OPINION

Packet-based communication in the cortex

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Abstract | Cortical circuits work through the generation of coordinated, large-scale activity patterns. In sensory systems, the onset of a discrete stimulus usually evokes a temporally organized packet of population activity lasting ~50–200 ms. The structure of these packets is partially stereotypical, and variation in the exact timing and number of spikes within a packet conveys information about the identity of the stimulus. Similar packets also occur during ongoing stimuli and spontaneously. We suggest that such packets constitute the basic building blocks of cortical coding.

Neurons are capable of generating spikes with great temporal precision[1]. Spike-timing is thought to be important for information processing in a large number of cortical areas (including visual[2,3], auditory[4,5], somatosensory[6] and olfactory[7] cortices and the hippocampus[8,9]). Of course, the spike times of any one neuron are just one component of much-larger, population-level activity patterns. It has recently become possible to investigate these population patterns by recording tens to hundreds of neurons in parallel[10,11].

One of the most often-reported findings from such parallel-recording studies in the cortex is that neuronal populations display stereotypical and repeating spike-timing patterns. Such recurring patterns of sequential neuronal activity have been observed in cortical cultures[12,13], acute cortical slices[14–17] and *in vivo* in the cortex of multiple species[18–23]. These patterns have also been observed in computational models of cortical circuits[24–30].

However, the existence of repeating patterns of activity has been controversial[31–34], mostly owing to difficulties in the statistical methods that are required to detect repeating patterns. Nevertheless, application of simpler statistical approaches based on analysing neuronal patterns triggered by external stimuli[35] or internal spontaneous events[36] strongly suggests that cortical spike times are nonrandom, with certain temporal sequences occurring at frequencies above those attributable to chance alone. Indeed, the existence of stereotypical firing sequences is not surprising: the observation that sensory stimuli evoke stereotypical sequential population responses is simply a reflection of the fact that individual neurons in the population respond to the stimulus with different latencies[35] that are consistent across different stimuli. These consistently different latencies may arise, for example, because of different synaptic delays in different neurons. Nevertheless, it is not

generally realized how remarkably similar are sequences generated by different stimuli and during spontaneous activity. Here, we explain that neuronal responses are not as diverse as is generally believed, but rather they are variations on a common theme.

In this Opinion article, we suggest that transient, sequentially organized packets of activity could constitute a basic building block of the cortical code. We first focus on the onset of neuronal responses to sensory stimuli and review evidence that cortical activity is composed of coherent and structured packets of population activity lasting a few hundred milliseconds. Next, we discuss evidence showing that the fine temporal structure of packets is largely conserved across spontaneous and stimulus-evoked conditions, and across different brain states, and describe how variations on a common sequential structure can encode information about sensory stimuli. We then take a global view, reviewing data from voltage-sensitive dye (VSD) imaging experiments and from electrode recordings spanning multiple cortical regions, which characterize how activity packets spread from one cortical area to another. We also discuss possible mechanisms of packet formation and suggest how the concept of a packet can provide a unifying framework for understanding cortical population coding and explaining multiple, seemingly unrelated, observations about information processing in the brain.

The local picture

Understanding the structure of population activity is particularly straightforward in the case of sensory responses, as the activity of multiple neurons can be analysed with respect to a fixed time point (the stimulus

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Glossary

Firing-rate coding
A coding scheme in which the features of a stimulus, such as its intensity, are coded by the number of spikes emitted within a specific period of time.

Network attractors
Activity patterns towards which a recurrent dynamical network evolves over time from a range of different initial conditions.

Quiet wakefulness
A period of drowsiness in which an animal is not moving and, for relevant species, not whisking.

Small-world topology
A type of network structure with highly interconnected local nodes and few long-range connections, which results in there being a short path between any two nodes while each node has relatively few connections.

Spike-time coding
A coding scheme in which information is transmitted by the exact timing of the action potential in reference to a specific event (for example, stimulus onset or spiking of another neuron).

Spike-timing reliability
A correlation-based measure that quantifies reproducibility of spike trains across trials. It decreases with spike-timing jitter and with spike count variability.
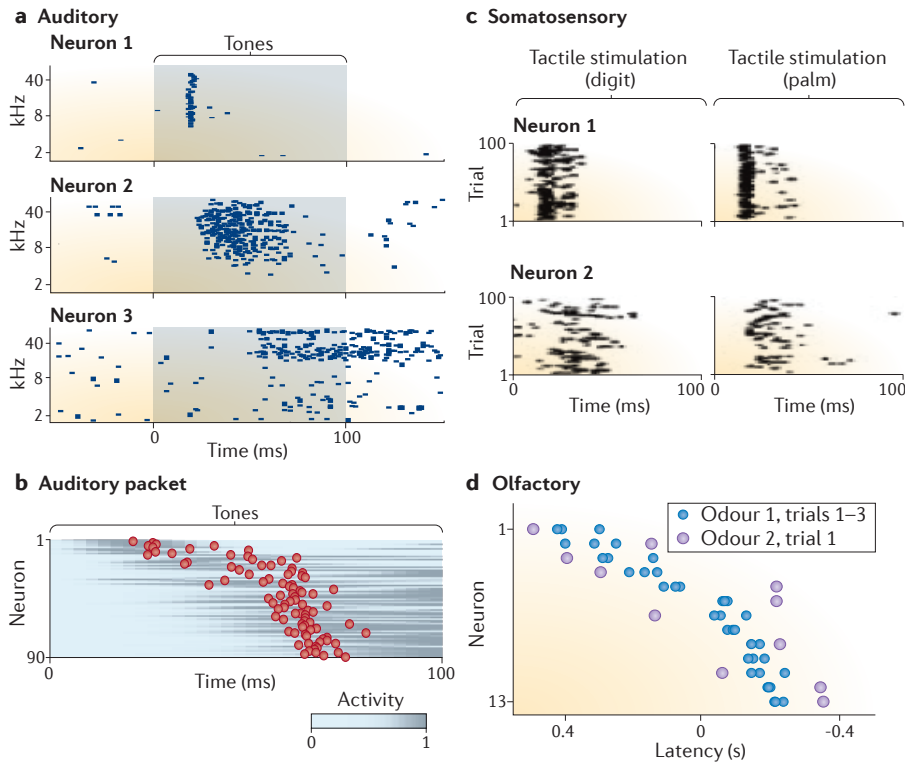
a Auditory

Neuron 1

Neuron 2

Neuron 3

b Auditory packet

c Somatosensory

Tactile stimulation (digit)   Tactile stimulation (palm)

Neuron 1

Neuron 2

d Olfactory

Figure 1 | **Consistent sequential packet structure in response to different stimuli. a** | The tone-evoked responses in the auditory cortex of unanaesthetized rats are heterogeneous across different neurons. The responses of three representative neurons to 60-dB tones at a range of frequencies are shown. Blue lines represent individual spikes and the grey region represents the tone duration (100 ms). **b** | A representative structure of a population packet. The sequential spread of the mean activity of 90 neurons, recorded simultaneously, in response to auditory tones is shown (the data are derived from a different study than that shown in part **a**). Grey horizontal lines are pseudocolour representations of each neuron's peristimulus time histogram (PSTH), and the red dots denote each neuron's mean spike latency, which is defined as the centre of mass of PSTH in the 100 ms after tone onset and corresponds to the typical duration of a packet. Individual neurons are ordered vertically by their mean spike time latency over all stimuli (five different tones and 100 repetitions) to illustrate sequential spread of activity. **c** | Heterogeneity in spike timing between different neurons is also evident in responses to somatosensory stimuli. The responses of two somatosensory cortex neurons to 100 repetitions of two different tactile stimuli applied to the palm or a digit of the contralateral forelimb are shown. Together with those of other studies[35,48], these findings indicate that somatosensory neurons also show stereotypical sequential order at stimulus onset. **d** | In the olfactory bulb, neuronal population patterns are similar in responses to different stimuli. The normalized response latencies of 13 olfactory neurons to two different odours are shown (three methionine trials are shown in blue; one arginine trial is shown in purple). Although the precise patterns are odour-specific, latencies are broadly similar across different stimuli for a given neuron (in this study, the mean correlation between neurons' latencies evoked by different stimuli was $r = 0.35$). Part **a** adapted from REF. 37. Part **b** adapted with permission from REF. 35, Elsevier. Part **c** adapted with permission from REF. 47, The American Physiological Society. Part **d** adapted with permission from REF. 55, Elsevier.

onset). Thus, we first describe the local structure of packets within a single area of the sensory cortex.

Sensory-evoked activity packets. Population activity evoked locally by sensory stimuli has a sequential structure that is clearly visible at the level of single-neuron recordings. This sequential structure arises because different neurons tend to fire at different latencies after stimulus onset and have different durations

of firing[37] (FIG. 1a). The diversity in the temporal structure of single-neuron responses to a stimulus suggests that population activity should have a sequential structure. This prediction is borne out by simultaneous recordings from large populations, which illustrate a continuum of response times of different neurons within a population, resulting in a packet of sequential neuronal activity after stimulus onset[35] (FIG. 1b). Although the latency of a stimulus-induced response in

individual neurons can depend on the precise characteristics of the presented stimulus (for example, the frequency of an auditory tone[5,38]), the variability of latency of a single neuron across stimuli is typically an order of magnitude smaller than the span of the mean latencies between different neurons (FIG. 1a). Thus, the sequential structure of population activity is broadly conserved, whatever the stimulus.

How long are the activity packets evoked by sensory stimuli? The duration of stimulus-evoked packets can be estimated as the period from response onset to the time at which most neurons cease their stimulus-driven activity. Although small changes in firing rate induced by stimuli can sometimes be found as late as 1 s after the offset of a sensory stimulus[39], the majority of cortical sensory neurons reach their peak firing rate within approximately 100 ms after a stimulus onset (FIG. 1a–c), and the firing rates of most neurons have returned close to baseline by approximately 200 ms in multiple modalities (for example, in visual[40], somatosensory[41] and motor[42] areas) across various species. Similarly, spontaneous fluctuations in spiking activity of approximately 50–300 ms have been observed in the neocortex[43]. Thus, it is reasonable to conclude that, in the sensory cortex, the typical duration of an activity packet is between 50 and a few hundred milliseconds.

Sequentially structured activity packets also form the building blocks of responses to more-complex, continuous stimuli, at least in the auditory cortex. For example, in the rat auditory cortex, the population response to complex sounds, such as an insect vocalization, comprises multiple activity packets evoked by acoustic transients[35]. These packets have a similar, although not identical, sequential structure to those evoked by simple, pure tones[35]. Similar results have been observed in the auditory cortex of awake cats in response to cat and human vocalizations[44]. The fact that population responses to spectrally complex stimuli have a similar sequential organization to those produced by pure tones is consistent with the fact that response latencies are similar across tone frequencies (FIG. 1a). Furthermore, most auditory cortical neurons have approximately separable spectro-temporal receptive fields[45], which means that the neuron response pattern to one tone frequency is similar to a scaled version of a response to any other tone frequency. This suggests that temporal relationships between neurons are likely to be preserved even in responses to spectro-temporally complex sounds.
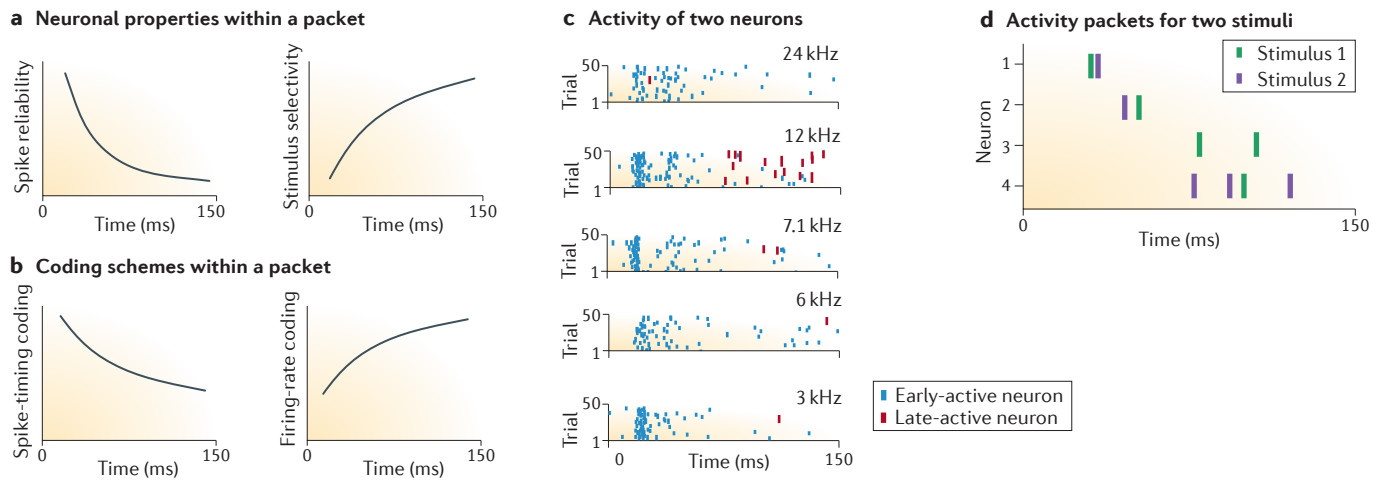
a Neuronal properties within a packet

b Coding schemes within a packet

c Activity of two neurons

d Activity packets for two stimuli

Figure 2 | **Information coding within packets. a** | Schematic representation of findings from several studies[36,39,67,68] that have shown that stimulus selectivity increases and spiking reliability decreases as a packet progresses over time. **b** | At the beginning of a packet, spike-time coding may be more important, whereas firing-rate coding may be more prominent later in a packet. Note that both codes are likely to be used at any point over the duration of the packet but their relative importance may progressively change over time. This panel is a schematic of our hypothesis based on the data summarized in part **a**. **c** | Representative responses of two auditory cortex neurons are shown. The spiking activity of the two neurons across 50 trials is shown for various tonal frequencies. The neuron shown in blue is active early in the packet; it responds with a similar firing rate to most stimuli but with a somewhat shorter spiking latency in response to a 7.1-kHz tone. By contrast, the neuron shown in red fires late in the packet and has high spike-timing variability across stimuli and across trials, yet its firing rate is highly tuned to its preferred stimulus (12 kHz). **d** | Schematic illustration of a simulated population response to two sample stimuli. Early-active neurons (labelled 1 and 2) have low stimulus selectivity and fire reliably to both stimuli but with slightly different latencies. Late-firing neurons (labelled 3 and 4) are activated more selectively and largely encode information by firing rate. Thus, although overall the population shows a similar sequential structure in response to both stimuli, variation in the precise pattern of spike-timing and firing rate can code for different stimuli.

Despite the similarities described above, different stimuli do not produce identical patterns of population activity, and indeed the differences in the spiking responses to different stimuli can encode information about the stimulus. In addition to differences in firing rate, it is well known that the precise spiking latency in the sensory cortex can differ between stimuli[6,38,46]. Nevertheless, for a single neuron, differences in response latency to different stimuli are typically considerably smaller than differences in latency between neurons[35,47,48] (FIG. 1a,c). Similarly, although different stimuli evoke different firing rates in individual neurons, population firing patterns show strong similarities across stimuli, as the mean rate[49] and correlation patterns[35,50] are largely preserved between stimuli. Thus, the activity sequences evoked by different stimuli consist of variations on a common spatiotemporal theme, with variations in spike count and timing conveying information about stimulus identity.

Sequential population responses to stimulus onsets are seen not only in auditory cortex. Close examination of published data from multiple brain regions suggests individual neurons have largely conserved response latencies across different stimulus conditions (for examples, see REFS 37,44,51–54). In the somatosensory

cortex, for instance, individual neurons fire with diverse latencies that are approximately conserved across different tactile stimuli[35,47,48] (FIG. 1c). Furthermore, analogous sequential packets have been observed outside cortical structures. Different odours evoke similar sequential patterns in the olfactory bulb on presentation; although these sequences are most similar for repeated presentation of the same odour, similarities are also seen in the sequential structure of responses to different stimuli[55] (FIG. 1d). Thus, sensory responses in several brain areas consist of transient activity packets, the structures of which vary on a theme: neuronal response latencies are approximately conserved between responses to different stimuli, but slight variations in the response pattern encode information about the stimulus identity.

Information coding within packets. The nature of the cortical code changes over the duration of a packet in multiple ways (FIG. 2). First, the spike-timing reliability progressively decays during a packet[36]. This can be seen at the level of single-cell responses (FIG. 1a): spikes of early firing neurons are timed extremely accurately, whereas later-firing cells show progressively broader responses, resulting from larger variability of times of individual spikes[36,56]. That spike-timing reliability progressively decreases within a packet

suggests that different information-coding schemes are used during different phases of the packet.

Specifically, spike-time coding may be used primarily by early firing neurons, whereas firing-rate coding may be used predominantly by late-firing neurons (FIG. 2b). In support of this idea, studies in multiple cortical regions suggest that, for many neurons, the timing of the first spike is much more informative about the stimulus identity than is the timing of subsequent spikes[6,46,57,58]. However, it should be noted that spike-timing and firing-rate codes are not mutually exclusive, but can coexist and contribute unique information about the stimulus[52,59–61]. Together, these data suggest that temporal and rate coding coexist within packets in a time-dependent manner (FIG. 2c,d). In response to different sensory inputs, the overall sequential structure of the packet is preserved but fine-scale temporal and firing-rate changes within packets carry information about stimulus identity, with late-firing neurons showing higher firing-rate selectivity and early firing neurons showing higher reliability and lower firing-rate selectivity.

In addition to weighting temporal and rate coding differently, the early and late phases of cortical activity packets also seem to encode different types of information. It was shown that short-latency responses correlate with

simple stimulus features, but later responses seem to represent more-refined and complex features. For example, in one study of the temporal cortex of macaque monkeys, information on basic stimulus categories (for example, faces versus geometric shapes) was conveyed in the earliest part of the neuronal response, and fine-grained information (such as that about face identity or expression) was conveyed, on average, 51 ms later[62]. Similarly, analysis of neuronal responses to complex shapes in the macaque inferior temporal cortex showed that activity immediately after stimulus onset carried information only about individual object parts (simple contour fragments), but over the course of the following ~60 ms information about specific multipart configurations gradually emerged, producing a more-explicit representation of the full object shape[63]. Studies in several other sensory areas have also reported that spiking activity becomes more stimulus-selective[39,64–68] (FIG. 2a) and conveys more-refined, high-level features as time progresses.

The later phases of stimulus-evoked packets may also contain information about the animal's behavioural choice. For example, in one study of the mouse primary somatosensory (S1) barrel cortex, early (<50 ms) sensory responses during a tactile detection task reliably encoded the presence of a stimulus but did not predict the mouse's behaviour. However, neural activity in a later response period (50–400 ms) correlated with the animal's behavioural response[69]. Similarly, in the primate secondary visual (V2) cortex, neural responses to binocular disparity stimuli correlate with the animal's behavioural choice only in the later phase of the sensory response[70]. As discussed below, it is likely that this more-complex coding in later stages of sensory-evoked packets represents integration of sensory input with feedback coming from elsewhere in the brain.

Spontaneous activity packets

Much of the activity in the cortex is generated spontaneously[71]. Population recordings in the sensory cortex of resting animals indicate that activity packets similar to those evoked by sensory stimuli can also occur without external stimulation (FIG. 3). These spontaneous packets occur sporadically at rates that depend on the animal's behavioural state: every few hundred milliseconds in quiet wakefulness but less frequently during sleep (the case of active behaviour is discussed below).

The structures of spontaneous activity packets within a single cortical layer are remarkably similar to those evoked
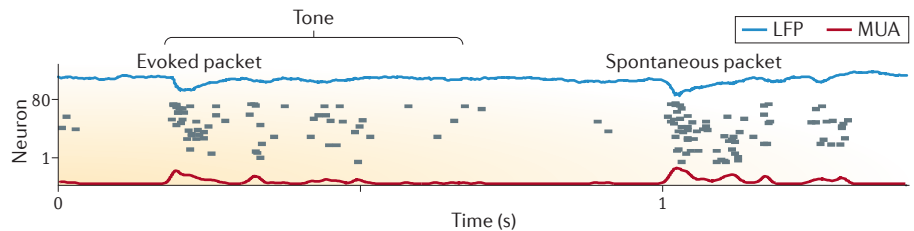

Figure 3 | Spontaneous packets have a similar structure to stimulus-evoked packets. A representative raw-data plot shows a tone response and a spontaneous firing event in the rat auditory cortex. The duration of a tone stimulus is shown at the top of the plot, the blue traces indicate local field potential (LFP) and the raster plot shows the spike trains of simultaneously recorded neurons. The multiunit activity (MUA; shown in red) was computed by averaging the activity of all recorded neurons. Neurons are ordered according to their spike latency within spontaneous packets, to facilitate visual examination of temporal patterns. Note the similarity of temporal structure of spontaneous and evoked packets. Adapted with permission from REF. 35, Elsevier.

by sensory stimuli. Their durations are approximately the same[72–75], and they are subject to similar constraints in terms of the sequence in which the involved cells fire[50] and the range of rates at which they can fire[35,36]. Moreover, spontaneous and evoked activities exhibit similar firing-rate statistics, described as neuronal avalanches, which maximize information capacity[76–78]. Nevertheless, spontaneous and sensory-evoked packets move through cortical layers in different ways. Sensory-evoked packets are first seen in layer 4 and at the layer 5–layer 6 border, the layers that receive the strongest input from thalamic primary relay nuclei. By contrast, spontaneous packets are usually first seen in the deep layers[79,80]. This suggests that the spontaneous activity packets observed in the sensory cortex are not driven by thalamic input but are instead either generated locally in deep-layer circuits or arise owing to propagation from other regions via corticocortical connections (which heavily target deep-layer neurons)[81–83]. As discussed below, imaging studies suggest the latter type of spontaneous cortical packet is more common.
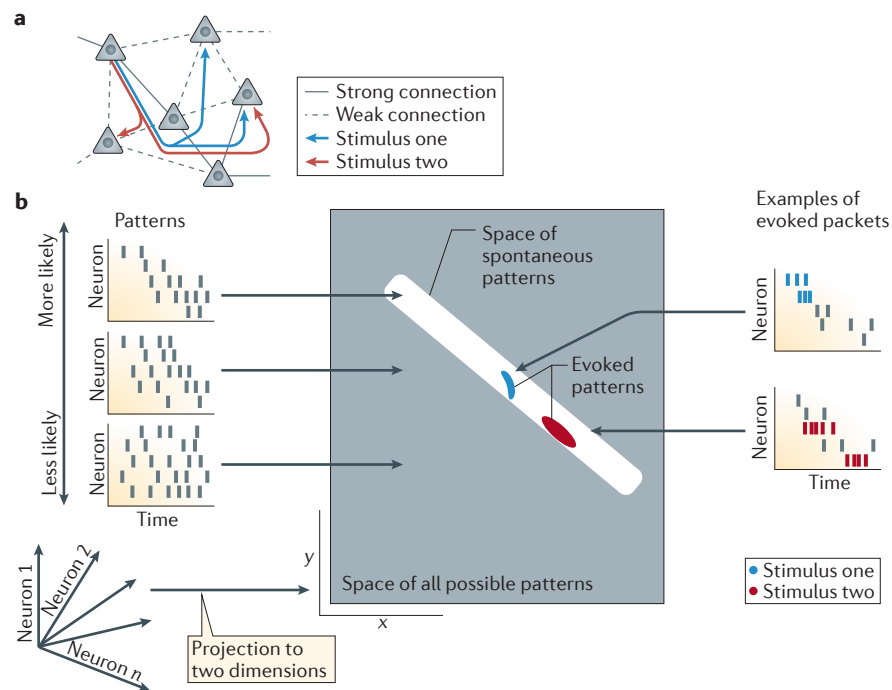
It is often proposed that spontaneous cortical activity reflects 'replay' of previously experienced firing patterns that occur during waking. However, the structure of spontaneous packets in the sensory cortex cannot exclusively reflect such replay events. In the auditory cortex for example, spontaneous activity packets have a similar structure to packets evoked by sounds that the animal had never heard before[35] (for example, in laboratory rats, packets evoked by sounds of a swamp played for first time were similar to spontaneous packets). This similarity cannot reflect replay of a previous sensory stimulus-induced packet, but instead more likely reflects hard-wiring constraints of the underlying circuitry, which can produce

only a limited number of activity patterns[84] (BOX 1). Nevertheless, there is considerable evidence that the patterns observed spontaneously in the sensory cortex are more similar in structure to patterns of activity that correspond to stimuli that the animal has most-recently experienced[85–88]. In rats, for example, repeated sensory stimulation was shown to modify, in a stimulus-dependent manner, the following spontaneous activity up to several minutes after stimulation[87,89]. Owing to neuronal network constrains, the spontaneous activity packets before stimulation already had a similar structure to that of the sensory-evoked packets; however, the similarity in sequential structure became greater after stimulation. Together, these data suggest how circuit constraints and replay interact. The wiring of the cortical circuit imposes certain constraints on cortical activity patterns; that is, there is a realm of possible activity patterns that a given cortical circuit can produce[35]. Sensory stimulus-induced and spontaneous activity patterns must all lie within this realm (BOX 1). However, the spontaneous patterns that occur are not evenly distributed among all possible patterns within this realm, but instead occur in a biased manner, with a higher probability of spontaneous packets occurring in areas of the realm that represent neuronal activity patterns evoked by recent sensory experience.

Spontaneous packets can also provide a simple explanation for the observation of precisely repeating spiking patterns[14,20,90] that occur without sensory stimulation. First, the reported duration of repeated patterns usually falls within the typical range of packet duration[20,91] (50 to a few hundred milliseconds), and spontaneous repeated patterns often have a similar structure and duration to stimulus-evoked patterns[87–89]. Moreover, most reoccurring precise spike patterns in

Box 1 | **Constraints on packet structure**

Cortical networks have a nonrandom structure. A small number of strong connections are embedded in a pool of weaker connections (see the figure, part **a**). These connectivity constraints may result in different stimuli producing similar activity packets, because neuronal activity preferentially propagates through the strongest connections. As a consequence, certain activity patterns are more likely to occur than others (see the figure, part **b**). The grey area illustrates the space of all spiking patterns theoretically possible for a packet. The white area represents the space of spontaneous packets actually generated in the cortex, which is much smaller than that for all the theoretically possible patterns, owing to physical network constraints. Packets evoked by different stimuli occupy smaller subsets within this subspace. The overall structure of the packets evoked by different stimuli is similar, but relatively small variation in the firing rates and spike-timing of particular neurons encode information about the identity of the stimulus. In the examples of evoked packets shown on the right, neurons most driven by a particular stimulus are colour-coded accordingly. Part **b** adapted with permission from REF. 35, Elsevier.

the auditory and somatosensory cortex can be predicted from the sequential structure of the packets[36]. Note that it is not necessary that packets have millisecond precision structure to observe statistically significant repeats at this resolution. For example, if neuron 1 tends to fire 50 ms ± 20 ms standard deviation after neuron 2, there is still a higher-than-chance possibility of observing neuron 1 firing, for instance, exactly 53 ms after neuron 2, when compared with a random distribution of spikes. Thus, sequentially structured packets are consistent with experimental data showing precisely repeating spiking patterns[20,23], which provided support, for instance, for the synfire chain model[18,92]. Nevertheless, some aspects of packet organization are not fully consistent with the original synfire chain model itself as, contrary to the model's predictions, spiking precision progressively decays after packet onset[36]. Thus, packets provide both convincing evidence that spike patterns show precise repetition and a simple explanation for this phenomenon.

Packet structure across brain states.
Electroencephalography (EEG) recordings in humans and in several other species reveal that different stages of arousal or sleep correspond to different states of global brain activity, which are characterized by their EEG power spectra[93,94]. These differing EEG patterns arise from a specific structure of cortical population activity[73,95,96]. Brain states seem to span a continuum from synchronized states that are characterized by large, slow fluctuations in population activity to desynchronized states that exhibit smaller and faster fluctuations (FIG. 4a). Although the most striking changes in brain state are seen between waking and sleep, more-subtle variations in brain state are also seen within waking,
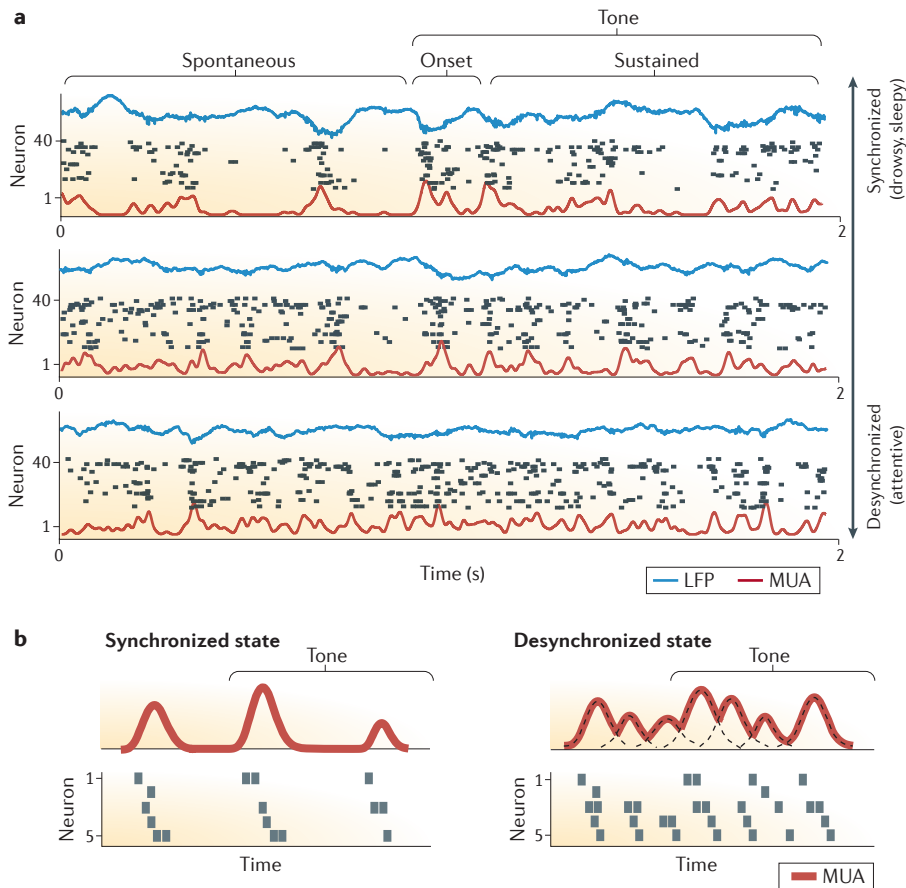
with more-desynchronized states accompanying behaviours such as whisking and more-synchronized states being observed during quiet wakefulness[97–99]. The steadier pattern of population activity seen in desynchronized states is accompanied by a reduction in the size of low-frequency fluctuations in local field potential (LFP) and in intracellular membrane potential[97,98]. In desynchronized states, the size of fluctuations in summed population activity can be extremely small[100]. Nevertheless, this lack of large fluctuations in summed activity does not mean that population firing in desynchronized states is unstructured. Indeed, recent evidence suggests that population activity in desynchronized states consists of packets similar to those observed during synchronized states, but that in desynchronized states the packets overlap in time, reducing the total size of fluctuations. There are several reasons for this conclusion, which we now discuss.

First, the temporal patterns evoked by the onset of sensory stimuli are highly similar across brain states. The size and fine structure of onset-evoked activity packets in awake auditory and somatosensory cortices are similar across states[73,89]. This similarity in the structure of onset-evoked packets also extends to sensory responses that occur during sleep: for example, in the auditory cortex, individual neurons respond to external stimuli with highly similar temporal profiles during wakeful, rapid-eye-movement sleep and slow-wave sleep states[101,102].

Second, even during responses to temporally unstructured stimuli (such as the presentation of a continuous tone), cortical population activity still consists of transient packets[73] (FIG. 4a). Such packets generated during the sustained period of a tone presentation show similar precise relative timing of spikes to that of onset-evoked packets, and information about the tone frequency is conveyed not only by the firing rates of cells within the packets but also by their precise relative timing[73]. Human EEG studies are also suggestive of packet-based organization: in the auditory cortex, acoustic signals are segmented in windows of approximately 200 ms[103], thus supporting the idea that the cortex may process sustained sensory stimuli in discrete packets.

Finally, the similarity of the fine temporal structure of population activity across different states extends beyond the stimulus onset. In the sustained period (>200 ms) after onset of long-lasting (over ~1 s) stimuli, packets may occur at unpredictable times and, because prolonged silent periods do not occur in highly desynchronized states, it is difficult to determine the onset of any

Figure 4 | **Sequential spiking pattern within packets is preserved across different brain states.** **a** | Examples of population raster plots showing 1 s of spontaneous population activity in the auditory cortex, followed by population activity in that area during presentation of a 1-s tone. The three rows show responses in the same neurons during different brain states; each raster plot shows spikes of simultaneously recorded neurons (black), local field potential (LFP; blue trace) and the multiunit firing activity (MUA; red trace), which is computed as the smoothed summed activity of all neurons. The time between 200 ms and 1 s after stimulus onset is referred to as the sustained period (shown at the top of the chart). Note that the population tends to fire in transient bursts of 50–100 ms duration at times including, but not limited to, the onset of the tone. Activity during desynchronized states shows weaker global fluctuations but still exhibits complex fine structure. To illustrate sequential activity within packets, neurons are shown in the order of their mean spike-timing within the packet (latency); neuron order is the same across all three panels. **b** | Schematic illustration of packet activity across different brain states. In a synchronized brain state, packets of population activity are separated by periods of global silence. Stimulus onset reliably induces an activity packet, but packets can also occur sporadically throughout the sustained and spontaneous periods. Within each packet, neurons fire with a stereotyped sequential pattern. 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 that are individually similar to those observed in the synchronized state are superimposed to produce a firing pattern that exhibits smaller fluctuations in global activity but retains a fine temporal structure. Republished with permission of Society for Neuroscience, from Gating of sensory input by spontaneous cortical activity, Luczak, A., Bartho, P. & Harris, K. D., **33**, 4, 2013; permission conveyed through Copyright Clearance Center, Inc.

particular packet. However, the fine temporal structure of packets during long-lasting stimuli can be investigated using cross-correlation analysis. Cross-correlograms calculated separately during synchronized and desynchronized brain states have similar temporal profiles[73]. Moreover, even during strong spindle oscillatory activity (~12 Hz),

the temporal relationships between neurons within a 50 ms window are remarkably stable, suggesting that packets have a highly conserved sequential structure even during large changes in oscillatory brain activity[104,105].

Together, these data are consistent with the hypothesis that activity during all brain states is composed of similar sequentially

organized packets but that, in a desynchronized state, the presence of a large number of packets overlapping in time creates the impression of continuous spiking patterns (FIG. 4b).

Packet-like activity in the hippocampus. Although the neocortex and hippocampus may have distinct primary functions[106–108], both structures seem to process information in a similar manner using activity packets of 100–200 ms. In animals that are not moving, spontaneous activity in the hippocampus is dominated by packets of firing known as sharp wave–ripple complexes (SWRs)[109,110]. SWRs have a similar duration to that of cortical activity packets and also have a sequential structure[111]. In addition, during active locomotion, hippocampal activity changes and becomes dominated by an ~7–8 Hz theta rhythm (at least in rodents[112]), and spiking activity on each cycle of this rhythm can be conceived as a single activity packet. Theta cycles have a similar duration (~100 ms) to hippocampal SWRs and sensory-evoked and spontaneous neocortical packets, and temporal sequences within theta packets and SWRs can also be very similar[106,113].

Interestingly, it was found that spontaneous hippocampal packets can be surprisingly similar to patterns evoked by a later novel experience[114]. This phenomenon (termed preplay) suggests that hippocampal packets may be constrained to a broadly predefined realm of possible activity patterns, similarly to packets in sensory cortices (BOX 1). It also seems consistent with the path-integration model of Samsonovich and McNaughton[115], in which preplay of future space trajectories could arise as a natural consequence of the prewired configuration of place fields on a 'chart'. Nevertheless, examination of the variability of temporal sequences in the hippocampus (for example, phase precession[8,9]) suggests that the realm of possible activity patterns could be orders of magnitude larger in the hippocampus than in the sensory cortices. Thus, although hippocampal activity is organized into ~100–200 ms packets in a manner similar to activity in the sensory cortices, the sequential order of packets seems to be modified by external and internal inputs to a larger extent in the hippocampus than in the cortex.

The global picture
Microelectrode array recordings can reveal the patterns of spiking activity occurring in local populations, but different techniques are required to understand how cortical activity packets are organized at a global level, across multiple cortical areas. Studies

using wide-field imaging with VSDs and studies using electrode recordings in multiple brain regions have shown that activity packets in sensory areas, as described above, are the local manifestation of large-scale waves that spread over the cortical surface.

The presentation of sensory stimuli often evokes waves of activity that spread outwards from the sensory cortex and reaches most of the cortical mantle[116]. For example, the response to a whisker stimulus is first seen in the corresponding whisker barrel but, over the next tens of milliseconds, propagates to a large number of other cortical regions. Stimulation of auditory and visual modalities causes distinct traveling patterns of global activity, appearing first in the corresponding primary sensory region and spreading over the next tens of milliseconds to additional areas[87,116,117]. Although this activity can be described as a travelling wave, it does not propagate simultaneously to all adjacent areas: for example, one of the earliest regions beyond the barrel cortex to see whisker-evoked activity is the vibrissa motor cortex[116,118]. As the activity packet continues to spread (>20 ms after the packet has started in the sensory cortex), the activity there is affected by feedback from other areas where the packet has already propagated, owing to recurrent connectivity between these regions[119,120]. This top-down feedback can differentially activate subsets of neurons[119], which might contribute to the higher stimulus selectivity shown by neurons that are active later within the packet in the sensory cortex, as discussed above. By approximately 70 ms after the presentation of a stimulus, the entire cortical sheet may be depolarized[116] (FIG. 5a), which may thus allow for global exchange of stimulus-relevant information.

However, as described above, not all packets are triggered by sensory stimuli. Packets can be initiated spontaneously in a wide range of cortical regions, including the sensory and association areas[116]. The hippocampus produces spontaneous packets in the form of sharp waves, but electrophysiological recordings in the hippocampus (which cannot be recorded with wide-field imaging) indicate that sensory-evoked packets also spread to the hippocampus[121–123]. Thus, it seems that activity packets originating in the sensory cortex are broadcast via direct and polysynaptic pathways to the entire cortical mantle, including the hippocampal cortex. Studies that have attempted to determine whether hippocampal spontaneous activity leads neocortical activity or vice versa have led to conflicting
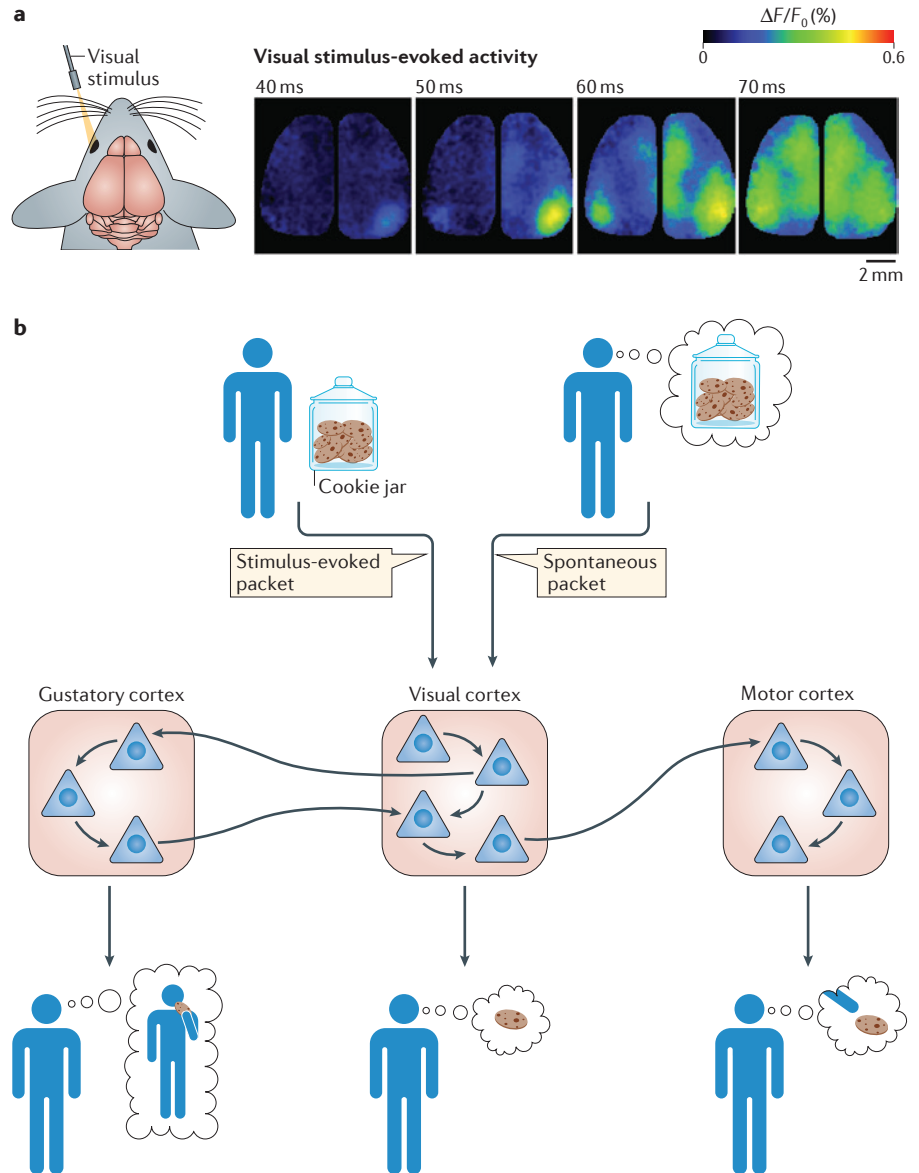

Figure 5 | **Global propagation of packets. a** | Population packets propagate as a complex wave spanning the majority of cortical regions. The schematic illustrates an experiment using voltage-sensitive dye in the cortex to assess neural activity in response to visual stimulation using an LED. A single, brief visual stimulus evokes early localized activation in the contralateral visual cortex. Over tens of milliseconds, the activity spreads to most parts of the cortex. **b** | Schematic illustration of the possible function of globally propagating stimulus-induced and spontaneous activity packets. When a visual stimulus (for example, a jar of cookies) is present, it may trigger a stimulus-induced packet of activity in the visual cortex, which then spreads from the visual cortex to other cortical areas. Activity triggered in different cortical areas may correspond to different associations of this particular stimulus. For example, activity triggered in the gustatory cortex might represent the taste and reward value of eating a cookie, late-phase activity in the visual cortex might represent an image of the target (for example, a single cookie, rather than the whole jar), and firing in the motor cortex might represent the preparatory activity required to generate the movements required to eat the cookie. At a later time, when the jar of cookies is no longer in sight, a spontaneous activity packet may occur. Such a spontaneous packet may again be initiated in the visual cortex and would consist of a very similar spike pattern to that which accompanied the original visual stimulus (that is, the spontaneous packet may reflect the 'replay' of a prior sensory-evoked pattern). The global activity and behavioural consequences of this spontaneous packet would be very similar to those of a sensory-evoked packet caused by the direct presence of the visual stimulus: activity in the gustatory cortex would convey the taste value of eating a second cookie, the visual cortex would again represent the target image, and the motor programme required to eat a cookie would again be initiated. Part **a** from REF. 116, Nature Publishing Group.

results[124–129]. In view of the VSD imaging results, this is not surprising: in the neocortex, it is not easy to determine whether activity in one area leads activity in another area, as activity can propagate in all directions. We hypothesize that the relationship between spontaneous activity in the hippocampus and cortex is like the relationship between different cortical areas: activity may start in any one area but, wherever it starts, it usually spreads to the whole cortex. Some spontaneous patterns may therefore be triggered by hippocampal sharp waves and spread to the neocortex; others may be triggered in the neocortex and spread to the hippocampus.

Possible function of packets

We hypothesize that activity packets may serve as fundamental building blocks of global cortical communication. Each packet can be conceived of as a discrete 'message' initiated by a particular cortical region and broadcast to all areas it projects to. Such packets can be evoked by sensory stimuli but can also arise spontaneously in almost any region of cortex and spread globally from there.

These packets presumably have a wide range of functions. For example, a packet originating spontaneously in the hippocampus might encode coordinated recall of a previous experience, triggering activity in wide regions of the neocortex. When this activity spreads to sensory areas, it might encode the sensory aspects of recalled memories; when it spreads to association cortices, it might trigger firing patterns encoding actions taken during the previous experience, and the consequences of these actions (for example, rewards). Spontaneous packets initiated in sensory areas might correspond to the recall or imagination of particular sensory stimuli and trigger activity in other areas reflecting associations of those stimuli, and they might even potentially trigger the same behaviours that the stimuli themselves would evoke (FIG. 5b). For example, in the motor cortex, neuronal activity packets are similar during both execution and observation of a movement[130]. In addition, spontaneous packets initiated in higher-order areas might reflect processes such as attention, transiently boosting the representation of specific modalities or stimuli[99].

In the sensory cortex, the 50–200 ms duration of an activity packet may provide a timeframe for the integration of feedforward and feedback inputs, in which feedback could provide 'context' for local processing[131]. As discussed above, the 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 the stimulus, and prepare downstream neurons for the more-refined information that follows later in the packet[63,69]. Thus, the function of cells active early in the packet could be to initiate global information exchange. Such early-active cells also may directly depolarize relevant late-active cells to facilitate integration of feedback information[119]. Thus, if early-active neurons are not appropriately activated, this might cause failure of signal integration, leading to incorrect behavioural decisions[132]. With a temporal window of 50–200 ms and a sequential activation structure, packets may thus be ideal for effectively combining relevant bottom-up and top-down signals.

Constraining spiking activity to small temporal windows may improve information transfer between brain areas by synchronizing neuronal firing[133,134] and may stabilize information carried by spatial and temporal spike patterns[135]. Thus, 'packeting' spikes into small temporal windows could enhance their effect on downstream activity[136]. Interestingly, the duration of packets is comparable with the time windows for long-term potentiation and long-term depression[137]. Therefore, such synchronous activity not only may increase information transfer efficiency but also may have a crucial role in plasticity, as the induction of synaptic plasticity is favoured by coordinated action-potential timing across populations of neurons[138].

In addition, structured packets could provide a temporal reference frame for information coding; that is, a temporal scaffold against which spike-timing variations could code for different stimuli[139,140]. The precise timing of spikes relative to stimulus onset can provide information about stimulus identity in multiple sensory modalities (including auditory[5,38,46], visual[54,141] and somatosensory systems[6,142]). However, it remains unclear how the brain could assess the time difference between actual time of stimulus onset and time of spikes signalling it. One suggestion is that a subset of neurons firing at a precisely constant latency relative to stimulus onset could provide a reference for decoding information from spikes in which timing differs with stimuli[143]. More generally, variations in the relative spike-timing of any one neuron compared to a broadly conserved timing pattern could convey information about sensory stimuli, even if there is no well-defined onset response. Indeed, the amount of information provided by the spike latency increases when spiking latency is referenced to population activity[55,57]; similarly, spike-timing in relation to LFP phase can provide information about stimulus identity in the hippocampus[9,144] and neocortex[60,61,135,145]. Because LFP fluctuations are strongly correlated with spiking activity[146,147], this suggests that spike-timing coding in relation to packet onset could be directly related to LFP-phase coding[73].

We therefore suggest that the default temporal structure of a packet provides a reference for downstream neurons to read out the precise timing of individual neurons. In support of this hypothesis, the relative timing of neurons within the packet during the sustained response to a long tone stimulus varies depending on the tone frequency[73]. It is not possible that this code could be read with respect to the stimulus onset, as the packets during the later part of the sustained tone occur at unpredictable times relative to the tone onset. Instead, the spike timing of any one neuron can only be read out with respect to the reference frame provided by the packet.

Possible mechanisms of packet formation

In this Opinion article, we present evidence that neural population responses to different stimuli are subject to conserved spatiotemporal constraints. One can imagine several ways in which the physical properties of a neural circuit could impose constraints on the spike patterns it can generate. First, different cortical neurons have diverse intrinsic physiological properties, which may contribute to the diversity of cellular firing patterns[148–150]. For example, cells with higher intrinsic excitability might fire earliest in sequence. Indeed, it was found that different cell types differ consistently in their response to the same current injections[151,152] or sensory stimuli[79,153] and in relation to the onset of spontaneous population bursts[154,155]. Moreover, the response latency of neurons in the superficial barrel cortex to whisker deflection systematically differs according to their projection target[156], with primary motor cortex-projecting neurons responding more rapidly than secondary somatosensory cortex-projecting neurons in response to the same stimulus. This raises the intriguing possibility that the timing in the packet sequence may correlate with the input and output projections of a neuron, which is also consistent with other studies[157–159].

Second, connectivity within cortical circuits is far from homogenous[160–162]. The cortex is thought to have a skeleton of

stronger connections immersed in a sea of weaker ones[163,164], and densely connected local neuron networks are supplemented by a small fraction of long-range connections[165], which is reminiscent of small-world topology[166–168]. Thus, the stereotypical temporal structure of cortical activity packets may be due in part to constraints imposed by the connectivity of the cortical microcircuit. For instance, activity may preferentially propagate through such stronger pathways, resulting in stereotypical sequential spiking patterns. Indeed, it has been suggested that packets are the functional manifestation of 'default microcircuits' — local patterns of connectivity that impose similar spatiotemporal constraints on spontaneous and stimulus-evoked flow of activity[84,169] (BOX 1). This hypothesis is also supported by modelling studies that show that the synaptic connections between neurons can determine the repertoire of spatial patterns observed during spontaneous activity, and indeed the dominant spatial patterns of the spontaneous activity, calculated as its principal component, do coincide remarkably well with those patterns predicted from the network connectivity[170]. It has been suggested that consistent activity patterns observed in the experimental studies described in this Opinion article may be a manifestation of network attractors[14], which are emergent features of some recurrent neural network models[171]. The realm of possible cortical activity patterns may be shaped to a large degree by prior experience, such as behavioural training[172,173], or even by passive exposure to an environment[174,175]. Thus, although the exact mechanisms of sequential pattern formation are not yet clear, multiple lines of evidence suggest that neuron latency to fire within a packet is determined by intrinsic properties of the neuron and its place in the circuit, rather than by the processing of any particular sensory stimulus[15,16].

Conclusions

Most studies of sensory coding focus on differences in single-neuron responses to a range of stimuli; however, they tend to overlook the similarity in responses to different stimuli. Here, we fill this void and describe findings to suggest that, despite such variability in responses to different stimuli, at the population level the overall sequential pattern is remarkably consistent across various stimuli. This may have an important function in neuronal coding by providing a common reference frame. That similar sequential packets are observed even during spontaneous activity suggests that the cortex

may process information not continuously, but rather in the form of such similarly structured, discrete packets.

Thus, we propose that cortical communication occurs as a series of packets of neural activity. Each packet is initiated in one cortical region and from there is broadcast to the rest of the cortex. A salient sensory event, such as a stimulus onset, results in initiation of a packet in the relevant primary sensory cortex, and packet activity soon spreads to all cortical areas. The earliest phase of this neural response reflects low-level processing of the sensory input relayed from thalamus and occurs exclusively in the relevant sensory region. In this early phase, cortical spikes are timed with high precision, so information can be encoded by these spike times in addition to firing rates. However, in the later phases of the packet, neural activity spreads over the entire cortical surface. Thus, spiking in the late phase of the packet reflects an integration of thalamic input with feedback from elsewhere in cortex and therefore encodes a more-highly processed interpretation of the sensory stimulus (for example, the meaning of an image). We note that packets not only are evoked by sensory stimuli but also can occur spontaneously, originating in almost any region of cortex or hippocampus before spreading globally. These spontaneous packets may facilitate a wide range of functions, including memory recall, the selection of goals and the direction of attention towards specific modalities or stimuli.

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