

Metadata of the chapter that will be visualized online

| | | |
|--------------------------------|---|---|
| Chapter Title | Packets of Sequential Neural Activity in Sensory Cortex | |
| Copyright Year | 2015 | |
| Copyright Holder | Springer Science+Business Media New York | |
| Corresponding Author | Family Name | Luczak |
| | Particle | |
| | Given Name | Artur |
| | Suffix | |
| | Division | Department of Neuroscience |
| | Organization | University of Lethbridge |
| | Address | 4401 University Dr., Lethbridge, AB, Canada, T1K 3M4 |
| | Email | Luczak@uleth.ca |
| Abstract | <p>Either spontaneously or in response to stimuli, neurons are active in a coordinated fashion. For example, an onset response to sensory stimuli usually evokes a 50–200 ms long burst of population activity. In this chapter, we summarize recent papers of the author showing that such bursts of neuronal activity are not randomly organized, but rather composed of stereotypical sequential spiking patterns. To underline this fine-scale internal organization of such population bursts, we will refer to them as “packets.” It has been shown that packets are ubiquitous feature of spontaneous and stimulus-evoked network activity and are present across different brain states. Although these packets have a generally conserved sequential spiking structure, the exact timing and number of spikes fired by each neuron within a packet can be modified depending on the stimuli. In this chapter, we provide a detailed description of packets, and we discuss how the packet-like organization of neuronal activity may provide an explanation for multiple puzzling observations about neuronal coding. It is interesting to note that organizing population activity into packets resembles how engineers designed information transfer over Internet, where information is divided in small, formatted network packets to increase communication efficiency and reliability.</p> | |
| Keywords (separated by “-”) | Auditory cortex - Somatosensory cortex - Population coding - Temporal coding - Upstate - Slow wave oscillation - Silicon microelectrodes - Brain state - Memory replay | |

Chapter 8

Packets of Sequential Neural Activity in Sensory Cortex

Artur Luczak

Abstract Either spontaneously or in response to stimuli, neurons are active in a coordinated fashion. For example, an onset response to sensory stimuli usually evokes a 50–200 ms long burst of population activity. In this chapter, we summarize recent papers of the author showing that such bursts of neuronal activity are not randomly organized, but rather composed of stereotypical sequential spiking patterns. To underline this fine-scale internal organization of such population bursts, we will refer to them as “packets.” It has been shown that packets are ubiquitous feature of spontaneous and stimulus-evoked network activity and are present across different brain states. Although these packets have a generally conserved sequential spiking structure, the exact timing and number of spikes fired by each neuron within a packet can be modified depending on the stimuli. In this chapter, we provide a detailed description of packets, and we discuss how the packet-like organization of neuronal activity may provide an explanation for multiple puzzling observations about neuronal coding. It is interesting to note that organizing population activity into packets resembles how engineers designed information transfer over Internet, where information is divided in small, formatted network packets to increase communication efficiency and reliability.

Keywords Auditory cortex • Somatosensory cortex • Population coding • Temporal coding • Upstate • Slow wave oscillation • Silicon microelectrodes • Brain state • Memory replay

Introduction

Progress in recording from a large number of neurons [1–3] allowed to advance our knowledge on how the activity of a single neuron is shaped by the action of other neurons [4, 5]. It has been found that even in the absence of external stimuli,

A. Luczak, Ph.D. (✉)
Department of Neuroscience, University of Lethbridge,
4401 University Dr., Lethbridge, AB, Canada, T1K 3M4
e-mail: Luczak@uleth.ca

29 population activity can exhibit complex self-organized patterns [6]. Its complex
30 nature and general similarity with activity evoked by sensory input [7–10] suggests
31 that spontaneous activity may play an important role in information processing [11,
32 12]. By studying spontaneous activity, a lot has been learned about the structure of
33 cortical population spike patterns. During resting and sleep, cortical circuits (both
34 in vitro and in vivo) spontaneously produce periods of activity known as “upstates”
35 [13–17]. In vitro experiments have shown that neural activity within upstates has a
36 sequential structure, with the order in which neurons fire largely conserved from
37 one upstate to the next, reflecting the interaction of recurrent circuitry and intrinsic
38 cellular dynamics [10, 18, 19]. Early evidence for sequentially structured spiking
39 activity in vivo came from studies detecting the presence of precisely repeating
40 spike motifs [20]. However, the statistical methods employed, as well as the long
41 duration and high temporal precision of the detected motifs, have been controversial
42 [21–23]. Recent analyses of in vivo population data have confirmed using straight-
43 forward statistical methods that population bursts such as upstates are indeed
44 sequentially patterned for a period of the order of 100 ms, with temporal precision
45 decaying as the upstate progresses [14].

46 Here we summarize a series of recent studies conducted by the author, describing
47 the fine structure of sensory responses and spontaneous activity. By simultaneously
48 recording from tens of neurons, it has been found that neuronal activity is composed
49 of transient but coherent and structured bursts of population activity, which we
50 termed “packets.” Firstly, we will describe how packets contribute to the global
51 structure of population activity. Next, we will analyze the sequential structure of
52 packets and show how it is conserved across different brain states. We will then
53 describe how sequential structure of packets encodes information about sensory
54 stimuli. In the following sections, we will discuss possible mechanisms of packet
55 formation and present a graphical summary of the main results. Lastly, we will
56 describe how the concept of a packet can provide unifying model for neuronal cod-
57 ing, which binds together multiple seemingly contradictory observations about
58 information processing.

59 **Cortical Activity Is Composed of Population Activity Packets**

60 The brain exhibits different patterns of activity depending on the behavioral state.
61 On one extreme is a synchronized brain state which occurs during slow wave sleep
62 or during deep anesthesia, where bursts of population activity called upstates are
63 interspersed with periods of global neuronal silence (downstates) [17]. On the other
64 extreme, when an animal is attentive to a task or stimuli, cortical activity is in desyn-
65 chronized state, which is characterized by seemingly continuous population activity.
66 This variability in cortical state can be also observed in quiescent waking animals
67 [16, 24], which is illustrated in Fig. 8.1a. Note that even in a desynchronized state
68 (Fig. 8.1a-bottom), population activity still exhibits coordinated 50–100 ms long

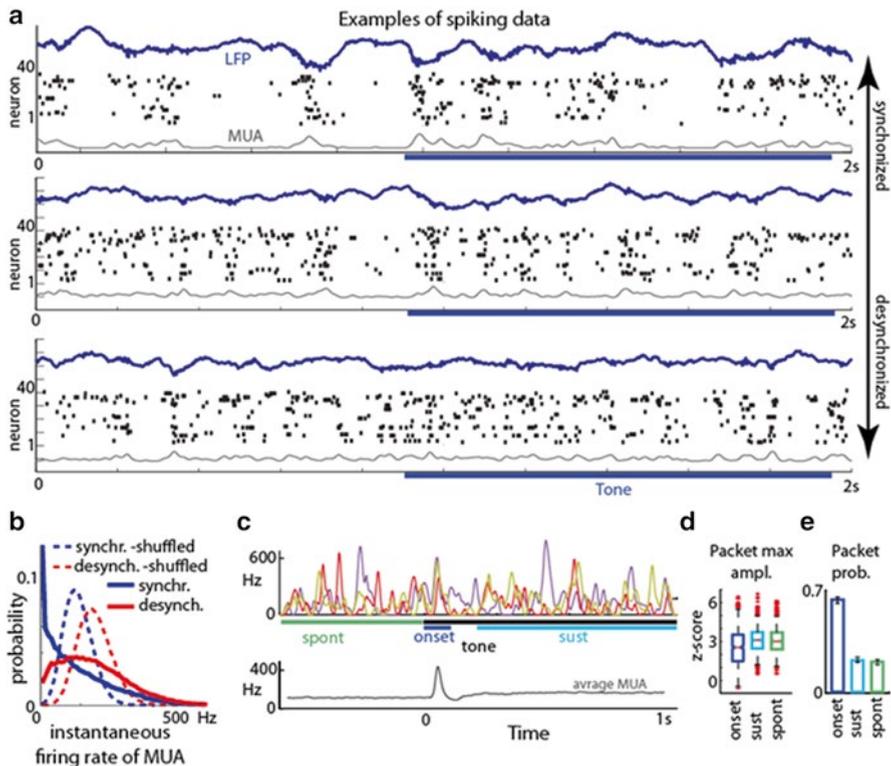


Fig. 8.1 Population activity in the auditory cortex shows coordinated bursts of activity (packets). (a) Examples of raster plots with periods of spontaneous activity followed by periods with tone presentation. Data recorded in auditory cortex in awake rat. Plots are sorted by cortical state. The raster shows spikes of simultaneously recorded neurons and the *blue trace* shows local field potential. At the *bottom* of the figure is the multiunit firing rate (MUA) computed as the smoothed summed activity of all neurons. Note that neurons tend to fire in transient bursts of 50–100 ms duration, with burst times including but not limited to tone onset. Activity during desynchronized states shows weaker global fluctuations but still exhibits complex fine structure. To visualize sequential activity within packets, neurons are sorted by latency in the same order in all three panels (see following section and Fig. 8.2f for more details). (b) Histogram of instantaneous MUA rates during sustained tone responses for desynchronized and synchronized trials. *Dotted lines* indicate the same analysis for trial-shuffled data. (c) *Top* of the panel shows examples of population rate on three single trials. Note that activity packets occur reliably at tone onset but sporadically during spontaneous and sustained periods. *Bottom* of the panel shows the trial-averaged population rate triggered at tone onset. (d) Box-and-whisker plots summarizing distributions of onset-evoked packets, and the distribution of amplitudes of the largest packets in the sustained and spontaneous periods. The central mark is the median, the edges of the box are the 25th and 75th percentiles. (e) Probability of occurrence of large activity packets (mean + 2 SD) during spontaneous, onset, and sustained periods. These analyses suggest that packets have similar amplitude for onset, sustained, and spontaneous periods but occur more reliably at stimulus onset. Figure reproduced from [24]

69 bursts which are also accompanied by a deflection of local field potential (LFP).
70 These bursts are larger than expected from random fluctuation in firing rate, which
71 is illustrated in Fig. 8.1b. This figure shows histograms of the distribution of popula-
72 tion firing rate for the synchronized and desynchronized states (solid lines) as com-
73 pared to trial-shuffled data (dashed lines) [24]. For synchronized data, the histogram
74 (blue) shows a clear mode at 0, indicating the presence of prolonged down phases,
75 and a “tail” corresponding to large bursts of activity. For desynchronized trials, the
76 distribution of multiunit (MUA) was less skewed but still markedly different from
77 the shuffled data, confirming the existence of smaller but still significant population
78 bursts in the desynchronized state ($p < 0.001$ two-sample Kolmogorov-Smirnov
79 test). We will call these population bursts “packets” to emphasize that each popula-
80 tion burst has a fine-scale organization that carries stimulus-specific information,
81 which we will describe in the following sections.

[AU1]

82 *Activity Packets Occur More Reliably at Stimulus Onset but Are* 83 *Not Larger than During Sustained or Spontaneous Periods*

84 We will begin analyzing packets by looking at onset responses evoked by sensory
85 stimulation. Figure 8.1c (top) plots the population rate in the auditory cortex for 3
86 trials with tone presentations. It suggests that the packets of activity accompanying
87 tone onsets are not larger in amplitude than those occurring either within extended
88 tone presentations or in silence. This might at first appear to contradict the fact that
89 one sees clear onset responses when activity is averaged across multiple trials
90 (Fig. 8.1c-bottom). The reason for this is that onset responses in averaged activity
91 occur not because the activity packets triggered by tone onsets are larger than those
92 occurring spontaneously or during sustained tone epochs but because activity pack-
93 ets are reliably evoked by tone onsets and occur at random times during sustained
94 tone responses and spontaneous activity. To quantify this, we calculated, for each
95 tone presentation, the height of the population rate peak after stimulus onset
96 (0–100 ms), the height of the highest population rate peak in the preceding period
97 of silence (–800–0 ms, to avoid offset responses from the previous tone), and the
98 highest population rate peak in the sustained response period (200 ms–1 s after tone
99 onset). Statistical test revealed that population rates at onset were significantly
100 smaller than the highest peaks during 800 ms immediately before or after onset
101 response at each trial (Fig. 8.1d; rates are expressed as z-scores to combine data
102 from different experiments; $p_{\text{onset-sust}}, p_{\text{onset-spont}} < 0.0001$; $p_{\text{sust-spont}} = 0.2$, two-sample
103 Kolmogorov-Smirnov test; [24]). This indicates that the population was typically
104 more active at some moment during the sustained period or silence preceding each
105 tone than at onset. However the probability of seeing an activity packet (measured
106 as an instantaneous MUA rate larger than the mean + 2 SD) was significantly higher
107 at onset as compared to any time point during spontaneous or sustained periods

(Fig. 8.1e). To verify that these results did not simply occur from occasional random spiking coincidences during the sustained and spontaneous periods (which are longer than the onset periods), we performed the same analyses on trial-shuffled data. This confirmed that the detected activity packets reflected true synchronous firing events [24]. Therefore, we concluded that the onset responses seen in activity averaged across trials reflect a stimulus-locked increase in the probability of activity packets, rather than an increase in their size.

Similarity of Sequential Spiking Activity of Stimulus-Evoked and Spontaneous Packets

So far we have only looked at population activity which reflects the sum of activity of all recorded neurons. Next, we will examine more closely the activity of individual neurons within packets and begin again by analyzing onset responses. Figure 8.2a–c shows raster plots and superimposed peri-event time histograms (PETHs) of three individual neurons in response to five different tones. Although the firing rate evoked in any given neuron varied with tone frequency, PETH shapes were largely conserved across tone frequencies. However, between neurons, PETH shapes differed considerably. To quantify the preservation of temporal structure across stimuli, we computed for each PETH a mean spike latency (MSL), defined as the mean spike time in the 100 ms after stimulus onset [9]. Figure 8.2d plots each neuron's MSL to its preferred tone frequency versus its average MSL to all other tones. For neurons with short latency (MSL below 40 ms for best frequency), the majority of points are below the diagonal, suggesting that for such neurons preferred stimuli often induce earlier firing ($p < 0.001$, paired Wilcoxon signed rank test). Robust correlation between MSL for preferred and non-preferred tones (mean $R = 0.72 \pm 0.24$; $p < 0.001$) confirms that temporal profiles are diverse between neurons and largely conserved within the responses of each cell to different tones. Thus, if a neuron is driven to fire in response to a given tone, it will do so with a stereotyped cell-specific temporal profile but with precise timing and firing rate affected by stimuli.

Next, we asked whether spike patterns within spontaneously occurring packets are also temporally structured as packets evoked by sensory stimuli. Figure 8.2e (top) shows raster plots of two of the individual neurons' responses evoked by tone onset, and Fig. 8.2e (bottom) shows average activity of 30 simultaneously recorded neurons to tone stimuli. For comparison, Fig. 8.2f shows raster plots and PETHs of the same neurons as in Fig. 8.2e, triggered at the beginning of spontaneously occurring packets (upstates). Again, a similar sequential ordering was seen. To statistically confirm this similarity, a slightly different approach was used, as the beginnings of spontaneous packets are not experimentally controlled. To measure a cell's position in the firing sequence within a packet, we defined a measure μ_{cc} , the center of mass of its cross-correlogram with the summed activity of all other neurons within

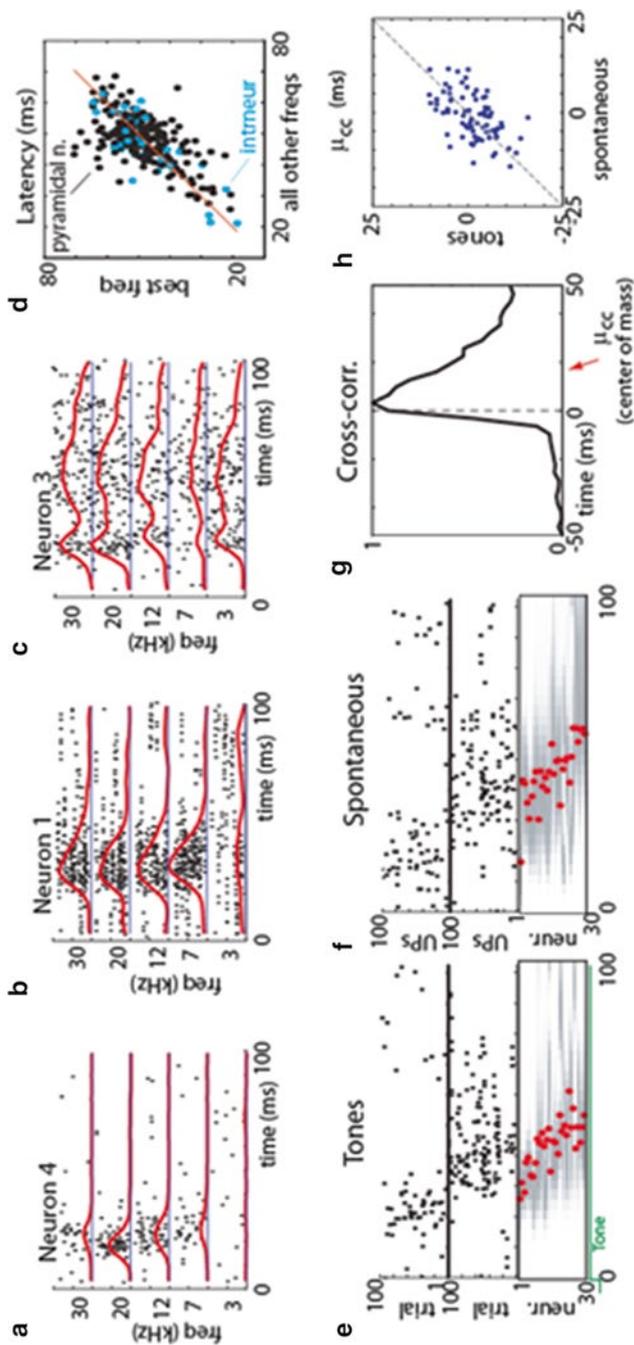


Fig. 8.2 Similarity of stimulus-evoked and spontaneous packets of sequential spiking activity. (a–c) Raster plots showing responses of representative neurons to presentations of 5 pure tones (100 trials for each tone). *Red lines* represent peri-stimulus time histograms. It shows that individual neurons respond to different tones with stereotyped temporal profiles but varying firing rates. (d) Scatterplot showing each neuron's mean spike latency to its preferred tone frequency versus to all other tones. The *red line* corresponds to equal latencies. *Blue dots* represent putative interneurons as defined by spike width. While neurons typically show earlier firing to their preferred tone, this difference is an order of magnitude smaller than the differences between cells. (e–top) Raster plots showing spike times for two representative neurons to repeated presentations of a pure tone stimulus. (e–bottom) Average activity of 30 simultaneously recorded neurons to tone stimuli. *Gray bars* show pseudocolor representations of each neuron's peri-event time histogram (PETH); *red dots* denote each neuron's mean spike latency in the 100 ms after tone onset. Neurons are ordered vertically by the mean latency over all stimuli to illustrate sequential spread of activity. (f) Raster plots and average activity for the same neurons as in panel (e), triggered by upstate onsets. Note the similar temporal pattern to panel (e). (g) Normalized cross-correlograms of one neuron's spike times with the summed activity of all other cells. *Arrow* shows the center of mass (mean spike time) of correlograms (μ_{cc}). (h) Conservation of μ_{cc} across different stimuli and spontaneous events, indicating preservation of sequential order. Each point represents the values of μ_{cc} for a given cell in the conditions indicated on the axes. Reprinted from Neuron, 62(3), Luczak A, Barthó P, Harris KD, Spontaneous events outline the realm of possible sensory responses in neocortical populations, 413–425, copyright 2009, with permission from Elsevier

148 ± 50 ms (Fig. 8.2g; see Experimental Procedures in [9]). Values of μ_{cc} were corre- [AU3]
149 lated between spontaneous events and stimulus classes, demonstrating that firing
150 order is consistent between stimulus-evoked packets and spontaneous packets
151 (Fig. 8.2h; $R_{\text{unanesth: spont-ton}} = 0.53 \pm 0.17$; $p < 0.001$). Similar consistent temporal pat-
152 terns were also observed in the somatosensory cortex [9] and in the visual cortex
153 [25] indicating that the sequential structure of spontaneous and evoked packets is a
154 general feature of cortical processing.

155 **Sequential Packet Structure Is Robust with Respect** 156 **to Different Brain States**

157 Patterns of population activity can change substantially with brain state as illus-
158 trated in Fig. 8.1a (compare top and bottom rasters). Does this change in population
159 pattern also affect the internal structure of packets? To investigate this question, we
160 again employed cross-correlation analyses between a single neuron and MUA as
161 illustrated in Fig. 8.2g, i. We found that cross-correlograms calculated separately
162 during synchronized and desynchronized brain states had similar temporal profiles.
163 Figure 8.3a, b shows the cross-correlograms for 45 neurons recorded simultane-
164 ously, with the order of neurons sorted by μ_{cc} measure in the synchronized state and
165 the desynchronized state, respectively. μ_{cc} was strongly correlated between these
166 states (Fig. 8.3c; $R = 0.67 \pm 0.23$ SD). This shows that packets in the synchronized
167 and desynchronized states have largely preserved sequential spiking patterns. This
168 also suggests that activity in both states is composed from the same type of packets,
169 but in a desynchronized state, the time between consecutive packets decreases and
170 creates an impression of continuous spiking patterns.

171 ***Relation to Local Field Potential (LFP)***

172 The above analyses have indicated that a given neuron fires with largely stereotypi-
173 cal timing relative to the 50–100 ms long activity packets regardless of brain state.
174 Because summed population activity is strongly correlated with the (negative) local
175 field potential (as seen in raw data in Fig. 8.1a), we would expect that a neuron's
176 timing with respect to these packets was related to its phase of firing with respect to
177 the LFP. Figure 8.3d shows examples of the cross-correlogram of the same neuron
178 with MUA (equivalent to spike-triggered MUA) and with LFP (Fig. 8.3e) in the
179 synchronized and desynchronized states. It shows that this neuron fired after the
180 majority of other neurons and after the maximum deflection in LFP in both states.
181 The relationship between the μ_{cc} measure and LFP phase for simultaneously
182 recorded neurons is presented in Fig. 8.3f; $R_{\text{syn}} = 0.73 \pm 0.17$ SD, $p_{\text{syn}} < 0.05$, circular-
183 linear correlation [26]. It indicates that the importance of spike timing in relation to
184 the LFP phase which was recently reported [27] could be the consequence of the
185 sequential organization of activity packets.

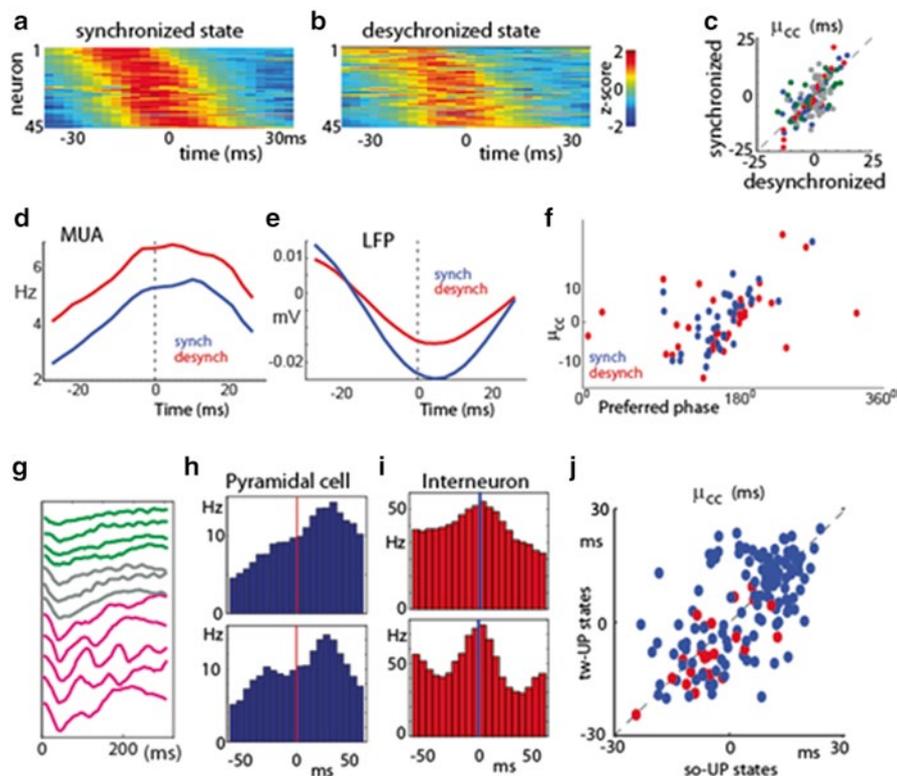


Fig. 8.3 Sequential spiking order within packets is preserved across different brain states. **(a, b)** Pseudocolor representation of CCGs for all neurons of a representative experiment, during synchronized **(a)** and desynchronized **(b)** periods. Each *horizontal line* of the pseudocolor matrix corresponds to the CCG of one neuron, vertically arranged in the same order for each plot, according to the value of μ_{cc} in the sustained period. For visualization, CCGs are normalized to mean 0 and unit variance. **(c)** μ_{cc} for each neuron calculated during sustained tone responses, in synchronized and desynchronized trials. Neurons from different animals are shown with different colors. The distribution of points along the *equality line* shows that each neuron's temporal relationship to the population is preserved across states. **(d)** Spike-triggered MUA histogram for an example neuron and **(e)** spike-triggered LFP for the same neuron during synchronized *(blue)* and desynchronized *(red)* brain state. Note that the (negative) peak of this curve occurs at a similar time to the peak of the spike-triggered MUA in the top panel. LFP was band-pass filtered between 8 and 12 Hz. **(f)** Relation between μ_{cc} and mean LFP phase at 8–12 Hz. Each dot represents a single neuron. It shows that the phase relationship of spike timing to LFP mirrors the timing relationship to population activity. **(g)** Representative examples of upstate-triggered LFPs sorted by first peak amplitude from a single shank. **(h)** Cross-correlogram between a single neuron and multiunit activity during first 150 ms of upstates for putative pyramidal cells (activity of the analyzed cell is triggered at multiunit activity spikes). Note that each cell has a different timing relation to multiunit activity but that the timing relation is similar for upstates with and without 12 Hz modulation. **(i)** The same analysis for putative interneurons. As compared to putative pyramidal cells, putative interneurons show a less diverse timing in relation to multiunit activity. **(j)** Comparison of latencies calculated for upstates with and without 12 Hz modulation (latency is defined as the center of mass of the cross-correlogram; [28]). *Red* and *blue* dots denote putative interneurons and putative pyramidal cells, respectively. Distribution of points along the *identity line* (*dashed*) shows that regardless of upstate type, neurons have a consistent temporal relation to population activity. Figure reproduced from [24, 28]

[AU4]

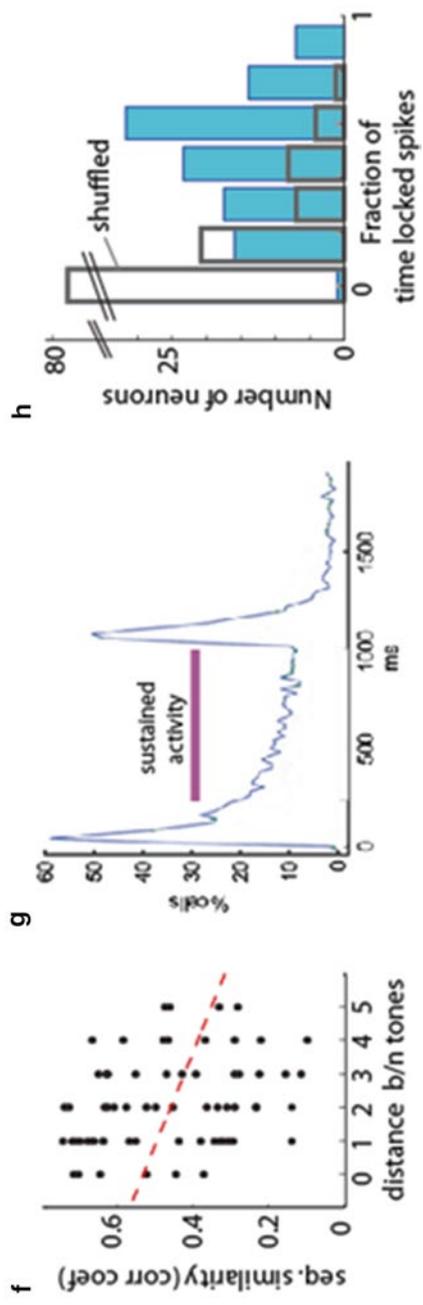
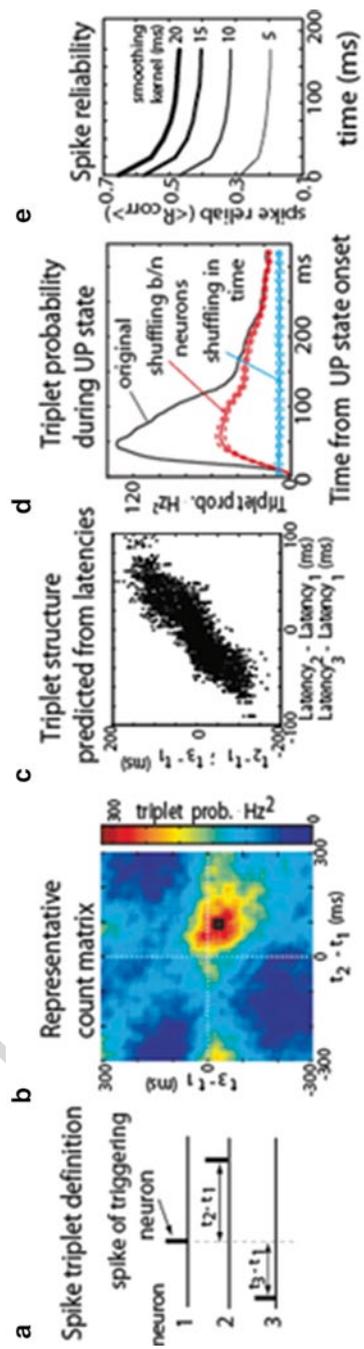


Fig. 8.4 Spike precision and information coding within packets. **(a)** For every trio of neurons, a spike triplet is described by two inter-spike intervals (t_2-t_1 and t_3-t_1). **(b)** Count matrix for a representative triplet of neurons, indicating the probability of different ISI combinations. *Black square* denotes triplets occurring within ± 10 ms of the mode. **(c)** Triplet structure reflects individual neural latencies. Each triplet is represented by two points: (latency of neuron 2—latency of neuron 1 and latency of neuron 3—latency of neuron 1). The strong correlation indicates that the structure of the triplets is predicted by the sequential structure of packets. **(d)** Occurrence of precisely repeating triplets peaks shortly after the start of UP states. *Blue* and *red curves* denote shuffled data for independent Poisson and common excitability models, respectively (the *dashed lines* indicate SD; [14]). **(e)** Spike timing reliability measure decays as a function of time after packet onset. Line width indicates the size of smoothing kernel. **(f)** Sequential structure of activity packets depends on tone frequency. Sequential similarity was measured as the correlation coefficient of μ_{seq} across the population for all pairs of tone frequencies. Note that the greatest similarity is seen between responses to different presentations of the same frequency (distance 0), whereas a smaller but nonzero similarity is seen for widely separated tone frequencies (distance 5). **(g)** Percentage of cells in the auditory cortex showing significant excitatory response to at least one tone stimulus, as a function of peri-stimulus time [54]. *Purple line* denotes sustained epochs. **(h)** Fraction of spikes, time-locked to population activity during sustained periods of tone presentations. Higher spike-locking values for the majority of neurons as compared to shuffled data (*gray line*) show that during sustained period neurons prefer to fire spike time-locked to packets [24]. Figure reproduced from [14, 24]

[AU5]

186 *Relation to Spindle Activity*

187 Another example of strongly preserved sequential packet structure can be found in
188 somatosensory cortex of ketamine-anesthetized rats, where population activity pat-
189 terns occurring at ~ 1 Hz can switch to faster ~ 12 Hz oscillatory patterns (spindles)
190 [28]. Figure 8.3g illustrates representative examples of upstate-triggered LFPs dur-
191 ing periods with and without 12 Hz oscillations (denoted by pink and green colors,
192 respectively). To examine in more detail the temporal relationship between neurons'
193 activity during different types of upstates, for each neuron, we calculated its cross-
194 correlogram with MUA, as described in the previous section. Figure 8.3h, i shows
195 such sample cross-correlograms for both periods, for representative pyramidal cell
196 and for representative interneuron, respectively [29]. Cross-correlograms had simi-
197 lar skewness for upstates with and without 12 Hz modulation, which was also the
198 case for the majority of recorded neurons (Fig. 8.3j; $R=0.59$, $p<0.01$). This shows
199 that even with drastic changes in oscillatory brain activity, temporal relations
200 between neurons with ± 50 ms window are remarkably stable, suggesting highly
201 conserved sequential structure within packets.

202 **Spike Precision and Information Coding**

203 *Precisely Repeating Spike Triplets*

204 We have seen that neurons display consistent temporal relationships within packets,
205 indicating that certain precise spike patterns should occur above chance level.
206 Precisely repeated spike patterns have been reported in a number of cortical systems
207 [10, 18, 19, 29–31], although the interpretation of these results has been controver-
208 sial [21, 23]. We hypothesized that the consistent timing of individual neurons in
209 relation to the onset of a packet could account for precisely repeating spike patterns
210 seen at the population level. Confirmation of this hypothesis would provide both
211 convincing evidence for the precise repetition of spike patterns and a simple expla-
212 nation for it.

213 For computational tractability, we restricted our search to spike triplets occurring
214 across three distinct cells [32] (Fig. 8.4a). For each cell trio, one cell was designated
215 the trigger for calculation of the joint distribution of spike times of the other two
216 [32]. Often, a clear mode was seen in these plots, suggesting that a particular
217 sequence occurred preferentially (e.g., Fig. 8.4b). The location of the mode could be
218 predicted from the neurons' individual latencies to packet onset (Fig. 8.4c). Note
219 that spiking precession is not within 1 ms; therefore these results are not fully con-
220 sistent with the concept of "synfire chains" which generally implies repeating pat-
221 terns to have a millisecond-level precision [20]. Repeating triplets (defined as those
222 whose inter-spike intervals (ISIs) were within ± 10 ms of the mode, indicated by the
223 black square in Fig. 8.4b) occurred preferentially shortly after UP state onset
224 (Fig. 8.4d), with the highest precision of spikes at the beginning of the packets (see

[AU6] Fig. 8.4e showing reliability of spiking over time; method adopted from [33]). This 225
 finding is consistent with [34] where the highest spiking precision was found shortly 226
 after stimulus onset and decreased thereafter. Therefore, we conclude that the tim- 227
 ing and structure of repeating triplets is predicted by the relationship of individual 228
 neurons to packet onsets. 229

Temporal and Firing Rate Coding Within Packets 230

[AU7] It is well documented that sensory stimuli can affect spike timing, especially for 231
 onset responses (see Fig. 8.2a or, e.g., [35]), but it is not clear if packets also show 232
 modification of temporal structure depending on stimulus. Thus, we next asked 233
 whether different tone stimuli caused variations around this common sequential 234
 structure. To test this idea statistically, we assessed the similarity of the sequential 235
 structure between the first and second half of the data set. Figure 8.4f shows the 236
 mean sequence similarity as a function of distance between frequencies, based on 237
 tonal order. Sequences become less correlated with increasing frequency difference 238
 between tones (Fig. 8.4f; $R = -0.22 \pm 0.08$ SD) which was not observed for shuffled 239
 data [24]. Thus, as observed with onset responses, even during sustained periods, 240
 the packets have a broadly conserved 50–100 ms sequential structure, but this struc- 241
 ture exhibits further variations depending on tone frequency. 242

It is also well documented that information about external stimuli can be encoded 243
 by the firing rates of neurons. Closer examination of population activity revealed 244
 that in response to preferred stimuli, a neuron fires additional spikes but only when 245
 it is coordinated with the activity of other neurons. As an example, let's consider the 246
 population activity during sustained tone presentations which is composed of pack- 247
 ets of activity as illustrated in Fig. 8.1. Theoretically, the extra spikes evoked by 248
 preferred stimuli could occur uniformly throughout the tone presentation, without 249
 regard to global network activity, or alternatively, extra spikes could occur specifi- 250
 cally during packets of high network activity ("time-locked" to packets). To address 251
 this question, we estimated the fraction of spikes locked to packets during sustained 252
 tone presentation (Fig. 8.3g). For this, we used a measure-based MUA cross- 253
 correlogram with single neuron activity normalized by an autocorrelogram (for 254
 details, see [24]). Figure 8.3h shows values of the fraction of spikes time-locked to 255
 packets, which is significantly larger than would be expected for trial-shuffled data 256
 ($p < 0.001$). Thus, this analysis suggests that the additional spikes a neuron fires in 257
 response to its preferred tone are primarily occurring at neuron-specific timing 258
 within packet. 259

Possible Mechanisms of Packet Formation 260

Sequentially structured activity packets are seen in computational models of corti- 261
 cal circuits [36–38], in cortical slices [10, 19, 39], as well as in response to sensory 262
 stimuli in vivo [9]. We found that population responses to different stimuli are 263

264 subject to conserved spatiotemporal constraints, consistent with results in other
265 modalities indicating conserved timing patterns in pairwise cross-correlograms
266 [25]. One can imagine a number of ways in which the physical properties of a neural
267 circuit could impose consistent constraints on the spike patterns it can generate.
268 Firstly, cortical neurons have diverse intrinsic physiological properties [40–42]
269 which may contribute to the consistent cellular timing which we and others observed
270 [14, 43]. For example, cells with lowest threshold could be firing earliest in sequence
271 [44]. Secondly, connectivity within cortical circuits is far from homogenous, for
272 example, with strong reciprocal connectivity occurring more than expected by
273 chance [45], suggesting that the stereotypical temporal structure of cortical activity
274 packets may be also imposed by the connectivity of the cortical microcircuit. We
275 suggest that these activity patterns are the functional manifestation of “default
276 microcircuits”—local patterns of connectivity that impose similar spatiotemporal
277 constraints on spontaneous and stimulus-evoked flow of activity, as illustrated in
278 cartoon form in Fig. 8.5a [46].

[AU8]

279 Summary Illustration of Packets

280 Our main findings can be summarized by Fig. 8.5. Connectivity and cellular proper-
281 ties of neurons impose constraints on types of spiking patterns which can be pro-
282 duced by the local circuit (Fig. 8.5a). Thus, certain activity patterns will be more
283 likely to emerge than other patterns (Fig. 8.5b-left). This can be illustrated as geo-
284 metrical interpretation, where each population spiking pattern is represented as a
285 single point (Fig. 8.5b-center). Experimentally observed spontaneous patterns are
286 confined only to a small subregion of space of all possible patterns. Stimulus-evoked
287 patterns are subject to the same circuit constraints and form subspace within spon-
288 taneous patterns [9]. Each type of stimuli results in a different firing rate of neurons,
289 and to a smaller degree different timing, but with preservation of the overall struc-
290 ture within the activity packet (Fig. 8.5b—right).

291 In synchronized states, stimulus onsets usually evoke reliable activity packets
292 with a duration of 50–100 ms, and similar packets occur irregularly during sus-
293 tained tone responses and spontaneously (Fig. 8.5c). As described above, these
294 packets have a broadly preserved sequential structure across stimuli and across
295 onset, sustained, and spontaneous periods. However, both the firing rates and pre-
296 cise timing of the constituent neurons can vary with stimulus type (Fig. 8.5b-right).
297 The additional spikes fired in response to preferred stimuli occur within packets
298 rather than spread evenly throughout the stimulus duration. In desynchronized
299 states, fluctuations in population rate are reduced, but timing relationships between
300 neurons remain preserved (Fig. 8.5d). This suggests that population activity is built
301 from discrete packets whose content conveys information about the stimulus, occur-
302 ring reliably at onset and irregularly at other times, with desynchronized activity
303 consisting of multiple overlapping packets rather than continuous, unstructured
304 activity as previously assumed.

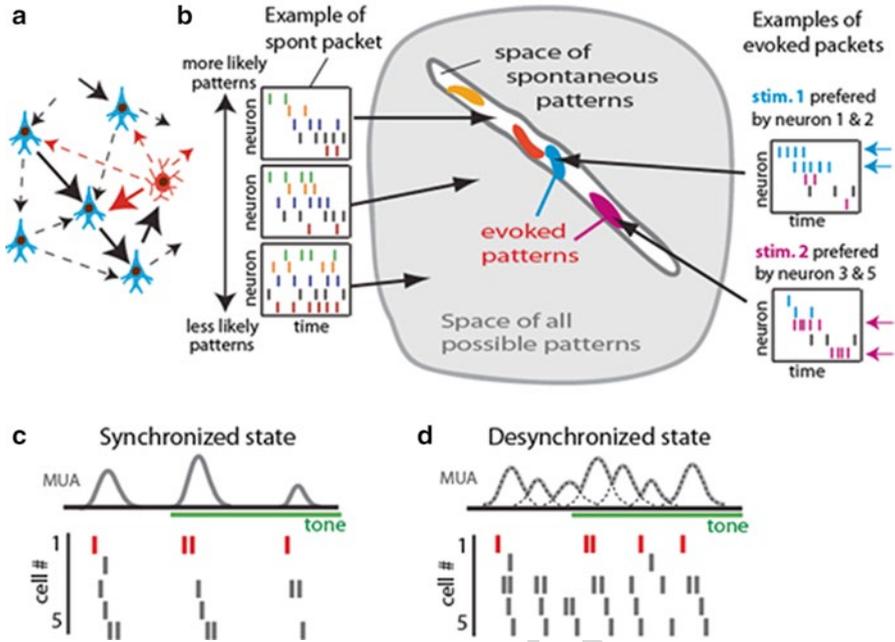


Fig. 8.5 Activity packets in graphical summary. (a) Cartoon illustration of the possible mechanism of packet formation. Due to constraints on connectivity, different inputs will result in similar spiking activity, which propagates preferentially through the strongest connections (*solid arrows*) embedded in a pool of weaker connections (*dashed arrows*). As a consequence of the connectivity pattern of the network, certain activity patterns are more likely to occur than others as illustrated in panel (b) (*left side*). (b-center) Cartoon illustrating the geometrical interpretation of our findings. The *gray area* illustrates the space of all spiking patterns theoretically possible for a packet. The *white area* represents the space of spontaneous packets; this is shown elongated and of small volume to illustrate strong constraints on patterns of activity imposed by a network. Packets evoked by different stimuli occupy smaller subsets within this (*colored blobs*). (b-right side) Illustration of stimulus-evoked packets. The overall structure of evoked packets is similar to the spontaneous packets; but the firing rate, and to a smaller degree, the spike timing of neurons, encodes information about stimulus identity. (c) Packets of population activity in a synchronized state are separated by periods of global silence. Tone onset reliably induces an activity packet, but packets also occur sporadically throughout the sustained and spontaneous periods. Within each packet, neurons fire with a stereotyped sequential pattern. Presentation of a neuron's preferred tone causes that neuron to fire at higher rates (*red*) but only during specific phase of activity packets. (d) In a desynchronized state, population activity does not show long periods of silence, but temporal relationships between neurons are similar to those in the synchronized state. This can be explained by a model in which many packets, individually similar to those seen in the synchronized state, are superimposed to produce a firing pattern that exhibits smaller fluctuations in global activity but retains a fine temporal structure. Figure reproduced from [24, 46]

305 Packet Structure May Explain Multiple Puzzling 306 Observations About Neuronal Coding

307 Below we address the significance of packets. We list some of the most puzzling
308 phenomena about neuronal coding, and we discuss how it could be understood in
309 light of the sequential structure of packets. We argue that the “packet theory” pre-
310 sented here could provide a unifying concept on how information is processed in the
311 brain.

- 312 – A packet structure provides time reference for temporal coding. It was shown
313 that precise timing of spikes after stimulus onset can provide information about
314 stimulus identity [35, 47]. Although an experimenter knows what the exact time
315 of a stimulus onset is, it remains unclear how the brain could access this informa-
316 tion to use spike timing in reference to onset. It was proposed that there could be
317 neurons always firing with the same latency to any stimuli, thus providing refer-
318 ence for decoding information from spikes in which timing differs with stimuli
319 [48]. Considering that many natural stimuli change gradually and do not have
320 well-defined sharp onset, the above-described mechanism may not have general
321 applicability. On the other hand, assuming that there exists a “typical” or
322 “default” sequential activity pattern imposed by cortical microarchitecture, any
323 variation in timing among neurons in this sequence can encode stimuli. Therefore,
324 the “default” temporal structure of a packet can provide reference for the brain to
325 interpret the timing of neurons.
- 326 – Packets show how temporal and firing rate coding coexists. As illustrated in
327 Fig. 8.5b-right, in response to preferred stimuli, a neuron fires more spikes, but it
328 is mostly restricted to the neuron-specific phase within a packet.
- 329 – Packets and cell assembly hypothesis. The idea introduced by Donald Hebb in
330 the 1940s [49] proposes that neurons are active collectively in groups produced
331 by Hebbian plasticity. Furthermore, Hebb postulates that different stimuli are
332 represented by unique neuronal assemblies with completely different temporal
333 patterns depending on task or stimulus. However, evidence for the conserved
334 structure of packets necessitates a partial revision of Hebb’s theory. Specifically,
335 conserved activity patterns imply that *neuronal assemblies are like a variation*
336 *on a one master theme rather than unique themes* for each stimulus or object. For
337 example, auditory neurons in Fig. 8.5b (right) respond with similar temporal
338 sequences to different tones, although each tone evokes a different variation of
339 that pattern [9].
- 340 – Stereotypical activity within packets provides an explanation as to why precisely
341 repeated spiking pattern can occur significantly more often than expected by
342 chance [20, 29].
- 343 – Preplay. In behaving animals, task-induced patterns of neuronal activity are
344 replayed during following rest which is believed to be a hallmark of memory
345 formation [50]. Recent studies have shown that replayed patterns are also similar
346 to spontaneous patterns that precede behavioral task. This phenomenon is termed

“preplay” and was elegantly shown in the hippocampus by [51]. Similarly, in ([52], Figure 1, 2007), the pre-task spiking patterns in the medial prefrontal cortex have an obvious similarity to patterns during the task and patterns replayed after the task. The data presented here is consistent with these results. Due to the connectivity constraints of local microcircuits, new experience does not create completely different patterns, but rather creates modification of existing patterns. Such task-induced gradual change of existing spiking patterns results that general structure of activity packets is preserved [53]. Also note that the timescale of preplayed and replayed patterns spanning up to a few hundred milliseconds is similar to the duration of packets. Thus, we hypothesize that memory replay could be the manifestation of, as described here, packets carrying information about past experience.

[AU9]

Function of Packets

What could be the function of the sequential structure of packets? One perspective could be that it has no function as the system has to generate sequential patterns given the constraints imposed by network connectivity [46]. A different possibility from an engineering point of view could be that dividing neuronal activity in packets could serve similar function as Internet protocol (IP) packets, where splitting data in small chunks with a specific format improves communication efficiency and transmission reliability. Indeed, it was observed that in the brain constraining spiking activity to small temporal windows (e.g., only to a negative phase of underlying oscillatory activity) can improve information transfer between areas by synchronizing neuronal firing, and that mechanism is commonly used across the brain [11]. Moreover there are evidences that sequential organization of activity within packets may also have functional significance. For instance, broad tuning and highest spiking precision at the beginning of a packet may be designed to signal the beginning of a message with only general information about stimuli (roughly analogous to header of IP packets). Consequently, later activity within a packet may contain more precise information. Indeed, it was observed that activity that occurred later after stimulus onset is more stimulus specific, with finer tuning of neurons [54, 55], likely due to top-down modulation [56]. In result, our perception of continuous stimuli may be an illusion, as cortical activity may carry information not continuously, but rather in a form of discrete and structured packets.

References

1. Buzsaki G. Large-scale recording of neuronal ensembles. *Nat Neurosci.* 2004;7(5):446–51.
2. Gomez Palacio Schjetnan A, Luczak A. Recording large-scale neuronal ensembles with silicon probes in the anesthetized rat. *J Vis Exp.* 2011;(56). pii: 3282
3. Luczak A, Narayanan NS. Spectral representation – analyzing single-unit activity in extracellularly recorded neuronal data without spike sorting. *J Neurosci Methods.* 2005; 144(1):53–61.

- 387 4. Harris KD, Bartho P, Chadderton P, Curto C, de la Rocha J, Hollender L, Itskov V, Luczak A,
388 Marguet SL, Renart A, Sakata S. How do neurons work together? Lessons from auditory
389 cortex. *Hear Res.* 2011;271(1–2):37–53.
- 390 5. Luczak A, Hackett T, Kajikawa Y, Laubach M. Multivariate receptive field mapping in mar-
391 maset auditory cortex. *J Neurosci Methods.* 2004;136(1):77–85.
- 392 6. Buzsaki G, Draguhn A. Neuronal oscillations in cortical networks. *Science.* 2004;
393 304:1926–9.
- 394 7. Kenet T, Bibitchkov D, Tsodyks M, Grinvald A, Arieli A. Spontaneously emerging cortical
395 representations of visual attributes. *Nature.* 2003;425:954–6.
- 396 8. Tsodyks M, Kenet T, Grinvald A, Arieli A. Linking spontaneous activity of single cortical
397 neurons and the underlying functional architecture. *Science.* 1999;286:1943–6.
- 398 9. Luczak A, Barthó P, Harris KD. Spontaneous events outline the realm of possible sensory
399 responses in neocortical populations. *Neuron.* 2009;62(3):413–25.
- 400 10. MacLean JN, Watson BO, Aaron GB, Yuste R. Internal dynamics determine the cortical
401 response to thalamic stimulation. *Neuron.* 2005;48:811–23.
- 402 11. Buzsaki G. *Rhythms of the brain.* New York, NY: Oxford University Press; 2009.
- 403 12. Destexhe A, Sejnowski TJ. *Thalamocortical assemblies how ion channels, single neurons, and*
404 *large-scale networks organize sleep oscillations.* Oxford: Oxford University Press; 2001.
- 405 13. Battaglia FP, Sutherland GR, McNaughton BL. Hippocampal sharp wave bursts coincide with
406 neocortical “up-state” transitions. *Learn Mem.* 2004;11:697–704.
- 407 14. Luczak A, Barthó P, Marguet SL, Buzsáki G, Harris KD. Sequential structure of neocortical
408 spontaneous activity in vivo. *Proc Natl Acad Sci.* 2007;104(1):347–52.
- 409 15. Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. The sleep slow oscillation as a traveling
410 wave. *J Neurosci.* 2004;24:6862–70.
- 411 16. Petersen CC, Hahn TT, Mehta M, Grinvald A, Sakmann B. Interaction of sensory responses
412 with spontaneous depolarization in layer 2/3 barrel cortex. *Proc Natl Acad Sci U S A.*
413 2003;100:13638–43.
- 414 17. Steriade M, Contreras D, Curro Dossi R, Nunez A. The slow (<1 Hz) oscillation in reticular
415 thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting tha-
416 lamic and neocortical networks. *J Neurosci.* 1993;13:3284–99.
- 417 18. Cossart R, Aronov D, Yuste R. Attractor dynamics of network UP states in the neocortex.
418 *Nature.* 2003;423:283–8.
- 419 19. Mao BQ, Hamzei-Sichani F, Aronov D, Froemke RC, Yuste R. Dynamics of spontaneous
420 activity in neocortical slices. *Neuron.* 2001;32:883–98.
- 421 20. Abeles M. *Corticomics: neural circuits of the cerebral cortex.* Cambridge: Cambridge
422 University Press; 1991.
- 423 21. Baker SN, Lemon RN. Precise spatiotemporal repeating patterns in monkey primary and sup-
424 plementary motor areas occur at chance levels. *J Neurophysiol.* 2000;84:1770–80.
- 425 22. Mokeichev A, Okun M, Barak O, Katz Y, Ben Shahar O, Lampl I. Stochastic emergence of
426 repeating cortical motifs in spontaneous membrane potential fluctuations in vivo. *Neuron.*
427 2007;53:413–25.
- 428 23. Oram MW, Hatsopoulos NG, Richmond BJ, Donoghue JP. Excess synchrony in motor cortical
429 neurons provides redundant direction information with that from coarse temporal measures. *J*
430 *Neurophysiol.* 2001;86:1700–16.
- 431 24. Luczak A, Bartho P, Harris KD. Gating of sensory input by spontaneous cortical activity. *J*
432 *Neurosci.* 2013;33(4):1684–95.
- 433 25. Jermakowicz WJ, Chen X, Khaytin I, Bonds AB, Casagrande VA. Relationship between spon-
434 taneous and evoked spike-time correlations in primate visual cortex. *J Neurophysiol.*
435 2009;101:2279–89.
- 436 26. Berens P. CircStat: a MATLAB toolbox for circular statistics. *J Stat Softw.* 2009;31:1–21.
- 437 27. Panzeri S, Brunel N, Logothetis NK, Kayser C. Sensory neural codes using multiplexed tem-
438 poral scales. *Trends Neurosci.* 2010;33(3):111.
- 439 28. Luczak A, Barthó P. Consistent sequential activity across diverse forms of UP states under
440 ketamine anesthesia. *Eur J Neurosci.* 2012;36(6):2830–8.

29. Ikegaya Y, Aaron G, Cossart R, Aronov D, Lampl I, Ferster D, Yuste R. Synfire chains and cortical songs: temporal modules of cortical activity. *Science*. 2004;304:559–64. 441
442

30. Abeles M, Gerstein GL. Detecting spatiotemporal firing patterns among simultaneously recorded single neurons. *J Neurophysiol*. 1988;60:909–24. 443
444

31. Prut Y, Vaadia E, Bergman H, Haalman I, Slovin H, Abeles M. Spatiotemporal structure of cortical activity: properties and behavioral relevance. *J Neurophysiol*. 1998;79:2857–74. 445
446

32. Abeles M, Gat I. Detecting precise firing sequences in experimental data. *J Neurosci Methods*. 2001;107:141–54. 447
448

33. Schreiber S, Fellous JM, Whitmer D, Tiesinga P, Sejnowski TJ. A new correlation-based measure of spike timing reliability. *Neurocomputing*. 2003;52–4:925–31. 449
450

34. Churchland MM, et al. Stimulus onset quenches neural variability: a widespread cortical phenomenon. *Nat Neurosci*. 2010;13:369–78. 451
452

35. Petersen RS, Panzeri S, Diamond ME. Population coding in somatosensory cortex. *Curr Opin Neurobiol*. 2002;12:441–7. 453
454

36. Izhikevich EM, Gally JA, Edelman GM. Spike-timing dynamics of neuronal groups. *CerebCortex*. 2004;14:933–44. 455
456

37. Buonomano DV, Maass W. State-dependent computations: spatiotemporal processing in cortical networks. *Nat Rev Neurosci*. 2009;10:113–25. 457
458

38. Fiete IR, Senn W, Wang CZ, Hahnloser RH. Spike-time-dependent plasticity and heterosynaptic competition organize networks to produce long scale-free sequences of neural activity. *Neuron*. 2010;65:563–76. 459
460

39. Buonomano DV. Timing of neural responses in cortical organotypic slices. *Proc Natl Acad Sci U S A*. 2003;100:4897–902. 461
462

40. Storm JF. K⁺ channels and their distribution in large cortical pyramidal neurones. *J Physiol*. 2000;525:565–6. 463
464

41. Sugino K, Hempel CM, Miller MN, Hattox AM, Shapiro P, Wu CZ, Huang ZJ, Nelson SB. Molecular taxonomy of major neuronal classes in the adult mouse forebrain. *Nat Neurosci*. 2006;9:99–107. 465
466

42. Vervaeke K, Hu H, Graham LJ, Storm JF. Contrasting effects of the persistent Na⁺ current on neuronal excitability and spike timing. *Neuron*. 2006;49:257–70. 467
468

43. Volgushev M, Chauvette S, Mukovski M, Timofeev I. Precise long-range synchronization of activity and silence in neocortical neurons during slow-wave sleep. *J Neurosci*. 2006;26(21):5665–72. 469
470

44. Kang S, Kitano K, Fukai T. Structure of spontaneous UP and DOWN transitions self-organizing in a cortical network model. *PLoS Comput Biol*. 2008;4:e1000022. 471
472

45. Song S, Sjöström PJ, Reigl M, Nelson S, Chklovskii DB. Highly nonrandom features of synaptic connectivity in local cortical circuits. *PLoS Biol*. 2005;3:e68. 473
474

46. Luczak A, MacLean JN. Default activity patterns at the neocortical microcircuit level. *Front Integr Neurosci*. 2012;6:30. 475
476

47. Heil P. First-spike latency of auditory neurons revisited. *Curr Opin Neurobiol*. 2004;14:461–7. 477
478

48. Brasselet R, Panzeri S, Logothetis NK, Kayser C. Neurons with stereotyped and rapid responses provide a reference frame for relative temporal coding in primate auditory cortex. *J Neurosci*. 2012;32(9):2998–3008. 479
480

49. Hebb DO. *The organization of behavior*. New York, NY: Wiley; 1949. 481
482

50. Wilson MA, McNaughton BL. Reactivation of hippocampal ensemble memories during sleep. *Science*. 1994;265(5172):676–9. 483
484

51. Dragoi G, Tonegawa S. Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature*. 2010;469(7330):397–401. 485
486

52. Euston DR, Tatsuno M, McNaughton BL. Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. *Science*. 2007;318(5853):1147–50. 487
488

53. Bermudez Contreras EJ, Schjetnan AGP, Muhammad A, Bartho P, McNaughton BL, Kolb B, Gruber A, Luczak A. Formation and reverberation of sequential neural activity patterns evoked 489
490
491
492
493

- 494 by sensory stimulation are enhanced during cortical desynchronization. *Neuron*. 2013;
495 79(3):555–66.
- 496 54. Barthó P, Curto C, Luczak A, Marguet S, Harris KD. Population coding of tone stimuli in audi-
497 tory cortex: dynamic rate vector analysis. *Eur J Neurosci*. 2009;30(9):1767–78.
- 498 55. Sugase Y, Yamane S, Ueno S, Kawano K. Global and fine information coded by single neurons
499 in the temporal visual cortex. *Nature*. 1999;400(6747):869–73.
- 500 56. Lamme VA, Roelfsema PR. The distinct modes of vision offered by feedforward and recurrent
501 processing. *Trends Neurosci*. 2000;23(11):571–9.

Uncorrected Proof

Author Queries

Chapter No.: 8 0002201406

| Queries | Details Required | Author's Response |
|---------|---|-------------------|
| AU1 | Please check if “multiunit (MUA)” should be changed to “multiunit activity (MUA).” | |
| AU2 | Please note that the tem “+–” has been changed to “±” in the sentence “summed activity of all other neurons within ±50 ms”. Please check for correctness. | |
| AU3 | Please check if inserted closing parenthesis is okay. | |
| AU4 | Please check and specify the part figure no, having “top panel”, which is explained in the sentence “peak of the spike-triggered MUA in the top panel”. | |
| AU5 | Please check and specify whether the term “dashed line” can be changed to “solid line” in Fig. 8.4d. | |
| AU6 | Please check if inserted closing parenthesis is okay. | |
| AU7 | Please check if inserted closing parenthesis is okay. | |
| AU8 | Please check if edit to sentence starting “Secondly, connectivity within...” is okay. | |
| AU9 | Please check if edit to sentence starting “Thus, we hypothesize...” is okay. | |