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RESEARCH ARTICLE

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Context-dependent force coding in motor and premotor cortical areas

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Abstract In three monkeys trained to finely grade grip force in a visuomotor step-tracking task, the effect of the context on neuronal force correlates was quantitatively assessed. Three trial types, which differed in force range, number, and direction of the force steps, were presented pseudo-randomly and cued with the color of the cursor serving as feedback of the exerted force. Quantitative analyses were made on 85 neurons with similar discharge patterns in the three trial types and significant linear positive (54 cells) or negative (31 cells) correlation coefficients between firing rate and force. An analysis of covariance (ANCOVA) showed that the population slopes for 2-step were steeper than for 3-step trials. Another ANCOVA at the population level, computed on the differences in firing rate and force between force steps, persistently disclosed a significant effect of trial type. For the first two force steps, the differences in firing rate were significantly larger in the 2-step than in the 3-step increase trials. Further analyses revealed that neither the force range nor the number of steps was a unique factor. A small group of neurons was tested in an additional trial series with a uniform cue for all three trials, leading to either a loss of context-dependency or to unexpected changes in firing rate. This demonstrates that the cue color was an important instruction for task performance and neuronal activity. The most important findings are that the context-dependent changes were occurring "online", and that neurons displaying context-dependency were found in all three lateral premotor cortex hand regions and in the primary motor cortex. Finger muscle activity did not show any context dependency. The context-dependent effect leads to a normalization of the cortical activity. The advantage of normalization is discussed and mechanisms for the gain regulation are proposed.

Key words Precision grip · Context-dependency · Force · Finger representation · Motor cortex · Premotor cortex

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Introduction

Neural correlates of static and dynamic force in the primary motor cortex (M1) have been investigated for more than 30 years (Evarts 1968, 1969; Schmidt et al. 1975; Thach 1978; Cheney and Fetz 1980; Hoffman and Luschei 1980; Evarts et al. 1983; Porter and Lemon 1993; Ashe 1997; for a review, see Hepp-Reymond 1988). Force coding has been demonstrated under various force conditions (isotonic, isometric, and auxotonic) for single-joint movements, such as wrist or elbow, and jaw movements. In the majority of the studies, monotonic relations between neuronal activity and static force were found, being linear over a restricted force range. Departures from linearity often occurred at high and more rarely at low forces. For multijoint movements in 2D space, a relation of firing rate to force has also been shown by Kalaska et al. (1989) under static conditions and by Georgopoulos et al. (1992) for dynamic force. Recently, the latter data have been expanded to the 3D space by Taira et al. (1996), leading to the conclusion that, for a majority of M1 arm neurons, the neuronal activity mainly or preferentially correlates with the direction of force rather than its magnitude.

The precision grip has been considered to serve as an appropriate model to investigate neuronal correlates of force in a natural situation, as the modulation of the force exerted between the thumb and index finger is required by every fine manipulation. This force is the resultant of the coordinate activity of many muscles, and

its control represents a challenging problem for the central nervous system. Neuronal correlates of dynamic and static isometric grip force have been demonstrated for many years, mainly for neurons in M1, but also for neurons located in the motor thalamus, pallidum, and somatosensory cortex (Smith et al. 1975; Hepp-Reymond et al. 1978; Anner-Baratti et al. 1986; Wannier et al. 1991; Maier et al. 1993). In recent years, neuronal correlates of grip force have also been found in various parts of the lateral premotor (PM) cortex (Hepp-Reymond et al. 1994). For this investigation, a more complex paradigm has been designed in order to reveal special premotor neuronal features. The experimental situation requires the production of two or three consecutive force steps, with the color of the exerted force serving as a cue for the number and direction of required force steps. Under these conditions, the slopes of the regression lines, taken as index of force-sensitivity, were steeper for the 2-step than for the 3-step trials covering a larger force range.

To explain this new finding, the simplest hypothesis was that the neuronal activity had non-linearities in the higher force range, showing some kind of saturation. As suggestive as this hypothesis might have been for tonic neurons displaying an increase of activity with force, it could not be applied as well to the numerous neurons with a decrease in firing rate with force. Another likely interpretation is that the neuronal activity may be context-dependent, and that changes in gain may occur depending on the instructions given in the task. These two interpretations have been quantitatively tested, and we report here on the statistical significance of context-dependent neuronal correlates of force in M1 and lateral PM cortex.

Materials and methods

Three alert female monkeys (*Macaca fascicularis*) were the subjects of the present study. The experiments were conducted in accordance with the principles of the Swiss Animal Protection Law on animal experimentation and care of experimental animals. The monkeys were not water deprived, but their dry food diet and weight were controlled.

Behavioral paradigm

Parts of the behavioral paradigm have been described in Hepp-Reymond et al. (1994). The monkeys sat in a primate chair in front of a computer-controlled video-screen (ca. 40 cm in front of the monkey) with forearms and wrists restrained in adjustable splints and the hands resting on platforms. They were trained to exert and control force isometrically on a transducer held between thumb and index finger, i.e., using the precision grip. The transducer could rotate around its vertical axis to prevent simple proximal push or pull movements. The visuomotor task consisted of a step-tracking paradigm that required the precise production of grip force within a relatively low force range in sequences of two or three variable force steps. Three different trial types were presented in a pseudo-random order during training and recording sessions. One trial type required two increasing force steps (2-step ↑trial), another type required three increasing steps (3-step ↑trial), and the third type had three steps, with a force decrease as the third step (3-step ↑↓trial). The paradigm is schematically represented in Fig. 1. On the video screen, a light-blue rectangle displayed the target force range, and a smaller colored one represented the actual force exerted on the transducer. Each trial type was cued by a different color ("color-cued" condition): magenta for 2-step↑, white for the 3-step↑, and blue for the 3-step↑↓ trials. A trial was initiated by the monkey closing its thumb and index finger on the transducer, producing force to reach the displayed target force, and maintaining it for a variable time (1.5–1.8 s). At the end of the hold period, an upward shift of the target instructed the monkey to increase the grip force within 2 s and reach a second force level that had to be maintained for 1–1.3 s. In the 3-step trials, the third shift of the target force window could either be in the upward or downward direction (increase or decrease). Some drops of fruit juice and a small piece of fruit or vegetable rewarded each correct trial. The force range covered by the 2-step↑ and the 3-step↑↓ trials lay between 0.25 and 0.85 N, and that of the 3-step↑ trials between 0.2 and 1.15 N. An effort was made to cover the whole force range by five to six trials with different target force ranges. The target force ranges varied slightly between monkeys. In one monkey, some neurons were additionally tested in a trial series in which all three trial types had the same cue color, the one cueing the 3-step↑ trials "uniformly" cued condition).

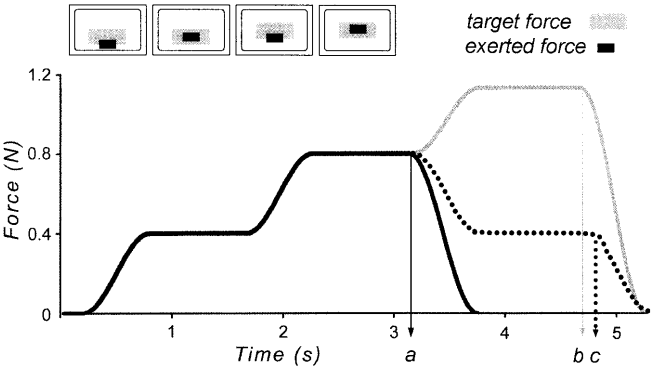

Fig. 1 Visuomotor force step-tracking task. *Top* Screen with required (target) and actual (exerted) force displayed at four different times during one two-step trial. *Bottom* Time course of idealized force curves (force scale in Newton, time scale in s). *Arrows* Occurrence times of the reward for two increasing force steps (2-step↑ trial) *a*, for three increasing force steps (3-step↑ trial) *b*, and for two increasing and one decreasing force steps (3-step↑↓ trial) *c*

Two pairs of strain gauges (DC 100 Hz, range 0–5 N) measured the one-dimensional force component of thumb and index finger separately, and these two forces were added electronically, yielding a resultant force, which was displayed on the video screen. A frequency-modulated tone proportional to the exerted force served as auditory feedback during training and during some recording sessions.

Surgery and recording

After completion of the training, a craniotomy was performed and a stainless-steel chamber (22 mm inside diameter) was stereotactically implanted contralaterally to the trained hand and centered slightly rostral to the M1 hand region. The chamber was implanted in two steps using a new technique based on titanium implants without any dental acrylic. Surgery was made under standard aseptic conditions and general anesthesia (30 mg/kg pentobarbital sodium after induction with 12 mg/kg of ketamine chloride). Full postoperative antibiotics and analgesic medication were provided.

Extracellular recordings of neuronal activity during the performance of the motor task were made following standard procedures, with the head of the monkeys immobilized mechanically

with a small helmet. Varnished tungsten microelectrodes (0.2 to max. 2 Ω impedance measured intracortically at 1 kHz) were inserted through the dura. In almost every recording site, intracortical microstimulation with a DC cathodal current up to 30 μA (60 ms trains, 0.2 ms duration at 300 Hz) was applied through a constant current isolator.

The peripheral receptive fields of the recorded neurons were assessed by stimulating the skin with a small probe and brush and by passive movements of muscles and joints. For two monkeys, the EMG activity of some finger and wrist muscles [first dorsal interosseous (1DI), extensor digitorum communis (EDC), flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), abductor pollicis brevis (AbPB), adductor pollicis (AdP)] were recorded either percutaneously or with surface electrodes in several sessions.

At the end of the recording period, the monkeys were given a lethal dose of pentobarbital and perfused through the heart with saline followed by paraformaldehyde (4%) and sucrose in phosphate buffer. The brains were prepared histologically, and the recorded region reconstructed on the basis of small electrolytic lesions.

Data collection, processing, and analysis

The action potentials were discriminated using a time-amplitude window discriminator. The output of the discriminator, together with other digital and analog signals, were stored on a digital tape and digitized on-line or off-line on a laboratory computer (LSI 11/73) and a new data acquisition system (MC 68030 with OS9 system). The sampling rate was 1 kHz for the spikes and 100 Hz for the analog channels (force and rectified smoothed EMG signals). The digitized data could be displayed trial-by-trial in a raster and peri-response time histograms all aligned on a selected digital signal. In general, the trials were aligned on the onset of force change from one level to the next (see Hepp-Reymond et al. 1994).

To assess the relation between firing rate and force, segments of constant force (300–1000 ms duration) were interactively chosen from the digitized data trial-by-trial in each force step. Only one segment per force step was selected, thus yielding two or three values per trial. Mean firing rate and mean resultant force were calculated within each segment. The significance of the correlation between firing activity and force was tested for each neuron by way of linear regression analysis, and the slope of the regression line taken as the index of force sensitivity (rate-force slope). In addition, general linear models with either a linear term or the combination of a linear and a quadratic term were applied. The corrected mean square error (MSE) was selected as a criterion for the fit quality (MSE = sum of squares/degrees of freedom).

To determine whether the correlation between firing rate and force could be influenced by the context (i.e., by the trial type), several statistical approaches were applied. On the *single-cell level*, the differences in firing frequency for each trial between the first two force steps were taken as the dependent variable, whereas the differences in force served as the covariate (to control for possible force bias) in an analysis of covariance, referred to in the text as $ANCOVA_{single}$. The trial type (2-step↑, 3-step↑, 3-step↑↓ trials) was the treatment and effect of interest. On the *population level*, both variables, force and frequency, were first z-transformed so that, for each single cell and variable, the mean of the data of the 2- and 3-step trials together was 0 and the standard deviation 1. This so-called z-standardization was carried out to cancel out cell effects for the further analyses. The subsequent statistical analyses focused on differences between the various trial types, taking into consideration only the first two force steps covering the same force range. To make inferences about the effect of trial type, an ANCOVA was conducted to test whether trial type (treatment) had a significant effect on the firing frequency (dependent variable) in relation to force (independent variable). A significant interaction between the independent variable and the treatment would then indicate a difference in population rate-force slopes. This analysis is referred to in the text as $ANCOVA_{slope}$. As a complementary statistical analysis, the standardized data, both force and frequency, were reduced to mean differences between the second and first force steps per trial type and per cell. To test the effect of trial type, the mean differences between the first two steps in 3-step trials (either 3-step↑ or 3-step↑↓) were subtracted from the mean differences between the first two steps in 2-step↑ trials. The same was also done between the two types of 3-step trials (3-step↑, 3-step↑↓). These differences were then analyzed applying an ANCOVA with the differences in frequency as the dependent variable and the differences in force as covariate, referred to in the text as $ANCOVA_{diff}$. A significant intercept indicates a difference in force scaling between the 2- and 3-step trials, irrespective of possible force variations. The same analyses were performed on the standardized EMG activity.

Results

Neuronal population and discharge patterns

A total of 1322 neurons were recorded in the M1 and lateral PM cortex contralateral to the performing hand. The distribution of the neurons over the various regions was as follows: 427 (32%) in M1, 371 (28%) in PM ventral rostral (PMvr), 231 (18%) in PM ventral caudal (PMvc), 275 (21%) in PM dorsal caudal (PMdc), 18 (1%) in the rostral PMd. Among these neurons, a selection of so-called "finger cells" was made on the basis of the motor reactions to microstimulation and the localization of the receptive fields. Whenever available, both criteria were considered; however, in case of lack of congruence or absence of reactions to microstimulation, the receptive field was the decisive factor. A total of 998 neurons were related to the fingers: 376 (38%) were located in M1, 249 (25%) in PMvr, 144 (14%) in PMvc, 225 (22%) in PMdc, and 4 (1%) in the rostral PMd.

Discharge patterns during task performance were first classified as phasic, phasic-tonic, tonic, decreasing, and mixed (Wannier et al. 1991). The cells with either a tonic increase or decrease of firing rate with force were further subdivided into two classes. The neurons displaying similar discharge patterns and force coding in all trial types were called "same", and the others were grouped under the label "complex" (Hepp-Reymond et al. 1994). From the 362 neurons with a tonic component, 138 (38%) belonged to the class "same" and were the object of the present investigation. The rest with more complex variations will be presented in another publication.

Linearity of relation between firing rate and static force

Of the 138 analyzed cells related to finger movements and displaying "same" discharge patterns, a significant majority (85, 62%) exhibited a significant linear force modulation when the data of the 2-step↑ and 3-step↑ trials were pooled (χ^2=7.4, df=1, P<0.01). Among those, 54 (64%) were positively and 31 (36%) negatively correlated with static force. In addition, the linear regression analysis revealed for a majority of these neurons a higher force sensitivity for the 2-step↑ than for the 3-step↑ tri-

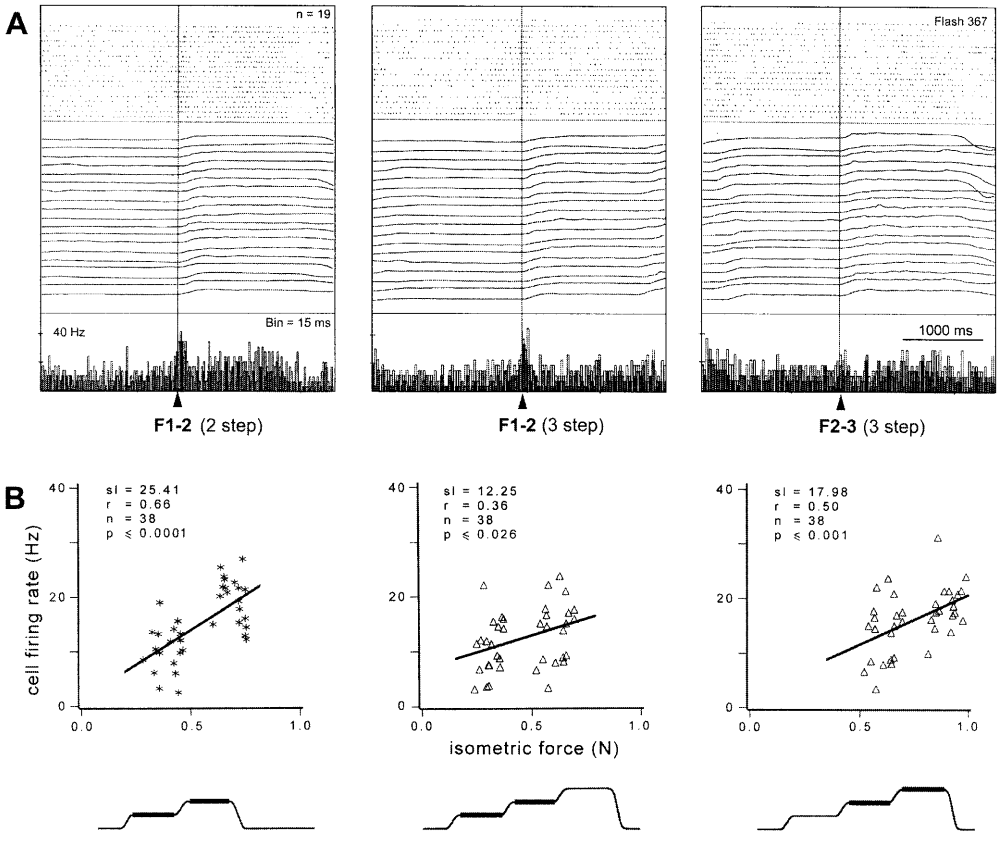

Fig. 2A, B Relation between firing rate and static force for one phasic-tonic M1 neuron with "same" discharge pattern. *Left* 2-step↑ trials. *Middle* 1st and 2nd force levels in 3-step↑ trials. *Right* 2nd and 3rd force levels in 3-step↑ trials. **A** Raster of cell activity with corresponding force traces and peri-response time histograms, aligned on the force change between the 1st and 2nd steps (*F1–2*) in the *left and middle diagrams* and on the force change between the 2nd and 3rd steps (*F2–3*) in the *right diagram*. Time scale inserted above right histogram. **B** Scatter diagrams displaying mean neuronal firing rate (Hz) as a function of mean static force (N) within selected segments during the holding phase. Each *symbol* corresponds to the data point of one segment. *sl* rate-force slope in Hz/N, *r* regression coefficient, *n* number of data points, *p* probability level

als. Figure 2 displays the activity rasters and peri-response time histograms for a M1 neuron with phasic-tonic activity and significant correlations to static force in the 2- and 3-step↑ trials.

Several analyses were performed in order to find out the origin of such differences in index of force-sensitivity. A first working hypothesis was that these differences were due to non-linearities in the higher force range covered only by the 3-step↑ trials. To test this hypothesis, the fits of the data to a linear and quadratic regression model were compared. Of the 85 cells with a significant "same" force modulation, a significant number (53, 62%) exhibited a better fit to the linear model than to the quadratic one, as expressed by the corrected MSEs (χ^2=5.2, *df*=1, *P*<0.05). When tested for statistical significance, the main effect of the quadratic component rarely reached significance, i.e., only in three positively and one negatively force-correlated cells. Non-linearities in the higher force thus may only occasionally account for the higher force-sensitivity in the 2-step↑ as compared with the 3-step↑ trials.

Context-dependent gain changes

We tested therefore the second hypothesis, according to which the context may induce changes of gain in the neuronal encoding of grip force. This hypothesis predicts that the slopes of the regression lines in the various "color-cued" trial types should differ, even when equal force ranges are compared. An example of this analysis is shown in Fig. 2B, which demonstrates that the regression slopes over the first two force steps are steeper for the 2-step↑ than for the 3-step↑ trials. $ANCOVA_{single}$ on the differences in mean firing activity and force between the first and second force step were performed at the single-cell level for all 85 neurons and yielded overall statistical significance in 18% of the neurons. An example is displayed in Fig. 3A. The frequently small sample size may account for the lack of statistical significance in most remaining neurons, although clear differences in activity between trial type are revealed by the displays and scatter diagrams.

For this reason and in order to identify the behavior of the whole neuron population, an $ANCOVA_{slope}$ was computed for 54 positively and 31 negatively correlated cells with "same" discharge patterns and significant linear force correlations in order to compare the regression coefficients. A significant interaction between the independent variable (force) and the treatment (trial type) indicates the heterogeneity of the population slopes. This interaction proved to be highly significant for both positively [F(1,2965)=42.03, P<0.0001] and negatively correlated M1 and PM cells [F(1, 1774)=13.43, P<0.0003]. As can be seen in Fig. 4A and B, the population slopes for the first two steps were obviously less steep in the 3-step↑ than in the 2-step↑ trials.

The complementary $ANCOVA_{diff}$ on the frequency and force differences between the first two force steps with force as covariate (see Methods) was carried out on the same neuron populations. This analysis disclosed a significant intercept effect for the positively correlated

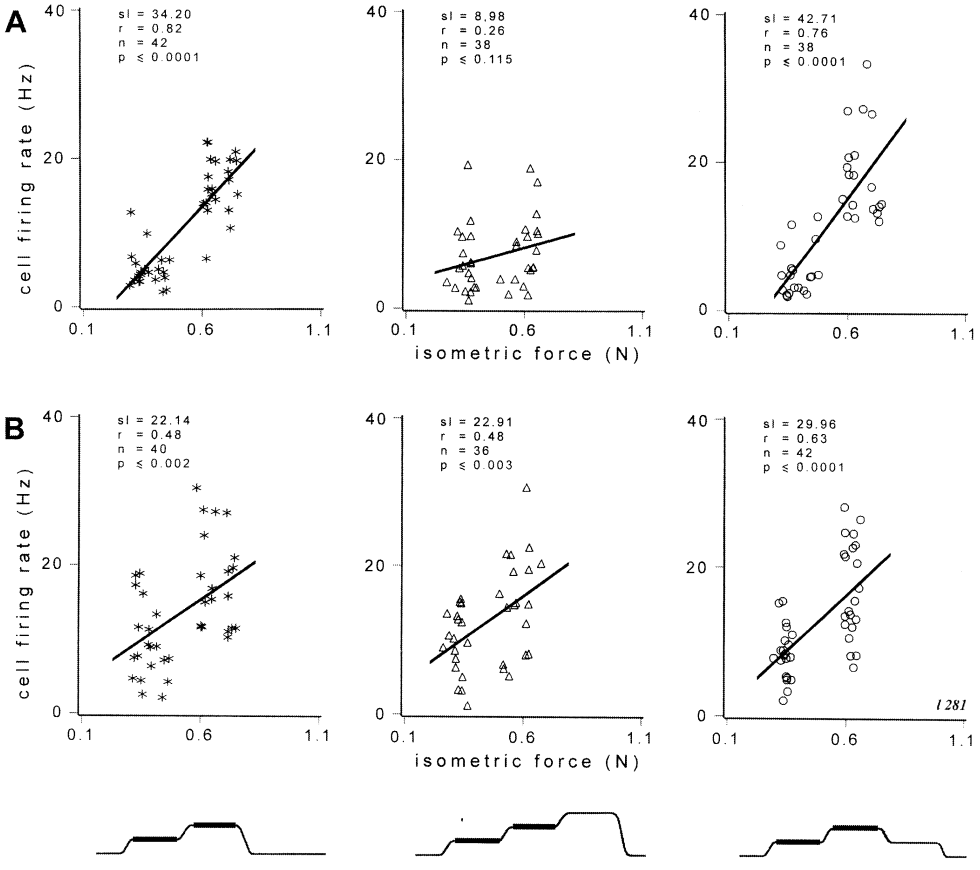

Fig. 3A, B Scatter diagrams and regression slopes over the first two force steps for one phasic-tonic, neuron with "same" discharge pattern. *Left* 2-step↑ trials. *Middle* 1st and 2nd force levels in 3-step↑ trials. *Right* 1st and 2nd force levels in 3-step↑↓ trials. **A** "Color-cued" condition. **B** "Uniformly cued" condition. Same displays and abbreviations as in Fig. 2B

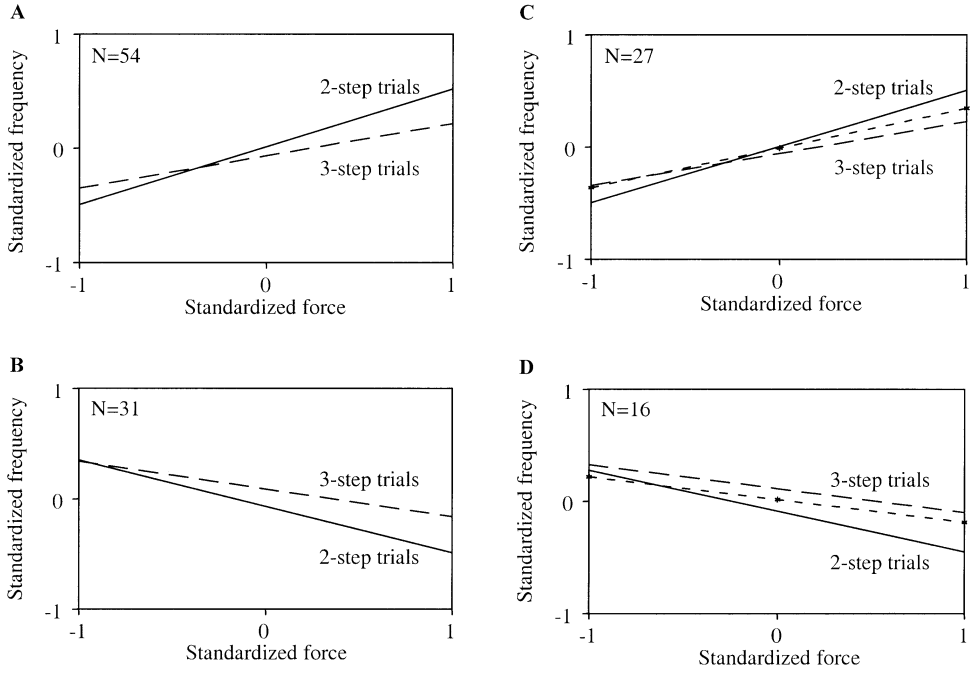

Fig. 4 Population rate-force slopes for the first two force steps in two (**A, B**) and in three (**C, D**) trial types under "color-cued" condition. **A**, **B** Data of three monkeys for 54 positively correlated (**A**) and 31 negatively correlated (**B**) (M1) and (PM) neurons. **C**, **D** Data including the 3-step↑↓ trials for a subset of 27 positively correlated (**C**) and 16 negatively correlated (**D**) M1 and PM neurons recorded in two of the three monkeys. *Solid line* 2-step↑ trials, *dashed line* 3-step↑ trials, *finely dashed line* 3-step↑↓ trials, *x-axis* differences in standardized mean force, *y-axis* differences in standardized mean firing rate

neurons [$F(1,52)=43.52$, $P<0.0001$] as well as for the negatively correlated neurons [$F(1,29)=41.16$, $P<0.0001$]. This effect is shown in Fig. 5A and C, which display that the mean firing rate differences between the first two force steps significantly differ when the 2-step↑ and 3-step↑ trials are compared. This is in line with the first analysis of covariance ($ANCOVA_{slope}$).

Similar analyses were performed with the 3-step↑↓ trials. If the differences observed above were due to the number of steps in a sequence, no significant difference

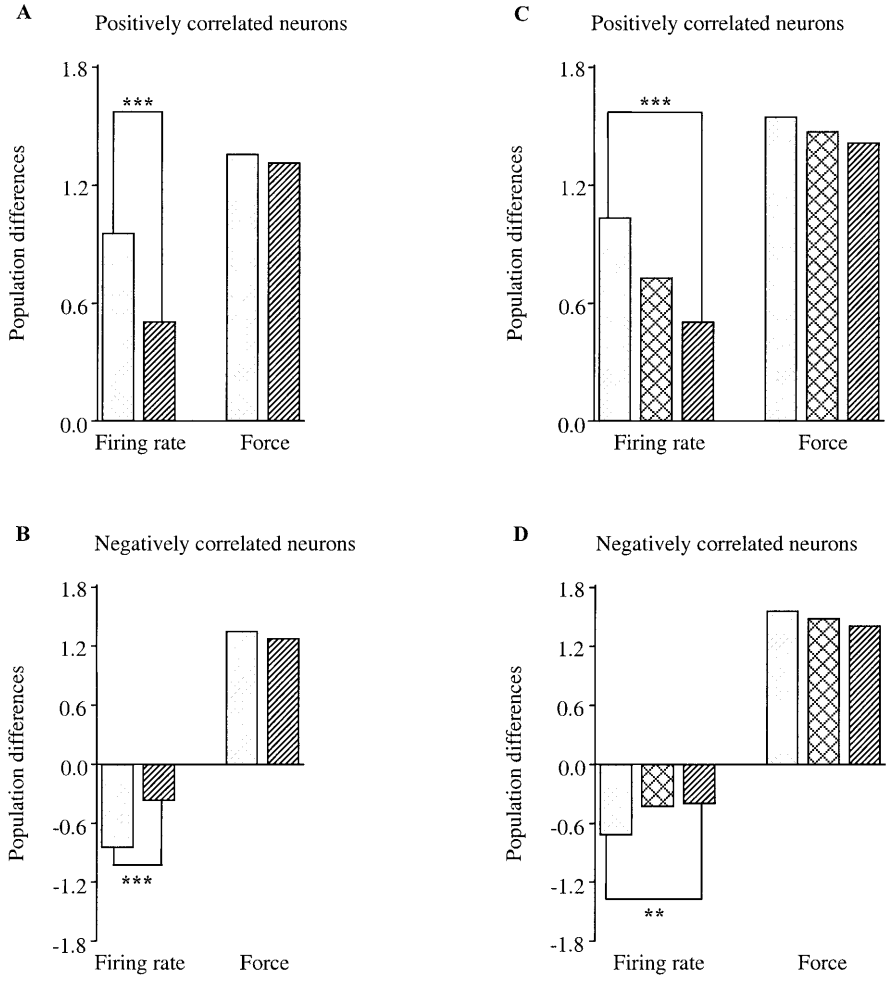

Fig. 5A–D Context-dependent gain changes in "color-cued" condition for populations of M1 and PM neurons. *Bars* represent differences between the 1st and 2nd force step in standardized mean firing rate and force (z-scores). **A**, **C** Positively correlated neurons. **B**, **D** Negatively correlated neurons. *Dotted bars* 2-step↑ trials, *stripped bars* 3-step↑ trials, *crossed bars* 3-step↑↓ trials. **A**, **B** ANCOVAs$_{diff}$ on a population of 54 positively correlated neurons (**A**) and 31 negatively correlated neurons (**B**) from three monkeys. **C**, **D** ANCOVAs$_{diff}$ on a subpopulation of 27 positively correlated neurons (**C**) and 16 negatively correlated neurons (**D**) from two of the three monkeys (see text). ** P<0.01, *** P<0.001

in the comparison between 3-step↑↓ and 3-step↑ trials should be found. If the differences, in contrast, were caused by the prediction of the force range covered by the motor sequences, no difference should appear between the 2-step↑ trials and the 3-step↑↓ trials, requiring almost the same lower force range. The scatter diagrams displayed in Fig. 3A show that the rate-force slope for the 3-step↑↓ was quite steep and, thus, more similar to the 2-step↑ than to the 3-step↑ trials. However, this effect is not obvious in Fig. 4C and D, which display population slopes in all three trial types, suggesting more similarity between the two types of 3-step trials (3-step↑ and ↑↓). The ANCOVA$_{diff}$ performed on the corresponding differences in activity between the first two force steps (Fig. 5C, D) did not reach significance when the 3-step↑↓ trials were compared to either the 2-step↑ or the 3-step↑ trials. This holds true for both the positively and negatively correlated neurons.

Table 1 Regional distribution of the context-dependent gain changes, as assessed with ANCOVAs$_{slopes}$ testing for differences in rate-force slopes between the 2-step↑ and 3-step↑ trials. *M1* Primary motor cortex, *PM* premotor cortex. Premotor cortex subregions: *PMd* dorsal, *PMvc* ventral caudal, *PMvr* ventral rostral. *n* Number of neurons

Area	n	*F*-Value	*P*≤
Positively correlated neurons			
M1	25	14.38	0.0002
PM	29	27.22	0.0001
PMd	5	5.24	0.02
PMvc	9	3.09	0.08
PMvr	15	18.63	0.0001
Negatively correlated neurons			
M1	11	2.55	0.1
PM	20	11.93	0.0006
PMd	10	5.44	0.02
PMvc	1	–	–
PMvr	9	10.78	0.001

Regional distribution of the context-dependent gain changes

The regional distribution of the neurons displaying context-dependent force coding in M1 and PM, and within the various PM hand representations, is shown in Tables 1 and 2. The ANCOVA$_{slope}$ disclosed significant differences in rate-force slopes between the 2-step↑ and the 3-step↑ trials for the positively correlated neurons in all regions and for the negatively correlated ones only in PM.

Table 2 Regional distribution of the context-dependent gain changes as assessed with ANCOVAs$_{diff}$ testing for differences in standardized mean firing rate (z-scores) in the various motor areas. Values for the 2-step↑ and 3-step↑ trials. Abbreviations as in Table 1

Area	n	2-step trial	3-step trial	Num,Den *df*	*F*-Value	*P*≤
Positively correlated neurons						
M1	25	1.00	0.53	1,23	23.62	0.0001
PM	29	0.91	0.47	1,27	18.87	0.0002
PMd	5	0.96	0.42	1,3	7.97	0.0665
PMvc	9	0.81	0.47	1,7	4.70	0.0669
PMvr	15	0.96	0.49	1,13	8.59	0.0117
Negatively correlated neurons						
M1	11	–0.72	–0.40	1,9	7.61	0.0221
PM	20	–0.92	–0.35	1,18	32.69	0.0001
PMd	10	–0.72	–0.28	1,8	20.42	0.0020
PMvc	1	–1.02	–0.66			
PMvr	9	–1.13	–0.38	1,7	19.00	0.0033

These results demonstrate that the context-dependency is not a specific feature of the PM neurons. However, the context-dependent effect was more significant for the PM than the M1 neurons, and within PM the strongest for the PMvr neuron population (Table 1). The complementary ANCOVA$_{diff}$ confirmed a significant difference in activity between the first two force steps of the 2-step↑ compared with the 3-step↑ trials for all regions in the negatively correlated neurons (Table 2B). The same was true for the positively correlated neurons, except for PMd and PMvc (Table 2A). This last finding may possibly be due to the small number of neurons in these two regions.

Effect of the cue color

To test the hypothesis that the color of the cursor served as a cue and helped the monkeys to predict the current trial type, we recorded in one monkey a small population of neurons in an additional series of "uniformly cued" trials. The cue color of the 3-step↑ trials (white) was mostly used in this test series. The working hypothesis was that, if the color was used as an instruction for the next step under the uniform cue condition, the differences in the slope of the regression lines should disappear, and the statistical analysis should no longer reveal any significant differences. So far, nine positively and three negatively correlated cells tested under these conditions were analyzed. Four positively correlated neurons showed significant context-dependent force coding and lost this effect in the "uniformly cued" condition. The scatter diagrams of one of them under "color-cued" and "uniformly cued" trials are displayed in Fig. 3A and B, respectively. This preliminary finding strongly supports the hypothesis that the color of the cursor is an important cue, as was predicted by the other data.

Muscle activity in the task

In several sessions, the EMG activity of some hand muscles were recorded together with single neurons or separately. The working hypothesis was that, if the context-dependent gain changes were only a cortical neuronal feature, the EMG activity should always have the same activity, regardless of the type of trial tested. A selection of finger and wrist muscles was recorded either percutaneously or with surface electrodes in 2–11 sessions each, depending on the muscles. A total of 47 EMG recordings were performed (eight 1DI, five AbPB, 17 EXT, 17 FLEX). Linear correlation coefficients between EMG amplitude and force (Maier and Hepp-Reymond 1995a) were computed, and the slopes of the regression lines, taken as an index of force sensitivity, were compared. Most EMG recordings (38, 81%) had significant linear correlation coefficients. Only three of them showed significant differences between trial types (ANCOVA$_{diff}$), pointing however, in the reverse direction as the differences displayed by neuronal activity. Moreover, this effect was not muscle specific, as it occurred in two muscle groups and only once per group (1/15 EXT and 2/13 FLEX).

To check whether the EMGs as populations may, however, have specific trends, ANCOVAs$_{diff}$ were performed on the difference in mean EMG activity between the first two force steps between the 2-step↑ and 3-step↑ trials for the four muscle groups. This analysis did not reveal any significant trend in mean EMG activity between 2-step↑ and 3-step↑ trials. These findings support our working hypothesis, according to which the cortical context-dependency should not be reflected in the EMG activity itself.

Discussion

The present investigation has brought forth three major new insights with respect to the control of isometric grip force in motor and premotor cortical areas. The first important and new finding is that the neuronal encoding of force is not in absolute firing rate, but is conditional on task requirements, such as the structure of the sequence and/or the force range required. In other words, context-dependent changes of gain exist, implying that a color cue indicating the trial type can induce significant modifications of the cortical activity. The second and least expected finding is that the neuronal activity can change its

gain in the task "on-line", that is trial-by-trial, thus displaying a high degree of cortical plasticity at the single-cell level. The latter finding suggests that this kind of normalization of the neuronal firing rate is a general feature of frontal motor areas, which can be found not only in the various PM hand representations, but in the M1 cortex as well.

Among the numerous neurons activated in the present visuomotor step-tracking task, one well-defined group of neurons displayed changes in force-sensitivity for the various trial types. This class of neurons had similar discharge patterns in the three trial types, their firing rate was monotonically related with the grip force, and the linear correlation coefficients, computed on the pooled data points of the 2-step↑ and 3-step↑ trials, were statistically significant. Within this class, the neurons with positive correlations between firing rate and force were more numerous than those showing negative correlations, confirming earlier findings (Wannier et al. 1991; Maier et al. 1993; Hepp-Reymond et al. 1994).

Neuronal correlates of force

The data reported here add a new important aspect to a well-documented field of research. In the numerous investigations devoted to the neuronal encoding of force, mainly of static force, monotonic and linear relationships have been generally stressed (Ashe 1997). However, non-linearities were observed in the lower and/or higher force range, and were interpreted as recruitment or as saturation, respectively (Cheney and Fetz 1980; Evarts et al. 1983). Evarts et al. (1983) proposed, for a pronation-supination movement of the forearm, the existence of two groups of pyramidal tract neurons (PTNs) with different force modulation and recruitment thresholds. In our earlier investigations, although the relationship between neuronal firing rate and grip force in linear regression displayed a high index of force sensitivity, non-linearities could be seen on individual scatter diagrams, but could not be systematically studied. The mean indices of force-sensitivity were confirmed in the successive investigations with different monkeys and slightly different experimental paradigms (Hepp-Reymond et al. 1978; Hepp-Reymond and Diener 1983; Wannier et al. 1991; Hepp-Reymond et al. 1994).

Adaptability of cortical neuronal discharge patterns

"On-line" changes of the relationship between firing rate and force have never been shown before, although it is a well-known phenomenon, when investigating parameters other than force, that the neuronal firing rate is modifiable under specific conditions. Most impressive were the pioneering findings of Fetz and Finocchio (1975), who were the first to suggest that changes in cortical activity could be induced experimentally, leading to an uncoupling from the muscle activity itself. Later, Muir and Lemon (1983) demonstrated that corticomotoneuronal cells (CM cells), though clearly connected to their target muscles, strongly modified their firing rate when a global grasp was compared with a precision grip, both of them requiring a constant force hold. Cheney and Fetz (1980) also reported differences in the behavior of CM cells and their relationship to force when slow controlled torques were compared with fast force pulses. In an earlier investigation on the precision grip, we also reported striking differences in dynamic force encoding during "ballistic" force ramps as compared with finely graded ones, suggesting that motor strategies can induce strong changes in the correlations between firing rate and dynamic force (Hepp-Reymond and Diener 1983). Similar observations, though not in force coding, had been previously published by Fromm and Evarts (1977) for precise small versus large movements. Finally, another drastic change in force related activity has been reported by Fetz and Cheney (1987) for some CM cells when the task required co-activation instead of reciprocal wrist movements.

Context-dependent changes of gain

In all the experiments discussed above, the changes in activity were induced by changes in movement or in motor task, which most probably activated different groups of muscles or the same muscles in a different manner. The present study, in contrast, reports context-dependent modulations of the relationship between firing rate and force in a motor task for which the muscle activity was the same regardless of the task requirements. These context-dependent changes in force-sensitivity, though significant in only a third of the finger neurons with similar discharge patterns for the 2- and 3-step trials, is a very robust and highly significant finding at the population level, as demonstrated by our statistical analysis. Basically, it demonstrates that the index of force-sensitivity is higher in the 2-step↑ than in the 3-step↑ trials. This can be considered as a normalization of the neuronal firing rate in such a way that the entire firing range will be used regardless of the force range covered (or of the number of force steps), thus leading to steeper regression lines in trials requiring less force. For a small group of neurons which displayed significant context-dependent gain changes and could be additionally tested with "uniformly cued" trials, the indices of force-sensitivity in all three trial types leveled down and the differences between trials were no longer statistically significant. These preliminary findings strongly support the hypothesis that the gain changes observed are tightly bound to the context, defined by the color serving as a cue for the trial type.

It is still an open question whether the force range itself or the number of steps in the trials is the main factor in the normalization observed. An answer to this question was expected from the 3-step↑↓ trials, which required three force steps but covered the same force range as the 2-step↑ trials. The behavior at the single-cell level was variable, showing the same force-sensitivity either

as in the 2-step↑ trials or as in the 3-step↑ trials. The analyses of covariance at the population level disclosed that neither the force range covered nor the structure of the sequence, i.e., number of steps, was a unique factor, but that the combination of both seemed to play a role in the gain changes.

The fact that an instruction, or a context, can modulate the neuronal activity in frontal motor areas is not a new finding as this has been clearly first shown by Tanji and Evarts (1976) for PTNs in M1 responding to a light signal indicating the direction of the next movement before its actual initiation. It is now firmly established that during motor preparation, i.e., during the set period following an instruction, the neurons can respond very specifically to the instruction content, in particular neurons located in PMd (Weinrich et al. 1984; Wise 1985; Riehle and Requin 1989; Riehle et al. 1994), occasionally in PMv (Boussaoud and Wise 1993). An important finding is that PM and M1 neurons can be activated without any muscle activation. More recent findings (Pellizzer et al. 1995) also revealed a clear switch of activity at the single-cell and population levels in a context-recall task in which the serial order played a major role. For instructional stimuli with univocal meaning, the go-signal triggered neuronal responses with clear directionality and with shorter timing, whereas for stimuli with ambiguous meaning the responses occurred at longer latencies and often with a switch in activity. An important methodological aspect was that the control and context-recall tasks were presented separately and not randomly. A new aspect revealed by our present findings with pseudo-random presentation of the various trials is that the context-dependent changes occurred from trial-to-trial. In other words, the neurons were increasing or decreasing their gain "on-line".

One could argue that the requirements of the present motor task and its execution are artificial and do not pertain to normal motor behavior, and that the effects observed were mainly related to the long training and steady performance of the monkeys. There is no doubt that learning plays a major role in the context-dependent automatic gain changes shown here. Recently, Nudo et al. (1996) have convincingly shown that the somatotopical organization of M1 can be modified by training. But, in fact, the special features of the motor behavior reported here are quite closely adapted to the daily requirements of most manipulations. Johansson and Westling (1984) have proposed an anticipatory control of grip force during manipulation, which depends on a sensorimotor memory of object features. Context-dependent gain changes in cortical activity may be one possible mechanism underlying the adaptations in grip behavior, which were elegantly demonstrated by Johansson (see 1996 for a review).

Regional distribution of context-dependent gain changes

Another important, present finding is that force-related neurons were found not only in M1, but also in several finger representations in the lateral PM cortex. So far, only few research groups have addressed the question of force encoding in PM (Werner et al. 1991; Riehle and Requin 1995). Werner and collaborators, in particular, reported that some postarcuate neurons, mainly PTNs and non-PTNs located in their vicinity, had significant and monotonic relationships between their static activity and the torque exerted against wrist flexion and extension. However, the percentage of neurons encoding force was lower in PM than in M1 and the mean firing rate-force slope of the PM neurons was significantly shallower than that of the M1 population. These findings could not be reproduced in the present investigation, in which M1 and PM neurons displayed no clear differences in their relationship with grip force. In fact, these neurons were distributed over all three PM finger regions, identified by microstimulation and peripheral localization of the receptive fields. The group with the highest context-dependency was located in PMvr with a large representation of thumb and index finger. However, a fair proportion of positively correlated M1 neurons also displayed context-dependency, albeit not as highly significant as in PM. The encoding of grip force appears to be a special feature of neurons in lateral PM, as the neuronal force coding in the other PM regions in the hemispheric midline is relatively rare and the relationship to force relatively poor (Cadoret and Smith 1997).

Firing rate normalization and its implications in motor control

Our data, which quantify a novel aspect of the cortical control of force, still raise many questions. The main ones concern the possible advantages of a normalization of the firing rate and its underlying mechanisms. In the visual system, normalization has been postulated to explain non-linear aspects of simple cell responses, mainly saturation at high contrast, and a model was proposed (Heeger 1992; Heeger et al. 1996; Carandini et al. 1997). According to the model, the non-linearities are caused by inhibitory interactions within the cortical cell pool. Important is the fact that the cortical neurons have a limited dynamic range and, therefore, an automatic gain control should occur to account for the entire contrast range. The effect of the normalization consists of a re-scaling of the cell activity with respect to stimulus contrast. Perception (spatial selectivity) should be the invariant without necessarily attending to the intensity values of the stimuli, i.e., to the light level itself. According to these authors, normalization should be fundamental to cortical function not only in visual cortex, but in other areas as well. This attractive model could be adapted to the motor cortical cells, following the idea that the invariant is not the exerted force per se, but some other factors such as the precision of the motor performance. In this case, the resultant force itself would be a product of the complex spinal network that computes descending and peripheral information, adapting its output to both central commands and muscle stiffness.

A predicted finding was that, if normalization is a purely cortical feature, the cortical context-dependent changes in gain should occur without any changes in the effectors, i.e., in the muscle activity itself. In monkey and man, the exertion of isometric static grip force is produced by a co-activation of at least 15 muscles organized in flexible synergies (Rufener and Hepp-Reymond 1988; Maier and Hepp-Reymond 1995a, 1995b). The lack of changes in EMG activity, which was the rule in the present investigation, is not surprising in view of the similar motor performance of the monkeys in the various trial types. However, this independence of the muscle activity from its cortical command requires the presence of a rectifier somewhere in the spinal cord or within the cortical network. Hultborn et al. (1979) proposed that the converging excitatory and inhibitory supraspinal inputs on the Renshaw interneurons allow the recurrent inhibition to serve as a variable gain regulator for the motor output at the motoneuronal level. During weak and finely tuned movements, the Renshaw cells would be more activated, thus leading to a low input-output gain. This mechanism, supported by data in humans (Hultborn and Pierrot-Desseilligny 1979), would act as an optimal force control during weak and strong muscle contractions. Such a theory is quite illuminating, but it is still questionable whether it could be applied to the present findings. Recently, the existence of Renshaw cells has been questioned for the distal forelimb of the cat (Scott et al. 1995; Illert et al. 1996), and there is no evidence yet that recurrent inhibition is functional in the control of the distal extremities in the monkey. However, this mechanism can serve as a model for some other interneuronal interactions in the spinal cord or within cortical modules.

In conclusion, the present investigation opens a new conceptual framework for the neuronal encoding of dynamic and, probably, kinematic movement parameters. At the same time, it raises a number of interesting questions concerning its functional relevance and its implementation in the central nervous system.

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