

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 firing³⁷ (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 onset³⁵ (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^{3,38}), 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 stimulus³⁹, 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 visual⁴⁰, somatosensory⁴¹ and motor⁴² areas) across various species. Similarly, spontaneous fluctuations in spiking activity of approximately 50–300 ms have been observed in the neocortex⁴³. 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 transients³⁵. These packets have a similar, although not identical, sequential structure to those evoked by simple, pure tones³⁵. Similar results have been observed in the auditory cortex of awake cats in response to cat and human vocalizations⁴⁴. 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 fields⁴⁵, 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.

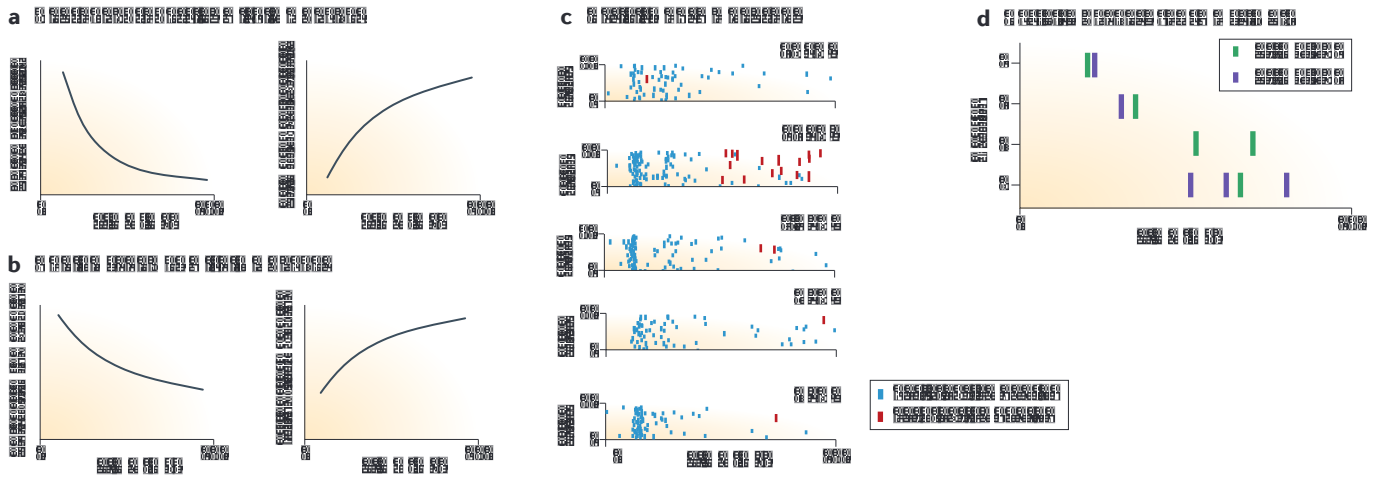


Figure 2 | Information coding within packets. **a** | Schematic representation of findings from several studies^{36,39,67,68} that have shown that stimulus selectivity increases and spiking reliability decreases as a packet progresses over time. **b** | At the beginning of a packet, spike-time coding 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.



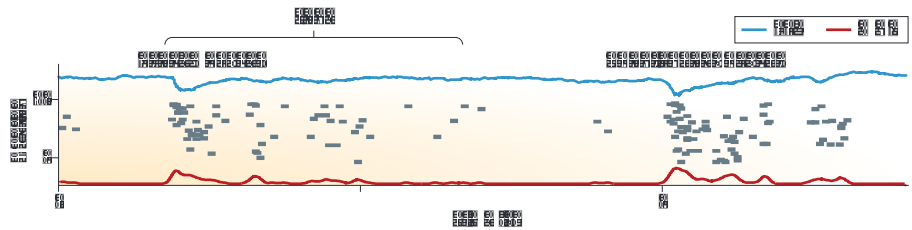


Figure 3 | **Spontaneous packets have a similar structure to stimulus-evoked packets.** A representative raw-data plot shows a tone response and a spontaneous firing event in the rat auditory cortex. The duration of a tone stimulus is shown at the top of the plot, the blue traces indicate local field 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 [10], Elsevier.

The auditory cortex is a highly organized region of the brain that processes sound information. It is composed of several distinct areas, each with its own specialized functions. The primary auditory cortex (A1) is the first cortical area to receive auditory input from the brainstem. It is characterized by a highly regular arrangement of neurons and is involved in the basic processing of sound features such as frequency and intensity. The secondary auditory cortex (A2) is located adjacent to A1 and is involved in more complex processing of auditory information, including the integration of sound with other sensory inputs and the generation of motor responses. The tertiary auditory cortex (A3) is the most posterior and lateral part of the auditory cortex and is involved in higher-level processing of sound, such as the recognition of speech and music. The auditory cortex is also involved in the generation of speech and the control of vocal production.

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Spontaneous activity packets

Spontaneous activity packets are brief, synchronized bursts of neural firing that occur in the absence of any external stimulus. These packets are thought to be generated by intrinsic neural circuits and are often observed in the auditory cortex. They have been shown to have a similar temporal structure to stimulus-evoked packets, suggesting that they may be generated by the same underlying mechanisms. Spontaneous activity packets are thought to play a role in the development and maintenance of neural circuits and in the generation of motor responses.

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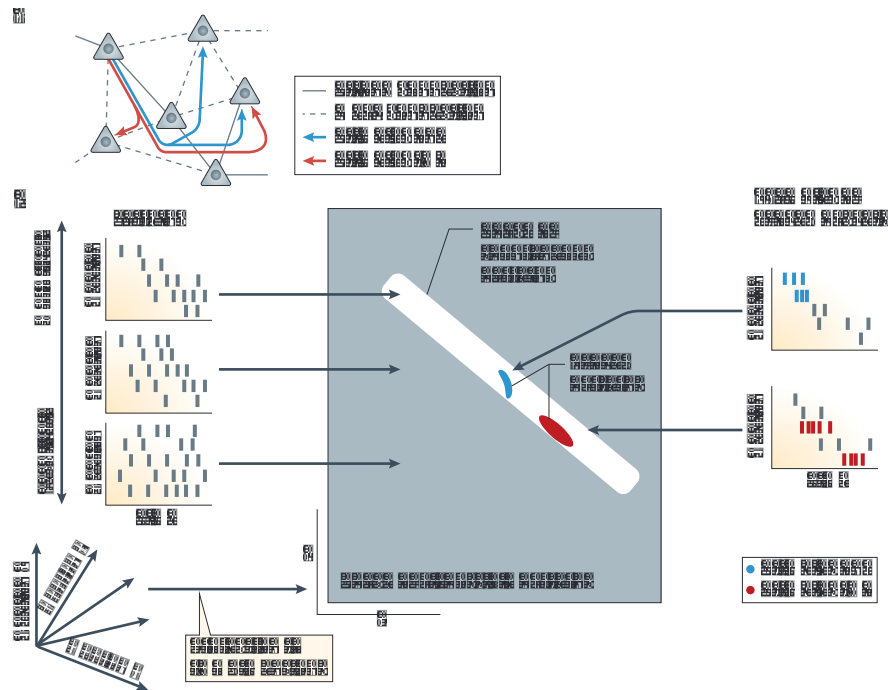
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Box 1 | Constraints on packet structure

neural activity in the cortex is 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 [1], Elsevier [2].



[1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61] [62] [63] [64] [65] [66] [67] [68] [69] [70] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102] [103] [104] [105] [106] [107] [108] [109] [110] [111] [112] [113] [114] [115] [116] [117] [118] [119] [120] [121] [122] [123] [124] [125] [126] [127] [128] [129] [130] [131] [132] [133] [134] [135] [136] [137] [138] [139] [140] [141] [142] [143] [144] [145] [146] [147] [148] [149] [150] [151] [152] [153] [154] [155] [156] [157] [158] [159] [160] [161] [162] [163] [164] [165] [166] [167] [168] [169] [170] [171] [172] [173] [174] [175] [176] [177] [178] [179] [180] [181] [182] [183] [184] 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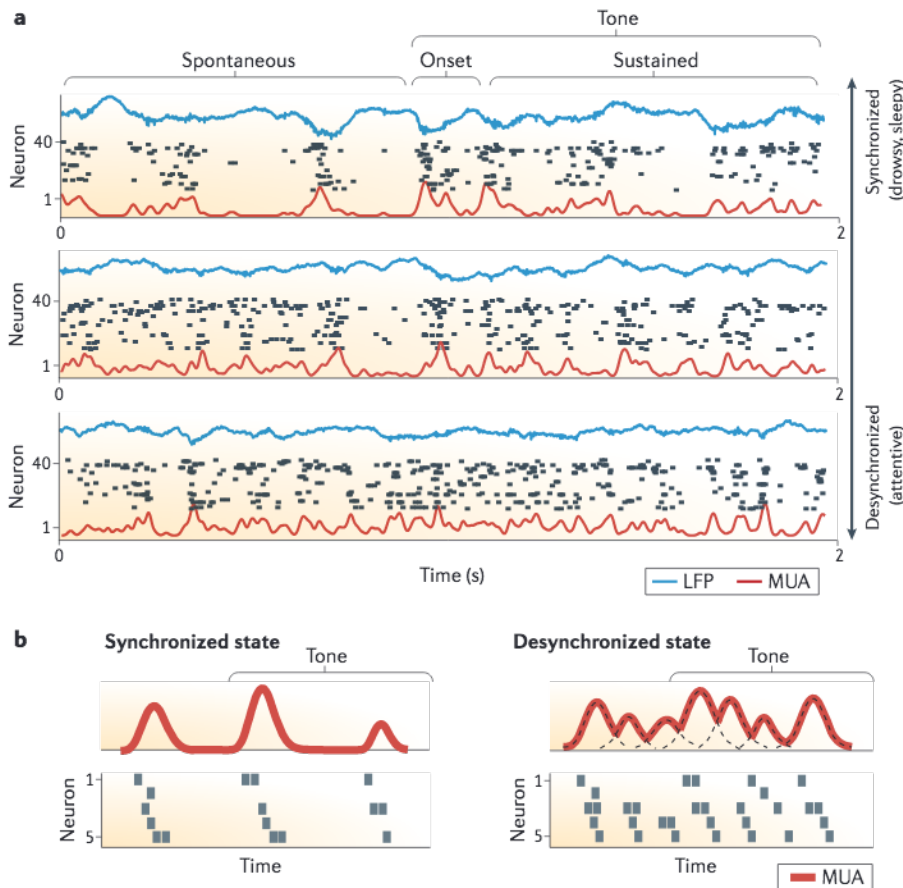


Figure 4 | Sequential spiking pattern within packets is preserved across different brain states. **a** | Examples of population raster plots showing 1 s of spontaneous population activity in the auditory cortex, followed by population activity in that area during presentation of a 1-s tone. The three 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 profiles⁷³. 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 structure¹¹¹. In addition, during active locomotion, hippocampal activity changes and becomes dominated by an ~7–8 Hz theta rhythm (at least in rodents¹¹²), 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 experience¹¹⁴. 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 McNaughton¹¹⁵, 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 mantle¹¹⁶. 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 neurons¹¹⁹, 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 depolarized¹¹⁶ (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 areas¹¹⁶. 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

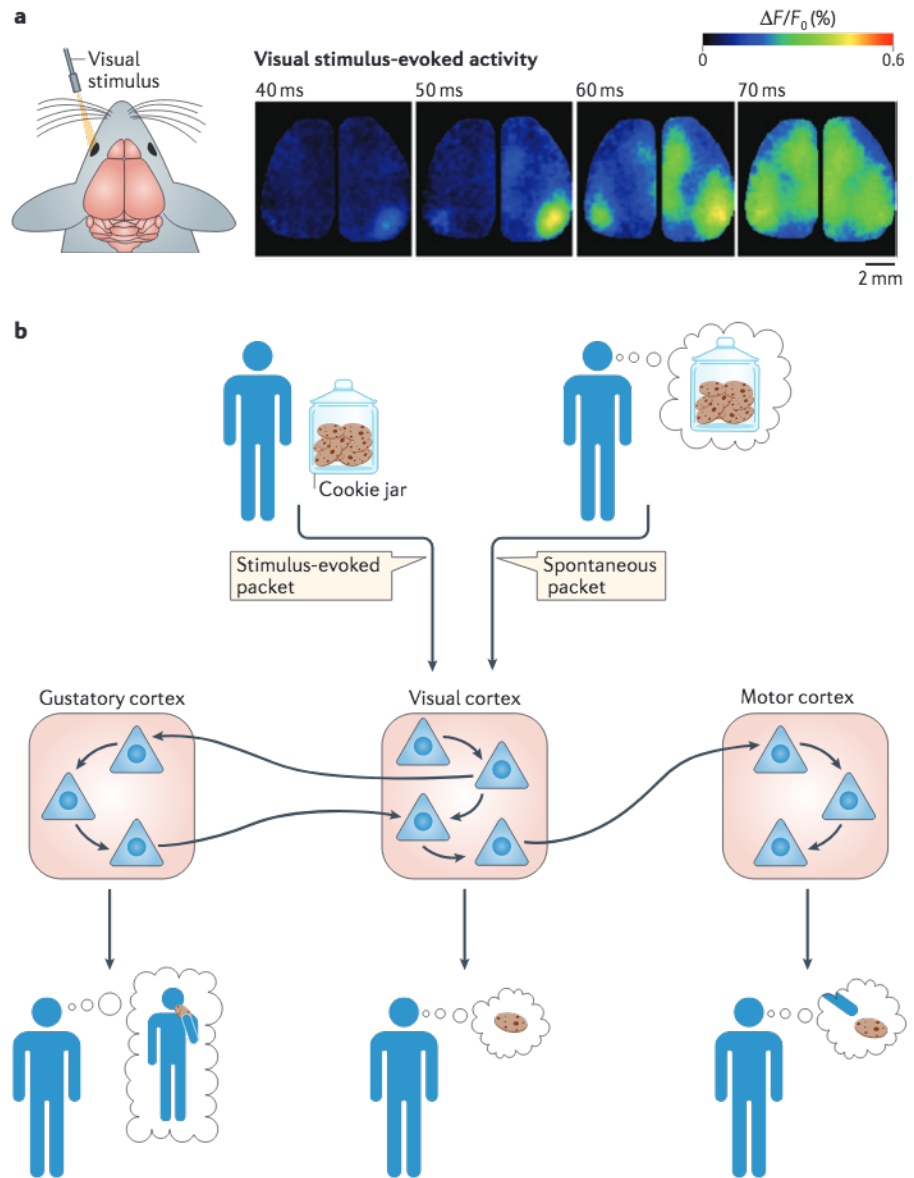


Figure 5 | Global propagation of packets. **a** | Population packets propagate as a complex wave spanning the majority of cortical regions. The schematic illustrates an experiment using voltage-sensitive dye in the cortex to assess neural activity in response to visual stimulation using an LED. A single, 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.

Abstract: This review discusses the possible functions of packets in the context of neural communication. It explores how packets of information are organized and transmitted within the nervous system, focusing on their role in signal processing and integration. The text highlights the importance of understanding these mechanisms for developing effective neural prosthetics and computational models of brain function.

Possible function of packets

The possible function of packets in neural communication is a topic of ongoing research. It is hypothesized that packets serve as discrete units of information that can be processed and integrated by downstream neurons. This mechanism could allow for more efficient and precise signal transmission compared to continuous analog signals. Further studies are needed to clarify the exact nature and function of these packets.

Understanding the function of packets is crucial for developing advanced neural prosthetics. By mimicking the natural organization of neural signals, researchers can create more effective interfaces between artificial devices and the brain. This knowledge also informs the development of computational models that aim to replicate the complex dynamics of neural networks. The review discusses various experimental approaches and theoretical models that have been used to investigate this phenomenon.

The review concludes by emphasizing the need for interdisciplinary collaboration between neuroscientists, engineers, and computer scientists to advance our understanding of neural communication. By combining experimental data with theoretical modeling and computational simulations, we can gain deeper insights into the mechanisms underlying the function of neural packets.

The review also discusses the implications of these findings for the development of neural prosthetics. By understanding how the brain naturally organizes and transmits information, researchers can design prosthetic devices that more closely resemble natural neural signaling. This could lead to improved functional outcomes for individuals with neurological impairments. The text also touches upon the broader implications for our understanding of the brain's computational capabilities.

Further research is needed to explore the role of packets in different types of neural circuits and across various species. This could help to identify common principles of neural organization and communication. The review also discusses the challenges associated with studying these phenomena, such as the difficulty of measuring individual packets in vivo. Innovative experimental techniques and computational models are being developed to address these challenges.

The review highlights the importance of these findings for the development of neural prosthetics and computational models. By understanding the natural mechanisms of neural communication, we can create more effective and biologically inspired artificial systems. This knowledge is also essential for understanding the brain's role in cognitive functions and behavior. The review provides a comprehensive overview of the current state of research in this field and identifies key areas for future investigation.

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Possible mechanisms of packet formation

The possible mechanisms of packet formation in neural communication are a topic of ongoing research. It is hypothesized that packets are formed through the integration of multiple signals or the activation of specific neural pathways. This process could involve the recruitment of different cell types or the activation of specific neurotransmitters. The review discusses various experimental approaches and theoretical models that have been used to investigate this phenomenon.

The review concludes by emphasizing the need for interdisciplinary collaboration between neuroscientists, engineers, and computer scientists to advance our understanding of neural communication. By combining experimental data with theoretical modeling and computational simulations, we can gain deeper insights into the mechanisms underlying the function of neural packets.

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Conclusions

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Abstract: This review discusses the current state of research on the role of the gut microbiome in mental health. It highlights the bidirectional relationship between the gut and the brain, and the potential for probiotics and prebiotics to improve mental health outcomes. Key findings include the impact of gut bacteria on neurotransmitter production, inflammation, and the stress response. The review also discusses the challenges of studying the gut microbiome and the need for further research to establish causal links between gut health and mental health.

Introduction: The gut microbiome, a complex community of microorganisms residing in the human gastrointestinal tract, has emerged as a key player in various aspects of human health, including mental health. This review explores the intricate connections between the gut and the brain, often referred to as the gut-brain axis. It discusses how the gut microbiome influences brain function through various mechanisms, such as the production of neurotransmitters, modulation of the immune system, and regulation of the stress response. The review also examines the potential of probiotics and prebiotics as interventions to improve mental health outcomes, and highlights the challenges and future directions in this field of research.

Conclusion: The gut microbiome plays a significant role in mental health, and its modulation through probiotics and prebiotics offers a promising avenue for improving mental health outcomes. However, further research is needed to establish causal links and to develop targeted interventions. The gut-brain axis represents a complex and dynamic system, and a deeper understanding of its mechanisms is essential for advancing our knowledge of the role of the gut in mental health.



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