

Spatiotemporal activity patterns of rat cortical neurons predict responses in a conditioned task

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ABSTRACT Precise and repeated spike-train timings within and across neurons define spatiotemporal patterns of activity. Although the existence of these patterns in the brain is well established in several species, there has been no direct evidence of their influence on behavioral output. To address this question, up to 15 neurons were recorded simultaneously in the auditory cortex of freely moving rats while animals waited for acoustic cues in a Go/NoGo task. A total of 235 significant patterns were detected during this interval from an analysis of 13 hr of recording involving over 1 million spikes. Of particular interest were 129 (55%) patterns that were significantly associated with the type of response the animal made later, independent of whether the response was that prompted by the cue because the response occurred later and the cue was chosen randomly. Of these behavior-predicting patterns, half (59/129) were associated with an enhanced tendency to go in response to the stimulus, and for 11 patterns of this subset, trials including the pattern were followed by significantly faster reaction time than those lacking the pattern. The remaining behavior-predicting patterns were associated with an enhanced NoGo tendency. Overall mean discharge rates did not vary across trials. Hence, these data demonstrate that particular spatiotemporal patterns predict future behavioral responses. Such presignal activity could form templates for extracting specific sensory information, motor programs prespecifying preference for a particular act, and/or some intermediate, associative brain process.

The cerebral cortex is a highly interconnected network of neurons in which the activity in any neuron is necessarily related to the combined activity in the neurons that are afferent to it. Because of the presence of reciprocal connections between cortical areas, re-entrant activity through chains of neurons occurs. Furthermore, certain pathways through the network may be favored by nonhomogeneity in the number or efficacy of synaptic interactions between the neural elements as a consequence of developmental and/or learning processes (1). In cell assemblies interconnected in this way, some ordered sequences of intervals within spike trains of individual neurons and across spike trains recorded from different neurons will recur (2). Such recurring, ordered, and precise (on the order of a few milliseconds) interspike interval relationships are referred to as spatiotemporal patterns of discharges (3). This term encompasses both their precision in time and their occurrence across different neurons (even recorded from separate electrodes). Such patterns have been predicted on theoretical grounds (4), although the fundamental mechanisms leading to their generation remain controversial (5).

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Since the development of techniques able to detect and evaluate the statistical significance of this kind of precisely patterned activity (6–10), many studies have shown their occurrence in association with sensory stimuli (11), movement (12), and short-term memory task (13). Association with task performance also has been established for other related neurophysiological phenomena. For instance, brain activity related to processes occurring during preparatory mental processes produce synchronization of local field potentials in the cerebral cortex (14). Magnetoencephalographic recordings in humans revealed that specific changes in neuromagnetic fields were related to the preparation of the overt movements (15, 16). Furthermore, coherent local field potentials (17), coordinated timing of spikes (18), and exact spike synchronization of different neurons (19) have recently been revealed to occur in association with the expected moment of cue presentation. Yet, the available data demonstrate merely the presence of synchronized neural activity (20), whereas the presence of any causal relationship with behavior is not clear.

To prove that spatiotemporal patterns do indeed have a specific behavioral function, data are required that establish causal relations between the occurrence of precise temporal relationships and cognitive or motor processes. We therefore investigated whether the occurrence of patterns during a waiting period before a cue that would prompt a particular response were associated with variables of subsequent behavior, such as correctness of responses and reaction time. The data presented here demonstrate that such patterns do indeed exist.

METHODS

All procedures were performed according to Swiss guidelines for the use of laboratory animals and with the approval of the Swiss veterinary authorities.

Behavioral Task. Long-Evans (hooded) rats ($n = 3$, weighing 200–225 g) were trained to perform a complex auditory discrimination Go/NoGo task, in which reward was asymmetrical (reward only for correct Go trials; ref. 21). Details of task, training, and performance in this task will be presented elsewhere. In brief, animals (maintained at about 90% normal body weight) performed the task in a 380 mm wide \times 600 mm long \times 400 mm high box placed in a sound-attenuating room. They were conditioned to wait behind a stripe on the floor at the back of the box for the simultaneous delivery of two frequency-modulated sounds, one from each side of the box, either of high (12-kHz) or low (3-kHz) pitch. Sounds were delivered after the rat had been in the waiting area for a randomized interval of 10–14 s.

The animals were trained (through a sequence of simpler steps) to move from the waiting area to a response zone at the other end of the box (within a maximum allowed reaction time

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of 6 s) only when a sound of one specific pitch was delivered at one speaker, independent of what was delivered at the other. Four possible pitch-location combinations existed, two of which signaled a Go response (see Fig. 1B). For both Go and NoGo combinations, there was one simple (same pitch both sides) and one conflictual (different pitch on each side) combination. Performances to the simple combinations were usually >80%, whereas those to the conflictual stimuli were less, reflecting their high cognitive loading (both pitch and location analysis required, in the face of high motivation to respond). A sunflower seed was immediately delivered to the response zone following a correct response. Incorrect responses and failure to relocate to the waiting zone was signaled by a flashing light delivered at the response zone. No punishments were employed. The position of the animal was monitored by a series of infrared light beams that traversed the work space and the response area. Reaction time was defined as the time from onset of the sound stimulus until breaking of the first light beam. The task was self-paced by the animal; timing of the waiting period started only when the animal entered the waiting zone.

Surgical and Electrophysiological Procedures. After 1 month of training, the subjects achieved an overall performance level >75% and were surgically operated on. All surgical wounds were infiltrated with 1.25% solution of procaine (effocaine). General anesthesia was induced by an i.p. injection (1.0 ml/kg body weight) of a 4:3 mixture of ketamine/xylazine hydrochloride. This dose corresponds to 57 mg/kg ketamine and 8 mg/kg xylazine. The limb-withdrawal reflex was checked regularly to monitor the depth of anesthesia. All animals were mounted in a stereotaxic frame without ear-bars such that the dorsal surface of the skull was horizontal (flat-skull position; ref. 22). The skin was incised in the midline, and the scalp was cleared of connective tissue before coating with a layer of dental bonding cement (Super Bond, Sun Medical, Toriyama, Japan). This was roughened to allow locking to the skull of the dental construction cements used to fabricate the headpiece and replaced the use of skull screws. A small hole was drilled over the frontal cortex for insertion of an epidural silver-wire earth electrode and larger holes drilled over the auditory cortex of both sides centered 3.75 mm rostral to λ and 7.25 mm lateral of the midline (cortical areas TE1 and TE2; ref. 22). On each side, the dura was incised and a bundle of 4 tungsten microwire, Teflon-insulated electrodes (1.2-mm external diameter, AM Systems, Everett, WA) attached to amphenol strip connectors, was introduced into the cortex under electrophysiological control. These were cemented in place by using carboxylate cement at a depth where action potentials of good signal-to-noise ratio were seen. Cells were tested during surgery for responses to simple auditory stimuli applied via miniature speakers at the external auditory meati. However, because secondary as well as primary auditory cortex was aimed at, strong auditory responses were not an absolute requirement for final placement. The headstage was completed with a layer of two part acrylic dental cement, and the animal was allowed to recover for several days before recording began.

For recording during the behavioral task, a suspended and counterbalanced 8-channel unity gain headstage was plugged into the two head plugs via short flexible leads. The counterbalance system ensured that the cable and headstage together had an effective net weight near zero. The animal was placed in the task box and performed the task as before. Signals from the wires were amplified, filtered (700 Hz–10 kHz), and viewed on an oscilloscope. Six of the 8 channels were selected and fed to a 6-channel spike-sorting system (Alpha Omega Engineering, Nazareth, Israel). This system sorts spikes on the basis of a template-match algorithm and is capable of separating up to three spikes per channel. A maximum of 18 spikes could therefore be discriminated, but only the best 15 were selected

for recording. The epoch of spike discharges at a time resolution of 1 ms, as well as behavioral parameters (infrared beam crossings, onset of stimuli, and reward delivery), were digitally stored to a file on an Apple Macintosh IIx microcomputer. All data acquisition and task control was performed by using software developed in-house based on the LABVIEW packages and NuBus acquisition boards of National Instruments (Austin, TX).

Data Analysis. Spatiotemporal patterns (subsequently referred to as patterns) are defined as sequences of intervals with high temporal precision (of the order of few ms) between at least three spikes (of the same or different neurons) that recur at levels above those expected by chance. The classical pattern-detection algorithm (8, 10) is formed from two parts: first, the detection—the algorithm finds all single or multineuron sequences of intervals that repeat two or more times within a record; second, the estimation of significance—the algorithm computes how many of such sequences of intervals can be expected by chance and provides confidence limits for this estimation.

To allow the detection of, and significance estimation for, specific patterns independently of all detected sequences of intervals, we developed and applied an extension of the algorithm. This extension, which we term the pattern-grouping algorithm, is briefly outlined here. In addition to the two steps indicated above, the pattern-grouping algorithm performs clusterization into one group of sequences of intervals with slight differences in spike timing. This operation is aimed at optimizing the time jitters for spikes forming patterns united into the same group and estimation of the significance of the group in such a way to select the most salient groups. The new algorithm considers those sequences of intervals detected by the standard algorithm as templates for searches of similar sequences of intervals in the spike-train data. The optimization of the time accuracy around each spike occurrence in the template increases the probability that a detected pattern is not significant by chance. The final output of the algorithm consists of a set of patterns, each of which contain all previously detected sequences of intervals falling within an allowable jitter of the template. Because of the jitter-optimization procedure, the allowed jitters vary from pattern to pattern but never exceed a defined value. The significance of the occurrence of the repeated interval sequences compared with that expected by chance was then calculated in the usual way (8, 10) and those exceeding 1% significance level were accepted as representing spatiotemporal patterns. For this study, the pattern-grouping algorithm was set to find patterns of three spikes (triplets) repeating at least seven times during the 10-s waiting period preceding stimulus delivery, provided the entire pattern lasted not more than 1,000 ms and was repeated with an accuracy of less than ± 3 ms.

RESULTS

General Observations. A total of 415 single units were recorded during 28 sessions from the cortical auditory areas of both hemispheres of three rats. The total recording time was approximately 49 hr (an average of 105 min per session). However, this study concerns only the 10-s period preceding stimulus onsets. Thus, the total analyzed time for this report was limited to 12 hr 47 min of recording time corresponding to an overall count of 4,607 trials. During this time we recorded 1,054,136 spikes. The firing rate of the single units ranged between 0.14 and 5.76 spikes per s (median = 1.50).

A total of 235 patterns (i.e., significant sequences of intervals) were found, of which 39% (91/235) occurred within the spike train of a single cell, 50% (118/235) were formed by spikes from two single units, and 11% (26/235) involved spikes from three different cells. When two or more spike trains were involved, these were most often (100/144) recorded from the

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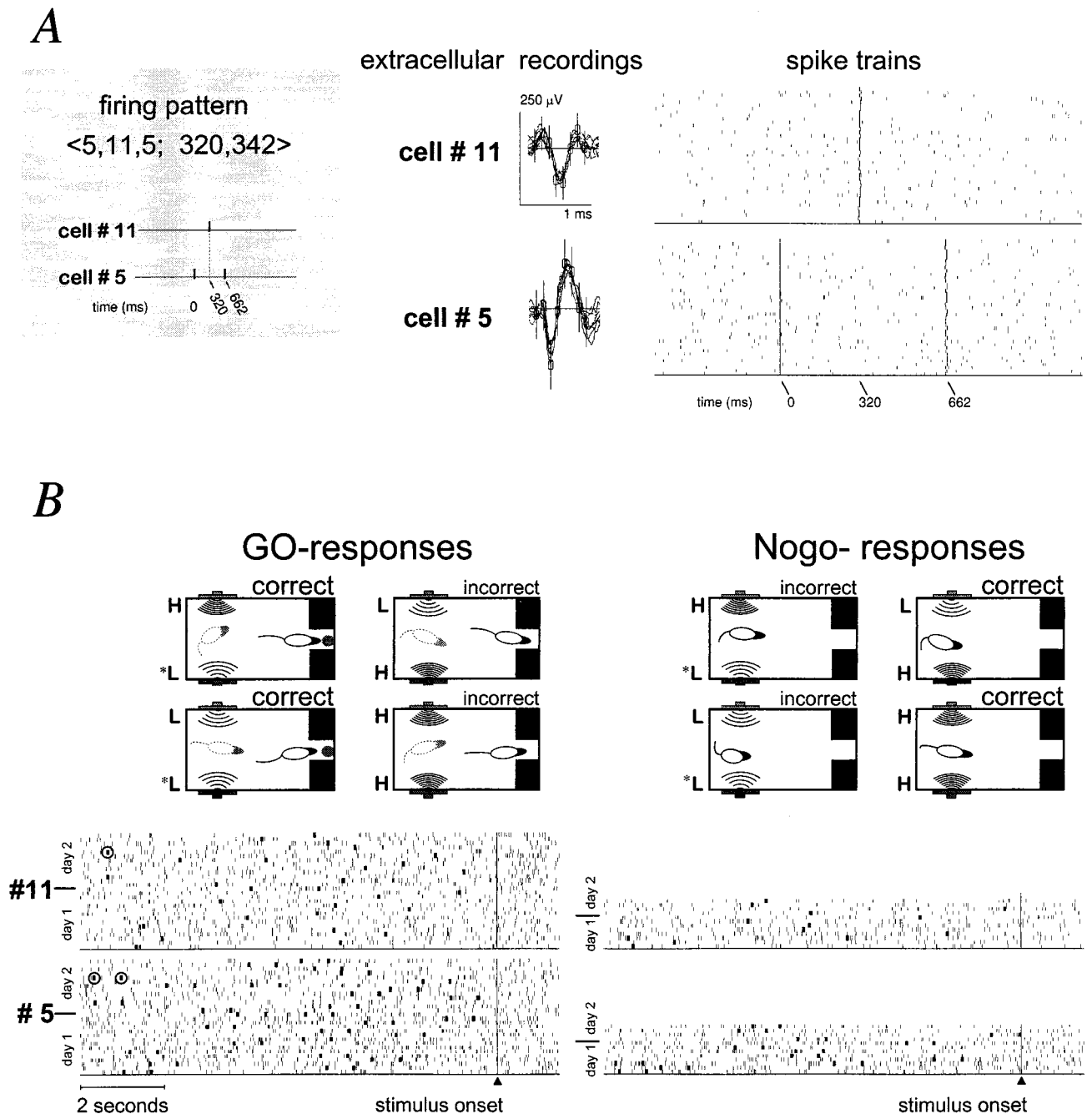


FIG. 1. (A) An example of a pattern formed by activity in two cells recorded from two different electrodes in the same hemisphere. Details of pattern timing are shown at *Left*. In the *Center*, several action potential waveforms from each cell are overlaid (scale bars for cell # 11 apply to both). Vertical lines on the traces are superimposed markers relating to settings of the template-matching software used to discriminate the waveforms. *Right*, all detected examples of the pattern formed by these cells displayed in rasters. Each tick mark shows the occurrence of an action potential, and each row shows a segment of data in which a pattern was detected. The rows have been slid past one another such that the first spikes of each occurrence of the pattern are aligned (a spike of cell # 5 at time 0). The accurate timing between that spike and a subsequent spike in cell # 11 and a later spike of cell # 5 causes these later spikes to also line up in the display, forming the nearly vertical lines at 320 ± 3 and 662 ± 3 ms delay. In this example, the data shown includes trials recorded on two consecutive days, as detailed in *B*. (B) Relationship of occurrence of pattern shown in *A* to Go-vs.-NoGo task performance. The possible behavioral situations in which Go and NoGo responses could occur are illustrated schematically (*Upper*). Go responses resulted both from correct movements to the feeder in response to low-pitch sound at the right speaker (*L) and from incorrect movements when a high pitch was delivered to this speaker (H). Conversely, NoGo responses could be correct (high pitch to right speaker) or incorrect (failure to move in response to low pitch to right speaker). *Lower* shows dot rasters of the same data shown in *A* but on a compressed time scale and aligned to the time of stimulus onset instead of to time of the first spike of the pattern. The trials are divided into those in which Go (*Left*) and NoGo (*Right*) responses occurred. Spikes involved in generating instances of the pattern during the waiting period (time to the left of the stimulus onset) are displayed as bars instead of ticks. Three spikes constituting one instance of the pattern are denoted by open circles. Note that there are more than twice as many Go trials ($n = 27$) with patterns than NoGo trials ($n = 12$), although the total number of Go and NoGo responses was nearly the same ($n = 283$ and 269 , respectively). In addition, in this example the reaction time for Go responses with a pattern (825 ± 60 ms) was significantly shorter than for Go responses with no pattern (985 ± 23 ms).

same wire or from two wires in the same bundle. However, it is of interest to note that nearly 20% (44/235) of all patterns included cells recorded across wires in opposite hemispheres. The total duration of the patterns ranged from 80 to 991 ms and was uniformly distributed. The spike intervals within the triplets ranged between 0 (i.e., synchronous firing of two cells participating in the pattern) and 870 ms. In a few cases it was possible to detect the very same pattern of three spikes on two consecutive days (as illustrated by Fig. 1), thus suggesting the stability of patterns over time as well as the reliability of our recording procedure.

Relationship of Patterns to Go/NoGo Performance. To determine whether certain patterns were associated with a particular behavioral choice (i.e., a Go or NoGo response to the cue signal), the following analysis was performed. First, we identified the records (i.e., sets of trials performed by an animal in one day) that contained one of the 235 sequences of intervals (noted above) that were found to be significant when considering all trials. We then divided the trials of each record into those in which a Go response occurred and those in which there was a NoGo response. Note that this division is independent of the nature of the cue signal because the animals made response errors in the task. A separate pattern-detection reanalysis was then run for each of these subsets of trials using the same criteria of significance as for the initial analysis. Of the 235 overall significant patterns, this procedure identified 59 (25%) patterns that were significant only in the Go trial subset (subsequently referred to as Go patterns, Fig. 1) and 70 (30%) that were significant only in the NoGo trial subset (NoGo patterns, Fig. 2), with the remaining patterns matching the significance criterion only when all trials were pooled. Thus, according to this analysis, considerable proportions of

patterns appear to be selectively associated with a particular behavioral outcome.

To obtain a more specific measure of the extent to which these patterns were predictive of behavior, we performed an analysis in which every occurrence was taken into account. A selected pattern repeated only seldom (<5% of all occurrences) within the same trial. Hence, on the basis of independent probabilities we could calculate the expected number of Go and NoGo patterns across all trials. This data (Table 1) confirmed a strong link between pattern category and subsequent behavior (Go or NoGo) on the trial-by-trial basis. Of 595 trials in which one of the 59 Go patterns occurred, 503 trials were indeed characterized by a Go response (only 459 were expected), whereas in 842 trials in which a NoGo pattern occurred, 695 NoGo behaviors were observed (compared with 594 expected).

Many of these Go and NoGo responses were in fact committed in error, and the effect of the patterns on the rate of errors is particularly illustrative of their association with behavior. The breakdown of the effect of pattern occurrence in relation to the four possible pitch-location cues is summarized in Table 1. As an example, consider the performance on the NoGo conflictual stimulus labeled HL. Here, there was an overall error rate (i.e., the rat made an incorrect Go response to the signal) of 38%. However, in the subset of trials in which a Go pattern occurred during the waiting period, the error rate was elevated to 80%. Conversely, the presence of a NoGo pattern reduced the error rate. The effect of NoGo patterns is particularly impressive in the case of the Go stimulus labeled LL, in which a correct Go response was observed in over 80% of the trials, thus showing that the rats found this an easy task to perform. However, in trials where a NoGo pattern was detected, correct performance fell to 58%. It is important to

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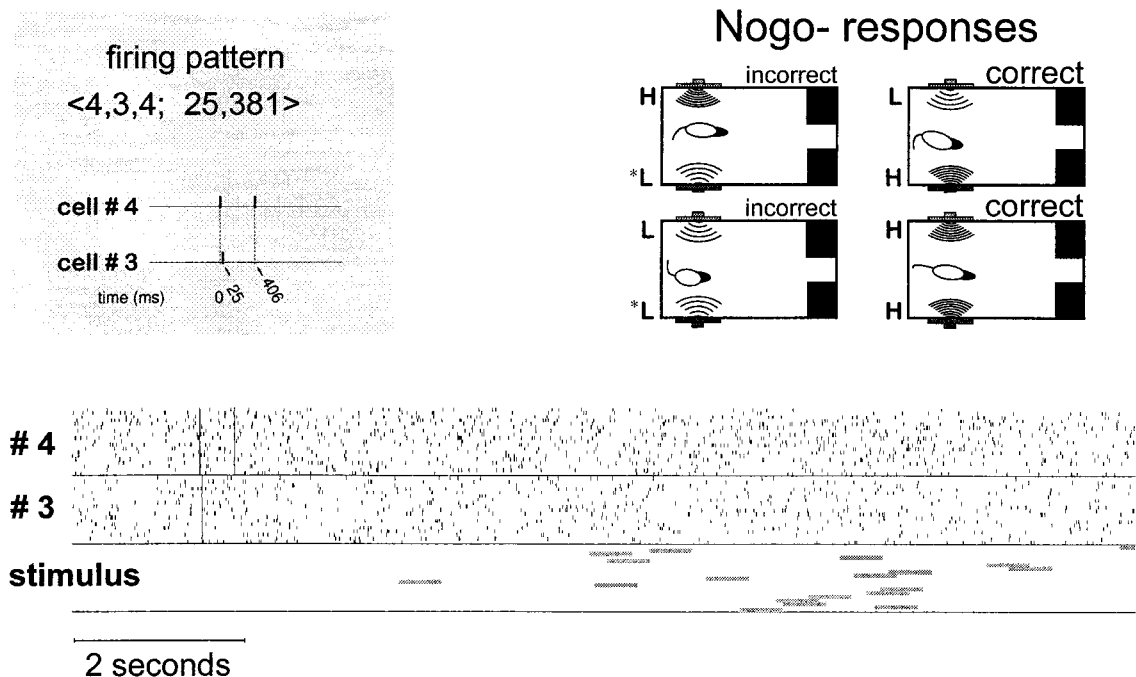


FIG. 2. An example of a NoGo pattern formed by activity in two cells recorded from the same electrode. Details of pattern timing are shown at *Upper Left*. *Upper Right* shows the behavioral conditions corresponding to the NoGo behavior (see Fig. 1). (*Lower*) Each small tick mark shows the occurrence of an action potential, and each row shows a segment of data in which a pattern was detected. The rows have been slid past one another such that the first spikes of each occurrence of the pattern are aligned (a spike of cell # 4). The accurate timing between that spike and a subsequent spike in cell # 3 and a later spike of cell # 4 causes these later spikes to also line up in the display, forming the nearly vertical lines at 25 ± 4 and 406 ± 2 ms delay with respect to pattern onset. Note that this pattern repeated 19 times but occurred only during the NoGo trials. In this session, the rat performed 29 Go trials and 90 NoGo trials.

Table 1. Effect of occurrence of selected firing patterns during the waiting period on the level of the subsequent Go response

Response stimulus	Go response as % of total stimuli received		
	All trials	Trials with Go patterns	Trials with NoGo patterns
Correct			
LL	83 (774/900)	99 (150/152)	58 (44/76)
HL	54 (739/1,368)	88 (149/187)	22 (46/301)
Incorrect			
LH	38 (621/1,629)	80 (199/225)	15 (55/251)
HH	3 (23/710)	16 (5/31)	1 (2/214)
All responses	46 (2,127/4,607)	85 (503/595)	17 (147/842)

Stimuli denoted by left-right speaker order. L, low; H, high. See Fig. 1B.

emphasize that the rat could not know in advance which randomly chosen stimulus would occur. Therefore, the distribution of pattern occurrences during the waiting period across the four possible pitch-location complex stimuli (see *Methods*) should be random. The distribution was tested by using contingency tables and found, as expected, to be not significantly different from the null hypothesis for either Go or NoGo patterns χ^2 test ($P > 0.05$ in both cases).

Relationship of Patterns to Reaction Time. To further investigate the influence of pattern occurrence on future behavioral performance, we also analyzed the reaction time (see *Methods*) for all trials ending with a Go response, irrespective of their correctness. Each of the 59 Go patterns were analyzed individually. For example, 1 such pattern was observed in the waiting period 21 times of 36 Go responses and 9 times of 23 NoGo responses. The reaction time to the 21 cues that followed a pattern occurrence was 760 ± 64 ms (mean \pm SEM), whereas for the other 15 Go responses with no pattern the reaction time was $1,115 \pm 124$ ms. Such accelerated response was found for 11 of 50 Go patterns, and the average difference in reaction time associated to these patterns was 250 ms \pm 38 ms.

DISCUSSION

These results show that the presence or absence of certain spatially and temporally organized sequences of intervals between spikes in cortical neurons have a bearing on subsequent behavior. In our experiments, precise spatiotemporal patterns appeared in the auditory cortex of freely moving rats waiting to perform an auditory discrimination in a reaction-time task. In contrast, consistent significant changes in overall firing rates were not observed over the same period. The patterns occurred before the auditory cue that prompted the rat to go or not to go and, as expected, were distributed independent of the nature of the randomly selected cueing stimulus. Certain patterns were specific for one of the two possible behavioral responses—Go or NoGo—irrespective of whether the response was correct. Furthermore, for some patterns associated with Go behavior, responses preceded by the pattern were performed significantly faster than those lacking them.

Data presented here complement and extend earlier work that established that such patterns can be found in conscious animals (3, 12, 13). However, although these studies established that patterns can occur selectively during particular phases of task performance, no definite behavioral impact or implication of their presence was observed. For instance, set-related activities in the auditory cortex of the rat (23) and motor regions in the monkey (24) have been described in terms of elevated rates of firing after an instruction stimulus, whereas an animal waits before making a movement in response to a later Go stimulus. In the present study, there were neither systematic changes in mean rate nor oscillatory patterns in the spike trains during the waiting period, yet we were able to

detect temporally organized activity predictive of subsequent response choice. These results do not rule out the possibility that large-scale neural activity is organized in oscillatory mode associated with auditory stimuli loaded with information, saliency, or task contingency as revealed in human auditory cortex by neuromagnetic methods (25).

Our results suggest that relevant information about future behaviors is carried by groups of specific neurons and expressed by the precise relative timing of individual spikes produced by members of the group independent of changes in firing rates. Nevertheless, it is not envisaged that the specific intervals that we find could in themselves be interpreted as bearing any particular information. They are instead seen as signposts toward a much larger integrated dynamic occurring in the cortex. The impact of the presence of specific spatio-temporal patterns on the responses of the animal suggests that such patterns participate in set-related activities that prime a particular response and thus bias the subject's response choice regardless of appropriateness. Alternate but not mutually exclusive hypotheses can be proposed, although the subjacent dynamics can only be conjectured about. First, patterns may be considered as parts of templates generated by preparatory processes activated to extract the useful information from forthcoming sensory cues (auditory "objects" in cognitive contexts requiring difficult discriminations). Templates would be activated selectively prior to the stimulus—the Go or the NoGo sound—and allow faster match/mismatch recognition; consequently, they are comparable to the "preconceived ideas" that influence human perception. Go patterns, for example, would reflect states wherein stimuli are more likely to be interpreted as Go signals. Such fine structures of brain activity, coined in terms more precise than overall mean rates, could be related to the thalamocortical information processing. Several lines of evidence indicate that the auditory cortex exerts a dynamic control over the functional segregation of signals transmitted via the thalamocortical loops, and activity in such loops may generate precisely repeating interspike intervals (26, 27).

The above suggestion seems most likely because neurons were recorded in a sensory area. However, a second hypothesis that cannot be ruled out is that patterns may be parts of motor programs, each prepared for performing actively either a Go or a NoGo response. Comparable biasing of motor processes has been postulated for humans performing "stop-signal" paradigms, where subjects must interrupt responses when delayed stop signals are presented (28, 29). Conceivably, both programs might coexist and compete as postulated by "race" models (30). Finally, because the separation between sensory and motor processes is fuzzy, bias could be established within more intermediate processes (predominantly neither sensory nor motor) and loosely be called associative. The patterns could reflect processes, such as synchronous firing in convergent/divergent chains of neurons (4) or a global mechanism of grouping caused by synchronous neural activation (31), that may be able to bind different cortical populations

(e.g., at modular or columnar level) into large-scale information-bearing structures.

In conclusion, the results presented here provide definite evidence that precise temporal coding exists in the cortex of freely moving rats and that valuable information for achievement of a behavioral task can be carried by precise timing of activity in neuronal networks. Furthermore, this study shows that not all patterns should be considered equal and the simple detection of excess of repeating firing patterns might mask important sensory or cognitive correlates.

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