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RESEARCH NOTE

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Time-modulated neuronal activity in the premotor cortex of macaque monkeys

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Abstract A voluntary motor act, executed in response to a stimulus, requires both spatial and temporal computation. Even though electrophysiological and positron emission tomography (PET) investigations on humans suggest that SMA, medial prefrontal cortex and primary motor cortex play a role in temporal mechanisms, we have few data about neuronal time computation in the premotor cortex. The involvement of monkey premotor area (PM) in motor learning and cognitive processes, and the presence of buildup neurons, whose activity is closely related to the motor action, prompted us to investigate the involvement of these set-related neurons in the time domain. To this end we manipulated the duration of a pre-cue in a visuomotor task while recording unit activity. We found that, when the duration of the pre-cue was predictable and long (5 s), delay of the onset of cell activity in consecutive trials gradually increased. On the other hand, when the duration was unpredictable or predictable and short (1 s), this phenomenon could not be detected. The inconsistent discharge correlations with expected reward and attentional processes, and the specific discharge relationship to the time instruction, suggest that these buildup neurons reflect a learning process in the time domain.

Keywords Frontal cortex · Time computation · Anticipatory activity · Premotor area · Monkey

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Introduction

In planning and executing a voluntary movement in response to a stimulus, the brain computes the spatio-temporal features of the motor act. The time computation is particularly relevant when a motor act has to be performed in relation to an instruction. Electrophysiological investigations in humans have revealed that a motor act, performed in response to a sensorial instruction, is preceded by slow EEG potentials, recorded in the frontal lobe, called "contingent negative variation" (CNV) (Walter et al. 1964). CNV is also related to the duration of motor sequence preparation (Vidal et al. 1995). Moreover, electrophysiological and positron emission tomography (PET) studies on humans suggest that SMA, medial prefrontal cortex and primary motor cortex play a role in temporal mechanisms (Sasaki and Gemba 1982; Vidal et al. 1995; Maquet et al. 1996). The role of the SMA and premotor cortex in timing ability is confirmed by lesion studies in humans (Halsband et al. 1993) and functional magnetic resonance imaging (fMRI) investigations (Rao et al. 1997).

Electrophysiological studies on the monkey frontal cortex have shown the presence of buildup neurons closely related to the motor action (Vaadia et al. 1986; Matsuzaka et al. 1992; Moody and Wise 2000) and timing behaviour when a CNV takes place simultaneously (Niki and Watanabe 1979; Sasaki and Gemba 1982). Moreover, it is commonly held that the monkey premotor area (PM) is involved in motor learning and cognitive processes (Rizzolatti et al. 1983; Chen and Wise 1995; Bon and Lucchetti 1997; Lucchetti et al. 1998). In addition, buildup activity has been found in the primate superior colliculus in preparation of saccadic eye movements and in target selection (Munoz and Wurtz 1995; Horwitz and Newsome 1999). In view of these previous findings, we manipulated the duration of a pre-cue in a fixation task to determine whether the patterns of buildup activity in the premotor neurons reflect changes in the temporal structure of the behavioural task.

Materials and methods

Behavioural methods

The experiments were carried out on three monkeys (*Macaca fascicularis*) in four hemispheres. The animals were trained for different visuomotor tasks. In this set of experiments we used the fixation task in different spatial positions: the targets (nine in all) were displayed in the form of a cross on a tangent screen placed at a distance of 114 cm from the animal's face. One target was located at the intersection of the cross; the other eight were distributed two to each arm, 10° and 20°, respectively, from the intersection in an up-down, left-right configuration. The animal had to press a bar, positioned before it on the same side as the hand contralateral to the hemisphere being recorded; a target (a tricolored light-emitting diode, LED) would then go on red (red period), after which the LED turned yellow (yellow period) and then green (green period). In the first 500 ms of red period the animal had to direct its gaze towards the target and maintain fixation until the green light went on. During the green period the animal had to release the bar to receive some drops of sweetened water as a reward. In the training session (70% of trials) the red period lasted 1–1.5 s, the yellow period 0.5 s and the green period 0.5 s. In the remaining trials we used longer red periods (from 1.0 to 7.0 s) and different random periods. In this way, the animal accustomed itself to different red durations. Notwithstanding this, during the experimental sessions, the maximum duration of 5 s was chosen because the animals displayed no signs of discomfort and performed the blocks of trials correctly during the training. The red stimulus, representing a pre-cue, instructed the monkey to maintain fixation and keep the bar pressed, the yellow stimulus, representing a cue, instructed it to maintain fixation and prepare to release the bar, while the green stimulus was the signal to release the bar. Before the recording sessions, we trained the animals to use only the arm contralateral to the recording hemisphere for a long period of time, thereby eliminating co-contraction of muscles in the ipsilateral arm. We also monitored the monkey's behaviour during the experimental sessions by means of an infrared TV system.

In addition, the animal performed the classic visual saccade task and peripheral attention task without the yellow period. These tasks were interposed between the blocks of 15 fixation trials in order to interrupt the learning of temporal predictability or unpredictability of red period duration in the fixation task.

During the experiments, the recorded neurons were tested prevalently with the central target in two basic red period time modes: (1) fixed time, i.e. predictable condition, and (2) random time, i.e. unpredictable condition. In the predictable condition the time was fixed at either 5 s or 1 s for a block of 15 trials. In the unpredictable condition the time ranged randomly from either 1 to 5 s or 2 to 2.5 s for a block of 15 trials. The yellow period was fixed at 0.5 s.

All tasks were executed in total darkness. An acoustic cue was switched on at the beginning of each session and switched off at the end, thus signalling to the monkey the beginning and the end of the working period.

Surgical methods

Using aseptic techniques and under general anaesthesia (10 mg/kg ketamine and 0.1 mg/kg xylazine, i.m.), a stainless steel cylinder was attached to the skull with four screws and cemented (Palacos R) in place to allow a painless fixation of the head. A search coil was implanted subconjunctivally (Judge et al. 1980). The EMGs of masseter, supraspinatus, sternohydeus, sternomastoideus, rombocervicalis, spinodeltoideus, trapezius, palmaris, ulnaris, radialis, triceps and biceps were recorded by needle electrodes. A stainless steel chamber for the electrophysiological investigation was then implanted vertically above each hemisphere. After each surgery session, treatment with antibiotics, cortisone and analgesics was administered for up to 1 week.

Physiological methods

Single neurons were isolated with epoxilite-coated tungsten electrodes. Eye movements were recorded using a magnetic field technique (Remmel 1984). The horizontal and vertical components of eye position, the unit activity, the bar and LED status and the EMG activities were sampled (1 kHz) and stored on computer (Macintosh) for offline analysis. We utilized SuperScope II (GWI) software for data acquisition and analysis.

Coagulation marks were made using direct current (10 µA for 15 s) at some recording sites for histological reconstruction. At the end of the experiments, under deep anaesthesia (pentobarbital 50 mg/kg i.v.), the animal was perfused with a 0.9% NaCl solution followed by 5% formalin. The brain was then sectioned in 60 µm slices, stained with thionine and the map of penetrations was reconstructed.

All phases of the experimental procedure followed the standards established by the European Community and Italian law (DL 116/92). The project was approved by the Italian National Superior Institute of Health and received the authorization of the Italian National Ministry of Health.

Results

We recorded 809 cells in three monkeys and in four hemispheres in the PM. Twenty-nine percent (232/809) of the neurons recorded were related to arm movements, tested both by task (bar pressing and releasing) and by the presentation of natural stimuli (reaching and grasping of pieces of fruit). Sixty-four percent (148/232) were only task related; of these, 33% (49/148) presented a buildup activity during the red and yellow periods, while the remaining cells were active during the other instructions. Moreover, 16 cells (16/49) were tested in different spatial positions but no significant differences were observed.

Histological reconstruction, performed at the end of the experiments, showed that the recorded neurons were not segregated in one field but distributed throughout the PM: rostromedially (pre-SMA or F6), laterally (F7, SEF) and caudally (F2) (Matelli et al. 1991) (Fig. 1). Outside the experimental sessions, when task-related cells were recorded, EMGs were taken of the following contralateral muscles: masseter, supraspinatus, sternohydeus, sterno-mastoideus, rombocervicalis, spinodeltoideus, trapezius, palmaris, ulnaris, radialis, triceps and biceps (Fig. 2). We compared the level of activity in the rectified EMGs during the 500 ms preceding the yellow period with that during the yellow period itself and found no statistical significance (Wilcoxon signed rank test: $P>0.5$).

At first, the cells were tested in the predictable condition of 5 s. In 49 neurons, the histograms of the whole block of 15 trials clearly showed a buildup activity, reaching a maximum during the yellow period. In order to obtain a clearer picture of the trend in firing activity, the series of 15 trials was subdivided into 5 successive sets of 3, and 5 histograms were then calculated.

In all 49 neurons, firing activity was present from the start in the first trial, whereafter delay of cell discharge gradually increased as the trials proceeded (Fig. 3a). In order to ascertain whether increasing delay was related to the predictability of red period duration or to habituation

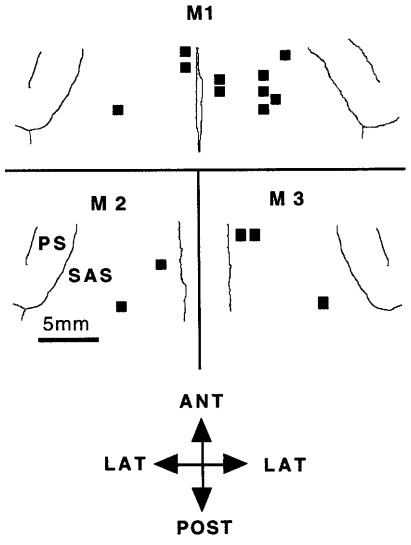

Fig. 1 Reconstructed maps of tracks in four hemispheres of three monkeys. *Each filled square* represents one penetration. In each penetration, from one to four buildup neurons were recorded (*PS* principal sulcus, *SAS* superior arcuate sulcus)

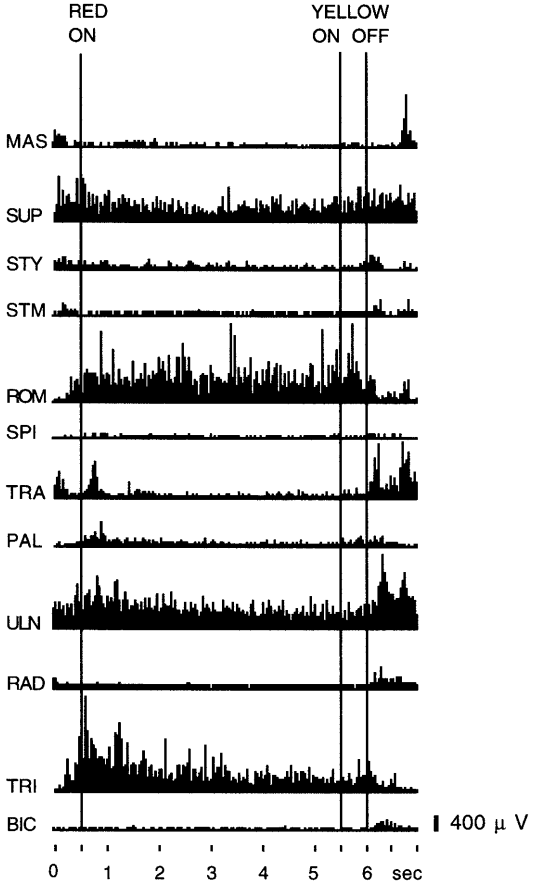

Fig. 2 Rectified EMG activities during task (predictable condition of 5 s) execution synchronized with yellow onset (*MAS* masseter, *SUP* supraspinatus, *STY* sternohydeus, *STM* sternomastoideus, *ROM* rombocervicalis, *SPI* spinodeltoideus, *TRA* trapezius, *PAL* palmaris, *ULN* ulnaris, *RAD* radialis, *TRI* triceps, *BIC* biceps)

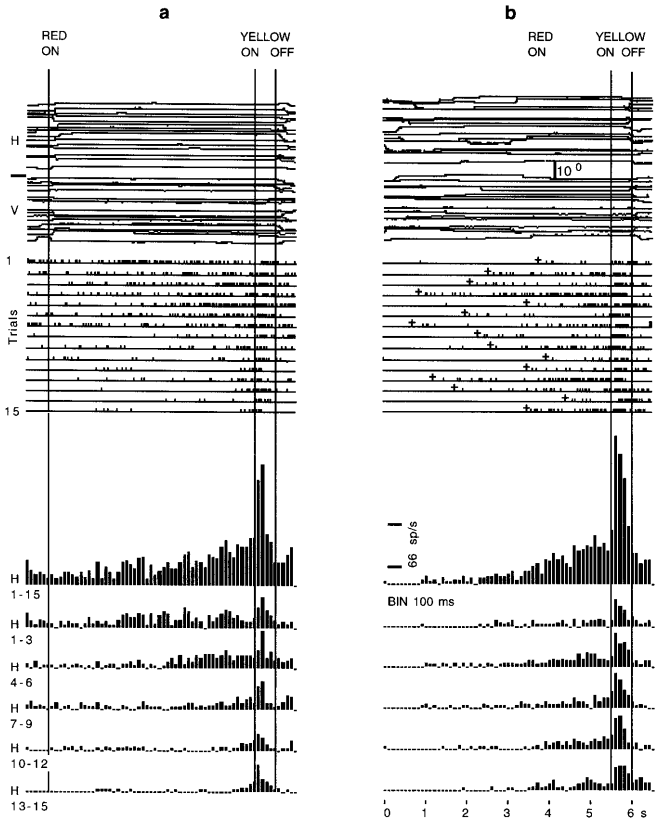

Fig. 3 a, b Discharge activity of a buildup neuron. **a** Neuronal behaviour in the predictable condition of 5 s. *Top* Rasters of 15 subsequent trials (from T1 to T15) aligned with the onset of the yellow light (*YELLOW ON*); *above the rasters*, the corresponding horizontal (*H*) and vertical (*V*) components of the eye position are reported. *Bottom* The first histogram represents the overall cell activity during 15 trials (H1–15); the following histograms represent the cell discharge in successive sets of three trials (from H1–3 to H13–15). **b** Neuronal behaviour in the unpredictable condition of 1–5 s. *The rasters* are aligned with the onset of the yellow light (*YELLOW ON*) and *the crosses* represent the onset of the red light

phenomenon, the cells were tested with red period durations ranging randomly from 1 to 5 s, since, in this condition, the duration was unpredictable. In this experimental condition, no increasing delay of the discharge was clearly observable (Fig. 3b). To ascertain whether a shorter and narrower red period duration range could affect the discharge pattern, we tested 22 (22/49) cells with a fixed red period duration of 1 s and with a random red period duration ranging from 2 to 2.5 s. The offline analysis revealed no increasing delay under either condition.

In order to identify the moment of statistically significant change in the discharge pattern in the individual histograms and in each experimental condition, the duration of the histograms was subdivided with a window of 0.5 s and the ANOVA test was then applied. Under the predictable condition of 5 s, in the overall histogram (15 trials), the 12th time interval (corresponding to the yellow period) always presented a statistically significant difference with at least the first eight time intervals (ANOVA, $F_{(12,53)}=9.774$, $P<0.01$). Then, using the yellow period as reference, the intervals that presented a statistically

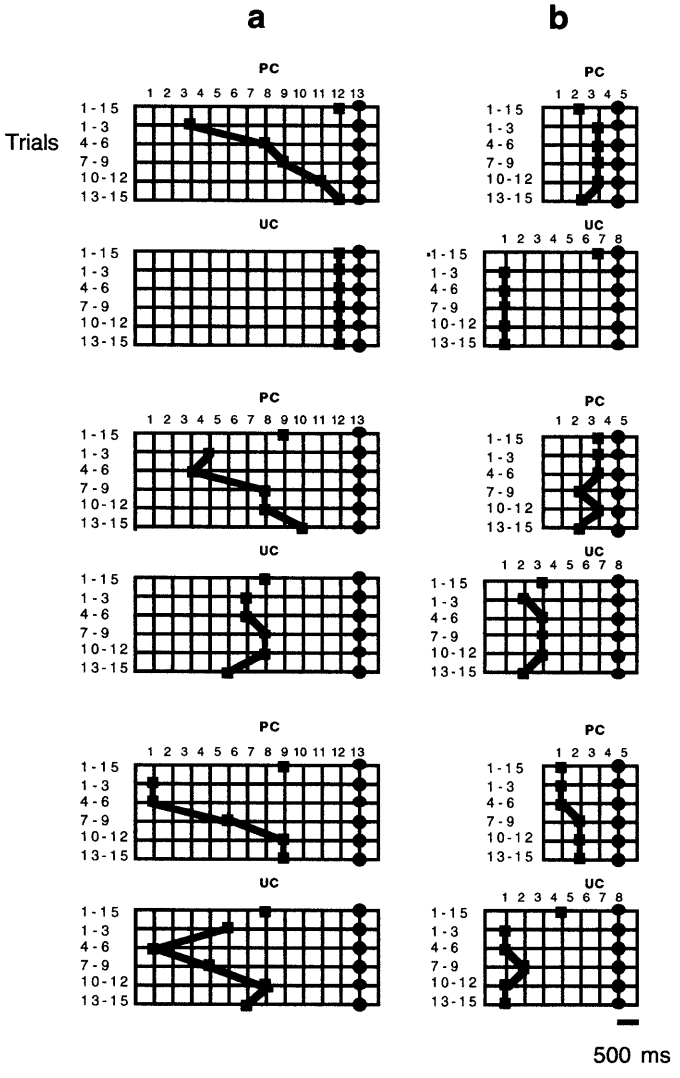

Fig. 4 a, b Graphic representation of statistical analysis of the data obtained from three buildup neurons under each experimental condition (the first neuron is the same one presented in Fig. 3). Each neuron displays a peculiar trend in the delay of the onset of cell discharge. In each graph, *the horizontal parallel lines* represent the histograms, including red, yellow and green periods (the overall one, trials 1–15, and the partial ones, from trials 1–3 to trials 13–15); *the vertical parallel lines* represent the intervals of 0.5 s. *Each filled dot* corresponds to the yellow period; *each filled square* separates the intervals presenting a statistically significant difference ($P<0.01$) with respect to the yellow period, *on the left*, from those presenting a statistically non-significant difference ($P>0.01$) *on the right*. *The oblique lines, joining the filled squares,* show the trend in discharge delay from a statistical point of view. **a** Graphic representation of statistical analysis of the data in the predictable condition, *PC* (5 s), and unpredictable condition, *UC* (1–5 s). **b** Graphic representation of statistical analysis of the data in the predictable condition (1 s) and the unpredictable condition (2–2.5 s)

significant difference ($P<0.01$), and those presenting a statistically non-significant difference ($P>0.01$) with respect to the yellow period, were identified for each histogram. Finally, these time intervals were plotted to obtain a visual representation of the trend in the discharge delay for each cell (Fig. 4a, PC).

In addition, we compared the overall activity of the five histograms and found a statistically significant difference (ANOVA, $F_{(4,320)}=23.058$, $P<0.001$).

Proceeding in the same way in the unpredictable condition of 1–5 s, the discharge presented neither an increasing delay nor a significant variation between subsequent histograms (ANOVA, $F_{(4,320)}=0.936$, $P>0.44$) (Fig. 4a, UC). In the predictable condition of 1 s and the unpredictable condition of 2–2.5 s, the discharge pattern was similar (predictable condition ANOVA, $F_{(4,120)}=0.469$, $P>0.76$; unpredictable condition ANOVA, $F_{(4,195)}=0.251$, $P>0.90$) (Fig. 4b).

Each neuron displayed a peculiar trend in the delay of the onset of cell discharge, as shown by the three examples in Fig. 4a: U496 had a very fast shift compared to U361 and U497 in the predictable condition and all the intervals

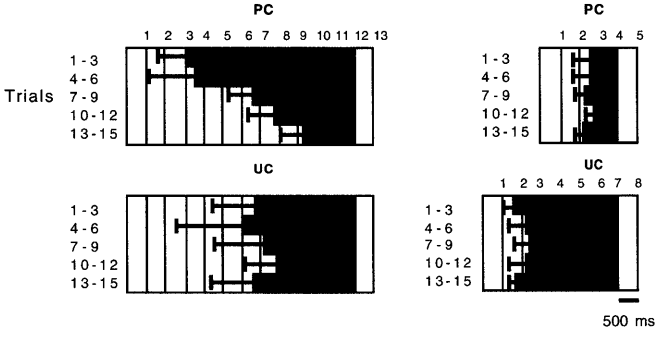

Fig. 5 Graphic representation of the statistical analysis of the cumulative data obtained from the 22 buildup cells tested in the predictable condition, *PC* (5 s), the unpredictable condition, *UC* (1–5 s), the predictable condition, *PC* (1 s), and the unpredictable condition, *UC* (2–2.5 s). *Each black rectangle* is made up by those intervals which do not present a statistically significant difference with respect to the yellow period ($P>0.01$). *The black bars* indicate standard deviations

presented a statistically significant difference with respect to the yellow period in the unpredictable condition. Owing to this variability, the average value for the 22 cells, indicating the onset of the intervals which did not show a statistically significant difference, was calculated for each histogram. This analysis showed a clear increase in the discharge delay only during the predictable condition of 5 s (Fig. 5).

In addition, to ascertain whether the changes in activity reflected the animals' motor performance, the eventual relationship between the monkeys' reaction time (RT) in bar releasing and the discharge delay was statistically analyzed by Spearman's test. No correlations were observed under any of the experimental conditions (P>0.1).

Discussion

The premotor cortex may be considered a set of sensorimotor fields that are involved in the preparation for or execution of movement, in the control of postural muscles and in the coordination of movement (Rizzolatti et al. 1981; Weinrich and Wise 1982; Goldshalk and Lemon 1983; Humphrey 1979; Goldberg 1985; Rizzolatti et al. 1998). In addition, recent investigations have revealed further functions in the different fields of the premotor cortex. Some of these studies have postulated a role in attentional processes and visuomotor learning (Rizzolatti et al. 1983; Chen and Wise 1995; Vaadia et al. 1986; Petrides 1986; Bon and Lucchetti 1997; Lucchetti et al. 1998) as well as in eye motor control (Schlag and Schlag-Rey 1987; Schall 1991; Bon and Lucchetti 1992; Tehovnik and Lee 1993; Mushiake et al. 1996; Olson et al. 2000).

In the literature, the data on the neuronal discharge relating to a visuomotor instruction during the delay period are interpreted in different ways. The results and conclusions depend on the task per se and on the manipulation of the task parameters. Some experimental evidence suggests that the premotor cortical cells process the preparation of limb movements in a specific direction (Riehle and Requin 1989; Crammond and Kalaska 2000). Moreover, Kurata and Wise (1988) tried to dissociate the set-related cells by means of an arbitrary and a directional motor task. However, they found that the set-related cells did not differ substantially in the two tasks, and they suggest that the premotor cortex activity reflects both aspects of motor preparation and behavioural adaptability.

Other authors describe the anticipatory activity in the premotor cortical cells as being related to a predictable event (Mauritz and Wise 1986) and the findings of Vaadia et al. (1988) support the hypothesis that the precue activity is independent of the post-cue activity. The pre-cue activity is a general instruction that does not include a motor instruction (direction of movement) but may represent motor preparation in a general sense. The pre-cue activity may reflect: (1) a general anticipation of an imminent sensory or motor event or (2) a general anticipation of "when" the event will occur.

In the light of the above, we exploited the respective predictability and unpredictability of the duration of a pre-cue in a visuomotor task to study the role of time in the motor preparation.

The three colours used in the task represent three behavioural instructions: a pre-cue (red), a cue (yellow) and a trigger stimulus (green). The pre-cue may be considered a waiting period before the change of colour instruction; the cue represents an instruction to prepare for the release of the bar; the trigger stimulus is a "go" command for bar release. Since the pre-cue instruction may be considered as related to time processing (Fraisse 1957; Vaadia et al. 1988), in this set of experiments we manipulated its duration. The yellow instruction, on the other hand, was kept fixed, to avoid any time interference with the red instruction, and short, because the early component of CNV starts more than 0.5–0.8 s prior to the onset of the movement.

The main finding of our study is that the delay of the onset of cell activity gradually increases in successive trials. This phenomenon may be the expression of a time modulation related both to the predictability of the duration of instruction and to the learning processes. The increasing delay of discharge during the predictable condition of 5 s is disrupted if the red period duration is randomized or fixed at 1 s. We may therefore speculate that these neurons contribute to the neural circuitry from which the conscious state of awareness of timing emerges, whereas the absence of a gradually delayed discharge in the predictable condition of 1 s may be explained by the limitation in the time available for computation, as suggested by the graphic representations in Figs. 4 and 5.

Moreover, the phenomenon consisting of markedly decreasing neuronal activity in successive trials present only in the predictable condition of 5 s may be due either to the delay of the discharge itself or to a general deactivation phenomenon. Statistical analysis shows that the first hypothesis is more convincing, since a significant overall decrease was found only when the histograms showed a marked delay in the onset of discharge. This further analysis supports the notion that these cells have a temporal learning function and not only one of general anticipation.

A similar delay effect was found by Fuster et al. (1982) in the prefrontal cortex during a delayed matching-sample colour task. The authors proposed the participation of these neurons in the temporal structuring of behaviour.

Alternatively, this pre-cue activity could be considered related to: (1) expected reward and (2) attention. We may discard the first possibility since the instruction is closely related to the motor act and the masseter EMG activity appears about 0.5 s after release of the bar. As regards the second issue, previous neuropsychological experiments in which the engagement of attention modifies the RT in relation to the predictability of sensory events need to be borne in mind (Umiltà 1988). The inconsistent correlation between RT and the pre-cue activity suggests that the delay in discharge onset cannot be directly related to the

attentional processes even though the animal directs its attention at the visual instruction. This may appear to be in contrast with previous experiments in which a correlation was found in some neurons between their activity, during a preparatory period, and RT. In those investigations the correlation was found for the activity related to a cue, and not, as in our experiments, for the activity related to a precue, which does not give any instruction for a subsequent movement (Riehle and Requin 1993).

In conclusion, the different behavioural patterns exhibited by the cells presented in this report suggest that these buildup neurons are involved in a learning process in the time domain.

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