Behavioral/Systems/Cognitive

Spike Timing, Spike Count, and Temporal Information for the Discrimination of Tactile Stimuli in the Rat Ventrobasal Complex

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The aim of this work was to investigate the role of spike timing for the discrimination of tactile stimuli in the thalamic ventrobasal complex of the rat. We applied information-theoretic measures and computational experiments on neurophysiological data to test the ability of single-neuron responses to discriminate stimulus location and stimulus dynamics using either spike count (40 ms bin size) or spike timing (1 ms bin size). Our main finding is not only that spike timing provides additional information over spike count alone, but specifically that the temporal aspects of the code can be more informative than spike count in the rat ventrobasal complex. Virtually all temporal information—i.e., information exclusively related to when the spikes occur—is conveyed by first spikes, arising mostly from latency differences between the responses to different stimuli. Although the imprecision of first spikes (i.e., the jitter) is highly detrimental for the information conveyed by latency differences, jitter differences can contribute to temporal information, but only if latency differences are close to zero. We conclude that temporal information conveyed by spike timing can be higher than spike count information for the discrimination of somatosensory stimuli in the rat ventrobasal complex.

Introduction

Understanding the neural code is a major challenge for system neuroscientists. To attempt a definition, the neural code is "a system of signals or symbols for communication"—which is the Merriam-Webster's lemma for "code"—applied to the nervous system. The field of neural coding relies on two main assumptions: information is carried by neurons, and neural "symbols" are made of spikes. The fundamental problem of neural coding is therefore to understand how spikes construct the symbols that neurons use to communicate information.

Spikes are stereotyped events precisely defined in time. The simplest way to construct symbols with such events is to use spike count, i.e., to count the number of spikes occurring in a given time window (Adrian, 1928). Using spike count, a neuron can only construct as many symbols as the number of spikes it is able to fire within the time window. A potentially more powerful way to construct symbols with spikes is to use spike timing, i.e., to consider exactly when spikes occur within the time window (Opticam and Richmond, 1987; Bialek et al., 1991; Hopfield, 1995; deCharms and Merzenich, 1996; Victor and Purpura, 1996; de Ruyter van Stevenick et al., 1997; Borst and Theunissen, 1999;

Reich et al., 2001; Chase and Young, 2006; Butts et al., 2007). The maximum number of symbols a neuron can construct with spike timing is limited only by the temporal resolution of the code (MacKay and McCulloch, 1952). In formal terms, the information capacity of spike timing is much higher than the information capacity of spike count.

The rat trigeminal system offered an attractive model that contributed to uncover the role of spike timing in the neural code. Two main problems have been investigated: (1) discrimination of stimulus location, when the same stimulus was delivered to different whiskers; (2) discrimination of stimulus dynamics, when stimuli with different dynamical content were delivered to the same whisker. In the whisker cortex, spike timing was consistently shown to convey more information than spike count alone (Ghazanfar et al., 2000; Panzeri et al., 2001; Foffani and Moxon, 2004; Arabzadeh et al., 2006). This importance of spike timing was extended to the forepaw cortex, suggesting a more general principle of sensory processing (Foffani et al., 2004, 2008; Blanc and Coq, 2007).

All tactile information reaching the cortex, however, has to pass through the thalamus. Consistently with the high temporal precision of thalamic responses to whisker stimuli (Nicolelis and Chapin, 1994; Deschênes et al., 2003; Aguilar and Castro-Alamancos, 2005), spike timing is more informative than spike count alone in the trigeminal thalamus (Ghazanfar et al., 2000; Montemurro et al., 2007). We have previously shown that thalamic neurons of the ventroposteromedial nucleus (VPM), which represents the whiskers, and of the ventroposterolateral nucleus (VPL), which represents the rest of the body, exhibit essentially the same magnitude/latency structure in their responses to ste-

reotyped tactile stimuli (Aguilar et al., 2008). Here, we apply information-theoretic measures and computational experiments on the same data, investigating the nature of spike timing information in the entire ventrobasal complex.

Materials and Methods

Experimental procedures. Experimental data have been previously published (Aguilar et al., 2008). Data were obtained from 13 male rats (250–350 g) anesthetized at stage III-3 (Friedberg et al., 1999). The level of anesthesia was monitored by electrocorticogram recording from the primary somatosensory cortex and by tail-pinch reflex. The experiments were performed under a predominant frequency of 3–4 Hz in the electrocorticogram recording, which represents a less synchronized state compared with the deeper anesthesia levels characterized by rhythmic bursts at lower frequencies. If rhythmic bursts were detected during the experimental protocol, the stimulation protocol was aborted. The level of anesthesia was kept constant at stage III-3 throughout the course of the experiments by applying supplemental doses when required (1/4 of original doses). Stage III-3 was chosen because it allows consistent single-neuron recordings to be performed through long stimulation protocols, and it retains at least part of the spatiotemporal complexity that characterizes the responses of thalamocortical neurons in active states (Aguilar and Castro-Alamancos, 2005).

Thalamic extracellular single-unit recordings were obtained from VPM and VPL (anteroposterior, −2.3 to −4.0; lateral, 2–4; dorsal, 5–7) using tungsten electrodes with 4MΩ impedance (at 1 kHz). We studied the responses to whisker stimulation for VPM neurons and the responses to cutaneous stimulation in forepaw or hindpaw for VPL neurons. Once a neuron was isolated, we located the receptive field center, defined as the whisker or cutaneous area that consistently elicited the response with greater magnitude (number of spikes/stimulus) and shorter latency ($n = 39$ neurons). In a subset of VPL cells ($n = 11$ neurons), we located not only the center of their receptive field (e.g., one digit) but also a responsive surround location (e.g., an adjacent digit).

We then applied our ON–OFF tactile stimulation protocol, which consisted of a set of 100 square-pulse stimuli of 0.5 Hz frequency and 500 ms duration. All stimuli were generated using a Master8 electrical stimulator (A.M.P.I.) with an ISO-Flex stimulus isolator (A.M.P.I.). Electrical pulses were delivered to a custom-made piezoelectric sensor attached to a rigid tungsten bar (0.5 mm in diameter, 2.5 cm long, with the tip curved at 90° for 5 mm). The piezoelectric sensor transduces electrical pulses into mechanical movements, whose range depends on the voltage. We used a voltage of 90 V, which imposed a final vertical movement of 0.5 mm to the tungsten bar. The tungsten bar was situated manually under microscopic control (Leica M300; Leica Microsystems) just a few micrometers over, but never touching, the whisker or the cutaneous area selected previously. The output of the Master8 stimulator was sent to the CED Power 1401 and recorded in Spike2 together with the signals to trigger the subsequent data analysis.

Neurons were meticulously discriminated off-line using filtering, voltage threshold methods and spike-sorting protocols in a complementary way. For the purpose of the present study, we considered two datasets: (1) the reduced dataset of 11 VPL neurons stimulated both in the center of their receptive field and in the responsive surround location; (2) the full dataset of 39 neurons stimulated only in the center of their receptive field.

Data analysis. Our basic problem was to quantify how much information can be extracted about the discrimination of stimulus location and the discrimination of stimulus dynamics from the single-trial responses of individual thalamic neurons, using either spike count or spike timing. As a model of discrimination of stimulus location, we considered the problem of discriminating between center and surround stimuli. As a model of discrimination of stimulus dynamics, we considered the problem of discriminating between ON and OFF stimuli delivered to the same location. The main difference between the discrimination of ON versus OFF stimuli compared with the discrimination of stimulus location is the following: independently of whether the dynamical difference of ON versus OFF stimuli (i.e., opposite movement direction of the stimulator) activates different peripheral receptors, ON and OFF stimuli remain con-

fined within a single cutaneous area (or whisker) somatotopically corresponding to the same thalamic cluster (or barreloid); conversely, in the discrimination of stimulus location, stimuli delivered to different fingers (or whiskers) somatotopically correspond to different thalamic clusters (or barreloids). Nonetheless, the basic coding principles under investigation are the same for the discrimination of stimulus location and for the discrimination of ON vs OFF stimuli.

By "information," here and throughout the study we specifically refer to Shannon's mutual information between the single-neuron responses and the stimuli. To discriminate two stimuli is a binary problem, so the maximum information, i.e., the entropy of the stimuli, is 1 bit. To say that a neuron conveys 1 bit of information means that from any single-trial response we can infer with full certainty which of the two stimuli generated that response. Indeed, spike timing information is more likely to emerge when the full information capacity of spike timing can be exploited, which happens in the discrimination between a high number of stimuli. The fact that we used binary discrimination problems is thus conservative for our purposes. To corroborate that our main results are not specific for binary discrimination, in neurons stimulated both in the center of their receptive field and in the responsive surround location we also performed the discrimination between all four stimuli available (ON center, ON surround, OFF center, OFF surround). In this case, the entropy of the stimuli is 2 bits.

Spike count information. To extract spike count information, for each neuron we considered a 40-ms-long poststimulus time window, counted the number of spikes the neuron emitted in each single trial, estimated the conditional probabilities of the responses given the stimuli, and directly calculated the mutual information between responses and stimuli as follows:

$$I(r,s) = \sum_s \sum_r P(s)\, P(r|s) \log_2\!\left(\frac{P(r|s)}{P(r)}\right), \qquad (1)$$

where $P(s)$ is the prior probability of occurrence of the stimulus s, which was always 0.5 for both stimuli because the number trials per stimulus was the same (100), $P(r|s)$ is the conditional probability of the response r to occur given the stimulus s, and $P(r)$ is the probability of the response r to occur given any stimulus. Because the responses of our neurons almost never exceeded 4 spikes in any given trial, the upward bias of the mutual information attributable to finite sampling was experimentally minimized by using 20 times as many trials per stimulus (100) as the number of possible responses (five).

Spike timing information. To extract spike timing information, we divided the poststimulus time window into 40 bins of 1 ms and registered the presence or absence of a spike in each bin as 1 or 0. With 40 1 ms bins, a neural response to a stimulus looks something like this: 0000000100010000000000000000000000000000.

The above response represents a neuron that fires two spikes, the first one 8 ms after the stimulus and the second one 12 ms after the stimulus. To calculate the mutual information with these types of responses is somewhat problematic, because the number of possible responses is too high for their probabilities to be precisely estimated from the finite number of trials experimentally available (in our case 100), which produces upward bias in the mutual information measure (Panzeri et al., 2007; Nemenman et al., 2008). To avoid this problem, we reduced the dimensionality of the responses by using them to classify the stimuli. To this end, we used the peristimulus time histogram (PSTH)-based classification method (Foffani and Moxon, 2004), which consists of creating a set of templates based on the average neural responses to the stimuli delivered (i.e., PSTHs), and classifying each single-trial response by assigning it to the stimulus with the "closest" template in Euclidean distance sense. The outcome of the classification is then used to calculate the mutual information between the predicted stimuli σ and the real stimuli s, as follows:

$$I(\sigma,s) = \sum_s \sum_\sigma P(s)\, P(\sigma|s) \log_2\!\left(\frac{P(\sigma|s)}{P(\sigma)}\right), \qquad (2)$$

where $P(s)$ is again the probability of occurrence of the stimulus s (i.e., 0.5 for both stimuli in our case), $P(\sigma|s)$ is the probability of predicting stim-

ulus σ when stimulus s was delivered, and $P(\sigma)$ is the probability of predicting stimulus σ independently of what stimulus was actually delivered. The way by which the conditional probabilities $P(\sigma|s)$ are estimated using the PSTH-based classifier can be formalized as follows:

$$P(\sigma = 1|s = j) = \frac{1}{N}\sum_{t \in j}(\min_{s'}[X(s',t)] \equiv i)$$

$$X(s',t) = \begin{cases} \sum_b (r_b(t) - \bar{r}_b(s'))^2 & s' \neq j \\ \sum_b \left(r_b(t) - \left(\bar{r}_b(s') - \frac{r_b(t)}{N}\right)\frac{N}{N-1}\right)^2 & s' = j \end{cases} \quad (3)$$

where N is the number of trials per stimulus ($N = 100$), $t \in j$ indicates the trials corresponding to stimulus $s = j$, the minimum is calculated across all stimuli s' (in our case two), $r_b(t)$ represents the single-trial response in bin b ($b = 1{:}40$) of trial t, and $\bar{r}_b(s')$ is the PSTH value of bin b corresponding to stimulus s' (i.e., the template), calculated as follows:

$$\bar{r}_b(s' = k) = \frac{1}{N}\sum_{t \in k}r_b(t). \quad (4)$$

Importantly, when the single-trial response $r_b(t)$ corresponding to stimulus j is compared against the PSTH $\bar{r}_b(s')$ corresponding to the same stimulus $s' = j$, the single-trial response is subtracted from the PSTH in the calculation of the Euclidean distance $X(s', t)$ to guarantee complete cross-validation in the classification (Foffani and Moxon, 2004). The upward bias of the mutual information, because of finite sampling, was experimentally minimized by using 50 times as many trials per stimulus as the number of possible stimuli (two). The mutual information $I(\sigma, s)$ between predicted stimuli and real stimuli represents a rigorous lower bound of the mutual information between the binned neural responses and the stimuli (Kjaer et al., 1994; Rolls et al., 1997; Furukawa and Middlebrooks, 2002; Schneidman et al., 2003). We thus used this conservative measure to extract spike timing information in our data.

Spike timing information, spike count information, and temporal information. The concept of spike timing implicitly considers both how many spikes occurred and when they occurred. Intuitively, there is no timing if there is no spike. This concept of spike timing is not related to the particular method we used to estimate spike timing information (the PSTH-based classification method), but is intrinsic in the way the responses are considered to construct the symbols of the code (i.e., binning at 1 ms bin size). This is consistent with previous studies applying information measures in the rat somatosensory system (Panzeri et al., 2001; Petersen et al., 2001; Foffani et al., 2004; Arabzadeh et al., 2006; Montemurro et al., 2007; Foffani et al., 2008).

In the present work, we explicitly considered that spike timing information includes both spike count information (how many spikes occurred) and temporal information (when they occurred). In general, temporal information and spike count information are not independent. Defining ΔI as the synergy/redundancy between temporal information I_{temporal} and spike count information $I_{\text{spike-count}}$, we can write the following intuitive relation (Nelken et al., 2005): $I_{\text{spike-timing}} = I_{\text{spike-count}} + I_{\text{temporal}} + \Delta I$.

The synergy/redundancy term ΔI is zero not only when spike count information and spike timing information are independent, but also when spike count information in zero. In these cases all spike timing information is temporal information.

To reach the conclusion that temporal information alone is greater than spike count information, we thus performed two analyses. (1) The first analysis consisted of considering only the first spike in each single-trial response and only responsive trials (i.e., trials with spikes) (Nelken et al., 2005). In this condition, spike count information is identically zero, so all spike timing information estimated with the PSTH-based classification method is indeed temporal information. (2) The second analysis consisted of selecting neurons that exhibited similar response magnitudes to the stimuli. In these neurons, spike count information should be close to zero, so the difference between spike timing information and spike count information will represent a tight lower bound of the tem-

poral information, i.e., most spike timing information will indeed be temporal information.

Simulations with latencies and jitters. To further investigate the basic elements of the temporal code, we performed a set of computational experiments. Using the physiological data as the starting point, the simulations allowed us to explore a larger range of response parameters than that available in the physiological variability. We modulated three main parameters of the responses: (1) the latency difference between stimuli, (2) the overall jitter of the responses, and (3) the jitter difference between stimuli. All three parameters represent the fundamental properties of the simulated responses, and the information obtained with these simulations will allow us to bring the results to a more general level.

To modulate the latency difference, for each neuron we first aligned the responses to the two stimuli so that the latency difference was 0 ms. We then moved the responses to one stimulus respect to the other, to impose a determined latency difference. This operation was repeated with increasing latency difference (0.2 ms steps). For each latency difference, we calculated the spike timing information that could be extracted about the discrimination between the two stimuli.

To modulate the overall jitter, defined as the SD of the first-spike latency averaged across the two stimuli, we added Gaussian noise to each single-trial first-spike latency, resulting in an increased overall jitter of the neural responses. This operation was repeated with increasing variance of the Gaussian noise (1 ms steps), resulting in an increasing overall jitter. For each jitter value, we calculated the spike timing information that could be extracted about the discrimination between the two stimuli. Importantly, adding jitter to the neural responses is formally equivalent to adding jitter to the temporal reference used to trigger the responses, which can be interpreted in terms of imprecision of a decoder. Our results will thus also provide basic requirements for a decoder to be able to extract temporal information from the neural responses.

To modulate the jitter difference, we added Gaussian noise to the single-trial first-spike latencies, only in correspondence to the stimulus with smaller jitter to reach a situation in which the jitter difference was approximately zero. We then increased the variance of the Gaussian noise (5 ms steps), resulting in an increasing jitter difference between the stimuli. For each jitter difference, we calculated the spike timing information that could be extracted about the discrimination between the two stimuli.

The simulations described above were also combined to investigate the joint contribution of latency differences, overall jitter and jitter differences to the temporal information.

Throughout the text values are given as mean $\pm$ SD. Statistical comparisons were performed with paired t tests or repeated-measures ANOVA. Results were considered significant at $p < 0.05$. All the analyses were performed in Matlab (version 7.1, The Mathworks).

Results

Spike timing information in VPL

We analyzed a dataset of 11 well discriminated VPL neurons responding to ON and OFF tactile stimuli delivered to two different locations: the center of their excitatory receptive field (e.g., one digit) and a responsive surround location (e.g., an adjacent digit). As a model of discrimination of stimulus location, we used the ON responses to discriminate between center and surround stimuli (Fig. 1A,D). Using spike count we could extract 0.18 ± 0.13 bits of information. Using spike timing we could extract 0.37 ± 0.30 bits of information, that is 106% more information than spike count. As a model of discrimination of stimulus dynamics we discriminated between ON and OFF stimuli delivered at the center location (Fig. 1B,E). Using spike count we could extract 0.38 ± 0.27 bits of information. Using spike timing we could extract 0.65 ± 0.18 bits of information, that is 71% more information than spike count. We also discriminated between ON and OFF stimuli delivered at the surround location (Fig. 1C,F). Using spike count we could extract 0.14 ± 0.13 bits of information. Using spike timing we could extract 0.31 ± 0.23 bits

A
ON center

B
ON center

C
ON surround

ON surround

OFF center

OFF surround
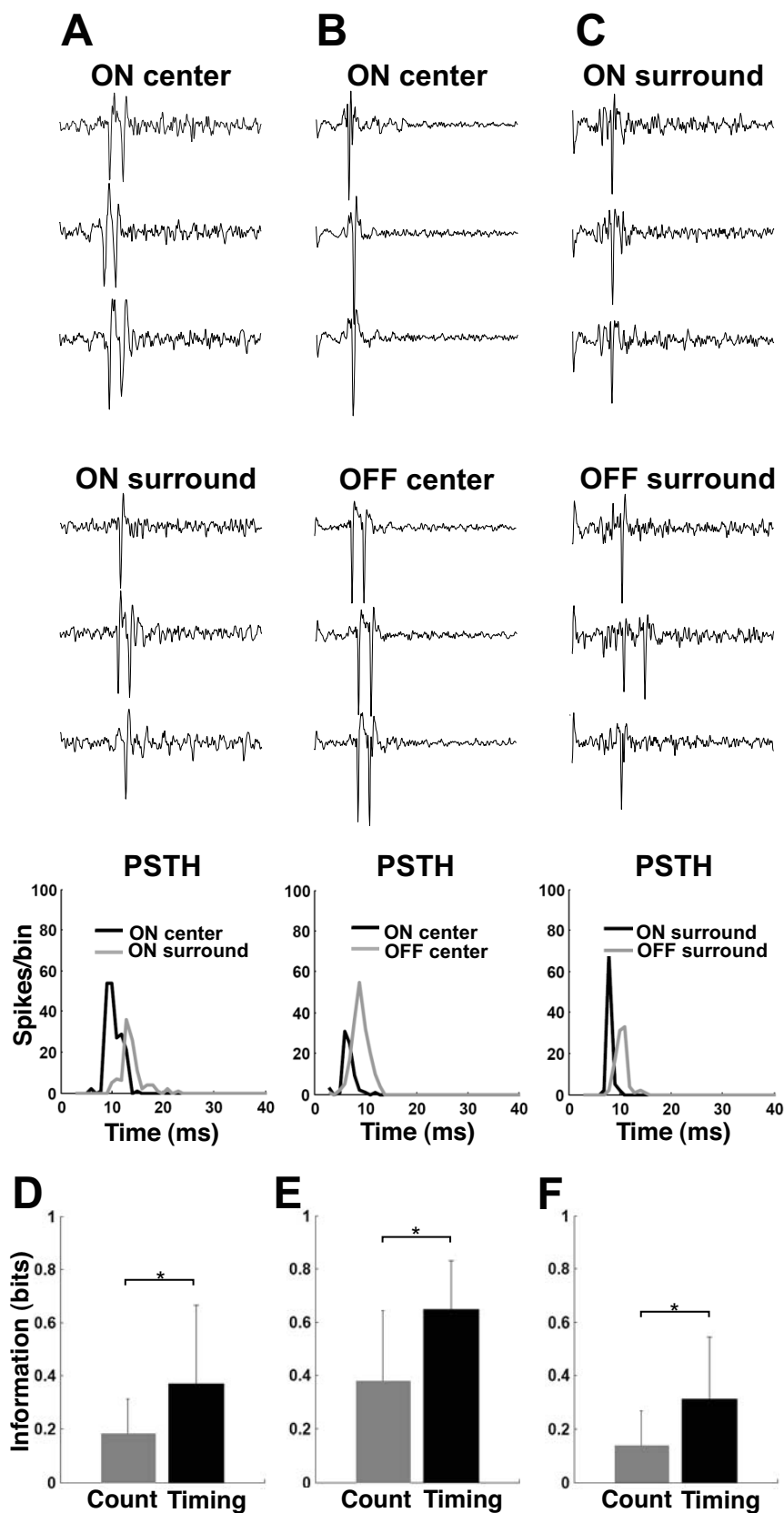
PSTH

PSTH

PSTH

Figure 1. Spike timing information in VPL. **A**, Discrimination of stimulus location. Representative neuron responding to ON stimuli delivered to its receptive field center (top three traces) and to a responsive surround location (middle three traces), with the corresponding PSTHs (bottom, calculated over all 100 responses/stimulus available). **B**, **C**, Discrimination of stimulus dynamics. Representative neurons responding to ON and OFF stimuli delivered (**B**) to the receptive field center, or (**C**) to a responsive

of information, that is 121% more information than spike count. Two-way repeated-measures ANOVA confirmed that spike timing information was significantly greater than spike count information in the three discrimination problems described above (first factor, spike count vs spike timing: $p = 0.0055$; second factor, the discrimination problem: $p = 0.0006$, interaction $p = 0.38$). Finally, we discriminated between all four stimuli: ON stimuli delivered to the center, ON stimuli delivered to the surround, OFF stimuli delivered to the center, OFF stimuli delivered to the surround. Using spike count we could extract 0.34 ± 0.20 bits of information. Using spike timing we could extract 0.78 ± 0.29 bits of information, that is 129% more information than spike count (paired t test: $p = 0.0017$).

Spike timing information, spike count information, and temporal information
The binned neural responses used to investigate the role of spike timing quantify both how many spikes occurred (spike count information) and when they occurred (temporal information). Let us consider two representative neurons (Fig. 2). One neuron responded to the two stimuli with different magnitudes and different latencies (Fig. 2A). The other neuron responded to the two stimuli with similar magnitudes and different latencies (Fig. 2B). In the first neuron, in which the response magnitudes to the two stimuli were different (1.4 vs 3.1 spikes/stimulus), spike timing did not provide additional information beyond spike count in our estimate, although the latency difference could clearly discriminate between the two stimuli. In this case, the information extracted with spike timing does not offer any insight about the temporal information obviously conveyed by latency difference and thus does not disambiguate it from spike count information. Conversely, in the second neuron, in which the response magnitudes to the two stimuli were similar (1.1 vs 1.3 spikes/stimulus), spike timing provided ~10 times more information than spike count. In this case, virtually all the information extracted with spike timing was temporal information conveyed by latency differences. In gen-

←

surround location. Top-to-bottom as in **A**. **D–F**, Spike count information (gray) and spike timing information (black) extracted about the discrimination of (**D**) stimulus location and (**E**, **F**) stimulus dynamics. Bars represent average values of all neurons ($n = 11$). Error bars represent SDs. Asterisks indicate significant differences ($p < 0.05$).

eral, to say that using spike timing we could extract more information than spike count means that in the neural responses there was some temporal information that was independent of spike count information, but it does not necessarily mean that temporal information alone was greater than spike count information.

To test whether in our experimental data temporal information alone was greater than spike count information, we performed two analyses. The first idea was to consider only the first spike in each single-trial response and only responsive trials (i.e., trials with spikes). In this condition there is no spike count information, so all spike timing information is indeed temporal information. We thus investigated the information conveyed by the first spikes of responsive trials in the same dataset of 11 neurons responding to ON and OFF stimuli delivered to the center of their receptive field and to a responsive surround location. Again, we first used the ON responses to discriminate between center and surround stimuli. Using spike count with all spikes of responsive trials we could extract 0.12 ± 0.11 bits of information. Using spike timing with only first spikes of responsive trials we could extract 0.26 ± 0.24 bits of information. Temporal information alone on average was thus at least 116% greater than spike count information. We then discriminated between ON stimuli and OFF stimuli delivered at the center location. Using spike count with all spikes of responsive trials we could extract 0.20 ± 0.16 bits of information. Using spike timing with only first spikes of responsive trials we could extract 0.53 ± 0.27 bits of information. Temporal information alone on average was thus at least 165% greater than spike count information. We finally discriminated between ON stimuli and OFF stimuli delivered at the surround location. Using spike count with all spikes of responsive trials we could extract 0.09 ± 0.10 bits of information. Using spike timing with only first spikes of responsive trials we could extract 0.40 ± 0.29 bits of information. Temporal information alone was thus on average at least 344% greater than spike count information. Two-way repeated-measures ANOVA confirmed that in responsive trials temporal information was significantly greater than spike count information in the three discrimination problems described above (first factor, spike count vs temporal: $p = 0.0028$; second factor, the discrimination problem: $p = 0.0136$, interaction $p = 0.24$).

The second idea was to select neurons exhibiting similar response magnitudes to the stimuli. In this condition, spike count information is expected to be very small, so that most spike timing information can be unambiguously considered temporal information. We investigated this idea in a dataset of 39 thalamo-
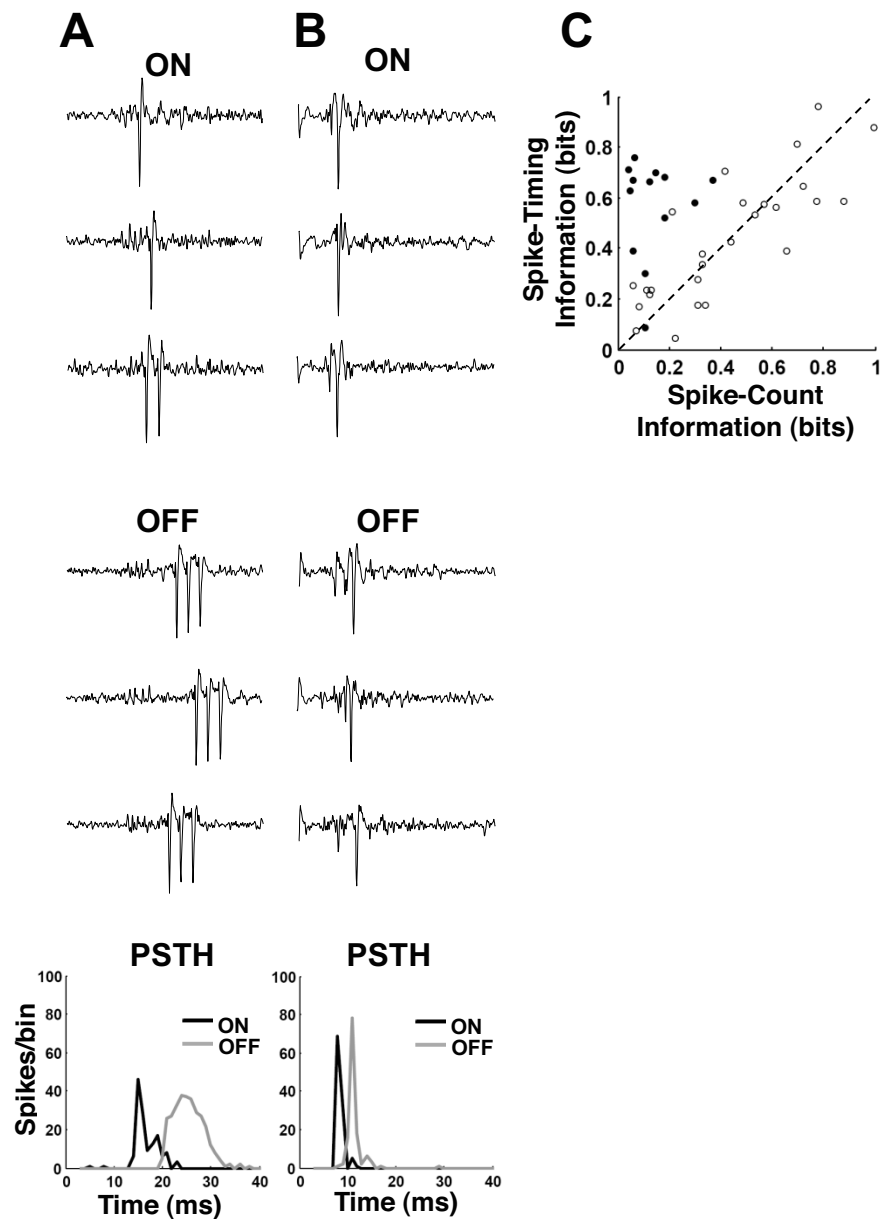

Figure 2. Spike timing information, spike count information, and temporal information. **A**, **B**, Representative neurons responding to ON and OFF stimuli (**A**) with different response magnitudes and (**B**) with similar response magnitudes. Top-to-bottom as in Figure 1 A–C. **C**, Scatter plot of spike count information and spike timing information for all 39 neurons responding ON and OFF stimuli delivered to the center of their receptive field. Empty symbols represent neurons exhibiting high magnitude difference between the responses to the two stimuli ($n = 26$); filled symbols represent neurons exhibiting low magnitude difference ($n = 13$). In most neurons exhibiting high magnitude difference it is not possible to disambiguate temporal information from spike-count information. In most neurons exhibiting low magnitude difference, most spike timing information can be unambiguously considered temporal information.

cortical neurons responding to ON and OFF stimuli delivered to the center of their receptive field. We sorted our 39 neurons into two groups: one group was composed by two-thirds of neurons exhibiting high magnitude difference between the responses to the two stimuli (1.1 ± 0.9 spikes/stimulus, $n = 26$), like the neuron in Figure 2A; the other group was composed by the remaining one-third of neurons exhibiting small magnitude difference (0.4 ± 0.3 spikes/stimulus, $n = 13$), like the neuron in Figure 2B (Table 1). We found that neurons that responded to the two stimuli with different magnitudes conveyed similar information with spike count (0.43 ± 0.27 bits) or spike timing (0.44 ± 0.25

Table 1. Neurophysiological properties of neurons responding to ON and OFF stimuli

	Neurons exhibiting high magnitude difference ($n = 26$)		Neurons exhibiting low magnitude difference ($n = 13$)	
	ON (range)	OFF (range)	ON (range)	OFF (range)
Response magnitude (spikes/stimulus)	1.49 ± 0.89 (0.32–4.79)	1.07 ± 1.11 (0.00–3.37)	1.60 ± 0.51 (0.90–2.64)	1.27 ± 0.59 (0.64–2.65)
Prestimulus activity (Hz)	2.2 ± 3.4	4.7 ± 4.9	1.0 ± 1.6	1.2 ± 1.3
% of first spikes	67 ± 21	50 ± 28	65 ± 21	70 ± 21
Latency of first spikes (ms)	10.3 ± 3.5	14.6 ± 6.0	9.2 ± 2.6	13.3 ± 4.7
Jitter of first spikes (ms)	1.7 ± 1.2	4.3 ± 3.7	1.0 ± 0.8	2.4 ± 1.4

The response magnitude was calculated as the average number of spikes per stimulus in the same 40 ms poststimulus time window used in the information analyses. The prestimulus activity was calculated in a 40 ms prestimulus time window and expressed in hertz. The % of first spikes was calculated as the percentage of spikes that are first spikes of the single-trial responses. Latencies and jitters of first spikes are also included.

bits, paired t test: $p = 0.4514$). In some neurons spike timing did provide some additional information over spike count, but in other neurons the estimated spike timing information was actually lower than spike count information because of underestimation (Fig. 2C). Overall, in this group it was not possible to disambiguate temporal information from spike count information. Conversely, neurons that responded to the two stimuli with similar magnitudes conveyed remarkably more information with spike timing (0.57 ± 0.20 bits) compared with spike count (0.14 ± 0.10 bits, paired t test: $p = 0.000004$). In this group the additional information conveyed by spike timing compared with spike count, which represents a conservative estimate of the temporal information, was 207% greater than the information conveyed by spike count.

To corroborate the relation between temporal information and first spikes, in the same dataset of 39 neurons responding to ON and OFF stimuli delivered to the center of their receptive field, we investigated the spike timing information conveyed by the first spike in each single-trial response. In the 26 neurons that responded to the two stimuli with different magnitudes the first spike conveyed 0.38 ± 0.24 bits, which corresponds to 86% of the information conveyed by all spikes. In the 13 neurons that responded to the two stimuli with similar magnitudes the first spike conveyed 0.55 ± 0.18 bits, which corresponds to 97% of the information conveyed by all spikes. In these 13 neurons, first spikes represented 65% of spikes in the ON responses and 70% of spikes in the OFF responses, which means that the remaining 35% and 30% of spikes provided little information that was not already conveyed by first spikes. When spike count is ambiguous, therefore, first spikes convey virtually all temporal information.

Taken as a whole, these results suggest that temporal information alone can be greater than spike count information, and support the idea of first spikes representing the basis of temporal information in the rat ventrobasal complex.

Informational contribution of first-spike latencies and jitters
To further investigate the nature of temporal information, we performed a set of computational experiments on the 13 neurons that responded with similar magnitudes to ON and OFF stimuli delivered to the center of their receptive field, using the first spikes of the single-trial responses. Because first spikes can be effectively characterized in terms of latencies and jitters, we modulated three main parameters of the responses: (1) the latency difference between stimuli (Fig. 3A), (2) the overall jitter of the responses (Fig. 3B), and (3) the jitter difference between stimuli (Fig. 3C). The rationale of these simulations is that they allowed us to explore a larger range of response parameters than that available in the physiological variability.

The first intuitive idea we tested is that temporal information arises from latency differences between the responses to different stimuli. As expected, information increased as the latency differ-

ence was increased, rapidly reaching a saturation point of 0.70 ± 0.18 bits. With physiological jitters, the latency difference that allowed the responses to convey 50% of the maximal information was 1.9 ± 0.9 ms, and the latency difference that allowed the responses to convey 95% of the maximal information was 3.8 ± 1.4 ms.

The second intuitive idea we tested is that the jitters of the neural responses limit the temporal information conveyed by latency differences. We observed that increasing the jitter of the neural responses rapidly reduced the information that could be extracted, from 0.55 ± 0.18 bits with the physiologic jitter of 1.7 ± 1.0 ms, to 0.10 ± 0.12 bits with an overall jitter of 4.4 ± 0.5 ms. Similarly, when the jitter was increased, the latency difference that allowed the responses to convey 50% of the maximal information increased from 1.9 ± 0.9 ms to 9.1 ± 1.8 ms, and the latency difference that allowed the responses to convey 95% of the maximal information increased from 3.8 ± 1.4 ms to 16.6 ± 3.2 ms. More in general, the latency difference that was necessary to allow neurons to transmit a given amount of information increased as the jitter of the neural responses was increased (Fig. 3D). If adding jitter to the neural responses is interpreted from a decoding perspective, these results also quantify how the temporal imprecision of a decoder can affect its ability to extract information conveyed by latency differences.

Latency differences are not the only possible source of temporal information. The third intuitive idea we tested is that at least some information unrelated to latency differences could be attributable to jitter differences between responses to different stimuli. This idea has physiological relevance in our dataset, as the jitter of the responses to ON stimuli (1.0 ± 0.8 ms) was significantly smaller than the jitter of the responses to OFF stimuli (2.4 ± 1.4 ms; paired t test: $p = 0.0004$, $n = 13$). For each neuron we first aligned the responses so that the latency difference was zero and therefore could not contribute any information. As expected, the information increased as the jitter difference was increased, reaching a saturation point much lower than what we observed by increasing latency differences. With a jitter difference of 12.8 ± 4.3 ms we obtained 0.26 ± 0.16 bits of information. We then investigated how the informational contribution of jitter differences changed as a function of the latency difference. We found that increasing the jitter differences increased the information only if the latency differences were very close to zero, whereas it always decreased the information if latency differences were sufficiently large (Fig. 3E).

Discussion
The main finding of the present work is not only that spike timing provides additional information over spike count alone, but specifically that the temporal aspects of the code can be more informative than spike count in the rat ventrobasal complex. Virtually all temporal information—i.e., information exclusively related to
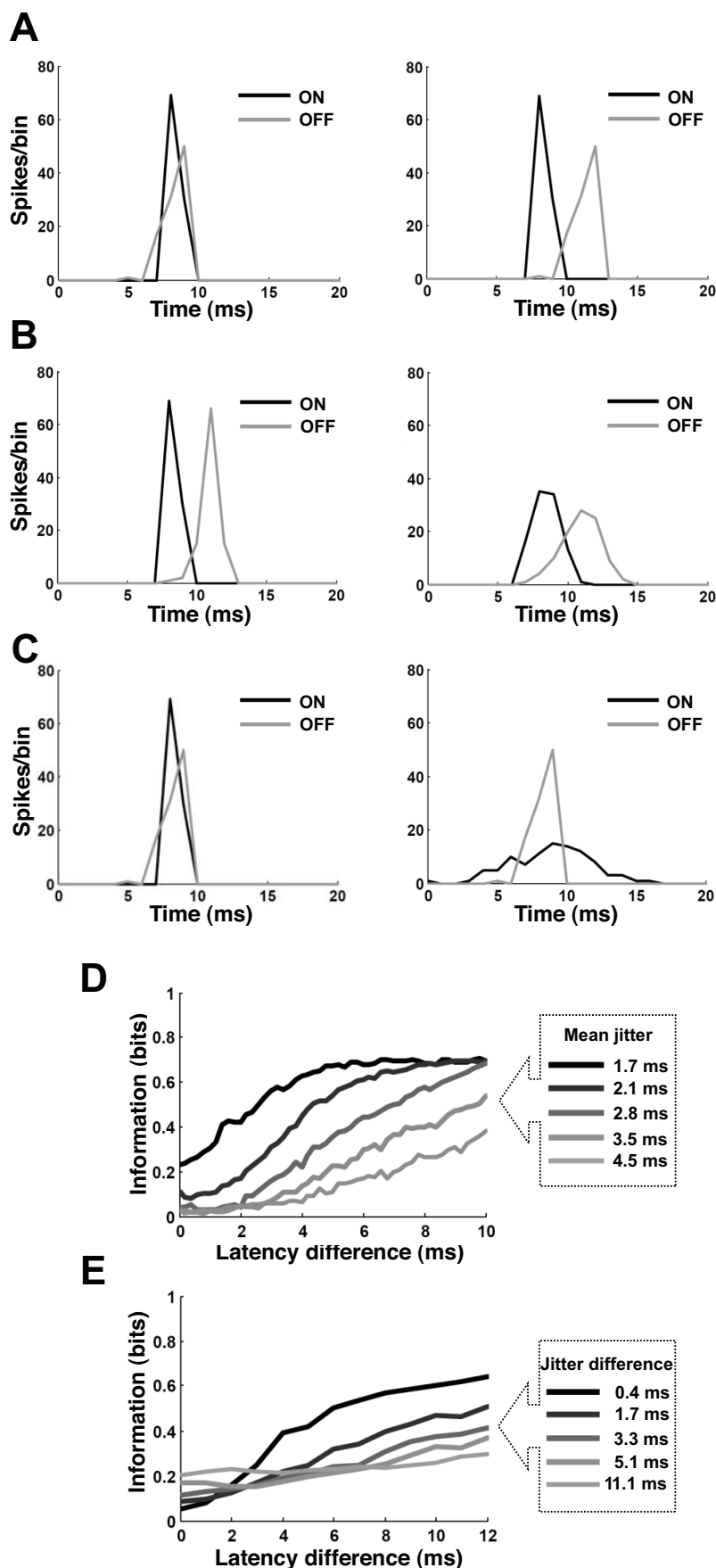
when the spikes occur—is conveyed by first spikes, arising mostly from latency differences between the responses to different stimuli. Although jitters are highly detrimental for the information conveyed by latency differences, jitter differences between stimuli can contribute to temporal information, but only if latency differences are close to zero.

Methodological considerations

Mutual information was used as a rigorous measure of statistical predictability between stimuli and neural responses. To estimate mutual information, we directly used Shannon's formula for spike count, whereas we recurred to PSTH-based classification for spike timing to avoid overestimating the information because of the bias problem. PSTH-based classification (Foffani and Moxon, 2004) has now been used in a number of studies (Foffani et al., 2004, 2008; Gutierrez et al., 2006; Malone et al., 2007; Engineer et al., 2008). Because PSTH-based classification provides a lower bound of spike timing information and has better sampling properties compared with the direct Shannon's formula, the additional information conveyed by spike timing over spike count in our data is a conservative estimate. PSTH-based classification does not explicitly take into account information represented by spike patterns, i.e., correlations between spikes in different bins. However, correlations between spikes seem to play a minor role for information encoding and decoding in the rat thalamus (Montemurro et al., 2007). Furthermore, first spikes conveyed virtually all information in our data, sug-

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Figure 3. Informational contribution of first-spike latencies and jitters. ***A***, Simulations with latency differences. The left panel shows PSTHs corresponding to the first spikes of a representative neuron in which the imposed latency difference between the responses to the stimuli is 0 ms. The right panel shows PSTHs corresponding to the responses of the same neuron when the latency difference is increased. ***B***, Simulations with overall jitters. The left panel shows PSTHs corresponding to the first spikes of a representative neuron with physiological values of latencies and jitters. The right panel shows PSTHs corresponding to the responses of the same neuron when the jitters are increased. ***C***, Simulations with jitter differences. The left panel shows PSTHs corresponding to the first spikes of a representative neuron in which the imposed latency difference is 0 ms. The right panel shows PSTHs corresponding to the responses of the same neuron when the jitter difference between the responses to the stimuli is increased. ***D***, The information conveyed by the responses increases as the latency difference is increased and decreases as the jitters are increased. ***E***, Spike timing information increases as the jitter difference increases, but only when the latency difference is close to zero.

gesting that any information conveyed by correlations between spikes was at most redundant to the information conveyed by first spikes.

The coding problem addressed in this study was to discriminate what stimulus occurred assuming that a stimulus did occur (see supplemental Results, available at www.jneurosci.org as supplemental material) and that stimulus onset was known. All our analyses thus assume an external temporal reference, which is a common assumption in the field (VanRullen et al., 2005). This assumption implies that the brain should have an equivalent internal temporal reference to decode the information in the spike timing codes described here. Intuitively, when a tactile stimulus is delivered, the brain could use the global thalamic response to generically detect that a stimulus occurred. It would then be feasible to use, for example, the beginning of such global response as an internal temporal reference to construct and decode latency codes for finer stimulus discrimination. Indeed, several works are now proposing possible internal references, including spikes emitted by other neurons (Chase and Young, 2007; Gollisch and Meister, 2008) or–less likely in our case–specific phase in the oscillations of local field potentials (Huxter et al., 2003; Buzsáki and Draguhn, 2004; Lee et al., 2005; Lisman, 2005; Fries et al., 2007; Montemurro et al., 2008). Importantly, spike timing information can even increase when an internal reference is used (Chase and Young, 2007), confirming that the knowledge of stimulus onset is not a limiting assumption.

Spike timing information in the ventrobasal complex of the thalamus

Two previous studies have shown that in the VPM spike timing conveys more information than spike count alone in the discrimination of stimulus location (Ghazanfar et al., 2000) and in the discrimination of stimulus dynamics (Montemurro et al., 2007), suggesting the presence of temporal information that was independent of spike count information. Here, we extended these results from the VPM to the VPL, thus bringing at the informational level the homogeneity that we previously investigated at the neurophysiologic level (Aguilar et al., 2008). Temporal information about stimulus dynamics in the ventrobasal complex implies that at least part of the remarkable spike timing precision observed in the responses of primary afferents to transient stimuli (Jones et al., 2004a, 2004b) is preserved in the thalamus (Desbordes et al., 2008; Petersen et al., 2008). Temporal information about stimulus location is trickier. Primary afferents selectively respond to a very circumscribed body area, e.g., one digit or one whisker (Leiser and Moxon, 2006). Primary afferents could thus exploit the spike timing precision of their responses only to discriminate between close locations within the body area they represent, e.g., within a fingertip (Johansson and Birznieks, 2004), but not to discriminate between separate locations such as different digits or different whiskers. Temporal information conveyed by spike timing about stimulus location between digits or between whiskers in the ventrobasal complex is thus a product of the basic transformations that occur in the brainstem (Panetsos et al., 1997; Aguilar et al., 2002, 2003; Fernández de Sevilla et al., 2006; Soto et al., 2006), which determine the enlargement of receptive fields at thalamic level. Importantly, the receptive field size of thalamocortical neurons is particularly large in active or awake states (Nicolelis et al., 1993; Nicolelis and Chapin, 1994; Friedberg et al., 1999; Aguilar and Castro-Alamancos, 2005). Larger receptive fields imply greater temporal information (Foffani et al., 2008), so the relative weight of temporal information over spike count information observed here in anesthetized con-

ditions is expected to increase in awake animals. Although our experimental anesthetized conditions represent a good model of passive unexpected stimuli during quiet behaviors (Krupa et al., 2004; Ferezou et al., 2006), it is important to remark that inferences about how stimuli are processed by behaving animals based on anesthetized data should be cautious. Nevertheless, the loss of spatial selectivity resulting from the large receptive fields—not only in the thalamus but also in the cortex (Ghazanfar and Nicolelis, 1999; Tutunculer et al., 2006; Moxon et al., 2008)— could be the price paid by sensory systems to fully benefit from the high information capacity of spike timing codes (Foffani et al., 2008).

Spike timing information, spike count information, and temporal information

A few recent studies hint at the intuitive idea of spike timing becoming particularly informative when the stimuli to be discriminated evoke similar response magnitudes (Arabzadeh et al., 2006; Foffani et al., 2008; Montemurro et al., 2008). In the present study, we explicitly considered that spike timing information includes both spike count information (how many spikes occurred) and temporal information (when they occurred), i.e., $I_{\text{spike-timing}} = I_{\text{spike-count}} + I_{\text{temporal}} + \Delta I$ (Nelken et al., 2005). Indeed, the experimental observation of different stimuli leading to similar spike counts with different latencies represents a limit case that is useful to intuitively show that temporal information can be much greater than count information. But the significance of our results is more general: using first spikes of responsive trials we were able to disambiguate the redundancy between temporal information and spike count information, showing that temporal information alone can be greater than spike count information even if different stimuli elicit rather different spike counts. The additional information obtained with spike timing compared with spike count in previous studies in the somatosensory system was therefore likely underestimating the real temporal information present in the code.

Informational contribution of first-spike latencies and jitters

In the somatosensory system and even in other sensory modalities, the very first spike emitted by single neurons in each single-trial response seems to convey most of the information about stimulus discrimination (Heil, 1997; Panzeri et al., 2001; Petersen et al., 2001; Furukawa and Middlebrooks, 2002; DeWeese et al., 2003; Foffani et al., 2004, 2008; Johansson and Birznieks, 2004; Nelken et al., 2005; Gollisch and Meister, 2008). First-spike coding is functionally appealing for rapid processing of sensory information (Thorpe et al., 2001; VanRullen et al., 2005), and is methodologically attractive because one spike represents the minimal element that is necessary to construct a spike timing code. In our data first spikes conveyed virtually all temporal information, suggesting that first-spike coding can operate in the ventrobasal complex of the thalamus. Our computational experiments confirm that temporal information is primarily caused by latency differences between the responses to different stimuli. These results support the importance of response latency as a fundamental element of the neural code (Amassian, 1953; Jones 1956; Gawne et al., 1996; Eggermont, 1998; Raiguel et al., 1999; Oram et al., 2002; Hurley and Pollak, 2005; Thomson and Kristan, 2006; Gollisch and Meister, 2008; Foffani et al., 2008).

Beside latencies, jitters clearly play a crucial role in neural codes based on spike timing (Mainen and Sejnowski, 1995; Berry et al., 1997; Hunter et al., 1998; Cecchi et al., 2000; Fellous et al., 2001; Szücs et al., 2004; Aldworth et al., 2005; Rokem et al., 2006;

Billimoria et al., 2006; Daw et al., 2006; Tiesinga et al., 2008). Our computational experiments formalize the intuitive idea of large jitters being detrimental for the information conveyed by latency differences. Importantly, increasing the jitter of the neural responses is also equivalent to increasing the jitter of the "clock" that the brain would need as an internal reference to decode spike timing information. Our simulations thus provide rigorous boundaries to the precision required for candidate clocks to extract temporal information from latency differences.

Our computational experiments also uncover a more subtle informational contribution by jitter differences between the responses to different stimuli. Jitter differences, however, can only contribute information if latency differences are close to zero. This suggests that jitter differences might be more difficult to be exploited at a functional level, whereas temporally precise first spikes synchronously emitted by multiple neurons within the same aggregate could be particularly efficient for transmitting tactile information from the thalamus to the somatosensory cortex (Bruno and Sakmann, 2006).

In conclusion, temporal information conveyed by spike timing can be higher than spike count information for the discrimination of somatosensory stimuli in the rat ventrobasal complex.

References

Adrian ED (1928) The basis of sensations. New York: Norton.

Aguilar J, Soto C, Rivadulla C, Canedo A (2002) The lemniscal-cuneate recurrent excitation is suppressed by strychnine and enhanced by GABAA antagonists in the anaesthetized cat. Eur J Neurosci 16:1697–1704.

Aguilar J, Rivadulla C, Soto C, Canedo A (2003) New corticocuneate cellular mechanisms underlying the modulation of cutaneous ascending transmission in anesthetized cats. J Neurophysiol 89:3328–3339.

Aguilar J, Morales-Botello ML, Foffani G (2008) Tactile responses of hindpaw, forepaw and whisker neurons in the thalamic ventrobasal complex of anesthetized rats. Eur J Neurosci 27:378–387.

Aguilar JR, Castro-Alamancos MA (2005) Spatiotemporal gating of sensory inputs in thalamus during quiescent and activated states. J Neurosci 25:10990–11002.

Aldworth ZN, Miller JP, Gedeon T, Cummins GI, Dimitrov AG (2005) Dejittered spike-conditioned stimulus waveforms yield improved estimates of neuronal feature selectivity and spike-timing precision of sensory interneurons. J Neurosci 25:5323–5332.

Amassian VE (1953) Evoked single cortical unit activity in the somatic sensory areas. Electroencephalogr Clin Neurophysiol 5:415–438.

Arabzadeh E, Panzeri S, Diamond ME (2006) Deciphering the spike train of a sensory neuron: counts and temporal patterns in the rat whisker pathway. J Neurosci 26:9216–9226.

Berry MJ, Warland DK, Meister M (1997) The structure and precision of retinal spike trains. Proc Natl Acad Sci U S A 94:5411–5416.

Bialek W, Rieke F, de Ruyter van Steveninck RR, Warland D (1991) Reading a neural code. Science 252:1854–1857.

Billimoria CP, DiCaprio RA, Birmingham JT, Abbott LF, Marder E (2006) Neuromodulation of spike-timing precision in sensory neurons. J Neurosci 26:5910–5919.

Blanc JL, Coq JO (2007) Coding processes involved in the cortical representation of complex tactile stimuli. J Physiol Paris 101:22–31.

Borst A, Theunissen FE (1999) Information theory and neural coding. Nat Neurosci 2:947–957.

Bruno RM, Sakmann B (2006) Cortex is driven by weak but synchronously active thalamocortical synapses. Science 312:1622–1627.

Butts DA, Weng C, Jin J, Yeh CI, Lesica NA, Alonso JM, Stanley GB (2007) Temporal precision in the neural code and the timescales of natural vision. Nature 449:92–95.

Buzsáki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926–1929.

Cecchi GA, Sigman M, Alonso JM, Martínez L, Chialvo DR, Magnasco MO (2000) Noise in neurons is message dependent. Proc Natl Acad Sci U S A 97:5557–5561.

Chase SM, Young ED (2006) Spike-timing codes enhance the representa-

tion of multiple simultaneous sound-localization cues in the inferior colliculus. J Neurosci 26:3889–3898.

Chase SM, Young ED (2007) First-spike latency information in single neurons increases when referenced to population onset. Proc Natl Acad Sci U S A 104:5175–5180.

Daw MI, Bannister NV, Isaac JTR (2006) Rapid, activity-dependent plasticity in timing precision in neonatal barrel cortex. J Neurosci 26:4178–4187.

deCharms RC, Merzenich MM (1996) Primary cortical representation of sounds by the coordination of action-potential timing. Nature 381:610–613.

de Ruyter van Steveninck RR, Lewen GD, Strong SP, Koberle R, Bialek W (1997) Reproducibility and variability in neural spike trains. Science 275:1805–1808.

Desbordes G, Jin J, Weng C, Lesica NA, Stanley GB, Alonso JM (2008) Timing precision in population coding of natural scenes in the early visual system. PLoS Biol 6:e324.

Deschênes M, Timofeeva E, Lavallée P (2003) The relay of high-frequency sensory signals in the whisker-to-barreloid pathway. J Neurosci 23:6778–6787.

DeWeese MR, Wehr M, Zador AM (2003) Binary spiking in auditory cortex. J Neurosci 23:7940–7949.

Eggermont JJ (1998) Azimuth coding in primary auditory cortex of the cat. II. Relative latency and interspike interval representation. J Neurophysiol 80:2151–2161.

Engineer CT, Perez CA, Chen YH, Carraway RS, Reed AC, Shetake JA, Jakkamsetti V, Chang KQ, Kilgard MP (2008) Cortical activity patterns predict speech discrimination ability. Nat Neurosci 11:603–608.

Fellous JM, Houweling AR, Modi RH, Rao RP, Tiesinga PH, Sejnowski TJ (2001) Frequency dependece of spike timing reliability in cortical pyramidal cells and interneurons. J Neurophysiol 85:1782–1787.

Ferezou I, Bolea S, Petersen CC (2006) Visualizing the cortical representation of whisker touch: voltage-sensitive dye imaging in freely moving mice. Neuron 50:617–629.

Fernández de Sevilla D, Rodrigo-Angulo M, Nuñez A, Buño W (2006) Cholinergic modulation of synaptic transmission and postsynaptic excitability in the rat gracilis dorsal column nucleus. J Neurosci 26:4015–4025.

Foffani G, Moxon KA (2004) PSTH-based classification of sensory stimuli using ensembles of single neurons. J Neurosci Methods 135:107–120.

Foffani G, Tutunculer B, Moxon KA (2004) Role of spike timing in the forelimb somatosensory cortex of the rat. J Neurosci 24:7266–7271.

Foffani G, Chapin JK, Moxon KA (2008) Computational role of large receptive fields in the primary somatosensory cortex. J Neurophysiol 100:268–280.

Friedberg MH, Lee SM, Ebner FF (1999) Modulation of receptive field properties of thalamic somatosensory neurons by the depth of anesthesia. J Neurophysiol 81:2243–2252.

Fries P, Nikolić D, Singer W (2007) The gamma cycle. Trends Neurosci 30:309–316.

Furukawa S, Middlebrooks JC (2002) Cortical representation of auditory space: information-bearing features of spike patterns. J Neurophysiol 87:1749–1762.

Gawne TJ, Kjaer TW, Richmond BJ (1996) Latency: another potential code for feature binding in striate cortex. J Neurophysiol 76:1356–1360.

Ghazanfar AA, Nicolelis MA (1999) Spatiotemporal properties of layer V neurons of the rat primary somatosensory cortex. Cereb Cortex 9:348–361.

Ghazanfar AA, Stambaugh CR, Nicolelis MA (2000) Encoding of tactile stimulus location by somatosensory thalamocortical ensembles. J Neurosci 20:3761–3775.

Gollisch T, Meister M (2008) Rapid neural coding in the retina with relative spike latencies. Science 319:1108–1111.

Gutierrez R, Carmena JM, Nicolelis MA, Simon SA (2006) Orbitofrontal ensemble activity monitors licking and distinguishes among natural rewards. J Neurophysiol 95:119–133.

Heil P (1997) Auditory cortical onset response revisited. I. First-spike timing. J Neurophysiol 77:2616–2641.

Hopfield JJ (1995) Pattern recognition computation using action potential timing for stimulus representation. Nature 376:33–36.

Hunter JD, Milton JG, Thomas PJ, Cowan JD (1998) Resonance effect for neural spike time reliability. J Neurophysiol 80:1427–1438.

Hurley LM, Pollak GD (2005) Serotonin shifts first-spike latencies of inferior colliculus neurons. J Neurosci 25:7876–7886.

Huxter J, Burgess N, O'Keefe J (2003) Independent rate and temporal coding in hipocampal pyramidal cells. Nature 425:828–832.

Johansson RS, Birznieks I (2004) First spikes in ensembles of human tactile afferents code complex spatial fingertip events. Nat Neurosci 7:170–177.

Jones FN (1956) Space-time relationships in somesthetic localization. Science 124:484.

Jones LM, Depireux DA, Simons DJ, Keller A (2004a) Robust temporal coding in the trigeminal system. Science 304:1986–1989.

Jones LM, Lee S, Trageser JC, Simons DJ, Keller A (2004b) Precise temporal responses in whisker trigeminal neurons. J Neurophysiol 92:665–668.

Kjaer TW, Hertz JA, Richmond BJ (1994) Decoding cortical neuronal signals: network models, information estimation and spatial tuning. J Comput Neurosci 1:109–139.

Krupa DJ, Wiest MC, Shuler MG, Laubach M, Nicolelis MA (2004) Layer-specific somatosensory cortical activation during active tactile discrimination. Science 304:1989–1992.

Lee H, Simpson GV, Logothetis NK, Rainer G (2005) Phase locking of single neuron activity to theta oscillations during working memory in monkey extrastriate visual cortex. Neuron 45:147–156.

Leiser SC, Moxon KA (2006) Relationship between physiological response type (RA and SA) and vibrissal receptive field of neurons within the rat trigeminal ganglion. J Neurophysiol 95:3129–3145.

Lisman J (2005) The theta/gamma discrete phase code occurring during the hippocampal phase precession may be a more general brain coding scheme. Hippocampus 15:913–922.

MacKay DM, McCulloch WS (1952) The limiting information capacity of a neuronal link. Bull Math Biophys 14:127–135.

Mainen ZF, Sejnowski TJ (1995) Reliability of spike timing in neocortical neurons. Science 268:1503–1506.

Malone BJ, Scott BH, Semple MN (2007) Dynamic amplitude coding in the auditory cortex of awake rhesus macaques. J Neurophysiol 98:1451–1474.

Montemurro MA, Panzeri S, Maravall M, Alenda A, Bale MR, Brambilla M, Petersen RS (2007) Role of precise spike timing in coding of dynamic vibrissa stimuli in somatosensory thalamus. J Neurophysiol 98:1871–1882.

Montemurro MA, Rasch MJ, Murayama Y, Logothetis NK, Panzeri S (2008) Phase-of-firing coding of natural visual stimuli in primary visual cortex. Curr Biol 18:375–380.

Moxon KA, Hale LL, Aguilar J, Foffani G (2008) Responses of infragranular neurons in the rat primary somatosensory cortex to forepaw and hindpaw tactile stimuli. Neuroscience 156:1083–1092.

Nelken I, Chechik G, Mrsic-Flogel TD, King AJ, Schnupp JW (2005) Encoding stimulus information by spike numbers and mean response time in primary auditory cortex. J Comput Neurosci 19:199–221.

Nemenman I, Lewen GD, Bialek W, de Ruyter van Steveninck RR (2008) Neural coding of natural stimuli: information at sub-millisecond resolution. PLoS Comput Biol 4:e1000025.

Nicolelis MA, Chapin JK (1994) Spatiotemporal structure of somatosensory responses of many-neuron ensembles in the rat ventral posterior medial nucleus of the thalamus. J Neurosci 14:3511–3532.

Nicolelis MA, Lin RC, Woodward DJ, Chapin JK (1993) Dynamic and distributed properties of many-neuron ensembles in the ventral posterior medial thalamus of awake rats. Proc Natl Acad Sci U S A 90:2212–2216.

Opticam LM, Richmond BJ (1987) Temporal encoding of two-dimensional patterns by single units in primate inferior temporal cortex. J Neurophysiol 57:162–178.

Oram MW, Xiao DK, Dritschel B, Payne KR (2002) The temporal precision of neural signals: a unique role for response latency? Philos Trans R Soc Lond B Biol Sci 357:987-

Panetsos F, Nuñez A, Avendaño C (1997) Electrophysiological effects of temporary deafferentation on two characterized cell types in the nucleus gracilis of the rat. Eur J Neurosci 9:563–572.

Panzeri S, Petersen RS, Schultz SR, Lebedev M, Diamond ME (2001) The role of spike timing in the coding of stimulus location in rat somatosensory cortex. Neuron 29:769–777.

Panzeri S, Senatore R, Montemurro MA, Petersen RS (2007) Correcting for the sampling bias problem in spike train information measures. J Neurophysiol 98:1064–1072.

Petersen RS, Panzeri S, Diamond ME (2001) Population coding of stimulus location in rat somatosensory cortex. Neuron 32:503–514.

Petersen RS, Brambilla M, Bale MR, Alenda A, Panzeri S, Montemurro MA, Maravall M (2008) Diverse and temporally precise kinetic feature selectivity in the VPm thalamic nucleus. Neuron 60:890–903.

Raiguel SE, Xiao D, Marcar VL, Orban GA (1999) Response latency of macaque area MT/V5 neuron and its relationship to stimulus parameters. J Neurophysiol 44:295–311.

Reich DS, Mechler F, Victor JD (2001) Temporal coding of contrast in primary visual cortex: when, what, and why. J Neurophysiol 85:1039–1050.

Rokem A, Watzl S, Gollisch T, Stemmler M, Herz AV, Samengo I (2006) Spike-timing precision underlies the coding efficiency of auditory receptor neurons. J Neurophysiol 95:2541–2552.

Rolls ET, Treves A, Tovee MJ (1997) The representational capacity of the distributed encoding of information provided by populations of neurons in primate temporal visual cortex. Exp Brain Res 114:149–162.

Schneidman E, Bialek W, Berry MJ 2nd (2003) Synergy, redundancy, and independence in population codes. J Neurosci 23:11539–11553.

Soto C, Martín-Cora F, Leiras R, Velo P, Canedo A (2006) GABA(B) receptor-mediated modulation of cutaneous input at the cuneate nucleus in anesthetized cats. Neuroscience 137:1015–1030.

Szücs A, Vehovszky A, Molnar G, Pinto RD, Abarbanel HD (2004) Reliability and precision of neural spike timing: simulation of spectrally broad-band synaptic inputs. Neuroscience 126:1063–1073.

Thomson EE, Kristan WB (2006) Encoding and decoding touch location in the leech CNS. J Neurosci 26:8009–8016.

Thorpe S, Delorme A, Van Rullen R (2001) Spike-based strategies for rapid processing. Neural Netw 14:715–725.

Tiesinga P, Fellous JM, Sejnowski TJ (2008) Regulation of spike timing in visual cortical circuits. Nat Rev Neurosci 9:97–109.

Tutunculer B, Foffani G, Himes BT, Moxon KA (2006) Structure of the excitatory receptive fields of infragranular forelimb neurons in the rat primary somatosensory cortex responding to touch. Cereb Cortex 16:791–810.

VanRullen R, Guyonneau R, Thorpe SJ (2005) Spike times make sense. Trends Neurosci 28:1–4.

Victor JD, Purpura KP (1996) Nature and precision of temporal coding in visual cortex: a metric-space analysis. J Neurophysiol 76:1310–1326.