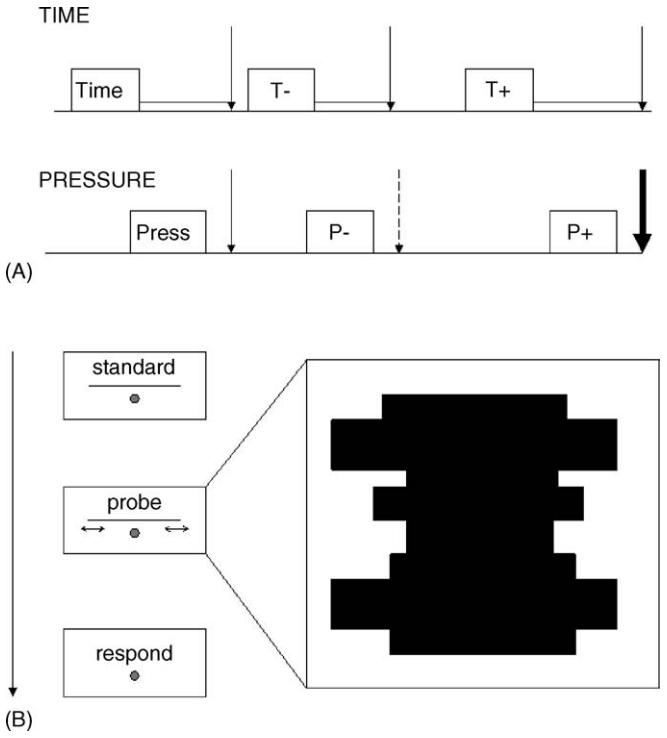

Fig. 1. (A) Schematic of behavioural tasks, experiment 1. The 'go' cues consisted of the word 'Time' or 'Press' and the instruction to produce a JND response was specified by a '+' or '−' sign as appropriate. All cues remained on the screen for 500 ms. In time subjects varied the interval between visual cues and responses according to T+/T− instructions; in the pressure block they varied the force of their button responses in the same way. The same number of responses, represented by vertical arrows, were made in each pressure block as in the corresponding time block, and the interval between responses in the pressure conditions was forced to match the intervals produced in the corresponding time block. (B) Schematic diagram of stimuli used for time and length comparison tasks in experiment 2. 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. A fixation point was present in the centre of the display at all times. Later training and testing in the magnet used the same paradigm, but without presentation of the standard.

To make a judgment about time, an entire temporal duration must be attended, however, it is possible to make a visual judgment about the length of a static line in under 300 ms (Essock, 1982). To force continued attention in the visual length judgment condition, we introduced dynamic fluctuations of line length (Fig. 3B). Subjects were required to attend the stimulus throughout, and make a decision based upon its mean length when the presentation terminated. In fluctuations, line length was increased or reduced by a random amount of the target mean length ($\leq$20% of the mean, with uniform distribution), with each new length presented for an interval chosen from a beta distribution (mean 322 ms; S.D. 207 ms). Fluctuations were identical in time and length conditions.

Before scanning, we found each subject's threshold for 85% accuracy using a 12-reversal Kaernbach psychometric staircase (Kaernbach, 1991). During fMRI scanning, subjects started at their previously determined threshold and continued to perform the staircase routine throughout the scanned blocks, with the aim of keeping performance near 85% accuracy throughout scanning. See Lewis and Miall (2002, 2003b) for further details on the procedure.

1.3. Subjects

Eight right-handed subjects participated in each experiment. For experiment 1, mean age was 29 and three subjects were female; for experiment 2, mean age was 26 and three subjects were female. One subject participated in both experiments. Both experiments were approved by the Central Oxfordshire Research Ethics Committee.

1.4. Task presentation

Behavioural tasks were presented and controlled by a PC laptop. During fMRI sessions, visual stimuli were projected onto a back-projection screen viewed from inside the magnet bore using 90° prism glasses. In experiment 1, responses were recorded using a force sensitive plastic button, in experiment 2, responses were recorded using a two button box.

1.5. 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 field of view, 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).

1.6. fMRI Data analysis

Data were analyzed using the Oxford Functional MRI of the Brain (fMRIB)'s in-house analysis tool 'FEAT', on a MEDx platform. Pre-statistics processing included 3D AIR motion correction to realign images, spatial smoothing with a Gaussian kernal of FWHM = 5 mm, 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 using cluster detection with an inclusion threshold of $z > 2.3$ and a probability threshold of $p < 0.001$, $p < 0.01$, or $p < 0.05$ as specified.

Probabilistic maps were masked by multiplying each map by a binary mask of significant [test–rest] activity to ensure that activation changes which correlated negatively with the control stimuli did not lead to false positives. Masked probability maps were then rendered onto the MNI canonical brain. Dorsolateral and ventrolateral prefrontal cortices were determined as defined in Rushworth and Owen (1998), frontal operculum was included in premotor cortex (Rizzolatti and Arbib, 1998).

1.7. Cluster area analysis

Voxels active at an uncorrected probability $p < 0.001$ ($z = 2.3$) were grouped into four categories: two regions of dorsolateral and one of ventrolateral prefrontal cortices, and anterior insula, as determined by the location of the local maximum in each cluster. The total volume of activity was then calculated by multiplying the number of voxels by the voxel volume in millimetres cubed.

1.8. Conjunction of fMRI datasets

To combine results from all three datasets (the [time − pressure] contrast from experiment 1, and [time − length] contrasts at 0.6 and 3 s from experiment 2), we performed a conjunction using inclusive masking (as in Prince et al. (2005)) with a cluster-based thresholding at $z > 2.3$ and $p < 0.001$. This analysis isolated areas, which were active at this threshold in all three datasets.

2. Results

2.1. Experiment 1

As reported previously (Lewis and Miall, 2002) behavioural data, averaged across subjects, show that JND deviations in the temporal interval were made in the cued direction on 94% of the trials in the time condition and 38% of trials in the pressure condition (significantly different, T-test, $p < 0.001$). Deviations in force produced were made in the cued direction on 90% of trials in the pressure condition and 72% of trials in the time condition (significantly different, $p < 0.001$). Functional data from the [time − pressure] contrast (Fig. 2A) showed activity in right hemispheric areas: posterior parietal cortex (superior, intraparietal sulcus, and inferior), dorsolateral prefrontal cortex, anterior cingulate, insula, and premotor cortex as well as in bilateral supplementary motor area (peaks of activity in pre, extending into proper) when thresholded at $p < 0.001$. Even when the inclusion threshold was raised to $p < 0.05$ no activity was observed in the basal ganglia or cerebellum.

Scrutiny of the task and the behavioural data suggests that some of the observed functional activity may be due to motor and attentional confounds rather than timing per se. Because the periods between the visual instruction and response are longer during time than pressure (Fig. 1A), it is likely that neurons involved in movement preparation (Wise et al., 1983) were active for longer periods in the former, leading to the observed activity in premotor and supplementary motor areas (Crammond and

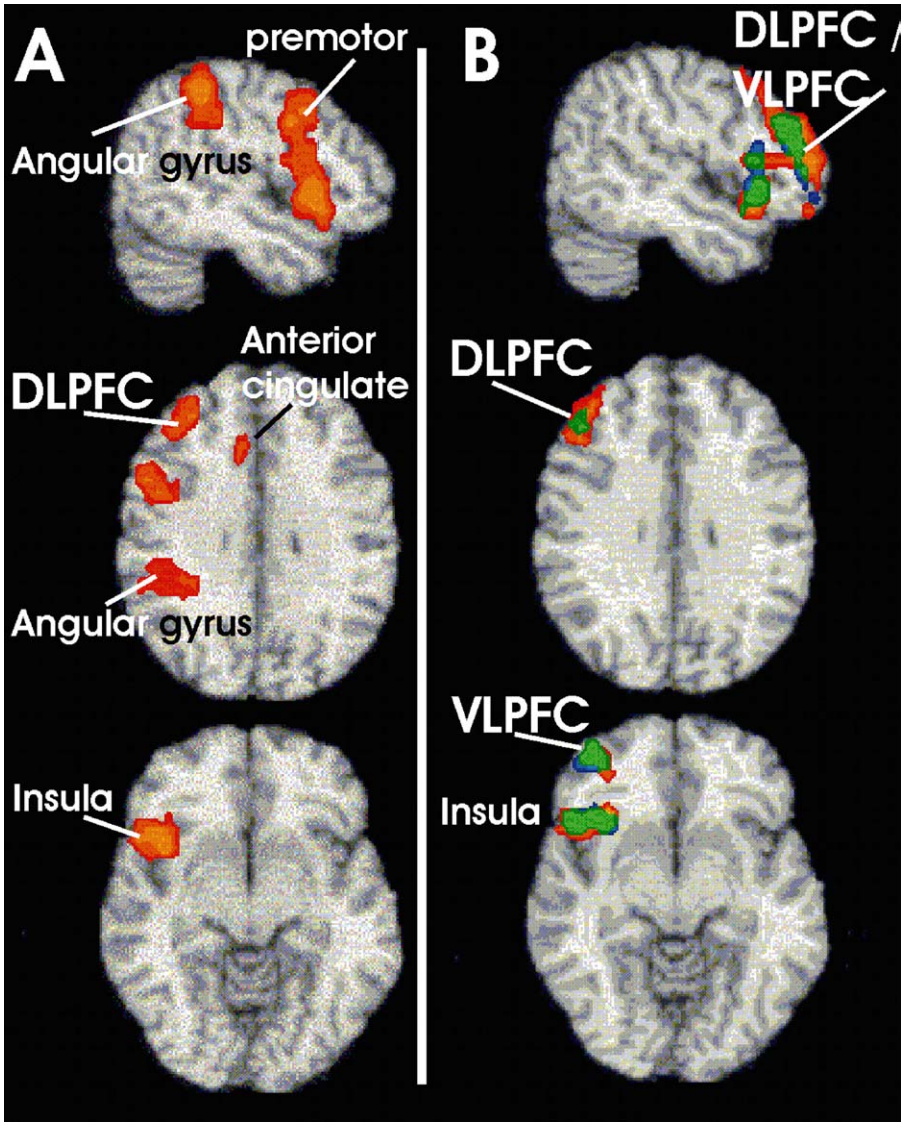

Fig. 2. Functional activity revealed by the [time − pressure] contrast in experiment 1 (A) and the [time − length] contrast in experiment 2 (B). Data were thresholded at $p < 0.001$ corrected for whole brain comparisons and rendered onto the MNI canonical brain in radiological convention (left and right are reversed). In B, data from 0.6 s are shown in red/orange, data from 3 s are shown in blue and areas of overlap appear in green. Coordinates (x, y, z): sagittal slices (top) and top axial slices (middle) 50 mm, 54 mm, 33 mm; lower axial slices (bottom) 30 mm, 14 mm, −7 mm.

Kalaska, 1996; Kalaska and Crammond, 1995). Furthermore, pressure required less attention than time since subjects had to attend to time throughout the produced intervals, but to pressure only for the brief duration of movement. Our data provide loose support for this difference in attentional demand since subjects modulated the force of finger presses in response to +/− cues even during the time condition when only temporal intervals should have been modulated (72% of deviations were made in the cued direction), but did not modulate the time of responses during the pressure condition (38% of deviations were made in the cued direction). This pattern suggests that the pressure task became nearly automatic after practice, and was thus performed even when not directly attended. The time task required more explicit attention and was only performed in the time condition.

Because the right hemispheric lateral frontal cortex, anterior cingulate, and posterior parietal cortex have all been shown to be involved in attention (Behrmann et al., 2004; Coull and Nobre, 1998; Mesulam, 1981; Mesulam, 1990), it is possible that the activity we observed in these areas is due to greater attentional requirements during the time condition, however, see Coull (2004), Coull and Nobre (1998), Coull et al. (2000) for data supporting a role for left parietal cortex in a distinct form of attention time, e.g. attention recruited in order to ensure that a motor response will occur at a specific moment in time.

2.2. Experiment 2

As reported previously (Lewis and Miall, 2003b), our data for 0.6 s showed a mean accuracy of 83% on the time task and 89% on the length task, the difference being just below significance ($p = 0.06$). At the 3 s interval, subjects achieved a mean accuracy

of 80% for time, and a significantly higher ($p = 0.008$) 92% for length.

Due to the altered analysis procedure, functional responses observed in the current report differed markedly from those previously reported for this data (Lewis and Miall, 2003b). Four areas of activity survived the [time – length] contrasts thresholded at $p < 0.001$ for both 0.6 and 3 s conditions. These were the right hemispheric orbitofrontal, dorsolateral, and ventrolateral prefrontal cortices, and the insula (Fig. 1B). Parietal cortex and anterior cingulate were not significantly activated by measurement of either interval at the $p < 0.001$ threshold. When the threshold was raised to $p < 0.01$, however, an area of weaker right parietal activity was detected in the 3 s data and an area of weaker anterior cingulate activity was detected in both the 3 s and 0.6 s data. When the threshold was raised still further, to $p < 0.05$, activity in the parietal area was also apparent in the 0.6 s condition. No basal ganglia activity was observed in either dataset using the [time – length] contrast, even at the lenient threshold of $p < 0.05$. No activity was observed in the cerebellum even at the lenient $p < 0.05$ threshold.

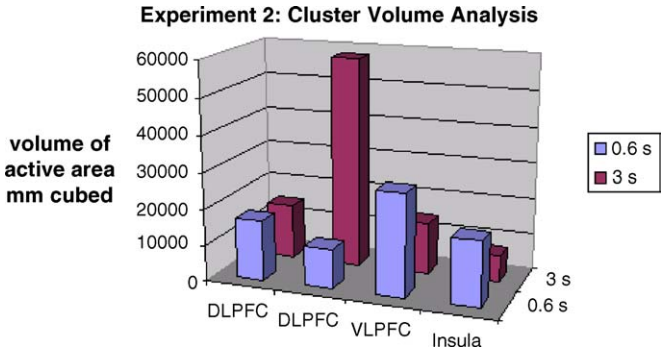

Fig. 3. The volumes of tissue activated in association with peaks in orbitofrontal, dorsolateral and ventrolateral prefrontal cortices and insula are shown for the two data-sets collected in experiment 2.

The cluster volume analysis (Fig. 3) showed that a larger volume of cortex was activated in the 3 s task than the 0.6 s task (94,986 mm cubed at 3 s and 73,872 mm cubed at 0.6 s). Much of this difference was in the dorsolateral prefrontal cortex where

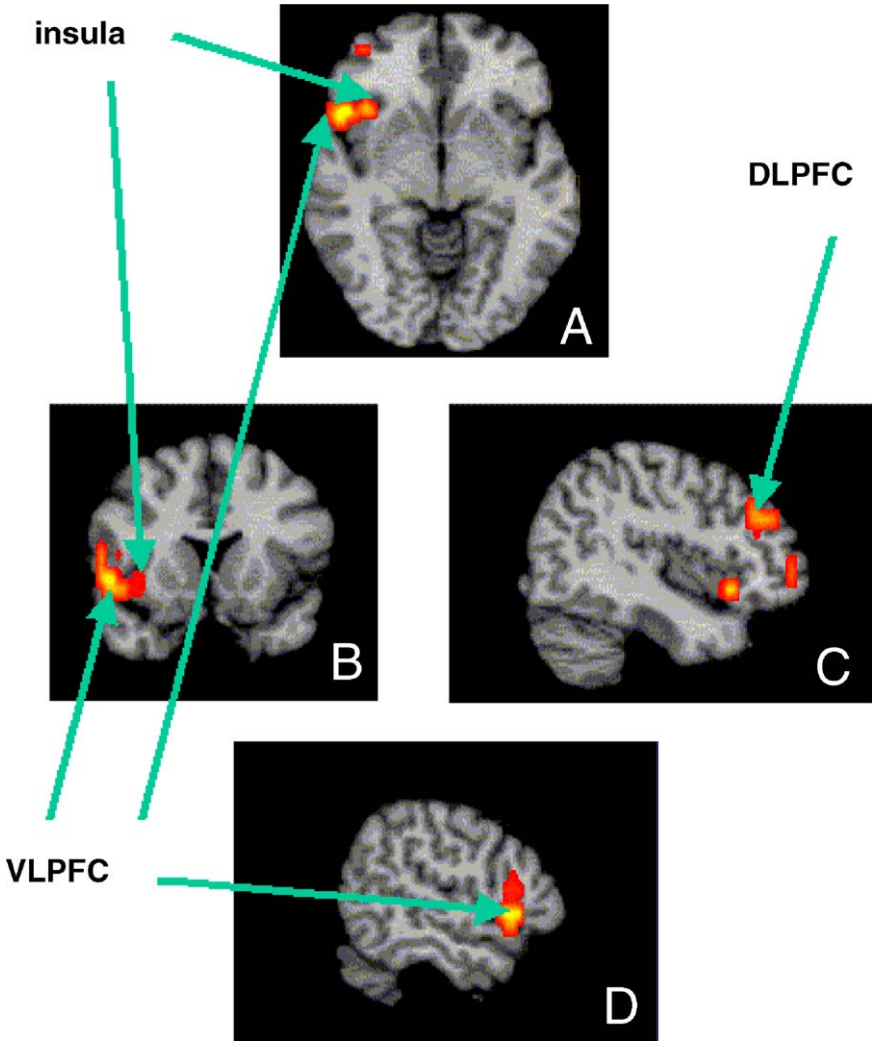

Fig. 4. Functional results from the conjunction via inclusive masking. Only the areas which were active at $p \leq 0.001$ in the [time – length] comparison for both 600 and 3000 ms in experiment 2 as well as the [time – pressure] comparison in experiment 1 are shown. Data are superimposed upon a high-resolution template brain in standard MNI space. Brain slices are shown in axial (A), coronal (B), and sagittal (C and D) orientations.

Table 1
The maximal mean z-scores from the conjunction across data from time > pressure in experiment 1 and time > length for both 0.6 and 3 s in experiment 2 shown in MNI coordinates

x	y	z	z-score	Functional area	Anatomical locus
Mean maxima from conjunction analysis					
42	54	0	3.1	Orbitofrontal	Middle frontal gyrus
44	39	30	3.6	DLPFC	Middle frontal gyrus
56	18	18	3.2	VLPFC	Inferior frontal gyrus
Insula					
44	21	−6	3.7	Insula	Insula

Key: DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex.

the volume activated was 47,142 mm cubed greater for the longer interval.

2.3. Conjunction analysis

The conjunction analysis, performed by inclusively masking all three datasets, (experiment 1 and both intervals from experiment 2) revealed voxels, which were active at $p < 0.001$ in all three cases. These fell in the right hemisphere and constituted two substantial clusters in dorsolateral prefrontal cortex, one in ventrolateral prefrontal cortices, and one in anterior insula (Fig. 4 and Table 1).

3. Discussion

Our conjunction of results from three separate datasets demonstrates the replicable involvement of right hemispheric dorsolateral and ventrolateral prefrontal cortices and anterior insula, both in two different time measurement tasks and at two different interval durations (sub- and supra-second). These findings argue for a general role of these three regions in cognitively controlled time measurement, supporting the conclusions of other authors who have examined similar tasks (Brunia et al., 2000; Coull et al., 2000; Coull and Nobre, 1998; Jueptner et al., 1996; Maquet et al., 1996; Rao et al., 2001; Roland et al., 1981; Tracy et al., 2000; Schubotz and von Cramon, 2001a,b; Schubotz et al., 2000).

In studying this type time measurement, we expected to find brain activity associated with working memory, retrieval from reference memory, attention, a time-varying process, and a temporal comparator. Analysis of the data from two different experiments using identical processing procedures allowed the comparison and contrasting of activities with respect to the differing demands of the three tasks upon attention and working memory. Such comparison facilitated interesting conjecture about the degree to which specific regions may be involved in attentional and memory related aspects of these tasks.

3.1. Differences between old and new analyses

It is important to note that the data discussed in this paper have previously been analyzed and published separately (Lewis and Miall, 2002, 2003b). In the case of experiment 1, we have not changed the analysis, thus the results presented here are identical to those already published (Lewis and Miall, 2002). In order to allow a valid comparison between data from the two studies, experiment 2 was re-analysed using methods identical to those of for experiment 1. Differences between old and new analyses include motion correction algorithms (MCFLIRT (Jenkinson et al., 2002) versus 3D AIR), implementation of the GLM analysis, and removal of autocorrelations via pre-whitening. The influence of such processing parameters upon results is a well-known weakness of research using fMRI and can lead to differences in the pattern of significant activity. The large number of analysis techniques available for fMRI processing often makes it difficult to select the most appropriate procedure, and in most cases a number of equally valid options are available. The analysis described in this paper corresponds to the original version of FEAT (see http://www.fmrib.ox.ac.uk/fsl/fsl/whatsnew.html).

The results we report for experiment 2 differ from those based upon our original analysis largely in that the original results showed significant dorsolateral prefrontal activation in both right and left hemispheres (Lewis and Miall, 2003b), while the new analysis reveals activity only in those regions of the original pattern which fell in the right hemisphere, and in right hemispheric ventrolateral prefrontal cortex. Although both old and new analyses are valid, and both sets of results should be considered carefully, the observation that right hemispheric dorsolateral prefrontal cortex and insula survive processing with two different sets of parameters argues for a more robust activation in these areas than in the left hemispheric regions or in the right ventrolateral prefrontal cortex, which appear in only one of the two analyses. Taken together with the observation that these regions were active in experiment 1 (Figs. 1 and 4 and Table 1), these data provide strong support for the involvement of right hemispheric dorsolateral prefrontal cortex and anterior insula cortex in cognitively controlled time perception.

3.2. Attention

Anterior cingulate and posterior parietal cortex, areas which have both been shown to be involved in attentional processing (Mesulam, 1981, 1990; Behrmann et al., 2004), were active at $p < 0.001$ during the task-difficulty confounded [time > pressure] contrast in experiment 1, but not during the more carefully balanced [time > length] contrasts of experiment 2. Assuming covariance between task difficulty and attention, this pattern is in keeping with a role for these areas in general attention during time measurement. For the right hemispheric posterior parietal cortex, this possibility is further supported by a correlation between the statistical strength of activity and the degree of performance imbalance between time and length conditions since this structure was active at $p < 0.01$ during the 3 s task of experiment 2 where the imbalance was 12% and only at $p < 0.05$ during the 0.6 s task where the imbalance was only 6%. This suggestion of a role for right parietal in attention to time is in keeping with previous neuroimaging (Rao et al., 2001) and lesion (Harrington et al., 1998b) studies, although left parietal has also been implicated in attention to time (see Coull (2004)).

3.3. Time-dependent process

Pharmacological work in both humans (Artieda et al., 1992; Harrington et al., 1998a; O'Boyle et al., 1996) and nonhumans (Meck, 1996) has suggested that the time-dependent process is dopamine-linked. This finding is supported by work in Parkinsonian (Artieda et al., 1992; Harrington et al., 1998a; Malapani et al., 1998; Elsinger et al., 2003), and Huntington's disease patients (Paulsen et al., 2004). The well established influence of dopamine upon subjective time measurement has led to the suggestion that the basal ganglia, a cluster of nuclei which are heavily innervated by dopamine, may house a time-dependent process, or at least be involved in timing. Cellular recordings showing that cells in this area can fire in a temporally specific manner (Matell et al., 2003) as well as a number of well controlled neuroimaging studies (Pouthas et al., 2005b; Nenadic et al., 2003; Coull, 2004; Coull et al., 2004a) reinforce this possibility. Support is not universal, however, as many other imaging studies have failed to find timing related activity in these structures (Macar et al., 2002; Tracy et al., 2000; Maquet et al., 1996; Sakai et al., 1999; Lewis and Miall, 2003a), or have found it only when control conditions are not subtracted from timing conditions (Rao et al., 2001; Coull and Nobre, 1998). This paper joins the ranks of these negative results as we did not observe striatal activity in any of the three datasets presented here, even at the lenient threshold of $p < 0.05$, so long as comprehensive subtractions were performed.

The basal ganglia are not the only candidate locus of a time-dependent process. A number of prefrontal regions are also modulated by dopamine (Porrino and Goldman-Rakic, 1982) and would thus be influenced by the pharmacological manipulations associated with altered timing. The dopaminergic perfusion of these regions is also altered in Parkinson's disease, so abnormal timing in Parkinsonian patients could also be explained by influences here. We have previously suggested (Lewis, 2002) a mechanism by which dorsolateral prefrontal cortex could serve as the time-dependent process. Under this model, dopaminergic influences on dorsolateral prefrontal cortex could explain some of the pharmacological and patient data on timing. Recent studies with Parkinsonian patients (Koch et al., 2005) and both transcranial magnetic (Koch et al., 2004b) and subthalamic stimulation (Koch et al., 2004a) have supported this idea by suggesting a connection between dopaminergic modulations of timing and the right dorsolateral prefrontal cortex.

3.4. Working memory and recall

The activity we observed in right hemispheric dorsolateral and ventrolateral prefrontal cortices may be associated with the memory demands of our timing tasks since these areas have been shown to be involved in memory functions (Smith and Jonides, 1999). A model of prefrontal cortex function (Petrides, 1991, 1994) supported by lesion work in monkeys (Petrides, 1991, 1994) as well as by neuroimaging, proposes different roles for dorso and ventrolateral prefrontal cortices in memory, suggesting that dorsolateral prefrontal cortex is important for functions such as self monitoring, primacy of events, or relative recency (Petrides, 1991, 1994) while ventrolateral prefrontal cortex is involved in memory storage (Mishkin and Manning, 1978) and active retrieval (Mishkin and Manning, 1978; Passingham, 1975). Under this model, the consistently observed activation of both dorsolateral and ventrolateral prefrontal cortices during discrete time measurement tasks could be interpreted respectively as working memory for the current interval and recall of stored values from prior experience of the interval.

3.5. Sub- and supra-second intervals

It has been proposed (Gibbon et al., 1997; Ivry, 1996) that different mechanisms may be used for measurement of temporal intervals at the sub- and supra-second range. We observed local peaks in the same areas for both 0.6 and 3 s (Fig. 2B), suggesting that the same timing system can be used to measure intervals at both ranges in this discrete time measurement task. The observation that a larger volume of dorsolateral prefrontal cortex was active during timing of 3 s than 0.6 s suggests that this area is more heavily involved in measurement of longer intervals. This is in keeping with the results of a study, which used fMRI to observe time measurement at 5 and 0.6 s and found activity in dorsolateral prefrontal cortex in the former but not the latter (Rubia et al., 1998). Our suggestion that this area is used in working memory during time measurement is also supported by this pattern since more information must be held online during the longer interval. It should be noted, however that this increase did not reach significance when activities associated with long and short intervals were compared directly using our original analysis (Lewis and Miall, 2003b). Furthermore, other authors examining brain activity associated with measurement of about 450 and 1300 ms using a similar comparison task did not find increased dorsolateral prefrontal cortex for the longer interval (Pouthas et al., 2005a).

3.6. Memory traces as the time-varying process

A family of clock models which show how working memory integration or decay can serve as a time-dependent process (Bugman, 1998; Miall, 1993; Staddon and Higa, 1999) provide a scheme by which activity in the dorsolateral prefrontal cortex may serve as the time-varying process in addition to its proposed working memory function. Under this scheme, any activity, which changes predictably over time can serve as the time varying process. This frequently takes the shape of integration or decay functions such as memory traces. Single unit recording studies have shown that some cells in the dorsolateral prefrontal cortex behave in a manner consistent with the integrator concept, systematically increasing or decreasing firing rates along a temporally predictable function during measured delay intervals (Niki and Watanabe, 1979; Matell et al., 2003). As discussed above, the suggestion that modulations of this type in dorsolateral prefrontal cortex are used as the time-varying process is in accord with the observed effects of dopamine upon time measurement (Artieda et al., 1992; Harrington et al., 1998a; Meck, 1996; O'Boyle et al., 1996) since dorsolateral prefrontal cortex receives modulatory dopaminergic inputs (Porrino and

Goldman-Rakic, 1982). The observation of increased activity in that region during the measurement of a longer interval is also compatible with this scheme and could be interpreted as evidence for recruitment of additional integration or decay functions.

4. Summary

Our data show consistent activity in right hemispheric dorsolateral and ventrolateral prefrontal cortices and anterior insula during two different cognitive time measurement tasks, and during measurement of both sub- and supra-second intervals. This provides strong evidence for the use of a flexible right hemispheric prefrontal timing system. The greater extent of dorsolateral prefrontal activity during measurement of the longer interval suggests a role for this structure in a memory related integrator/decay processes. Stronger responses in posterior parietal cortex when the control tasks place lower demands on attention raises the possibility that this region may be involved in attentional processing during timing.

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