

Brain activity during non-automatic motor production of discrete multi-second intervals

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It has been suggested that the different patterns of brain activity observed during paced finger tapping and non-movement related timing tasks, with medial premotor cortex (supplementary motor cortex, pre and proper) and ipsilateral cerebellum dominating the former, and dorsolateral prefrontal cortex (DLPFC) the latter, might be related to differing motor demands. Since paced finger tapping often consists of automatic movement (requiring little overt attention), while non-motor timing is attentionally modulated, the difference could

also be related to attentional processing. Here, we observed timing related activity in both medial premotor cortex and DLPFC, with non-timing related activity in other areas, including ipsilateral cerebellum, when subjects performed non-automatic motor timing. This result shows that, in time measurement, medial premotor activation is not specific to automatic movement, and DLPFC activity is not specific to non-motor tasks. *NeuroReport* 13:1731–1735 © 2002 Lippincott Williams & Wilkins.

Key words: Automatic movement; Cerebellum; Dorsolateral prefrontal cortex; Supplementary motor area; Temporal processing; Time measurement; Time perception

INTRODUCTION

The measurement of time is fundamental to most behaviours. Neural network modelling has shown that it can be performed using a variety of simple circuits [1,2], making the existence of multiple timers highly probable. It has also been suggested that different circuits may be used for motor and non-motor timing [3]. If motor timing is defined as the production of temporal intervals by movement, then this possibility is supported by the neuroimaging literature, which has shown that the medial premotor cortex, (the supplementary motor area, SMA and/or pre-supplementary motor area, preSMA) and ipsilateral cerebellum commonly activate in tasks such as paced finger tapping [4–8], while non-motor tasks such as temporal comparison [9–12] more frequently activate the dorsolateral prefrontal cortex (DLPFC).

Continuous paced finger tapping is often learned to such an extent that distraction does not reduce accuracy. At this point, it places little demand upon overt attention and hence can be thought of as automatic movement [13]. Conversely, timing tasks involving discrete, separated trials do require overt attention since performance is degraded by distraction [14]. Because the motor timing tasks leading to activity in medial premotor cortex and ipsilateral cerebellum mainly use continuous finger tapping, while the non-motor tasks leading to DLPFC activity use separate trials,

it is possible that the difference in pattern is not due to the motor/non-motor distinction, but instead to the difference between timing via automatic movement and other timing.

Existing studies [15,16] examining brain activity during timing by non-automatic movement have not convincingly settled this question. One [15] showed activation of the bilateral DLPFC associated with production of separate intervals, but the control task was a non-demanding button press. This, left uncertainty about whether this activity was associated with timing or attention. The SMA also activated in this study but the authors suggest this might be associated with the vibrotactile stimuli used rather than with timing. Another paper [16] found activity in DLPFC, SMA, and ipsilateral cerebellum when subjects were primed regarding the time they would wait before a cued movement, but none of these areas survived when a control with equivalent motor and attention requirements was subtracted.

Here, we aimed to find out whether the medial premotor cortex and ipsilateral cerebellum which are active in automatic motor timing also activate during non-automatic motor timing, and conversely to determine whether the non-motor associated DLPFC activates in this type of task. To control for activities related to movement processing, we included a task requiring greater motor precision than the timing condition.

MATERIALS AND METHODS

Task: We modified a temporal production task such that subjects would not repetitively produce the same interval, ensuring that automatic movement timing could not be used. Four conditions were used, each in eight randomly ordered 30 s blocks (5–6 trials/block): TIME, PRESSURE, MOTOR, and REST.

TIME: The word 'TIME' started temporal production intervals which subjects terminated by pressing a force-sensitive button to indicate their estimate. The target duration of trial 1 in each block was 3 s, but the target durations of subsequent trials were just noticeably longer/shorter than (JND +/-) the duration of the interval just completed, specified by time+ or time- cues (1 back design). **PRESSURE:** The word 'press' cued subjects to (promptly) press the button with attention to force. The target for trial 1 was a pre-trained median force, but target forces of subsequent trials were JND +/- the force produced in the preceding trial, as specified by press+ or Press- cues.

MOTOR: Subjects pressed the button promptly in response to MOTOR cues without attending to time or force.

In TIME and PRESSURE the + or - instructions were either selected randomly or, if the time/force diverged by > 20% from the target of trial 1, chosen to move estimates back towards that target. In TIME, inter-trial intervals were selected randomly to fall between 700 and 2200 ms. In PRESSURE and MOTOR, cues were shown one reaction time before the time of the button press produced for that trial number in the corresponding TIME block. In REST the word 'rest' appeared on the screen and subjects were asked to remain still and fixate.

Peak force/time of presses was recorded and modulation of time/force in the cued direction was used as a measure of accuracy. Subjects practised both TIME and PRESSURE with feedback until accurate in > 75% of trials before scanning. They were instructed not to count.

Subjects: Eight right-handed subjects (mean age 29 years, three female) gave informed consent. The experiment was approved by the Central Oxfordshire Research Ethics Committee.

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 force-sensitive plastic button calibrated outside the scanner and sampled at >1000 Hz with a 12 bit A/D converter.

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

fMRI data analysis: Data were analysed using the Oxford fMRI of the brain (fMRIB) 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 kernel of FWHM = 5 mm, and non-linear band-pass temporal filtering to remove global changes in signal intensity > 2.8 Hz.

Statistics were computed using a general linear model, convolved with a gaussian kernel to simulate haemodynamics, and including explanatory variables for TIME, PRESSURE, and MOTOR conditions with REST as unmodelled baseline. Statistical maps were produced for each subject by contrasting the parameters associated with each condition, then fit to the MNI canonical brain using the fMRIB 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 [17] with an inclusion threshold of $z > 2.3$ and a cluster based probability threshold of $p < 0.001$.

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. Cluster maxima were localised using anatomical landmarks on the MNI canonical brain. DLPFC and VLPFC were defined according to [18], SMA and preSMA according to [19].

RESULTS

Behavioural data, averaged across subjects, show that JND deviations in the temporal interval produced were made in the cued direction on 94% of trials in TIME and 38% of trials in PRESSURE (significantly different, paired *t*-test $p < 0.001$). Deviations in force produced were made in the cued direction on 90% of trials in PRESSURE and 72% of trials in TIME (significantly different, $p < 0.001$).

Functional data from the TIME–MOTOR contrast (Fig. 1, blue) showed peaks of activity in bilateral superior parietal lobe and intraparietal sulcus, inferior frontal sulcus (with associated activity extending into both DLPFC and VLPFC), premotor cortex (PMC), insula, and basal ganglia, in midline anterior cingulate (AC), and medial premotor cortex, (the peaks fell in preSMA and activity extended into SMA proper), in right hemispheric inferior parietal lobe, and VLPFC, and in left hemispheric DLPFC, primary motor cortex (M1) and cerebellar hemisphere, when thresholded at $p < 0.001$ (Table 1). The TIME–PRESSURE contrast (Fig. 1 red/green) showed peaks of activity in only a subset of these areas: right hemispheric PPC (IPS and inferior parietal), DLPFC, AC, insula, and PMC as well as midline medial premotor cortex, (the peak fell in preSMA and activity extended into SMA proper), when thresholded at $p < 0.001$ (Table 1). Even when the cluster level inclusion threshold was raised to $p < 0.05$ no activity was observed in the basal ganglia or cerebellum in this contrast.

DISCUSSION

Because both TIME and PRESSURE tasks called for modulation of time or force in a 1-back design (+/1 JND from previous response), they both involved processing

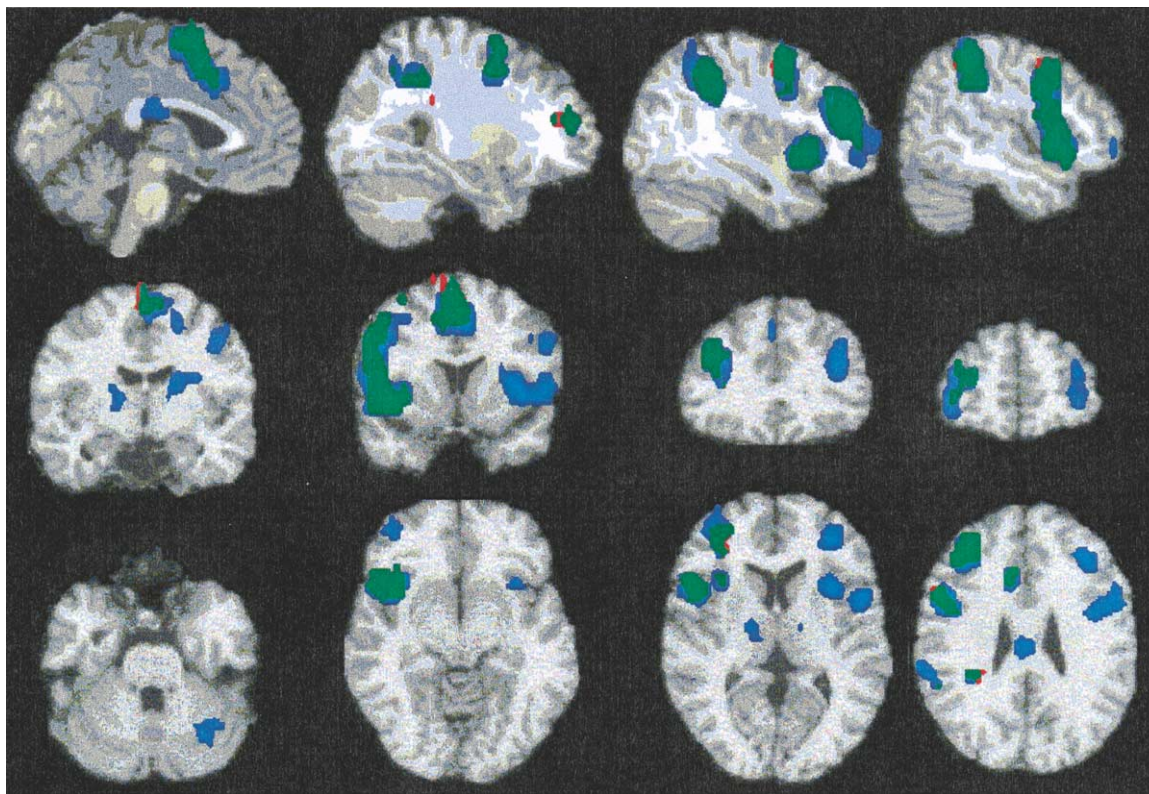


Fig. 1. Areas of activity surviving the TIME–MOTOR contrast are shown in blue, those surviving the TIME–PRESSURE contrast are shown in red, and areas of overlap are shown in green. Data have been thresholded at $p < 0.001$ and rendered onto the MNI canonical brain using radiological convention (right and left are inverted). From left to right, serial slices are taken at: sagittal $x = 0, 30, 40, 50$ mm, coronal, $y = -6, 14, 34, 54$ mm, and axial $z = -27, -7, 13, 33$ mm from the anterior commissure.

associated with working memory, comparison, and response to $+/-$ cues. The TIME–PRESSURE contrast should therefore control for activity associated with these processes; because MOTOR involved only a simple motor response and no memory or comparison processes, however, the TIME–MOTOR contrast should only control for activity associated with basic motor function. The activity observed in many sensorimotor areas in TIME–MOTOR but not TIME–PRESSURE illustrates the importance of this difference since these regions may be associated with any of the cognitive functions present in TIME and in PRESSURE but not MOTOR. The presence of ipsilateral cerebellum among these areas is particularly relevant since it implies that this region is not involved in temporal specific processing in our task. The remainder of our discussion will focus on results from the TIME–PRESSURE contrast as it provides a more stringent control for this type of confound.

Premotor areas: The medial premotor activation resulting from our TIME–PRESSURE contrast shows that this area can activate in non-automatic motor timing, thus rejecting the possibility that it is involved in timing during automatic movement alone. Two subsets of neurones called ‘set’ related cells and ‘buildup’ cells are found in the medial and lateral premotor cortices [20,21]. These are involved in movement preparation, firing between a cue to move and movement initiation [20,21]. Set related cells fire at a fairly

constant frequency during this interval, while buildup cells either increase or decrease firing [21]. In our experiment, the periods between the visual instruction and response were ~ 3 s longer during TIME than during PRESSURE, hence set related and buildup neurones were probably active for longer periods in the former. This inequality could have contributed to the extent of activity shown in medial premotor region as a result of the TIME–PRESSURE contrast.

The medial premotor activity observed in studies of paced finger tapping may also be due to set related and buildup activity, with each tap or pacing stimulus serving as a pre-cue for the next movement. This is especially probable in those studies using comparison with rest [4–8]. Since set and buildup activities are known to be involved in movement preparation [20,21], we might thus dismiss much of the reported medial premotor activity as movement associated confound, unrelated to time measurement. The possibility that this activity might be used to measure time during movement preparation, however, provides a compelling alternative interpretation. Neural network models of time measurement have described methods by which temporally predictable variation in any process, for instance the firing rate of buildup cells, can serve as the predictably time-varying component of a clock system [1,2,22]. Hence, it may be that while ramping activity in preparation for movement, these cells also provide an accurate temporal indicator.

Table 1. Coordinates, in mm from the anterior commissure, for local maximum Z-scores (value) representing peaks of activity from the TIME–MOTOR contrast and the TIME–PRESSURE contrasts.

| | x | y | z | Value | Functional area | Anatomical locus |
|-------------------------------|-----|-----|---|-------|----------------------|------------------------------------|
| TIME–MOTOR contrast | | | | | | |
| Prefrontal cortex | | | | | | |
| –36 | 36 | 24 | L | 4.8 | DLPFC/VLPFC | inferior frontal sulcus |
| –33 | 50 | 18 | L | 5.2 | DLPFC | superior frontal sulcus |
| 48 | 12 | 36 | R | 6.8 | DLPFC/VLPFC | inferior frontal sulcus |
| 50 | 18 | 6 | R | 7.6 | VLPFC | inferior frontal gyrus |
| Frontal cortex | | | | | | |
| –3 | 9 | 54 | L | 7.7 | preSMA | superior frontal gyrus |
| 3 | 21 | 48 | R | 7.0 | preSMA | superior frontal gyrus |
| –48 | –3 | 48 | L | 4.1 | PMC | middle frontal gyrus |
| 33 | 9 | 48 | R | 6.4 | PMC | middle frontal gyrus |
| Insular cortex | | | | | | |
| –36 | 18 | 6 | L | 5.5 | insula | insula |
| 42 | 15 | 0 | R | 7.3 | insula | insula |
| Primary motor cortex | | | | | | |
| –48 | –3 | 48 | L | 4.1 | MI | precentral gyrus |
| Limbic cortex | | | | | | |
| 9 | 24 | 30 | R | 4.8 | AC | anterior cingulate gyrus |
| Parietal cortex | | | | | | |
| –42 | –39 | 42 | L | 6.6 | intraparietal sulcus | intraparietal sulcus |
| 48 | –36 | 54 | R | 8.8 | intraparietal sulcus | intraparietal sulcus |
| –50 | –36 | 48 | L | 6.4 | superior parietal | superior parietal gyrus |
| 18 | –59 | 54 | R | 5.0 | superior parietal | superior parietal gyrus |
| 36 | –42 | 48 | R | 7.5 | postcentral gyrus | superior parietal gyrus |
| 36 | –48 | 66 | R | 3.7 | superior parietal | postcentral sulcus |
| 65 | –30 | 24 | R | 5.0 | inferior parietal | inferior parietal gyrus |
| Basal ganglia | | | | | | |
| –21 | –6 | 24 | L | 3.2 | caudate | – |
| 15 | –9 | 12 | R | 3.4 | putamen | – |
| Cerebellum | | | | | | |
| –42 | –56 | –30 | L | 4.5 | cerebellum | lobule VI/crus I |
| TIME–PRESSURE contrast | | | | | | |
| Prefrontal cortex | | | | | | |
| 36 | 45 | 18 | R | 5.0 | DLPFC | middle frontal gyrus |
| Frontal cortex | | | | | | |
| 3 | 9 | 66 | R | 6.3 | preSMA | superior frontal gyrus |
| 39 | 6 | 54 | R | 4.7 | PMC | middle frontal gyrus |
| Limbic cortex | | | | | | |
| 9 | 27 | 30 | R | 3.1 | AC | anterior cingulate gyrus |
| Insular cortex | | | | | | |
| 42 | 15 | 0 | R | 5.1 | insula | insula |
| Parietal cortex | | | | | | |
| 47 | –36 | 48 | R | 4.6 | intraparietal sulcus | deep intraparietal sulcus |
| 36 | –42 | 48 | R | 4.2 | inferior parietal | supramarginal gyrus |
| 36 | –36 | 36 | R | 3.6 | intraparietal sulcus | inferior bank intraparietal sulcus |
| 24 | –56 | 48 | R | 2.9 | intraparietal sulcus | superior bank intraparietal sulcus |

DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; PMC, premotor cortex; preSMA, pre-supplementary motor area; AC, anterior cingulate; MI, primary motor cortex; L, Left; R, Right.

The possibility of a central role for the medial premotor region in time perception was recently proposed by Macar and colleagues [15]. Their suggestion is in keeping with prior results showing that event related potentials in this region correlate with the subjective precept of how much time has passed [23]. They suggested that the region contains a temporal accumulator, which stores information likened to the ticks of a clock, as time passes. Because the accumulator concept is parallel to the idea of timing by temporally predictable functions [24], our suggestion regarding the use of buildup cells is in good keeping with these ideas [15,23].

Although PMC has not been strongly linked with motor specific timing, activity has been observed there in a wide range of time measurement studies [9,25,26]. Like medial premotor cortex, PMC contains set related and buildup cells [27], so activity there may also be due to firing of these cells.

Prefrontal cortex, parietal cortex, and anterior cingulate: Our task design did not guarantee that TIME and PRESSURE conditions would place equivalent demands upon attention. The right hemispheric lateral frontal cortex, AC, and PPC have all been shown to be involved in

attention (for review see [16]), thus activity observed in these regions as a result of the TIME–PRESSURE contrast may be due to general attention rather than time measurement alone. Accordingly, we cannot yet rule out the possibility that much of the prefrontal/parietal activation which has been observed in relation to time measurement [9–12] may be attentionally associated. Human perception of time has been shown to be modulated by attention [14], however, and timing associated activity in attentional areas should therefore be expected. If the DLPFC activity observed during non-motor timing [9–12] does serve an attentional function, it is not surprising that the region does not commonly activate during timing via automatic movement, since this task places minimal demands on the attention system.

CONCLUSION

Medial premotor cortex and ipsilateral cerebellum are frequently active in studies of timing by automatic movement, while DLPFC is frequently active in non-motor timing. We used a non-automatic movement timing task, the production of intervals near 3 s in duration, and observed timing related activity in both medial premotor cortex and DLPFC, with non-timing related activity in the ipsilateral cerebellum. These results demonstrate both that medial premotor activation during time measurement is not specific to timing via automatic movement, and that DLPFC activity during time measurement is not specific to non-motor tasks. We conjecture that the activity observed in medial and lateral premotor cortices may be associated with set related or buildup cells. Because the changing firing frequency of buildup cells can provide a temporally predictable function, we suggest that it may be used to mark time during movement preparation. Finally, we

conjecture that the observed DLPFC activity may be due to attentional modulation of the timing system.

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