Invariant neuronal activity associated to decision making in a rewarded choice reaction time task

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Abstract

Freely-moving rats were trained in a decision-making reaction time task to provide data that can be compared with noise-compatibility paradigms previously obtained in humans. A group of subjects was trained at first to positively discriminate an auditory pitch in a rewarded Go/Nogo response choice task. In a subsequent phase the same tones were simultaneously presented in different combinations from two locations, such that only the correct tone presented at the correct location is triggering a reward. Other subjects were trained either to discriminate at first the location cue, whereas the pitch cue was introduced in the subsequent phase or to categorize human vowels. At the end of the second phase the rats were chronically recorded with multiple electrodes located in the auditory and inferolimbic cerebral cortical areas. Invariant preferred firing sequences both within, and across cell spike trains tended to appear in association with the response predicted by the subject, as suggested by faster reaction times, or in association with specific errors of decision.

1 Introduction

Understanding the neural basis of decision making processes is a key question which is generally investigated by searching of where and how a "decision" is taken in a recursive way. It is not the dopamine cells, because current theories suggest that some input to them is responsible for suppressing their activity when a signal is not rewarding; so another structure of the circuit is likely to be where the "decision" is made. But how does that structure achieve that - perhaps by receiving information about learnt value from some other structure? Obviously, such an infinite regress cannot continue in a real brain. Decision making processes are usually studied with relatively simple stimulus-response tasks and inferences about these operations are generally based on experimental observables associated to the behavioral response. Such stimulus-response experiments are usually interpreted in terms of processing stages. Completion of a task is regarded as the execution of a series of distinct processes including perception, decision, and response initiation [1, 2].

The information flow between the processing stages, and the observed output resulting from manipulations of experimental variables, can be considered under various hypotheses, or models. Partially processed information is transferred continuously or in "chunks" following continuous [3] and asynchronous discrete models [4, 5]. On the opposite discrete models [6] assume that information processing in one stage has to be fully completed before the results are transferred to the next.

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The dimensional overlap model [7, 8, 9] attempts to encompass all classes of stimulus-stimulus and stimulus-response compatibility tasks by a full processing model consisting of two modules with stage-like characteristics. The response production module has two principal processing paths: automatic response activation and response identification [10].

According to this model it is rationale to investigate decision making by searching for invariant neural activity associated to either path of the response production. In order to avoid the pitfalls of the "grandmother cell" approach, where the information is coded by the activity of any one cell, the invariant neuronal activity can be investigated by searching subtle shifting of patterned neural activity of dispersed but interconnected elements. Learning processes are likely to potentiate or weaken certain pathways through the networks by affecting the number or efficacy of synaptic interactions between the neurons. Despite the plasticity of these phenomena it is likely that whenever the same information is presented in a network the same pattern of activity is evoked in a circuit of functionally interconnected neurons, referred to as "cell assembly". In cell assemblies interconnected in this way some ordered sequences of interspike intervals will recur. Such recurring, ordered, and precise (in the order of few ms) interspike interval relationships are referred to as spatiotemporal patterns of discharges or preferred firing sequences. For this to be true, temporal firing patterns must occur to a significant level above chance. Several evidence exist of spatiotemporal firing patterns in behaving animals, from rats to primates [11, 12, 13] where preferred firing sequences can be associated to specific types of stimuli or behaviors. The unlimited complexity offered by the unbounded number of possible temporal combinations of preferred firing sequences allows the build-up of a neural semantics to reach a level of complexity far enough to represent the highest brain activities that characterize human thoughts [14]. In this study we present evidence of invariant neuronal activity associated to specific mistakes in the response choice, not related to the cues carried by the stimulus.

2 Materials and Methods

2.1 Subjects

The subjects were Long-Evans rats *Rattus norvegicus* of either sex, aged 3–8 months at the begin of the experiment. The rats were housed individually with free access to water and restricted food supply. The rats were rewarded by sunflower seeds during the experimental sessions and were given supplemental pellets at the end of each session so to maintain their body weight at least at 90% of the *ad libitum* weight. All experimental procedures were carried out in accordance with the international guidelines for the care and use of laboratory animals and with governmental veterinary authorization.

2.2 Behavioral Training

The subjects were initially trained in a short-path black rectangular box (380 mm wide x 600 mm long x 400 mm high) inside a sound-proof room. At a later stage some subjects were trained in a long-path black box (750 mm wide x 800 mm long x 400 mm high). The box was open at the top, fitted with two loudspeakers (20 Watts, impedance 4-8 Ω, Poly Planar Inc., Warminster, PA) mounted on the outside of the box, on either side near one extremity A dispenser of sunflower seeds was mounted above the box at the level of a narrower section (80 mm) located at the extremity opposite to the loudspeakers. Several infrared beams are used to monitor the subject's position and to delimit a *stimulus delivery area* near the loudspeakers and a *feeder area* near the dispenser of sunflower seed. The reaction time (RT) was defined as the interval between the onset of the stimulus and the exit from the stimulus delivery area. The movement time (MT) was defined as the interval between the exit from stimulus delivery area and the entrance in the feeder area. A video camera on the ceiling over the box allowed for monitoring the rat's behavior from the outside of the sound-proof room.

Two habituation sessions of 15-30 minutes were conducted prior to training, in which the animals were placed individually in the experimental apparatus and allowed to move unhindered. The first step of training was aimed at conditioning the subjects to stay quietly in the stimulus delivery area and wait for an auditory stimulus before entering the feeder area and retrieve a sunflower seed. During the first 2 sessions (20 minutes/session), the acoustical stimulation was self-paced by the subject upon entering the feeder area and the sound was repeated in order to strengthen the sound-

reward association. The subjects were trained to exit the feeder area before a maximum allowed delay of 15 seconds. During the following sessions the subjects were trained to go in the stimulus delivery area and wait for the stimulus. Once the subjects had retreated to the rest area, a timer was started for a variable randomized time interval (6-15 seconds) before a new stimulus was delivered. The maximum delay for responding was decreased from 15 to 5 seconds in 4 sessions. Steady-state performance was determined by 3 successive sessions with performances over 90%. Overall, 7-10 sessions (at a rate of 2 sessions/day at 4 hours interval) were necessary to complete this phase.

During the discrimination training the response cues were introduced. In the case of the combined "pitch"-"location" paradigm the first cue was chosen between two choices (low vs. high pitch or right vs. left loudspeaker for the same pitch). The stimuli consist of complex frequency-modulated tones described in detail elsewhere [15]. In the case of vowels paradigm two sets of vowels, irrespective of the pitch of the speaker, were presented at both loudspeakers [16]. In both paradigms one set of stimuli was associated to the GO response (GO stimuli followed by a reward), whereas the other set was associated to the NOGO response (NOGO stimuli not associated to a punishment). The sequence of stimulus delivery was randomized using an algorithm to prevent biases described elsewhere [15]. A session lasted until the animal had made 27 correct responses to the rewarded stimuli. Overall, 26 sessions (at a rate of 1 session/day) were necessary to complete this phase with performances steadily >80%.

During the complex decision making task a set of new stimuli were introduced. If the subjects were initially trained to attend a low pitch from a certain loudspeaker then any combinations of same-pitch sounds delivered from two different locations are termed congruent (i.e., High pitch Right + High pitch Left, or Low pitch Right + Low pitch Left). Mixed pitch tone combinations were termed incongruent. Out of the four possible two-pitch combinations, two were associated with reinforcement, i.e. those which included the GO-pitch from the same loudspeaker used for training during the previous phase. The same procedure was applied to those subjects initially trained to attend the location and then exposed to the pitch cue. In the case of the subjects trained with the vowels this task included an additional set of the same vowels pronounced by new speakers. The test occurred at a rate of 1 session/day lasting an average of 40 minutes. A session was terminated after 27 correct GO responses or after an hour had elapsed.

2.3   Chronic Implantation of recording electrodes

After two weeks the subjects were surgically operated for the implantation of the microelectrodes. The subjects (weighing 280-330 g) were anesthetized by a mixture of ketamine (57 mg/kg) and xylazine hydrochloride (8 mg/kg) and mounted in a stereotaxic frame without ear-bars. Holes were drilled in the skull over the temporal cortex of both hemispheres. We preferentially aimed areas Te1 on one hemisphere and Te2, Te3 on the other hemisphere or the ipsilateral inferolimbic cortex, but the localization was assessed only after histological analysis of the site of electrolytic lesions performed before the sacrifice of the subjects. An epidural earth contact (flattened silver-wire) was introduced through a separate hole in the frontal bone. Bundles of 4 Teflon-insulated tungsten microwire electrodes were lowered into the cortex under electrophysiological recording-control at an angle of approx. 30 degrees from vertical (approaching normal to the cortical surface), to a depth where spike discharges of greatest signal-to-noise ratio were detected (usually around 700-1200 μm from the surface). Units were tested for responses to simple tone stimuli delivered from microphones (Bruel & Kjaer 4134) in the auditory canals. Electrodes were fixed in place with non-irritating carboxylate cement, and the contact sockets for electrodes and earth lead stabilized with acrylic cement. More details are described elsewhere [17].

2.4   Preferred Firing Sequences

Preferred Firing Sequences (PFS) were defined as sequences of intervals with high temporal precision between at least 3 spikes (triplets) of the same or different units that recurred at levels above those expected by chance by means of the "pattern grouping algorithm" (PGA) (Fig.1). PFS can be formed by spikes generated by one unit only. In this case PFS are referred to as 'single-unit patterns'. PFS that include spikes generated by different units are referred to as 'multi-unit patterns'. For the present study PGA [18, 19] was set to find patterns formed by three (triplets) or four spikes

(quadruplets), with a significance level $p = 0.10$, provided the entire pattern did not last more than $800\ ms$ and was repeated with a jitter accuracy of $\pm 5ms$.
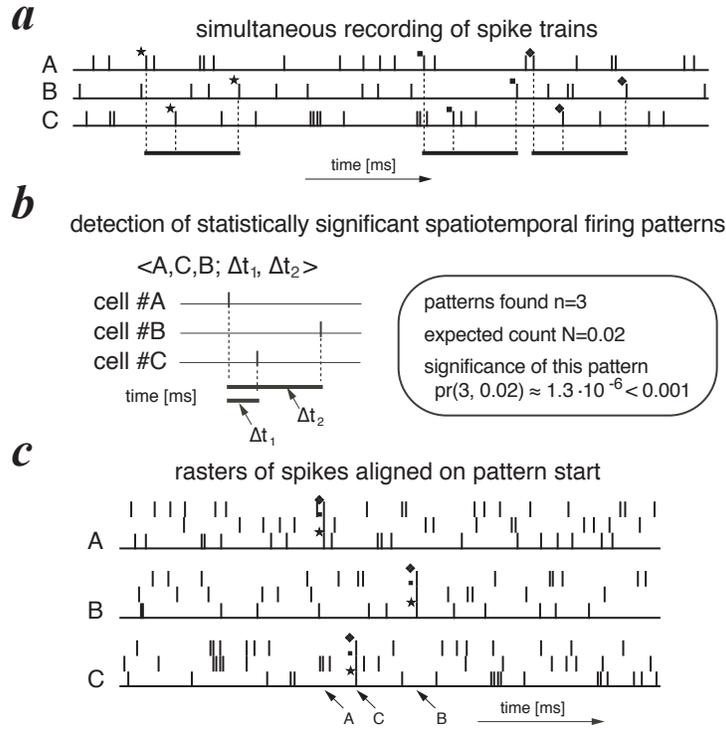
Figure 1: Outline of the general procedure followed by pattern detection algorithms. **(a)**: Analysis of a set of simultaneously recorded spike trains. Three cells, labeled A, B, and C, participate to a patterned activity. Three occurrences of a precise pattern are detected. Each occurrence of the pattern has been labeled by a specific marker in order to help the reader to identify the corresponding spikes. **(b)**: Estimation of the statistical significance of the detected pattern. **(c)**: Display of pattern occurrences as a raster plot aligned on the pattern start.

3 Results

A total of 2362 single units recorded from the cortical areas of both hemispheres of 17 rats were analyzed so far, corresponding to 188 sessions. Most spike trains included at least 10,000 events. The total recording time for each spike train was approximately 2 hours. The firing rate of the single units ranged between 0.05 and $24.44\ spikes/s$. The results here focus on the PFS that were found in the interval that immediately preceded or followed the stimulus onset.

About half of the PFS that we found could not be related to a stimulus feature nor to a motor behavior. The other PFS were mainly associated to a GO or to a NOGO response irrespective of its correctness, or associated to some class of stimuli determined by complex sensory features such as a specific set of pitches. Because of the lack of space we emphasize an examplar PFS of the latter case illustrated by the pattern $<\ 1,\ 1,\ B\ ;\ 16 \pm 2.0,\ 307 \pm 2.0\ >$ composed by spikes produced by two single units labeled #1 and #B (Fig. 2). This notation means that the PFS starts with a spike of unit #1, followed $16 \pm 2.0\ ms$ later by a second spike of the same unit, and followed by a spike of unit #B $307 \pm 2.0\ ms$ after the pattern onset. We observed 15 repetitions of this pattern during the whole session; 13 times this PFS was associated with the GO stimulus corresponding to vowel /ε/. In addition, this PFS occurred within 3 seconds after the stimulus onset 10 times out of 15.

Despite an overall excellent performance the rat responded incorrectly 11 out of 21 times when the stimulus was a GO stimulus characterized by a fundamental frequency $f_0 = 325\ Hz$, i.e. after stimulus /$\varepsilon_{(325)}$/. About half (5/11) of such mistaken trials occurred when the PFS $<\ 1,\ 1,\ B\ ;\ 16 \pm$

► stimulus Go -> response GO
■ stimulus Go -> response NOGO $/\varepsilon_{(325)}/$
◉ stimulus NOGO -> response NOGO
◇ stimulus NOGO -> response GO
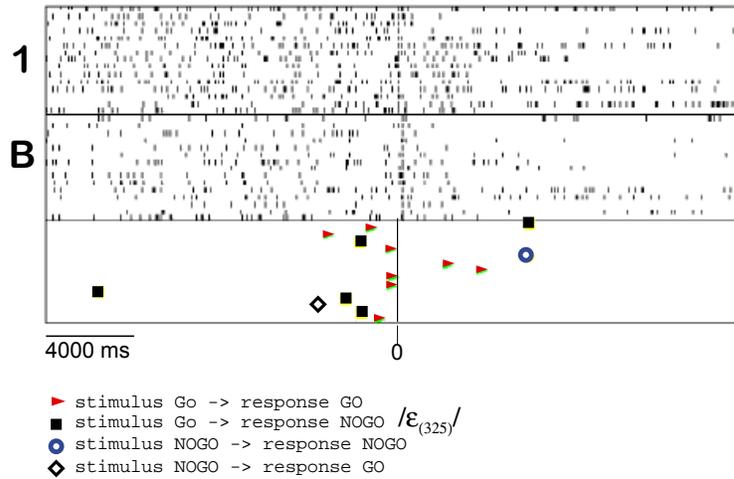
Figure 2: Raster display of the activities of two cortical neurons recorded from different electrodes, one in Te3 from the right hemisphere and the other one in the ipsilateral inferolimbic cortex. The rasters are aligned by displaying the first spike in the pattern $< 1, 1, B ; 16 \pm 2.0, 307 \pm 2.0 >$ at time 0. The PFS is repeated 15 times with a jitter of $\pm 2.0\ ms$.

$2.0, 307 \pm 2.0 >$ was observed (Fig. 2). The peristimulus time histograms (PSTH) of the cells participating to the pattern show that the evoked activity depended on the correctness of the trial (Fig. 3). It is important to note that the different PSTHs were different despite the very same sensory stimulation. Notice that during the incorrect trials the activity of both cells #1 and #B was decreased after about $300\ ms$ from stimulus onset.
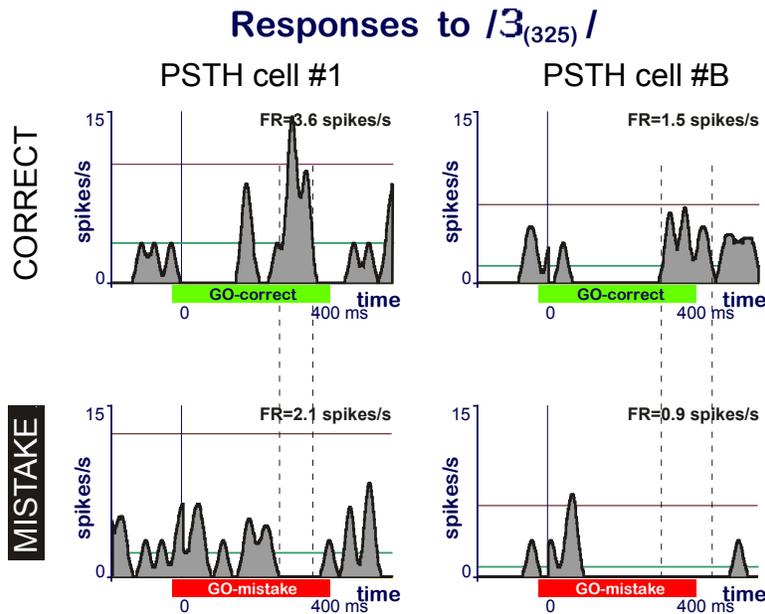
Figure 3: Peristimulus time histogram (PSTH) of the same cells participating to the pattern of Fig. 2. The PSTHs during the trials characterized by a subsequent correct response to the GO stimulus $/\varepsilon_{(325)}/$ is plotted in the upper row diagrams. The PSTHs during the trials characterized by a subsequent incorrect response to the same GO stimulus $/\varepsilon_{(325)}/$ is plotted in the lower row diagrams.

5

4 Discussion

At the level of the activity of cell assemblies the present study reports experimental observations that demonstrate, for the first time to our knowledge, the existence of invariant electrophysiological correlates that are associated to the outcome of the decision in a rewarded choice reaction time task. In particular it is remarkable that cells that were identified on the basis of their participation to preferred firing sequences were responding with a stimulus-onset triggered evoked activity that depended on the outcome of the decision. The electrophysiological investigation of decision making at the single unit level has been focused in studying dopamine mediated activity [20] in the striatum and cerebral cortex [21, 22]. Those studies described complex event-related response patterns associated to the reward expectation, prediction errors and motivation but could not reveal a precise link between those responses with the network activity.

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. Due to the cortico-basal ganglia-thalamo-cortical loop and the presence of reciprocal connections between cortical areas, re-entrant activity through chains of neurons occurs. Precise and repeating spike train timings within and across neurons define "spatio-temporal patterns" of activity corresponding to preferred firing sequences. The present results confirm the existence of PFS associated with precise stages of a behavioral task [11, 12, 13]. In addition, the present results establish a link between the cells that participate to recurrent neuronal networks likely to encode the information with high temporal accuracy with event-related activity. However, the fact that a custom made statistical analysis can detect significant firing patterns that are associated to cognitive processes does not tell much about the read-out mechanisms that should be embedded in the neural networks for decoding the transmitted information. The observation that the same stimulus may elicit different responses in the same cell according to the decision making could be related to the fact that the expectedness of an event or the emotion can affect its perception such that the brain builds-up a wrong representation of the expected stimulus [23, 24]

The behavioral strategies observed in our protocol suggest a competition between two processes: one involving stimulus evaluation, response preparation and execution, the other involving recognition of the stimulus features associated with inhibition of the Go-response [15]. It is worth reporting that in the current results single unit activity suggests that at latencies close to $300\ ms$ the decision making process suppressed or inhibited the stimulus-related response of selected cells. In humans the electrophysiological investigation of invariant correlates of decision making revealed a negative event-related potential [25] and error-related negativity [26] occurring near $250\ ms$ after outcome stimuli that inform human participants about gains and losses in a gambling task.

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