Spike-Phase Coding Boosts and Stabilizes Information Carried by Spatial and Temporal Spike Patterns

Christoph Kayser,[1,*] Marcelo A. Montemurro,[4] Nikos K. Logothetis,[1,3] and Stefano Panzeri[2,4,*]
[1]Max Planck Institute for Biological Cybernetics, Spemannstrasse 38, 72076 Tübingen, Germany
[2]Robotics, Brain and Cognitive Sciences Department, Italian Institute of Technology, Via Morego 30, 16163 Genova, Italy
[3]Division of Imaging Science and Biomedical Engineering, University of Manchester, Manchester M13 9PT, UK
[4]Faculty of Life Sciences, University of Manchester, Manchester M60 1QD, UK
*Correspondence: christoph.kayser@tuebingen.mpg.de (C.K.), stefano.panzeri@iit.it (S.P.)
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SUMMARY

Several neural codes have been proposed in order to explain how neurons encode sensory information. Here we tested the hypothesis that different codes might be employed concurrently and provide complementary stimulus information. Quantifying the information encoded about natural sounds in the auditory cortex of alert animals, we found that temporal spike-train patterns and spatial populations were both highly informative. However, the relative phase of slow ongoing rhythms at which these (temporal or population) responses occurred provided much additional and complementary information. Such nested codes combining spike-train patterns with the phase of firing were not only most informative, but also most robust to sensory noise added to the stimulus. Our findings suggest that processing in sensory cortices could rely on the concurrent use of several codes that combine information across different spatiotemporal scales. In addition, they propose a role of slow cortical rhythms in stabilizing sensory representations by reducing effects of noise.

INTRODUCTION

Perception is highly robust to the presence of sensory noise. When listening to someone over a cell phone, for example, our brain can comprehend the information provided by the voice despite a variety of distracting environmental noises. How the brain achieves this feat and what neural coding mechanisms allow a stable sensory representation despite noise is one of the central and much debated questions in neuroscience (Averbeck et al., 2006; Ermentrout et al., 2008; Stevens and Zador, 1995). The problem of generating stable representations is further exacerbated by the presence of internally generated fluctuations of neuronal excitability. Such fluctuations typically manifest in spatially patterned or rhythmic ongoing activity (Arieli et al., 1995; Azouz and Gray, 1999; Tiesinga et al., 2008) and can

affect neuronal responses as much as sensory stimuli do (Arieli et al., 1996; Tiesinga et al., 2008). Although such ongoing rhythms might relate to important functions like neuromodulation or cognitive feedback, they make neural responses state dependent and may thus act as noise in the process of forming reliable sensory representations (Shadlen and Newsome, 1998).

Several different candidate neural codes have been proposed to form sensory representations that are robust to internal or external noise (Ferster and Spruston, 1995; Softky, 1995). The golden standard in systems neuroscience is the spike rate over a predefined time window, which reduces noise by temporal averaging. Yet, it has been proposed that, depending on how internally generated activity and external inputs interact, other codes may be more advantageous. For example, temporal patterns of neuronal activity, such as precisely timed patterns of action potentials, can provide considerably more information than the firing rate of the same neuron (Abeles et al., 1994; Bialek et al., 1991; Optican and Richmond, 1987; Victor, 2000). Importantly, temporally structured activity can increase the reliability of information processing by facilitating the transmission of activity (Diesmann et al., 1999; Salinas and Sejnowski, 2001). In addition, the cooperative behavior of groups of neurons in the form of a population code can enhance the information carrying capability of sensory cortices and might possibly reduce the influence of noise by pooling across neurons (Averbeck et al., 2006; Harris, 2005; Pouget et al., 2000). And finally, internally generated network rhythms themselves might participate in sensory processing by allowing the encoding of information in the relative timing of neuronal activity to slow background rhythms (rather than to stimulus changes) (Brody and Hopfield, 2003; Hopfield, 1995; Lisman, 2005; O'Keefe and Recce, 1993).

Despite these various proposals, each promoting a different individual neural code, little is known about whether a single code or a combination of coding schemes provides the highest robustness to fluctuations in background activity or sensory noise. One possibility is that only one coding strategy is used and different apparent codes reflect the same underlying mechanisms and provide the same information. Another possibility is that different codes compete with each other, and for any given stimulus or task only one might win because of mutual incompatibility. For example, the precision of spike timing results from the balance of intrinsic reverberations and stimulus-locked input,

and hence individual spikes might lock to either the stimulus or internal rhythm (Tiesinga et al., 2008). A third possibility is that the nervous system does not rely on a single code alone, but actually employs different coding strategies either concurrently or even synergistically (Bullock, 1997; Fries et al., 2007; Lisman, 2005). For example, both a spike-train pattern as well as the relative timing of this pattern to slow rhythms might be informative. From a theoretical perspective, the concurrent use of different coding strategies is attractive, as it allows combining information across different spatiotemporal scales (Hopfield, 1995; Lisman, 2005).

There are two main reasons why the knowledge on the neural codes used for stable sensory representations has remained fragmented. One reason is methodological, since most studies consider only one or two selected coding mechanisms at a time. As a result, it is difficult to judge the relative contribution of different proposed codes to the information carrying capacity in a given sensory area. Another reason is that most studies use highly controlled stimuli, and thus do not allow gaining insights into the robustness of neural codes with respect to realistic sensory conditions in which actual stimuli are often mixed with noise. And third, we do not know to what extent slow background rhythms interfere with sensory processing, to what extent they reflect modulatory influences, or to what extent they directly participate in coding stimulus or task-related information.

The present study was designed to reconcile the different proposals of robust sensory coding by directly comparing the contribution of different codes to the encoding of natural stimuli in the alert animal. Importantly, we employed the same principled framework (information theory) and the same data set to compare different neural codes. We recorded single units and local field potentials from the auditory cortex of alert monkeys. First, we systematically quantified the information encoded by different temporal and population codes, as well as nested versions consisting of combinations of temporal and spatial codes (see Figure S1, available online, for an overview of the different codes). This systematic analysis allowed us to directly compare the information available in codes operating at different scales and to assess their complementary nature. Second, we used a stimulus paradigm that includes realistic sensory noise to quantify the robustness of each code to sensory noise. The auditory cortex was chosen as a model system, as natural sounds contain characteristic temporal features that facilitate the formation of complex neural codes (Nelken et al., 2005; Schnupp et al., 2006; Schroeder et al., 2008).

RESULTS

In the following, we first study the relation between slow rhythmic activity, stimulus drive, and spiking responses. To do so, we quantify how far rhythmic activity is related to sensory stimuli, and how far spikes of individual neurons exhibit a systematic relation to these rhythms. We then show how this relation translates into highly informative codes that combine firing rates and spike-train patterns of individual neurons with the phase of slow rhythms. Second, we quantify the information available in spatial population codes, and we ask whether spatial codes also gain information when the relative timing of population response

and slow rhythms is known. Finally, we devise a stimulus paradigm that combines repeated acoustic stimulation with sensory noise in order to determine the robustness of each code to noise.

Information in Local Field Potentials

Rhythmic activity patterns have been attributed an important role not only in sensory processing but also in higher cognitive functions (Buzsaki and Draguhn, 2004). Such rhythmic activity is often characterized using local field potentials (LFPs), which provide an aggregate measure of local subthreshold integrative processes and network state changes (Juergens et al., 1999; Logothetis, 2002). Field potentials are strongly influenced by somatodendritic potentials, voltage-dependent membrane oscillations, and spike afterpotentials and provide an index of neuronal processing that is not equivalent to measures of spiking activity (Belitski et al., 2008; Berens et al., 2008; Rasch et al., 2008). To separate individual rhythms, the LFP is usually divided into distinct frequency bands, each of which is characterized by a time-dependent amplitude and phase of the respective oscillation. These amplitudes and phases can, for example, be extracted using Hilbert transforms and can then be used to analyze each rhythm's role in sensory processing.

Field potentials might reflect purely internal network dynamics, which might effectively act as "noise" with regard to sensory representations. Alternatively, these rhythms might play an active role in sensory processing, for example by entraining the network to salient features of the stimulus (Lakatos et al., 2008; Schroeder et al., 2008) or by providing a time basis relative to which neuronal firing could encode information (Brody and Hopfield, 2003; Hopfield, 1995; Lisman, 2005; O'Keefe and Recce, 1993). To determine which out of the broad range of rhythms are stimulus related, we recorded LFPs in response to natural acoustic stimuli and analyzed the mutual (Shannon) information between individual LFP frequency bands and the stimulus. The mutual information quantifies the reduction of uncertainty about the stimulus that can be gained from observation of a single trial of the neural response. Importantly, information provides a principled framework to quantify and compare the relation between stimulus and different neural codes, and unlike correlation-based measures, information has the advantage of capturing all nonlinear dependencies of any statistical order. In addition, this information-based characterization does not make assumptions about which stimulus features drive the responses.

The acoustic stimulus consisted of a 52 s sequence of naturalistic sounds including environmental and animal sounds and segments of conspecific vocalizations (Figure 1A). The same stimulus sequence was presented repeatedly to allow statistically robust estimates of information theoretic quantities. Figure 1B displays example time courses of LFP phase and energy in the theta (4–8 Hz) frequency range, after both signals have been binned into four (color-coded) intervals, as used in the information analysis. This example suggests that the phase might provide information about the stimulus, since it is highly repeatable across trials; the energy, in contrast, seems more variable and less informative.

To quantify this, we computed the mutual information between LFP phase (or energy) and stimulus. This was done by dividing
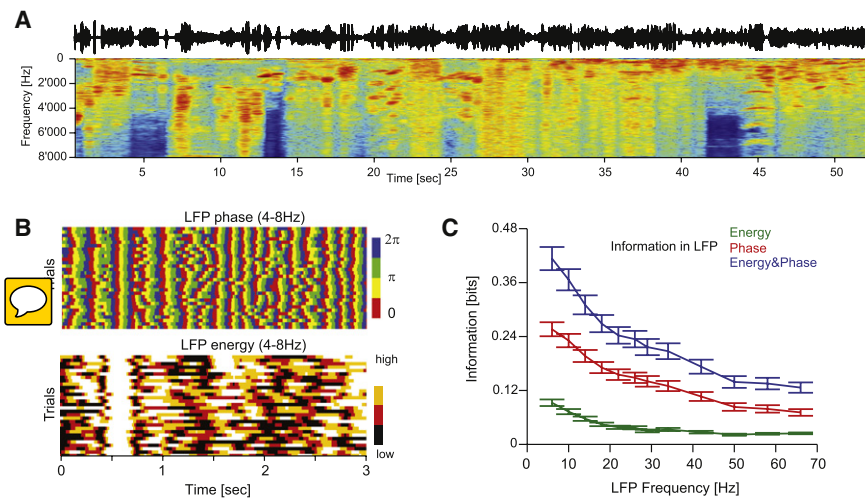
Figure 1. Information in Local Field Potentials

(A) Waveform and spectrogram (red, high power; blue, low power) of the acoustic stimulus sequence.

(B) Examples of low-frequency (4–8 Hz) LFP phase and energy for 30 subsequent trials. Both signals are binned into four bins.

(C) Mutual information between LFP (phase, energy, and the combined energy&phase signal) and stimulus.

Error bars indicate mean and SEM across sites (n = 86, T = 4 ms time window).

the time axis into nonoverlapping windows of length T, each of which was considered as a different "stimulus" (de Ruyter van Steveninck et al., 1997). Throughout this study, we used stimulus windows of length T from 4 ms to 48 ms. The resulting information estimates were corrected for limited sampling biases using a multistep procedure (full details of the analysis are provided in the Supplemental Data).

For both energy and phase, information was higher at lower frequencies and peaked at the lowest band investigated (4–8 Hz, Figure 1C). Overall, phase provided nearly three times more information than energy, resulting in a highly significant difference (4–8 Hz band: energy 0.1 ± 0.008 bits, phase 0.25 ± 6 bits, mean ± SEM, t test $p < 10^{-19}$). We further computed information for the combined energy&phase signal, which provided slightly more information than the summed information of energy and phase (4–8 Hz band; combined: 0.44 ± 0.028 bits; sum; 0.35 ± 0.016 bits), indicating that energy and phase provide complementary information.

These results have several implications. First, LFPs are not purely intrinsic signals, and while faster rhythms are stimulus unrelated, slow rhythms are stimulus locked and informative. Second, the precise timing (phase) of slow rhythms is related to the stimulus more than the amplitude, suggesting that phase might play a more important role in sensory coding than energy.

The Relation of Spiking Activity and LFP

Before investigating whether spiking activity and the phase of slow rhythms provide complementary stimulus information, we systematically quantified the relation between spikes and LFP phase. Figures 2A–2D display the spiking response of one neuron and the LFP phase recorded on the same electrode. Consistent with the above, the phase is coherent across trials (Figure 2B). Color coding spikes with the LFP phase at the time of spike reveals that often epochs with similar firing rate (peaks in the PSTH of same height) occur during different phases of the LFP (Figures 2C and 2D). In the figure, we highlighted three such pairs. In case a, for example, one peak (a1) occurs at a red phase angle while the other occurs at a green phase (a2).

This observation of a systematic relation between the occurrence of spikes and LFP phase not only suggests that slow rhythms relate to changes in network excitability but also that knowledge of their phase allows discriminating peaks in the PSTH that might not be discernable based on firing rates alone.

We further substantiated these results by a systematic analysis of the trial-to-trial consistency of LFP phase (Supplemental Results 2.1). Instances of high firing rates were often accompanied by a consistent phase across trials, and different stimulus epochs with similar firing rates can be associated with a different reliable phase angle, suggesting that the phase may be used to disambiguate stimuli that are equally effective in terms of spike rate. Further, we found that individual neurons have distinct preferred phase angles. These results suggest that the phase of firing might indeed be employed as neural code for acoustic stimuli, both at the single neuron and population level.

Information in Firing Rates and the Spike-Phase Code

Having established that slow rhythms are stimulus related and that spikes bear a systematic relation to LFP phase, we can now test the hypothesis that the relative timing of spikes and LFP phase provides additional information not contained in the firing rate. This would indicate that slow rhythms and their putative control over neuronal excitability can be exploited to enhance the information contained in a neural code. We quantified the information carried by the rate code (I_rate), which consists only of the spike rate, and the spike-phase code (I_rate&phase), which labels the spike rate with the phase quadrant of the LFP (see Supplemental Experimental Procedures 1.2 for details). A comparison of I_rate&phase and I_rate determines quantitatively whether the spike phase adds information beyond that available in spike rates.

Across the population of 104 SUA/MUA sites, the firing rate was well informative about the stimulus and provided 0.047 ± 0.0036 bits of information (0.0589 ± 0.006 bits, when restricted to n = 55 SUA). While these information values might seem low, one must note that they were obtained using short (T = 4 ms) time windows; in normalized units, these correspond to information rates of about 12 bits/s, which is in the range of
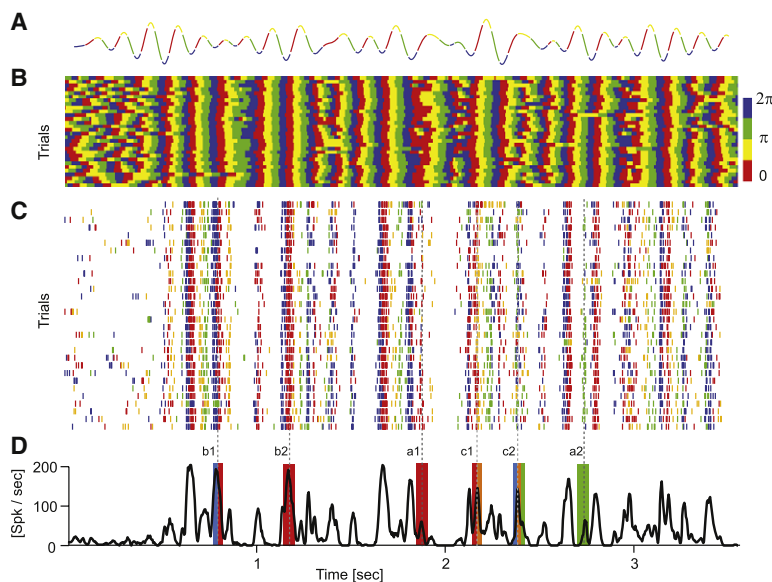
A

B

C

D

Figure 2. Slow Rhythms and Spiking Activity

(A) Low-frequency (8–12 Hz) LFP during a single trial. The phase angle is color coded.

(B) Binned LFP phase during 30 subsequent trials.

(C) Spike raster plot for one unit recorded during the same trials as in (B). Individual spikes are color coded according to the LFP phase at the time of spike.

(D) Mean firing rate (PSTH) at this site. The colored bars indicate the typical phase at each peak. Pairs of peaks in the PSTH with similar height but different phase angle are marked by gray lines. The two instances in each pair (e.g., a1, a2) can be distinguished based on LFP phase but not based on the firing rate.

previously reported values for neurons in sensory structures (Borst and Theunissen, 1999). Compared to the firing rate, the spike-phase code was even more informative: Figure 3A displays the information in I_rate versus I_rate&phase and reveals a considerable increase in information for many individual units. Indeed, the mean increase was 93% ± 9.1% (from 0.047 to 0.093 bits) and the difference between codes highly significant (t test, $p < 10^{-5}$). We systematically quantified this information gain of I_rate&phase for a range of LFP frequencies (Figure 3B): the gain was highest for low and gradually decreased toward higher frequencies. Statistically, the information gain was significant for frequencies up to 34 Hz (t test $p < 0.01$, Bonferroni corrected), but not for higher frequencies. Noteworthy, the information gain in the phase code was highly variable between individual units (scatter of individual dots in Figure 3B). An even stronger information gain by spike-phase coding was found when considering single units only (Supplemental Results 2.2). To confirm that information in phase is novel

with respect to information in rates, we verified that I_rate&phase provides information about stimuli that cannot be discriminated by rate alone. To do so, we computed information using only stimulus windows for which the (average) firing rate attained exactly the same value and hence for which there is no information in I_rate: while I_rate remained zero, I_rate&phase increased for stimulus windows with higher firing rate (Figure 3C).

The spike-phase code defined above combines neuronal firing with the phase of slow rhythmic activity. However, one could also envision a neural code in which it matters at what amplitude of the rhythm rather than at which phase angle a neuron fires. To assess the usefulness of such a code, we computed the information obtained when labeling spikes with the LFP energy or the combined energy&phase signal. However, neither of these putative codes provided more information than obtained from the phase label (Supplemental Results 2.3). Altogether, these results let us conclude that slow (<30 Hz) rhythmic activity does not act as internal "noise," but the phase of slow rhythms can be combined with spiking activity to form a highly informative code. The phase of higher frequencies (e.g., above 40 Hz), however, does not add further stimulus information than already contained in firing rates.
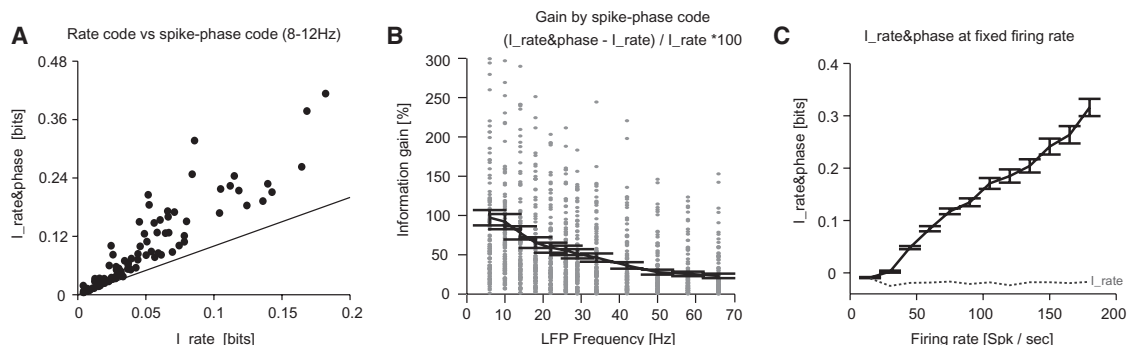
A Rate code vs spike-phase code (8-12Hz)

B Gain by spike-phase code (I_rate&phase - I_rate) / I_rate *100

C I_rate&phase at fixed firing rate

Figure 3. Information in Spike Rate and Spike-Phase Codes

(A) Information in spike rate (I_rate) versus the information in spike phase (I_rate&phase, 8–12 Hz phase label, T = 4 ms time window). Each dot denotes one unit.

(B) Information gain (in percent) of the spike-phase code relative to rate code. The black line indicates the mean and SEM across units (n = 104); dots denote individual units.

(C) Information in I_rate&phase, computed separately for windows of the same firing rate (for each neuron the stimulus was divided into segments of same average rate). While the spike-phase code still provides information (black line), information in spike rate is zero (dashed line).
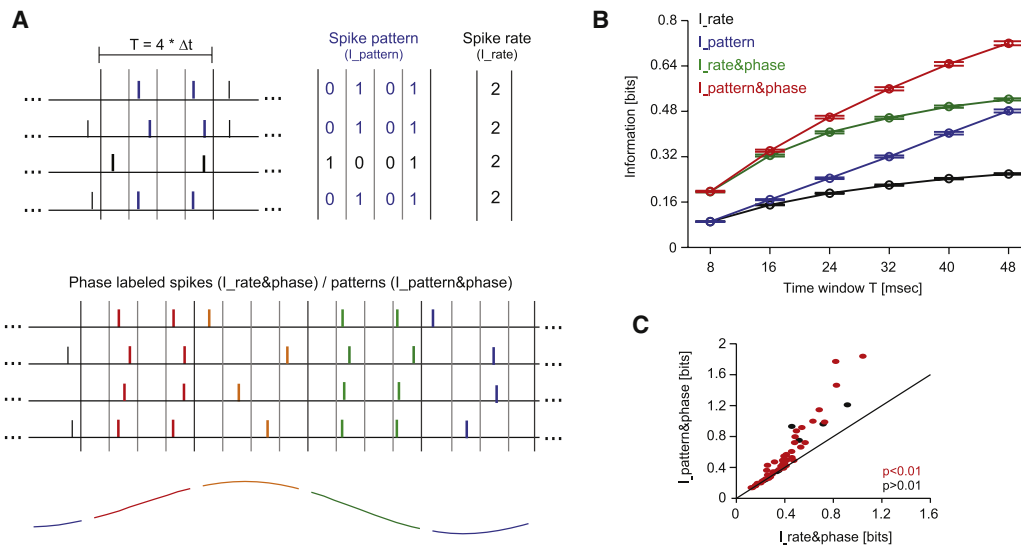
Figure 4. Information in Different Temporal Codes

(A) Schematic explaining different temporal codes. From the response in a given window, one can either extract the spike pattern (here a binary four-digit word) or the spike rate. Importantly, time windows of same rate can contain distinct spike patterns. In addition, one can label the rate or spike pattern with LFP phase (lower panels), resulting in nested codes. Red and green spikes form consistent spike patterns, while orange and blue spikes do not form consistent patterns. And while red and green patterns are identical, they occur during a different LFP phase (color code). Similarly, orange and blue spikes yield the same firing rate, but can be distinguished by phase.

(B) Information as a function of stimulus window length T (number of bins L times bin width Δt). Lines and error bars indicate the mean and SEM for single units (SUA, n = 55, Δt = 8 ms). The result for the combined MUA/SUA data set is presented in the Supplemental Results.

(C) Scatter plot of information in phase-labeled rate versus information in phase-labeled patterns. Red dots denote units with a significant increase in information (p < 0.01, bootstrap statistics for individual units).

Information in Temporal Spike Patterns

While there was no additional information in spikes locked to high-frequency oscillations, there might be fine temporal information in precisely stimulus-locked (rather than LFP-locked) spike patterns. We hence quantified the information in temporal spike patterns. Following Strong et al. (Strong et al., 1998), we subdivided each stimulus window (length T) into smaller time bins (Δt, the precision used to register spikes within a pattern) and counted the occurrence of spike patterns in windows of different lengths (Figure 4A). We employed bin widths Δt of 4 and 8 ms, as these were optimal to discriminate individual sound segments based on temporal responses (Supplemental Result 2.4). The following section presents the results of this analysis for single-unit (SUA) data only, since spike patterns might critically depend on the individual neuron. The results for the entire data set are shown in Supplemental Results 2.5.

Consistent with previous reports from other modalities (Panzeri et al., 2001), the information in spike rates (I_rate) and patterns (I_pattern) increased steadily with the size of the stimulus window (Figure 4B). However, I_rate grew more slowly than I_pattern. For a stimulus window of T = 48 ms and a precision of Δt = 8 ms, I_rate provided 0.26 ± 0.025 bits (mean ± SEM) while I_pattern provided 0.48 ± 0.04 bits, corresponding to an information gain of 109% ± 16% in the temporal code. Importantly, similar results held for other time windows, and I_pattern was significantly larger than I_rate when the pattern consistent of four (t test p < 0.01), five (p < 0.001), or six bins (p < 10^{-5}). Similar

results were also obtained when using bins of Δt = 4 ms and when including multiunit activity (Supplemental Results 2.5). This demonstrates that temporal spike patterns constitute a much more informative code than firing rates.

The information in I_rate&phase (8–12 Hz label) also increased with stimulus window (Figure 4B) but slower so than I_pattern. Still, for all stimulus windows considered, I_rate&phase was larger than I_pattern. For example, for T = 48 ms, I_rate&phase provided 0.52 ± 0.03 bits corresponding to an information gain of 168% compared to the rate code (Figure 4C). Even if the value of I_pattern is likely to be slightly underestimated for stimulus windows longer than 32 ms (due to a small residual negative bias, Supplemental Experimental Procedures), the information gain of I_rate&phase was significantly larger than the gain of I_pattern for all time windows (t test, at least p < 0.01). A comparable advantage of I_rate&phase over I_pattern was also found for the 4–8 Hz band and different temporal binning.

These results promote several conclusions. First, the nervous system may obtain a compelling performance gain by using temporal codes rather than spike rates. Second, I_pattern increased faster than I_rate&phase with increasing window length, suggesting that, for very long windows, spike patterns could be more informative. However, for windows shorter than 48 ms, I_pattern provided less information than I_rate&phase, suggesting that at the biologically relevant timescales of postsynaptic potentials and membrane time constants spike phase is the more informative temporal code.

Information in Nested Phase and Pattern Codes

The above shows that neuronal activity encodes information about acoustic stimuli on different timescales. On a fine scale, spike patterns provide information, while on longer scales the relative timing of spikes and slow rhythms is informative. This begs two questions. First, whether these two processes provide complementary information about the stimulus. And second, whether stimulus-locked spike patterns and phase-locked firing can coexist at the same time. Since both external stimuli and internal network activity control the excitability of cortical neurons, it might well be that the two processes are mutually incompatible (Tiesinga et al., 2008). To decide on these alternatives and to determine whether auditory cortex potentially could employ a "nested" code, we compared the information in spike patterns (I_pattern&phase) and spike rates (I_rate&phase) when both were tagged with the phase of slow rhythms (Figure 4A).

For all considered lengths T of stimulus time windows, I_pattern&phase was higher than I_rate&phase, which discards the precise spike pattern (Figure 4B). For example, for the T = 48 ms window, I_pattern&phase was 0.72 ± 0.048 bits while I_rate&phase was 0.52 ± 0.03 bits, resulting in a higher information gain for I_pattern&phase (238% of I_rate) than for I_rate&phase (168%). This difference between the phase-labeled patterns and phase-labeled rate was significant for all windows longer than 24 ms (at least p < 0.01). We further verified the potential of the nested code at the level of individual neurons using a bootstrap procedure: for 44 of 54 SUAs, I_pattern&phase was higher than I_rate&phase (at p < 0.01, 8–12 Hz LFP and T = 48 ms, Figure 4C). Similar results were obtained for other windows, the 4–8 Hz band, and for the entire MUA/SUA population (Supplemental Results 2.5).

These results highlight the computational advantages the nervous system could gain by concurrently employing several (nested) coding schemes that combine fast (spikes ~10 ms) and slower (low-frequency LFP ~100 ms) timescales. However, they leave open whether phase-locked and stimulus-locked epochs alternate and prevail each for different stimuli or whether both codes coexist in time but encode different features of the same stimulus epochs. We directly addressed this by quantifying the trial-to-trial consistency of spike patterns and spike-phase relations and testing whether consistent patterns and spike-phase relations occur simultaneously. On average, instances of reliable spike-phase relation were also accompanied by reliable spike patterns (Supplemental Results 2.6): across units, the consistency index of spike patterns and spike-phase relation correlated strongly (mean R^2 of 0.59 ± 0.16), demonstrating that stimulus-locked spike patterns and stimulus-related spike-phase relations coexist rather than alternate.

Information in Spatial Codes

Another possibility to combine information from different sources and to stabilize the sensory representation to external or internal noise is to join the activity of spatially separated neurons in the form of a population code (Pouget et al., 2000; Reich et al., 2001). In the following, we directly compare the information provided by two different population codes to the information in the above temporal codes. Both population codes are obtained from the same set of responses but make different
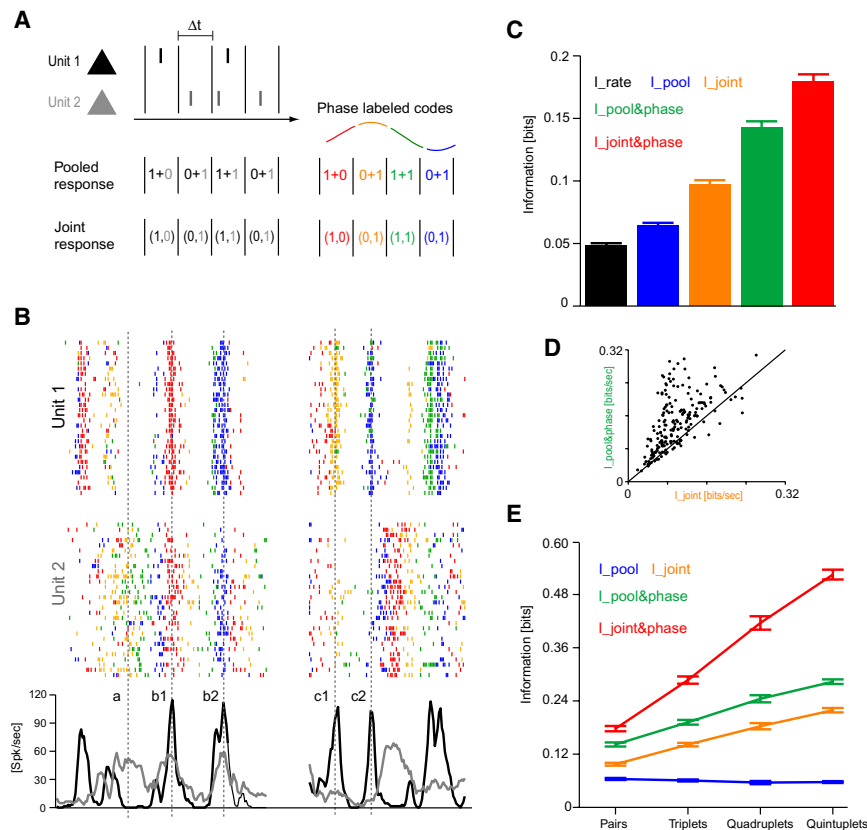
assumptions about the underlying mechanisms (Figure 5A). The pooled code (I_pool) assumes that the identity of the neuron eliciting a particular spike is lost and explicitly sums the activity of different neurons (Panzeri et al., 2003; Reich et al., 2001). In contrast, the labeled-line keeps track of each neuron's response and defines the informative variable as the vector comprising all responses (hence also called joint response, I_joint). In the following, we first consider populations consisting of two neurons (pairs) and later compute the information for population codes consisting of up to five simultaneously recorded neurons.

That a population code consisting of two neurons is advantageous over the responses of individual neurons is exemplified in Figure 5B: several epochs during which one neuron elicits the same response can be discriminated by knowing the response of the other neuron (e.g., points a and b1, see differences between gray and black traces). Indeed, combining the responses of pairs of neurons clearly increased the information beyond that available from individual neurons: both I_pool (0.064 ± 0.002 bits, mean ± SEM, n = 210 pairs, T = Δt = 4 ms) and I_joint (0.096 ± 0.004 bits) were significantly higher than I_rate (of the same neurons 0.048 ± 0.0012 bits, t tests p < 10^{-4}, p < 10^{-7}, Figure 5C). Noteworthy, I_joint was about twice I_rate, suggesting that individual neurons encode largely independent information. Indeed, comparing the sum of the information provided by individual neurons with I_joint (I_rate(S,r_1) + I_rate(S,r_2) versus I_joint(S,(r_1,r_2))) revealed no significant difference (t test, p = 0.47). Hence, in the present setting (units spaced at least 750 μm apart), a spatial population code mainly provides the summed information available by both neurons. While these results highlight another possibility to enhance the information bearing capacity of auditory cortex aggregating information across spatial scales, this begs the question of how spatial and temporal codes interact and in how far they can complement each other.

Information in Nested Spatial and Spike-Phase Codes

To investigate the complementary nature of temporal and population codes, we computed the information in a nested code consisting of spatial population activity and its relative timing to slow rhythms. Adding the (4–8 Hz) phase label to the population codes indeed showed that combining evidence from spatial and temporal dimensions allows distinguishing stimulus epochs that could not be distinguished otherwise. In the example of Figure 5B, the firing rates of each neuron are the same at time points b1 and b2; yet these can be discriminated by knowing the LFP phase (b1, red phase; b2, blue phase). While the pair c1 and c2 provides another such example, the combination of b2 and c2 illustrates the full power of the combined code: since the firing rate of unit 1 at b2 and c2 is the same, and both responses occur during the blue phase, neither the rate of unit 1 nor the spike-phase code suffices to distinguish these points. However, adding the firing rate of unit 2 allows distinguishing them. As a result, the example time points b and c can only be all distinguished when multiple coding schemes are employed.

Information analysis demonstrated that nested codes indeed consistently provide more information than spatial codes (Figure 5C, 4–8 Hz phase label, T = Δt = 4 ms): for the pooled

Figure 5. Information in Different Spatial and Nested Spatial and Temporal Codes

(A) Schematic of different population codes. The activity of two neurons can be combined by either summing their responses in each time window (pooled code) or by preserving the identity of the neuron eliciting each response (labeled-line code/joint response). In addition, the relative timing of either population response to slow ongoing rhythms can be taken into account, resulting in nested codes (color coding).

(B) Example data for one pair of units. The upper panels display the simultaneously recorded spikes of both units color coded by 4–8 Hz phase at the time of spike, while lower panels display the PSTHs. Dashed lines indicate instances at which the responses of both units differ clearly (a) or time points at which both units yield the same average response, but which can be distinguished based on the LFP phase (pairs b and c).

(C) Information provided by each code (mean and SEM values, n = 210, 4–8 Hz phase label, T = 4 ms stimulus time window).

(D) Scatter plot I_joint versus I_pool&phase. Information provided by the phase label was generally higher than information provided by knowing the identity of each neuron.

(E) Information in different codes for neuronal populations consisting of between two and five units. Lines indicate the mean and SEM across the respective number of populations (pairs, n = 210; triplets, n = 167; quadruplets, n = 61; quintuplets, n = 124; T = 4 ms stimulus time window).

code, information doubled from 0.064 ± 0.002 bits (I_pool) to 0.14 ± 0.004 bits (I_pool&phase, t test p < 10^{-20}), and for the labeled-line, information increased from 0.096 ± 0.004 bits (I_joint) to 0.18 ± 0.006 bits (I_joint&phase, p ≈ 0). The benefit arising from the phase label was further confirmed by a bootstrap analysis, which revealed that for all except three pairs of neurons I_pool&phase was significantly larger (p < 0.01) than I_pool (similar for I_joint). In addition, in a direct comparison, I_pool&phase was significantly more informative than I_joint (sign test p < 10^{-13}, Figure 5D). This demonstrates that the phase label adds information that cannot be retrieved from the labeled-line.

Given that the LFP constitutes a mesoscopic signal comprising the synaptic-related activity around the electrode, one could conceive that the phase label becomes redundant with the joint response of an increasing group of neurons (Latham and Lengyel, 2008). We addressed this by computing the information in population codes consisting of up to five simultaneously recorded neurons (Figure 5E). Pooling the activity of an increasing number of neurons led to a small reduction of information (I_pool 0.064 ± 0.002 bits for pairs, 0.057 ± 0.002 bits for quintuplets), suggesting that pooling reduces the specificity of the summed response. In contrast, information in the joint response increased linearly with increasing population size (I_joint 0.096 ± 0.004 bits for pairs, 0.22 ± 0.005 bits for quintuplets, t test p ≈ 0). Importantly, adding the phase label to this joint firing rate further enhanced the information for all population sizes (I_joint&phase 0.18 ± 0.006 bits for pairs, 0.52 ± 0.01 bits for quintuplets), resulting in a significant difference to I_joint

(p ≈ 0). We hence conclude that the spatial labeled-line is complementary to the temporal phase label and hence information in spatial codes can be enhanced by including information about the relative timing to slow rhythms.

Information Coding in the Presence of Sensory Noise

Any neural code that is to operate under realistic conditions must not only provide information about clearly audible sounds but must also be robust to external noise. During every day hearing, such noise could arise from a number of sources, such as background babble in a bar, traffic noises in a downtown area, or simply by wind whistling in the ear. We conducted a second experiment to directly quantify the impact of sensory noise on different codes. To this end, rather than delivering perfectly repeatable stimuli, we parametrically degraded, independently in each trial, the acoustic stimulus with noise of four different levels (Figure 6A). Since background noise is often of similar structure as the original stimulus that needs to be encoded (e.g., background voices in a bar), we designed the noise in our experiments to have a naturalistic frequency composition similar to the actual stimulus.

The impact of noise on neuronal responses is illustrated for one unit in Figure 6B: at time point a1, this unit responded vigorously to the "clean" stimulus, but the response was much reduced when adding noise. As a result, some time points (e.g., a1 and a2) could be discriminated based on the firing rate in the absence of noise, but no longer during the medium noise condition. However, when including the phase label,
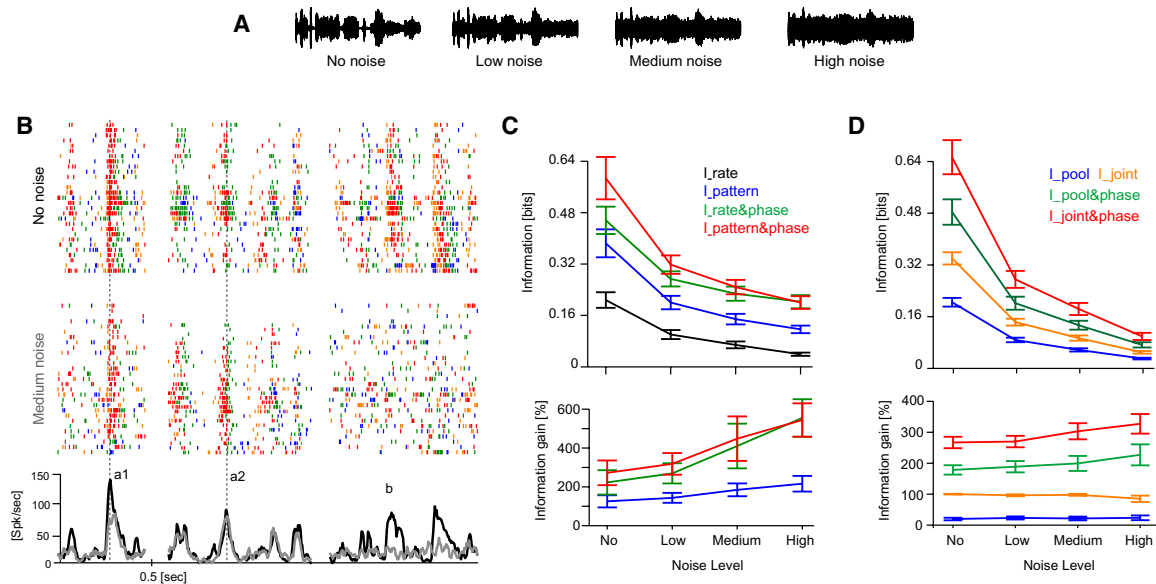
Figure 6. The Effect of Sensory Noise on Information Coding

(A) Example segments of the same stimulus mixed with noise of four different levels.

(B) Example data form one unit recorded during subsequent trials in no-noise and medium-noise conditions. Spikes are color coded with the LFP phase (4–8 Hz). Dashed lines indicate illustrative time points: (a) indicates instances that can be distinguished based on firing rate in the no-noise, but no longer in the medium-noise condition. Yet, they can be distinguished based on the spike phase during the noise condition. (b) indicates a period where individual time points become indiscriminable regardless of the code used.

(C) Information in the different temporal codes (color coded) as a function of noise level (mean and SEM, n = 25 units, Δt = 8 ms, T = 48 ms window, 4–8 Hz phase label). The lower panel displays the information gain with respect to the firing rate.

(D) Information and information gain in the different spatial and nested spatial and temporal codes (color coded, n = 40 pairs, Δt = 8 ms, 4–8 Hz phase label).

these time points still could be discriminated during noise: the response at a1 consistently occurred during the orange-to-red phase, while the response at a2 occurred during the red-to-green phase.

Confirming these observations, we found that the information in each code decreased with increasing noise level (Figure 6C). For example, I_rate decreased from 0.20 ± 0.024 bits (no noise, n = 26 units, Δt = 8 ms, T = 48 ms) to 0.039 ± 0.005 bits (high noise), resulting in a significant effect of noise (ANOVA, F = 57, p ≈ 0). The decreases in information were significant for all codes (Figure 6C).

The information gain provided by more complex codes over the firing rate, however, increased with increasing noise level (Figure 6C, lower panel). For example, the gain of I_pattern nearly doubled, resulting in a significant difference between no-noise and high-noise conditions (p < 0.001). For I_rate&phase, the gain more than doubled (p < 10^{-3}), and the same was true for I_pattern&phase (p < 10^{-3}, all computed with Δt = 8 ms, T = 48 ms, 4–8 Hz LFP). For the spatial population codes (Figure 6D), the information gain remained constant across noise levels (I_pool, p = 0.8; I_joint, p = 0.3). For the nested spatial and temporal codes, the information gain increased again with noise (I_pool&phase, p = 0.09; I_joint&phase, p = 0.05), although less pronounced that in the purely temporal codes above.

These results have several implications for sensory processing. First, they rule out the hypothesis that temporal averaging of responses is necessary to reduce noise (Shadlen and Newsome, 1998). Spike patterns locked to stimulus onset were far more robust to noise than spike rates, suggesting that precise spike patterns are generated robustly by the activation of internal mechanisms in response to salient stimuli (Diesmann et al., 1999; Harris, 2005). Second, the phase of slow rhythms is a critical variable to noise-robustness: tagging any considered neural code (spike rate, spike patterns, or population response) with the phase of slow rhythms greatly improved the robustness of its information in noisy conditions. This leads us to conclude that low-frequency rhythms provide a highly robust frame of reference upon which neuronal spiking activity carries additional information and which stabilizes neural codes to noise.

DISCUSSION

In this study, we compared the performance of different neural codes in encoding natural sounds in the auditory cortex of alert primates (c.f. Figure S1 for an overview of all codes). We systematically quantify and compare the information provided by different temporal and population codes, as well as by nested combinations of these, and both during repeated stimulation conditions and in the presence of sensory noise. Our results demonstrate that both temporal spike patterns and spatial population codes provide more information than firing rates alone and that codes operating on different scales provide complementary information. As a consequence, combining different coding mechanisms into a nested code provides significant gains of information. Our results highlight the nested combination of spiking activity with the phase of slow rhythms as an

especially promising code, as it was found to be most informative, it contained information complementary to both spatial and temporal patterns, and provided robustness to sensory noise. Hence, we conjecture that one role of slow rhythms might be to provide a stable frame of reference relative to which spiking activity (temporal or population pattern) can encode sensory information.

Stimulus-Locked and Phase-Locked Temporal Neural Codes

Two different neural codes that exploit the temporal response structure have been suggested: finely timed stimulus-locked patterns of spikes (Bialek et al., 1991; Optican and Richmond, 1987; Stevens and Zador, 1995) or the relative timing ("phase") of spiking activity to slow fluctuations of the cortical network (Hopfield, 1995; Lisman, 2005). Although both codes have received considerable experimental support, they are often regarded as incompatible because of their partly contrasting requirements: the more spike times are modulated by internally generated rhythms, the more difficult it appears to support precisely stimulus-locked spike times, and vice versa (Tiesinga et al., 2008). Our results highlight that both temporal codes coexist and provide complementary information about the same stimulus epochs.

We found strong quantitative support for phase coding: labeling spike rates with the phase of slow rhythms greatly enhanced the information encoded, and the information carried by the phase of firing was genuinely novel with respect to that carried by spikes. Noteworthy, the information gain by spike-phase coding was limited to slow (<30 Hz) fluctuations, while fast (gamma) oscillations did not play a role in spike-phase coding (in agreement with findings from somatosensory cortex [Ray et al., 2008]). Previous evidence for spike-phase coding relative to slow rhythms has been reported in the hippocampus (Hopfield, 1995; Lisman, 2005; Mehta et al., 2002; O'Keefe and Recce, 1993), olfactory structures (Brody and Hopfield, 2003; Laurent, 2002), and recently also in primary visual cortex of anesthetized animals (Montemurro et al., 2008). Our findings corroborate the notion that phase coding is also exploited in cortical areas, and prominently, also in alert animals. Indeed, the information gain of phase codes found here in the alert animal was much larger than that reported under anesthesia (Montemurro et al., 2008).

Previous reports of spike-phase coding considered only the relationship between the time-dependent firing rate and slow rhythms, but did not address whether spike-phase coding could be accompanied by precisely stimulus-locked spike patterns. Here we provide direct evidence for the simultaneous presence of stimulus information encoded in stimulus-locked spike patterns and phase-locked activity in sensory cortex of alert animals. We found that stimulus-locked spike patterns with precision of less than 10 ms were highly informative, in agreement with previous reports (Chechik et al., 2006; Engineer et al., 2008; Nelken et al., 2005; Schnupp et al., 2006; Walker et al., 2008; Wang et al., 2007). The excess information in spike patterns over firing rates increased with the duration of the stimulus window, suggesting that natural acoustic stimulation can impose extended and temporally precise patterns on the spiking responses of auditory cortex neurons.

Importantly, spike patterns and their relative timing to slow rhythms provided genuinely complementary sensory information, and combining both codes resulted in a considerable gain of information. The combination of both temporal codes constitutes an example of so-called nested coding, where different types of information are inserted on the neural response, embedded in different timescales. While nested codes could offer considerable computational advantages by exploiting the synergy of information at different scales, they have rarely been addressed in experimental work (Hopfield, 1995; Lisman, 2005).

That spike patterns and their relative phase to slow rhythms carry complementary information raises the question of how this combination is achieved. This might seem surprising since the mechanisms generating temporal and cell assembly patterns may be partly shared with the mechanisms generating slow network fluctuations (Harris et al., 2002). One possibility is that responses could alternate between stimulus-locked and phase-locked epochs (Tiesinga et al., 2008). Yet, this was not the case in our data, as spike patterns and spike phase were highly reliable in the same epochs. Alternatively, we suggest that different stimulus features (occurring in the same stimulus epoch) are represented by slow rhythms and finely timed spike patterns. In this way, the full bandwidth of cortical signaling capacity could be used efficiently to form information-rich representations.

How can spike times be precisely related to slow internal fluctuations and at the same time be stimulus driven? One possibility is that slow network rhythms themselves are reliably modulated by the stimulus. Indeed, we found that slow field potentials were stimulus locked and informative. Under this circumstance, it is no longer exclusive for spikes to lock either to slow rhythms or the stimulus, allowing them to participate simultaneously in both forms of temporal coding. A point worth noting is that our experiments employed prolonged stimulation periods using an ensemble of naturalistic sounds, in contrast to many studies that use briefly pulsed sounds separated by prolonged periods of silence. Continuous stimulation might better reflect typical every day conditions, where, for example, we often follow longer conversations or watch out for one particular sound in a prolonged sequence of other sounds. In addition, prolonged stimulation might facilitate the entrainment of slow rhythmic activity to sensory stimuli. Natural sounds, including speech and vocalizations, contain prominent rhythms on different temporal scales, which could directly drive the excitability of auditory cortex and map temporal stimulus properties onto the patterns of oscillatory activity taking important roles in information processing (c.f. Supplemental Discussion). Indeed, previous experiments have demonstrated that slow oscillations control the excitability and timing of faster oscillations and of spike times (Lakatos et al., 2005; Schroeder et al., 2008), both during spontaneous activity and during sensory stimulation. Our results demonstrate that this hierarchical control of the processing at faster timescales by slow oscillations translates into a highly informative nested coding scheme for the encoding of naturalistic sounds. Noteworthy, the interaction of slow oscillations and spiking activity might not only be relevant for sensory processing, but could also play a central role in cognitive and attentional modulation

of early sensory processing (see Lakatos et al. [2008] and Supplemental Discussion).

Information Coding Using Spatial Population Codes

It has been suggested that populations of neurons with diverse tuning properties increase the information they transmit by using so-called labeled-line codes, in which specific information is embedded into the label (e.g., the spatial coordinates) of the neuron firing the spike. Support for this notion has been reported in visual (Reich et al., 2001) and somatosensory cortex (Panzeri et al., 2003) of anesthetized animals. We extend these findings by showing that labeled-line coding is highly informative also in auditory cortex of alert animals.

Further, our results demonstrate that the information carried by the temporal spike-phase code is complementary to that carried by the spatial label. This suggests that the stimulus dependence of the phase of firing cannot be predicted simply by the activation of particular assemblies of neurons (Harris, 2005) and that information carried by the spike phase is complementary to information contained in (small) populations of neurons (Latham and Lengyel, 2008). This highlights further the notion that tagging spikes with the phase of slow network fluctuations is an efficient way to merge information locally available at individual neurons with complementary information spread over a larger (mesoscopic) scales.

Decoding Information Available in Nested Codes

Our results suggest that nested codes are advantageous over simpler codes, especially over firing rates. But can putative downstream neurons actually access the full information provided by nested codes, and which mechanisms are needed for such read out? To be able to exploit a specific code, the receiving (decoding) neurons need to be sensitive to the parameters constituting the code. For example, being able to "read" temporal spike pattern sensitivity to time intervals between individual postsynaptic potentials is needed (Salinas and Sejnowski, 2001). Hence, to exploit the relative timing of spikes to slow ongoing rhythms, a (decoding) neuron needs to have access to the phase of firing. Low-frequency rhythms are correlated over several millimeters and constitute a spatially extended signal that is available to other neurons in the same or a nearby region. Given that a large fraction of synapses in cortex connects spatially proximal neurons (Braintenberg and Schuetz, 1998), the slow rhythm is likely the same for the neuron eliciting the spike and the neuron receiving it; as a result, the phase of firing is available for a good number of the computations performed in cortex. For the present data, we verified that the spike-phase code is robust to the choice of the LFP: combining spiking activity with the LFP recorded on the same electrode or with an "average" LFP both yielded significant information gains (c.f. Supplemental Results 2.7). Since the membrane potential of many neurons fluctuates according to the LFP (Amzica and Steriade, 1995; Lampl et al., 1999), incoming postsynaptic potentials will also bear a particular temporal relation to the membrane potential. Combined experimental and modeling studies have shown that the responses of individual neurons indeed depend on this relative timing, and membrane potential oscillations can dramatically increase the temporal precision of spiking responses (Margrie

and Schaefer, 2003; Schaefer et al., 2006) and increase the information transfer by single neurons (Tiesinga et al., 2002). As a result, it is likely that neurons can indeed exploit the precise phase relation of slow rhythms and spiking responses. In addition, nonspecific thalamic nuclei, which may act as classic modulatory inputs in auditory cortex, project diffusely and nonspecifically to the superficial cortical layers of several cortical fields (Jones, 1998). This makes them an ideal candidate to coordinate the activity of neuronal populations in spatially separated up- and downstream areas, providing the right context in which the driving inputs are processed in the downstream area (Lakatos et al., 2007; Schroeder et al., 2008).

Information Coding in the Presence of Sensory Noise

To determine which neural codes may prevail in sensory cortical areas, it is important to consider realistic conditions. This not only requires that neuronal activity is recorded from alert animals but also that sensory stimuli conform to every day conditions. Acoustic stimuli are often corrupted by noise, such as downtown traffic noise or the babble of voices at a cocktail party. Despite this noise, we are still able to identify individual sounds or understand somebody talking. This raises the question whether the same neural codes, and if so which, can be used to represent clean and noise-corrupted stimuli. To explore the ability of neural codes to cope with sensory noise, we employed a separate stimulus paradigm during which the original stimuli were presented mixed with noise. While the information in all codes decreased with increasing noise, the information gain of nested spike and LFP phase codes increased with increasing noise. Hence, these findings suggest a crucial function for slow rhythmic activity: it might serve to stabilize the sensory representation to the detrimental effect of sensory noise.

Theoretical studies on neural networks show that correlated noise in the input to different units can generate stable oscillatory synchrony (Ermentrout et al., 2008; Galan et al., 2006). Such correlated trial-to-trial variations might for example occur in the elements participating in the generation of slow rhythms, making these a stimulus-related signal that by virtue of its aggregate nature could be highly robust to noise. In addition, combined modeling and experimental work has demonstrated that rhythmic input increases the firing precision of single neurons and increases their robustness to noise (Brody and Hopfield, 2003; Margrie and Schaefer, 2003; Schaefer et al., 2006; Tiesinga et al., 2002). Hence, slow rhythms could serve as a common frame of reference relative to which neuronal activity could encode additional sensory information regardless of the external sensory conditions. The results presented here provide experimental evidence that this may indeed be the case.

EXPERIMENTAL PROCEDURES

Electrophysiological Recording Procedures and Stimuli

Neuronal activity comprising local field potentials and spiking responses was recorded from auditory cortex of three rhesus monkeys (Macaca mulatta), using a multielectrode recording system (electrode spacing 750 μm). Recording sites covered regions of primary auditory cortex and the caudal belt. All procedures were approved by the local authorities (Regierungspräsidium) and were in full compliance with the guidelines of the European

Community (EUVD 86/609/EEC). Details of signal extraction, information estimates, and bias correction procedures are described in the Supplemental Data.

Sounds (average intensity of 65 dB SPL) were delivered from two free-field speakers while the animal was passively listening in an anechoic booth. In a first paradigm, a continuous 52 s sequence of various natural sounds (including animal vocalizations, environmental sounds, conspecific macaque vocalizations, and segments of speech) was repeated many times (usually >55) for each site. In a second paradigm, a 20 s chunk of this long natural sound was presented either in its original form or mixed with noise. The noise was obtained as a mixture of natural sounds and was either 6 dB softer than the original sound ("low noise"), had the same level ("medium noise"), or was 6 dB louder ("high noise"). Importantly, and to resemble true noise, a different background noise was randomly generated for each trial.

SUPPLEMENTAL DATA

The Supplemental Data include Supplemental Experimental Procedures, Supplemental Results, Supplemental Discussion, and nine figures and can be found with this article online at http://www.neuron.org/supplemental/S0896-6273(09)00075-0.

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