Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks

Marlene Bartos, Imre Vida‡ and Peter Jonas**

Abstract | Gamma frequency oscillations are thought to provide a temporal structure for information processing in the brain. They contribute to cognitive functions, such as memory formation and sensory processing, and are disturbed in some psychiatric disorders. Fast-spiking, parvalbumin-expressing, soma-inhibiting interneurons have a key role in the generation of these oscillations. Experimental analysis in the hippocampus and the neocortex reveals that synapses among these interneurons are highly specialized. Computational analysis further suggests that synaptic specialization turns interneuron networks into robust gamma frequency oscillators.

Divergence
The number of postsynaptic target neurons innervated by a particular neuron. By contrast, convergence is the number of presynaptic neurons innervating a given neuron.

Spatial coherence
The correlation between signals at two different locations for all times (whereas temporal coherence is the correlation between signals at two different times for the same location). The term was originally defined in physics, but is also widely used in neuroscience.

**Physiologisches Institut der Universität Freiburg, Abteilung 1, Hermann Herder Strasse 7, D-79104 Freiburg, Germany. ‡Institut für Anatomie und Zellbiologie der Universität Freiburg, Abteilung Neuroanatomie, Albertstrasse 17, D-79104 Freiburg, Germany. Correspondence to P. J. e-mail: peter.jonas@physiologie.uni-freiburg.de*
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Oscillatory activity is a hallmark of neuronal network function in various brain regions, including the olfactory bulb, thalamus, hippocampus and neocortex[1]. The frequency of network oscillations covers more than three orders of magnitude, from slow oscillations in the delta (0.5–3 Hz) and theta (3–8 Hz) ranges to fast oscillations in the gamma (30–90 Hz) and ultrafast (90–200 Hz) ranges[1]. Within this spectrum, gamma oscillations have received particular attention, because their relationship to higher brain functions is most evident[2,3]. Gamma oscillations have been proposed to represent reference signals for temporal encoding[4,5], sensory binding of features into a coherent percept[2], and storage and recall of information[6,7]. Conversely, disruption of gamma oscillations could underlie some psychiatric disorders, such as schizophrenia[8,9].

To understand how oscillations contribute to higher brain functions, it is essential to first consider the basic underlying mechanisms. A key requirement for the generation of network oscillations is regular and synchronized neuronal activity. If a neuron fires action potentials in a regular manner, rhythmic activation of output synapses generates a periodic fluctuation in the intracellular membrane potential of all postsynaptic target cells[10]. If several neurons fire action potentials both regularly and synchronously, this fluctuating output signal is amplified, defining temporal windows of increased and reduced excitability in a larger population of target cells. At the same time, the rhythmic synaptic activation pattern results in a fluctuating field potential signal, which can easily be measured using extracellular recording electrodes[11]. The divergence of synaptic connections leads to a high level of spatial coherence of network oscillations. Such highly coherent oscillations might be ideal reference signals for temporal encoding and sensory binding in large neuronal ensembles[2,5].

Although gamma oscillations occur in all cortical areas[1,2], they have been particularly well studied in the hippocampus[11–13]. There are several reasons for this. First, the power of extracellularly recorded gamma oscillations is higher in the hippocampus than in other brain regions, owing to the simple laminated architecture of the hippocampal circuit[14]. Second, gamma oscillations in the hippocampus are evoked under specific behavioural conditions, such as exploration, when they typically coexist with theta oscillations[12]. This allows researchers to analyse the relationship between network oscillations and behaviour. Finally, as the hippocampus is essential for spatial navigation and episodic memory, the relevance of network oscillations for coding, storing and recalling information can be investigated[7,15,16]. Although hippocampal gamma oscillations have been studied for decades, the underlying neuronal and synaptic mechanisms have only recently come to light.

In this article, we aim to summarize the synaptic mechanisms of gamma oscillations in the cortex, with a primary focus on the hippocampus. We review the dependence of gamma oscillations on synaptic inhibition and the role of fast-spiking, parvalbumin-expressing γ-aminobutyric acid (GABA)-containing interneurons. Next, we explain how mutual inhibition leads to

oscillations in inhibitory interneuron network models. We go on to describe the properties of GABA synapses between interneurons that experimental work has revealed, and we show that these properties increase the robustness of oscillations when incorporated into interneuron network models. Finally, we address interneuron excitation by gap junctions and fast glutamatergic synapses, and discuss extended network models that incorporate these aspects.

Reliance of gamma activity on inhibition

Intuitively, phasic excitation seems to be an ideal mechanism to generate synchronized oscillatory activity. However, this might not be the case for gamma oscillations. The contribution of excitation and inhibition to the generation of gamma oscillations can be systematically examined in acute hippocampal slices *in vitro* (FIG. 1). In these slices, gamma activity can be evoked by either electrical stimuli or chemical agonists, and the emerging

Parvalbumin
A calcium-binding protein that contains EF-hand (helix–loop–helix) motifs. In the hippocampus, parvalbumin is selectively expressed in fast-spiking basket cells and axo-axonic cells. Although the function of parvalbumin is not fully understood, its expression represents a reliable marker for interneuron identification.

Network models
Computational models of neuronal networks, in which individual neurons (integrate-and-fire or conductance-based elements) are coupled by inhibitory synapses, excitatory synapses or gap junctions.

Gap junctions
Morphologically specialized electrical and biochemical connections between two cells, which are formed by transcellular channels. A gap junction channel is composed of two hemichannels (connexons), each of which consists of six subunits (connexins). Gap junctions are blocked by octanol and carbenoxolone; however, these blockers are not absolutely specific.

Acute hippocampal slices
200–400-μm-thick sections of the hippocampus, typically cut with a tissue slicer in the transverse plane. In comparison to the *in vivo* brain, the acute slice offers easy access in electrophysiological experiments, excellent visibility and the possibility of fast solution exchange.

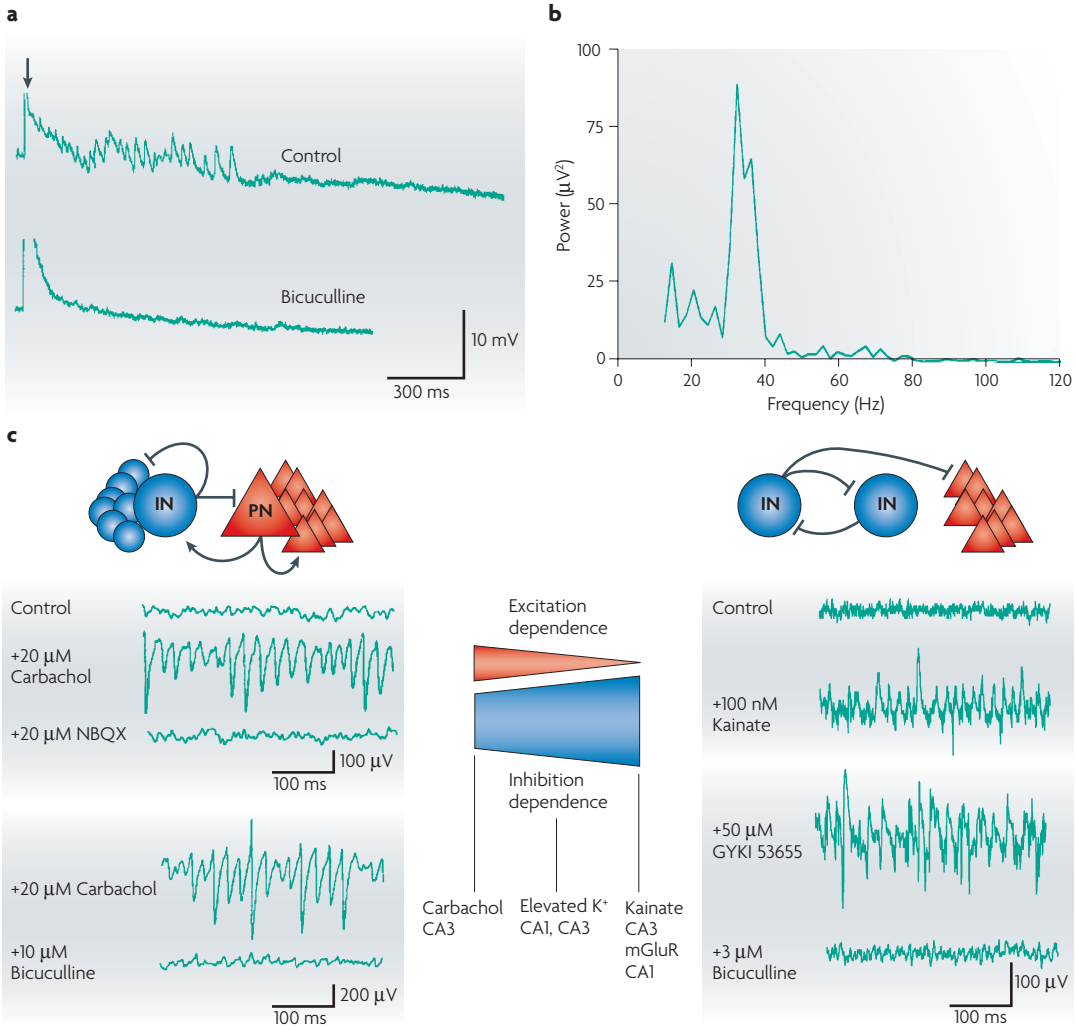

Figure 1 | **Networks of GABA-containing interneurons generate gamma oscillations *in vitro*. a** | Gamma oscillations in the hippocampal CA1 region evoked by tetanic stimulation (arrow) through activation of metabotropic glutamate receptors (mGluRs) *in vitro*. Gamma oscillatory activity was measured by whole-cell recording from a CA1 pyramidal neuron. Oscillations are blocked by the $GABA_A$ (GABA type A) receptor antagonist bicuculline. **b** | Power spectrum of the oscillations, showing the maximum at ~40 Hz. Similar oscillations can be recorded in the presence of blockers of fast excitatory synaptic transmission. **c** | Gamma activity in the hippocampus evoked by ionotropic or metabotropic receptor agonists *in vitro*. Left panel, carbachol-induced gamma oscillations in the CA3 subfield are blocked by both the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor antagonist NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulphonamide) and the $GABA_A$ receptor antagonist bicuculline. Right panel, kainate-induced gamma oscillations in the CA3 region are insensitive to the AMPA receptor antagonist GYKI 53655, but abolished by bicuculline. Gamma oscillatory activity was investigated with extracellular field potential recording. The schemes above the panels indicate putative mechanisms of gamma activity (IN, interneuron; PN, principal neuron). The red triangle and blue trapezoid (center) illustrate the relative dependence of oscillations on fast excitatory and inhibitory synaptic transmission in different paradigms. Panels **a** and **b** reproduced, with permission, from *Nature* REF. 17 © (1995) Macmillan Publishers Ltd. Panel **c** (left) reproduced, with permission, from *Nature* REF. 18 © (1998) Macmillan Publishers Ltd. Panel **c** (right) reproduced, with permission, from REF. 21 © (2004) Society for Neuroscience.

oscillations can be investigated using extracellular or intracellular recordings. Unexpectedly, an early study showed that gamma oscillations in the hippocampal CA1 region can be evoked by tetanic stimulation in the presence of blockers of ionotropic glutamate receptors[17], indicating that fast excitatory synaptic transmission is not necessary for this form of gamma oscillation (FIG. 1a,b).

Gamma oscillations can be evoked *in vitro* by agonists of various metabotropic or ionotropic receptors: metabotropic glutamate receptors (mGluRs)[17], muscarinic acetylcholine receptors (mAChRs, which mimic cholinergic input from the septum)[18,19] and kainate receptors[20,21]. They can also be induced through the application of a potassium-rich solution[22]. However, the gamma oscillations evoked under these conditions differ in their reliance on excitation and inhibition. mGluR-induced gamma oscillations in the CA1 region are completely blocked by the $GABA_A$ receptor (GABA type A receptor) antagonist bicuculline, but are maintained in the presence of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonists[17]. Likewise, kainate-induced oscillations in the CA3 subfield are completely blocked by bicuculline, but are maintained in the presence of AMPA receptor blockers[21]. By contrast, oscillations in the CA3 region induced by the cholinergic agonist carbachol have different pharmacological properties. Like mGluR- and kainate-induced oscillations, they are blocked by $GABA_A$ receptor antagonists; however, they are also inhibited by AMPA receptor antagonists[18,23]. Potassium-induced oscillations in both the CA1 and CA3 regions have intermediate properties, as they are completely blocked by $GABA_A$ receptor antagonists, but only partly inhibited by AMPA receptor blockers[22]. Gamma oscillations can also be evoked in the dentate gyrus[24,25], entorhinal cortex[26] and somatosensory cortex[27], although the underlying mechanisms have been less well investigated.

Therefore, GABA-mediated inhibition is necessary and sufficient for the generation of gamma oscillations induced by mGluR or kainate receptor activation, whereas it is necessary but not sufficient to generate gamma oscillations after carbachol application. Carbachol-induced oscillations require a combination of phasic inhibition and phasic excitation. Regardless of the means of induction, the power and frequency of gamma oscillations can be modulated by substances that modify $GABA_A$ receptor gating, such as benzodiazepines and barbiturates[17,21,28]. This underscores the importance of GABA synapses in the generation of gamma oscillations.

The differences in the reliance of gamma oscillations on fast inhibitory and excitatory synaptic transmission, depending on the method of induction, can be understood in terms of synaptic connectivity and the localization of receptors that activate the network. There is an extensive system of glutamatergic recurrent collateral synapses in the CA3 but not in the CA1 region. It is therefore plausible that phasic excitation is more important in CA3 than in CA1. Furthermore, mGluRs and kainate receptors are expected to preferentially activate interneurons[21,29,30], whereas mAChRs are believed to be mainly located on principal neurons[31]. As a result, mGluR and kainate receptor models do not require phasic excitation, because interneurons are activated directly, whereas mAChR models depend on phasic excitation, as interneurons are activated indirectly by pyramidal neurons. Application of a potassium-rich solution is likely to depolarize both interneurons and principal cells, and therefore potassium-induced oscillations have intermediate properties (FIG. 1c,d).

Finally, gap junctions seem to be important for some *in vitro* forms of gamma oscillations. Carbachol-induced gamma oscillations in the CA3 region are inhibited by the non-specific gap junction blocker octanol[32], and potassium-induced gamma oscillations in the CA1 region are reduced by the presumably more specific gap junction blocker carbenoxolone[33]. In addition, kainate-induced oscillations in CA3 are reduced in connexin-36-knockout mice, in which electrical coupling between interneurons is eliminated[34,35]. So, gap junction coupling increases the power of gamma oscillations, although it is not necessary for their generation.

In summary, mGluR- and kainate-receptor-dependent forms of gamma oscillation rely exclusively on fast inhibition mediated by $GABA_A$ receptors. By contrast, mAChR-dependent types of oscillation require both fast inhibition and rapid excitation. Although the diversity of *in vitro* forms of gamma oscillation might be unsatisfying from a reductionist perspective, all of these forms are likely to be relevant *in vivo*, possibly reflecting region- and state-dependence of mechanisms underlying hippocampal gamma oscillations.

Role of basket cells in gamma oscillations

The predominant reliance of gamma activity on $GABA_A$-receptor-mediated inhibition led to the view that a network of mutually connected inhibitory interneurons is a major generator of gamma oscillations. In a simple analogy, the interneuron network acts as a clock, providing a timing signal to the principal cell ensemble[5]. But do all interneurons participate in gamma activity, or only a subset? GABA-containing interneurons are diverse and differ in their functional properties, axonal arborization and expression of molecular markers in both the hippocampus[36–39] and the neocortex[40–42]. Interneurons can be broadly classified as fast-spiking versus non-fast-spiking and soma-inhibiting (which includes basket cells) versus dendrite-inhibiting cells. Moreover, interneurons can be subdivided into largely non-overlapping sets according to the expression of calcium-binding proteins (such as parvalbumin, calretinin and calbindin) and neuropeptides (such as cholecystokinin and somatostatin)[38]. On the basis of these criteria, 16 different interneuron types have so far been distinguished in the hippocampal CA1 region[39].

Several lines of evidence indicate that fast-spiking basket cells that express parvalbumin[43] are essential for the generation of gamma oscillations both *in vivo* and *in vitro* (FIG. 2). First, parvalbumin-expressing basket cells are abundant. In the hippocampus, they represent ~20% of all GABA-containing interneurons[38]. Second, fast-spiking, parvalbumin-expressing basket cells both form an extensive, mutually connected interneuron network[44–46] (BOX 1) and have a highly divergent

Basket cells
A well-defined type of soma-inhibiting GABA-containing interneuron, so named because of its formation of perisomatic 'baskets' around target cell somata. A large subset of basket cells have a fast-spiking action potential phenotype and express the calcium-binding protein parvalbumin.

Integrate-and-fire models
Simple models of the electrical behaviour of a single neuron, which is characterized by passive integration in the subthreshold voltage range and generation of a stereotypic spike above threshold. Networks with integrate-and-fire neurons can be treated analytically.

synaptic output to principal neurons[36,47]. This means that inhibitory synapses between basket cells could synchronize action potential activity within the basket cell network, whereas inhibitory synapses between basket cells and principal neurons could distribute this synchronized activity to the principal neuron population. Third, gamma activity is associated with alternating current sources and sinks in the perisomatic region, consistent with the involvement of basket cells, which innervate this subcellular domain[12,13,23,48]. Fourth, the fast signalling properties of basket cells, particularly the fast-spiking action potential phenotype[49] and the high intrinsic resonance frequency[50], seem to be optimal for the generation of gamma oscillations. Finally, basket cells are highly active during gamma activity. Action potentials are generated at a rate of ~1 per gamma cycle and are precisely phase-locked to the oscillations[12,13,23,51–53]. This activity pattern is very different from that of principal neurons, which fire at a markedly lower rate and with less precision.

In addition to fast-spiking, parvalbumin-expressing basket cells, other types of interneuron might contribute to the generation of gamma oscillations. For example, cholecystokinin-expressing basket cells could be involved[54]. Consistent with this hypothesis, agonists of cannabinoid (CB1) receptors, known to suppress GABA release from synaptic terminals of cholecystokinin cells, reduce gamma activity *in vitro*[20]. How the relatively low abundance of these neurons, their limited connectivity[38] and the less precise transmitter release from their output synapses[55] fit into this picture remains to be clarified. Furthermore, other interneurons inhibiting the perisomatic domain (such as trilaminar cells and axo-axonic cells), interneurons inhibiting the dendritic domain (for example, bistratified cells and oriens alveus–lacunosum moleculare interneurons) and interneuron-selective interneurons might also participate in gamma activity[38,39]. Consistent with this idea is the fact that several of these subtypes of interneuron fire action potentials during carbachol- and kainate-induced oscillations *in vitro* in a phase-locked manner[23,52,53]. However, the quantitative contribution of these subtypes to the generation of gamma oscillations remains to be determined.

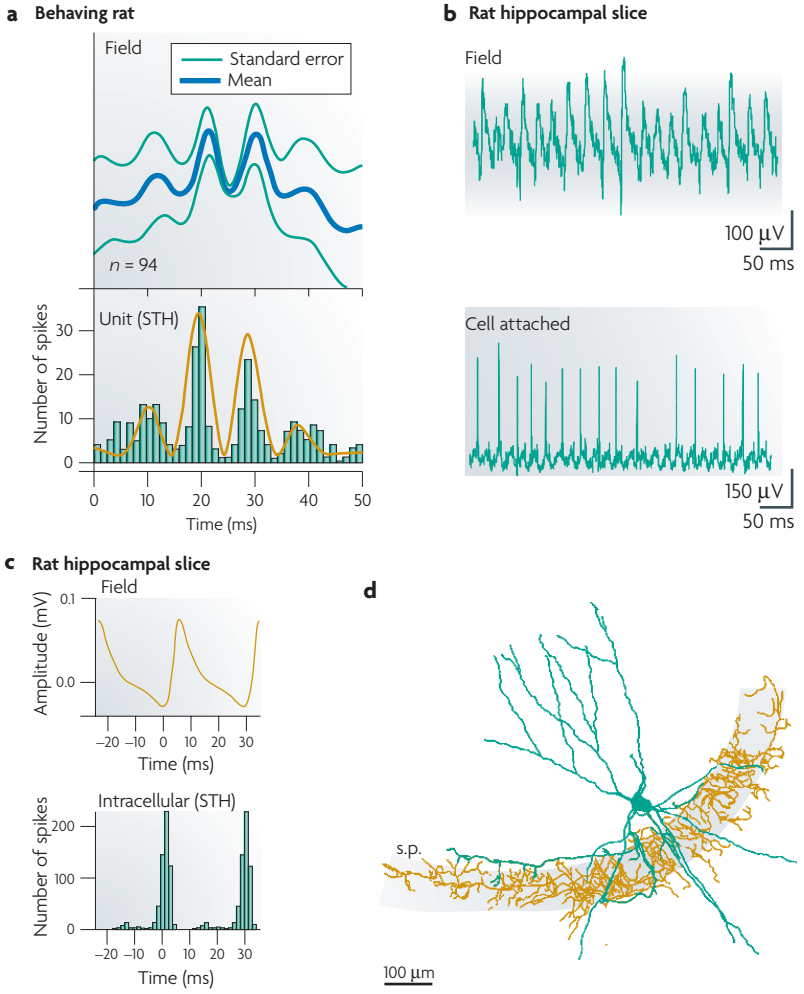

Figure 2 | **Basket cells fire action potentials that are phase-locked to gamma oscillations *in vivo* and *in vitro*. a** | *In vivo* extracellular recording from a putative hippocampal fast-spiking basket cell in the dentate gyrus in the behaving rat. Top, extracellularly recorded field potential; bottom, corresponding spike–time histogram (STH) of the recorded unit. Note that the interneuron fires at high frequency during gamma activity, phase-locked to the oscillations in the field potential. **b–d** | Cell-attached recording from an anatomically identified basket cell in the hippocampal CA3 region *in vitro* during carbachol-induced gamma oscillations. Panel **b** shows a field-potential recording (top) and corresponding action potentials (bottom). Panel **c** shows the average field potential (top) and corresponding spike–time histogram (bottom). Panel **d** shows the morphology of the recorded basket cell. Note the characteristic axonal arborization in stratum pyramidale (s.p.). Panel **a** reproduced, with permission, from REF. 12 © (1995) Society for Neurosicence. Panels **b–d** reproduced, with permission, from REF. 52 © (2005) Society for Neuroscience.

Build it, and you understand it?

How can networks of inhibitory cells generate synchronized gamma oscillations? One way to address this question is to follow Hopfield's suggestion: "build it, and you understand it"[56], and to develop network models.

The simplest possible model is a system of two synaptically connected neurons[57–62]. If single neurons are described by integrate-and-fire models[63] their synchronization properties can be determined analytically. In such a two-cell model, if the synaptic effects are instantaneous, excitatory coupling synchronizes the neurons very efficiently[59,64]. However, if the synaptic events rise more slowly (a biologically more plausible scenario), mutual inhibition is the better synchronizing mechanism[59]. Does this conclusion also hold in more complex systems with a larger number of neurons represented by conductance-based models[63]? Several studies have investigated the oscillatory behaviour of larger interneuron networks numerically[60,65,66]. These models made the general assumptions that inhibition between interneurons is slow, weak and hyperpolarizing, and that the network is homogeneous. Furthermore, network structure was not implemented. All of these studies concluded that inhibitory interneuron networks can generate coherent oscillations in the gamma frequency range if the neurons are exposed to a tonic excitatory drive[60,65,66]. Coherent oscillations are also generated if a random train of phasic excitatory events, instead of a tonic drive, is used to activate the network[67,68].

Box 1 | **Structure and delays in interneuron networks**

One way to obtain quantitative estimates of synaptic connectivity in inhibitory interneuron networks is to use paired recordings *in vitro* to probe connection probability. However, errors in the estimate will arise from the testing of closely spaced pairs of neurons (leading to overestimation) and from severing interneuron axons during the slicing procedure (leading to underestimation). Connectivity can be estimated anatomically by labelling an interneuron and counting either the number of output synapses and target cells of the same type (divergence)[44,45] or the number of input synapses from neurons of the same type (convergence)[46]; in the latter case, the number of contacts per connection has to be determined independently. A parvalbumin-expressing basket cell in the CA1 region labelled with biocytin provides a divergent output to 60 other parvalbumin-expressing basket cells[44]. A parvalbumin-expressing basket cell in the CA1 region identified by immunolabelling receives convergent input from ~360 parvalbumin-positive synaptic boutons ($868 \times 27.6\%$ (dendrites) + $177 \times 70\%$ (soma))[46]. Assuming three contacts per connection[75], the numbers obtained by the two approaches are comparable, as expected for a network with one type of neuron. Parvalbumin-expressing basket cells in the visual cortex have been found to provide divergent output to between 33 and 58 other parvalbumin-expressing basket cells[45].

Even if quantitative estimates of convergence and divergence are available, the precise structural rules of connectivity are unknown. Accordingly, assumptions have to be made when interneuron networks are assembled. The simplest assumption is all-to-all connectivity. However, given the morphological properties of interneuron axons, this seems to be too simple. Alternative rules are:

- Random connectivity with constant[65] or distance-dependent connection probability[68,76].
- A small number of long-range connections, which leads to a 'small world' network structure[118,119]. For interneuron networks, such a rule is based on interneuron subtypes with long-range projections[120–122].

In a structured network, distances between neurons correspond to delays in synaptic transmission. In interneuron network models, instantaneous inhibition fails to generate synchronization[59,123], and slowly rising inhibition without delay leads to only moderate synchronization[59,65]. However, if short delays are introduced and combined with rapidly rising and decaying inhibitory postsynaptic conductances, network coherence is substantially increased[67,76]. Delays also influence network frequency; it is reduced by longer delays and increased by shorter delays. This indicates that the preferred oscillation frequency of interneuron networks might be partly hard-wired[67,110].

Connectivity is a critical factor for the generation of gamma oscillations in interneuron networks[65]. Convergence increases compound conductances in target cells, whereas divergence enhances the spread of synchrony from a small subpopulation to a larger population.

As with many models, however, the devil is in the detail. In the original models, such as the Wang–Buzsáki (W–B) model, synchronization is sensitive to changes in kinetics of the synaptic conductance, connectivity and synaptic reversal potential[65]. Furthermore, synchronization is extremely sensitive to heterogeneity in the tonic excitatory drive[60,65]. Heterogeneity in the tonic excitatory drive translates into variability in the intrinsic action potential frequency, because of the monotonic relationship between firing frequency and driving current[65,69]. Therefore, heterogeneity in the drive will desynchronize the network. In the W–B network model, synchronized oscillations are abolished if the coefficient of variation of the tonic excitatory drive exceeds ~5% (REF. 65). However, the requirement for minimal heterogeneity is inconsistent with experimental data. Although activation of mGluRs and kainate receptors efficiently induces gamma oscillations *in vitro*[17,21], the corresponding tonic excitatory currents in interneurons are highly variable[21,30,70]. For example, the coefficient of variation of mGluR responses in fast-spiking CA1 interneurons is ~35% (REF. 30).

Conductance-based models
Models of the electrical behaviour of a single neuron in which active and passive properties are represented by voltage-dependent and leak conductances. The voltage dependency of sodium and potassium conductances, in turn, is often described in terms of Hodgkin–Huxley equations. Networks with conductance-based neurons require numerical analysis.

In the interneuron network models, robustness against heterogeneity can be improved substantially by incorporating fast and strong rather than slow and weak inhibitory synapses[71]. However, under these conditions a large excitatory drive is needed to counterbalance the increased inhibition[71]. Robustness against heterogeneity can be also increased by combining strong coupling with noise. In this case, interneurons fire stochastically during a small proportion of gamma cycles, leading to a weak synchronization regime[66,72]. However, whereas weak stochastic synchronization is compatible with low-frequency firing of principal neurons, it is not consistent with high-frequency firing of interneurons during gamma activity *in vivo* or *in vitro*[12,13,23,51–53] (FIG. 2). Furthermore, weak stochastic synchronization seems to be sensitive to randomness in network connectivity[73].

In conclusion, interneuron network models based on mutual inhibition can generate gamma oscillations. However, oscillatory activity in these models is highly sensitive to heterogeneity in the tonic excitatory drive. Furthermore, it is not clear how the model assumptions compare to the properties of basket cell–basket cell synapses in biological networks.

Fast inhibition between basket cells

The ideal experimental strategy to address whether the properties of synapses between basket cells are consistent with the assumptions of network models is paired recording in acute brain slices. This approach has two main advantages. First, it allows the experimenter to record unitary inhibitory postsynaptic potentials and inhibitory postsynaptic currents (unitary IPSPs and IPSCs), which, unlike compound IPSPs and IPSCs, are generated by the activity of a single presynaptic neuron. Second, if combined with biocytin labelling, paired recording allows the researcher to identify the presynaptic interneuron on the basis of its morphological properties and expression of molecular markers.

Paired recording experiments in acute slices *in vitro* have shown that basket cells are highly interconnected in both the hippocampus[74–76] and the neocortex[41,77–80]. For example, the probability of finding a chemical synaptic coupling between two closely spaced fast-spiking, parvalbumin-expressing basket cells in the dentate gyrus is ~50% (M.B., unpublished observations). An independent estimate of connectivity was obtained by neuroanatomical approaches, indicating that each parvalbumin-positive basket cell is connected to at least 60 other basket cells (BOX 1).

Furthermore, paired recording analysis showed that synapses between basket cells have specialized functional properties (FIG. 3). First, evoked $GABA_A$-receptor-mediated IPSCs in these cells show surprisingly rapid kinetics[75,76]. After a delay, caused by axonal action potential propagation (conduction delay) and transmitter release (synaptic delay; BOX 1), IPSCs rise almost instantaneously and decay with a time constant of ~2 ms at near-physiological temperature[75]. Fast inhibition is target-cell specific. IPSCs at basket cell–basket cell synapses are about twice as fast as IPSCs at basket cell–principal neuron synapses[75,76,81]. In addition, fast inhibition is region-independent, suggesting

that it represents a general principle of basket cell operation. Fast signalling at basket cell–basket cell synapses has been observed in all hippocampal subfields[76] and also occurs at synapses between fast-spiking parvalbumin-expressing interneurons in the neocortex[80].

Second, evoked IPSCs have a large amplitude[75,76]. Consistent with this result, immunocytochemical analysis showed that there are approximately three times more α1 and β2/3 $GABA_A$ receptor subunits at basket cell–basket cell synapses than at basket cell–pyramidal neuron synapses in the CA1 region[82]. Although basket cell–basket cell synapses show synaptic depression, a substantial IPSC component persists even during high-frequency trains of stimuli[75,81]. Similarly, although various presynaptic receptors (for example, mGluRs and mAChRs) are present at basket cell output synapses, the extent of modulation of GABA release by these receptors is subtle[83]. Therefore, synaptic transmission at basket cell–basket cell synapses shows high efficacy and stability.

Finally, there is accumulating evidence that $GABA_A$-receptor-mediated synaptic events are not hyperpolarizing, but 'shunting'[84,85] (BOX 2). In GABA-containing interneurons of the hippocampus, neocortex and cerebellum, the reversal potentials of single evoked IPSCs measured using gramicidin perforated-patch recording are between the resting potential and the action potential threshold[68,86,87]. In dentate gyrus basket cells, for example, the mean synaptic reversal potential is –52 mV (the resting potential is –59 mV and the threshold ~–40 mV)[68]. Network activity might induce intracellular accumulation of chloride and downregulation of chloride extrusion, which, in turn, would result in a further shift of the synaptic reversal potential in the depolarizing direction[88].

In conclusion, basket cells are extensively interconnected by GABA synapses, as implemented in previous interneuron network models. However, inhibition at synapses between basket cells is not slow, weak and hyperpolarizing but fast, strong and shunting, in contrast to the assumptions of these models.

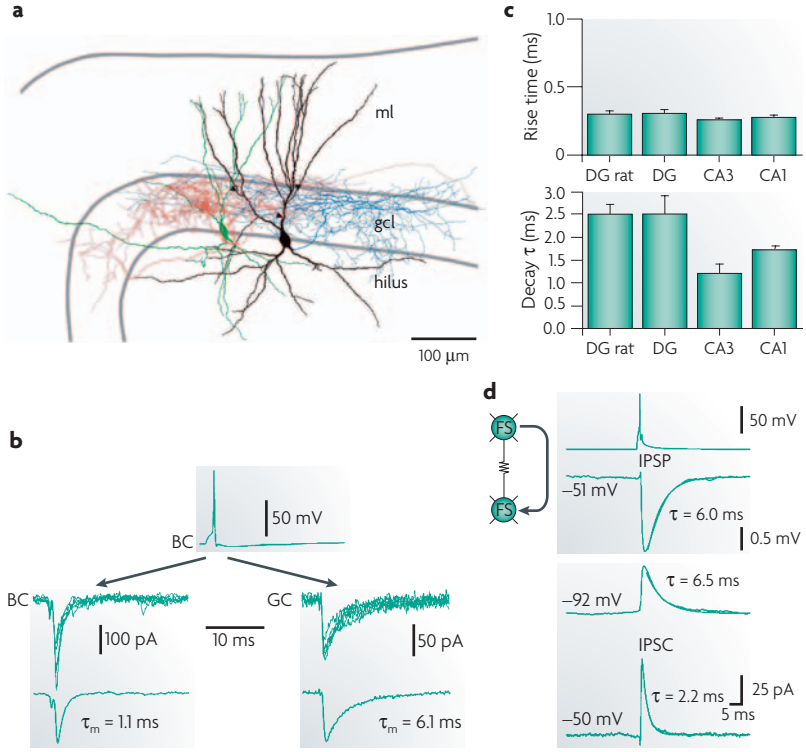

Figure 3 | **Functional specialization of GABA-mediated synaptic transmission in cortical interneuron networks *in vitro*. a** | *Camera lucida* reconstruction of a synaptically connected pair of basket cells in the dentate gyrus in a rat brain slice *in vitro*. Green indicates soma and dendrites of a presynaptic cell; red indicates axons of a presynaptic cell; black indicates soma and dendrites of a postsynaptic cell; blue indicates axons of a postsynaptic cell. Arrowheads indicate three synaptic contacts confirmed by electron microscopy. ml, molecular layer; gcl, granule cell layer. **b** | Fast, target-cell-specific inhibition at hippocampal basket cell (BC)–basket cell synapses at near-physiological temperature. Sequential triple recording from a presynaptic basket cell (top) and a postsynaptic basket cell (left) versus a postsynaptic granule cell (GC) (right). Because a chloride-rich intracellular solution was used for recording, inhibitory postsynaptic currents (IPSCs) are inwardly directed. Note the difference in IPSC kinetics between the basket cell and the granule cell. **c** | Fast inhibition at basket cell–basket cell synapses is region- and species-independent. Rise time and decay time constant of IPSCs at pairs between anatomically identified basket cells in the rat dentate gyrus (DG) and parvalbumin-expressing basket cells in the mouse dentate gyrus, CA3 and CA1 regions *in vitro* transgenically labelled by enhanced green fluorescent protein (EGFP). Bar graphs based on data from REFS 75,76. **d** | Fast inhibition at synapses between fast-spiking (FS), parvalbumin-expressing interneurons in the neocortex. Top trace, presynaptic action potential; centre traces, inhibitory postsynaptic potentials (IPSPs) at two different holding potentials; bottom trace, IPSC. Note the early components in the postsynaptic current of basket cell–basket cell pairs (**b**, left and **d**, bottom) generated by electrical coupling. Panels **a** and **b** reproduced, with permission, from REF. 75 © (2001) Society for Neuroscience. Panel **d** reproduced, with permission, from REF. 80 © (2002) National Academy of Sciences.

Models with fast, strong and shunting synapses

Do fast, strong, and shunting inhibitory synapses support synchronization in interneuron network models? In the absence of delays, they do not: interneuron networks with fast, strong and shunting synapses generate gamma oscillations with only low coherence under these conditions (FIG. 4). However, if delays (BOX 1) are introduced as a corollary of network structure (conduction delay) and synaptic properties (synaptic delay), the oscillatory behaviour of the network changes substantially[67,76]. In the presence of short delays, fast inhibition consistently supports synchronization, independently of whether delays are assumed to be constant[67,75] (FIG. 4) or distance-dependent[68,76] (FIG. 5). The high level of synchrony in this scenario is understandable, as a rapid inhibitory synaptic event generated after a short delay is a maximally effective synchronizing signal. It precisely defines an early time interval without inhibition and a late time interval with strong inhibition. Accordingly, temporal windows of firing and suppression follow in an alternating manner.

Early work emphasized that synchronization in interneuron network models can work only if inhibition is hyperpolarizing[65]. The conclusion that shunting inhibition (BOX 2) does not support synchronization has also been reached on theoretical grounds for models of two weakly coupled oscillators by phase–response analysis[58,61,62]. However, if shunting inhibition is incorporated into a multi-cell network with delays and fast synapses, coherent oscillations are generated, independently of the properties of active conductances in the neurons[68].

Box 2 | **How shunting inhibition promotes synchronization**

There is accumulating evidence that inhibition is not hyperpolarizing, but 'shunting' in various neurons, including GABA (γ-aminobutyric acid)-containing interneurons[68,84–87,124]. The nature of inhibition is defined by the reversal potential of the $GABA_A$ (GABA type A) receptor-mediated synaptic current (E_{syn}). Three regimes have to be considered:

- A hyperpolarizing regime, in which E_{syn} < resting membrane potential (rmp).
- A shunting regime, in which rmp ≤ E_{syn} < action potential threshold (thres).
- An excitatory regime in which E_{syn} ≥ thres.

$GABA_A$ receptors, which mediate fast inhibitory synaptic transmission, have high permeability to chloride but low permeability to other anions, including bicarbonate[125]. Therefore, the synaptic reversal potential is mainly determined by the chloride concentration gradient. The intracellular chloride concentration of neurons is primarily regulated by the activity of two transporters — the Na^+–K^+–$2Cl^-$ cotransporter 1 (NKCC1) and the K^+–Cl^- cotransporter 2 (KCC2). NKCC1 pumps chloride into neurons, whereas KCC2 removes it. Accordingly, the intracellular chloride concentration is determined by the expression ratio of these two transporters. In principal neurons, inhibition is depolarizing early in development[126], and later becomes shunting or hyperpolarizing, presumably because KCC2 is upregulated and NKCC1 is downregulated. By contrast, in interneurons inhibition remains shunting during development[68,127].

The somatodendritic integration rules for shunting inhibition differ from those for hyperpolarizing inhibition[124]. The effect of shunting GABA synapses consists of two temporal phases. In the first phase, the synaptic conductance leads to a reduction in the excitability of the cell, despite the concurrent depolarization. In the second phase, when the conductance has decayed but the membrane depolarization persists, excitability is increased. The contribution of the two temporal phases further depends on spatial factors[124]. If a shunting GABA synapse is close to the action potential initiation site, both phases are relevant. By contrast, if the shunting GABA synapse is remote from the action potential initiation site, only the second depolarization phase is significant, because the depolarization, but not the conductance, propagates electrotonically. Therefore, in this case, shunting inhibition can be purely excitatory.

Models based on shunting inhibition generate coherent gamma oscillations in a large region of the parameter space of mean tonic excitatory drive (I_μ) and synaptic peak conductance (g_{syn}; FIG. 5b), also covering experimental estimates of g_{syn}. Furthermore, they generate oscillations with greatly increased robustness against heterogeneity in the tonic excitatory drive. In comparison to the interneuron networks based on slow, weak and hyperpolarizing synapses, networks with fast, strong and shunting synapses tolerate a tenfold higher level of heterogeneity, up to ~70% (FIG. 5c). In addition, interneuron networks with shunting synapses require a smaller tonic excitatory drive and show less suppression of firing[68].

Why are interneuron network models with shunting inhibitory synapses highly robust against heterogeneity? Shunting inhibition consists of an early, conductance-dominated phase and a late, depolarization-dominated phase. At high levels of excitation the first phase dominates, shifting the subsequent action potential to later times. At low levels of excitation, the second phase acts to advance the following action potential. Therefore, shunting inhibition has differential, excitation-level-dependent effects on action potential timing. At the network level, this results in homogenization of action potential frequencies, which counterbalances the heterogeneity in the tonic excitatory drive[68]. This mechanism could also stabilize oscillations in heterogeneous networks comprising several interneuron subtypes.

Tonic excitatory drive
Constant current or conductance that depolarizes neurons in network models above threshold, mimicking activation by mGluR agonists and other stimuli during experiments. The tonic excitatory drive can be either homogeneous (neurons receive the same drive) or heterogeneous (neurons receive different drives, with heterogeneity being quantified by a coefficient of variation).

Unitary IPSPs and IPSCs
Synaptic events generated by the activity of a single presynaptic neuron. IPSPs are measured under current-clamp conditions and IPSCs are measured under voltage-clamp conditions.

In conclusion, an interneuron network model based on fast, strong and shunting synapses as well as synaptic delays is an efficient gamma frequency oscillator (FIG. 6). Furthermore, such a model tolerates a substantial level of heterogeneity in the drive. The model might depict forms of *in vitro* gamma activity that are independent of phasic excitation, such as mGluR-mediated gamma activity in CA1 or kainate-induced gamma activity in CA3 (REFS 17,21). Moreover, it might describe *in vivo* gamma activity under conditions in which principal cell activity is low.

Fast interneuron excitation

In the original interneuron network models, the tonic excitatory drive was the only source of excitation provided to the network[65]. However, other forms of excitation might be relevant, both *in vivo* and *in vitro*.

Paired recording experiments have identified two distinct forms of fast interneuron excitation. One form originates from other interneurons and is mediated by electrical coupling. Studies with electron microscopy first suggested the existence of electrical synapses between GABA-containing interneurons (in particular parvalbumin-expressing subtypes) throughout the cortex[78,89,90]. Subsequently, paired recording was used to directly reveal that interneurons are coupled by electrical synapses[75,76,78,79,91,92]. Electrical coupling is interneuron specific. It occurs in pairs of interneurons, but is not found between interneurons and principal neurons or between principal cells, although dye coupling of pyramidal cells at axo-axonic sites has been demonstrated[93]. The probability of finding electrical coupling between interneurons varies between ~20% and close to 100%, presumably depending on cell type, age and modulatory state[92].

Because gap junctions are resistive elements, slow depolarizations or hyperpolarizations evoked by long current pulses efficiently propagate across them. Using long pulses, the coupling coefficient (that is, the ratio of postsynaptic to presynaptic voltage change) is estimated to be between 2% and 11% (REFS 76,79,91,94). Action potentials also propagate across gap junctions, resulting in the generation of attenuated and filtered postsynaptic responses known as 'spikelets'. Unlike chemical synaptic events, which are characterized by synaptic delay, amplitude fluctuation and multiple-pulse depression or facilitation, spikelets show minimal delay and constant amplitude[75,76,79,91]. Electrical coupling between interneurons is abolished by gap junction blockers such as octanol[91] and is absent in connexin-36-knockout mice[34,95], indicating that it is largely mediated by connexin-36.

Another more conventional form of interneuron excitation is mediated by glutamatergic synapses formed by local and remote principal neurons. Synaptic transmission between local principal neurons and interneurons was extensively studied by paired recordings at granule cell–basket cell synapses in the dentate gyrus[96] and at pyramidal neuron–interneuron synapses in CA1, CA3 and the neocortex[97–103]. The probability of finding a synaptic connection is markedly lower for principal

Compound IPSPs and IPSCs
Synaptic events generated by a population of presynaptic neurons, for example, evoked by stimulation of multiple presynaptic axons or synchronized activity in an interneuron network. The compound conductance is the convolution of the unitary conductance and the distribution of spike times and delays. Therefore, compound conductances have a slower time course than unitary conductances.

neuron–interneuron pairs (less than 10%)[96,99] than for interneuron–interneuron pairs. However, the convergence is high, because of the large number of principal cells. Furthermore, effective connectivity might be enhanced by electrical connections between axons of principal cells[32,93].

Principal neuron–interneuron synapses, like the majority of glutamatergic synapses, rely mainly on AMPA receptors. However, their functional properties are highly specialized. First, unitary excitatory postsynaptic potentials (EPSPs) and excitatory postsynaptic currents (EPSCs) have a rapid time course. For example, EPSCs generated at granule cell–basket cell synapses rise almost instantaneously and decay with a time constant of ~1 ms at near-physiological temperature[96,104]. Fast excitation is target cell-specific — EPSCs at granule cell–basket cell synapses are approximately twice as fast as EPSCs at granule cell–principal neuron synapses[96,105]. Fast excitation also occurs at synapses between pyramidal neurons and fast-spiking interneurons in the neocortex[102,103], indicating that this is a general phenomenon.

Second, glutamatergic synapses on interneurons are stronger than those on principal neurons. In the CA3 region, a unitary synaptic event can be sufficient to drive the postsynaptic interneuron to firing threshold[97,98], whereas in the dentate gyrus coincident activation of five or more synaptic inputs is necessary[96]. Consistent with a high synaptic strength, immunocytochemical analysis revealed a high density of AMPA receptor subunits at

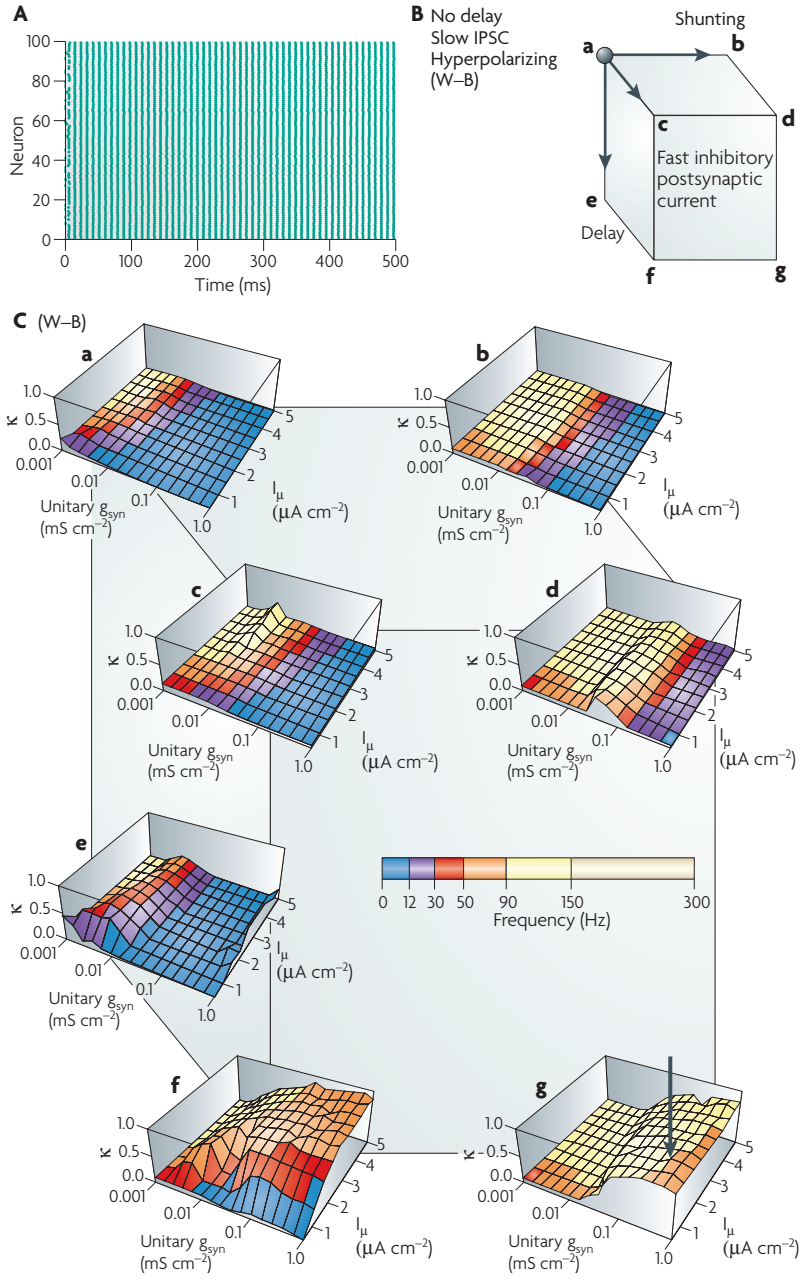

Figure 4 | **Synchronization properties of interneuron network models.** Synaptic delays, fast kinetics and shunting effects of inhibition promote gamma oscillations in interneuron network models. Simulations closely follow the procedures and assumptions of Wang and Buzsáki (W–B)[65]. Presentation of results is similar to those of previous publications[68,76]. For each parameter set, the network was initially in an asynchronous state. Synchrony was quantified as coherence (κ) during the last 100 ms of a 500-ms simulation period. Several simulations were run using different values of unitary synaptic peak conductance (g_{syn}) and mean tonic excitatory drive (I_μ), and three-dimensional plots of κ against g_{syn} and I_μ were generated. Finally, several κ–g_{syn}–I_μ plots were made, modifying the original W–B model by increasing synaptic delay (from 0 ms to 1 ms), decreasing the decay time constant of the postsynaptic conductance (from 10 ms to 2 ms), and shifting the synaptic reversal potential (from –75 mV (hyperpolarizing) to –55 mV (shunting)). All simulations were carried out using an unstructured model with 100 neurons. The connection probability was 0.6 and the coefficient of variation of the tonic excitatory drive (I_σ/I_μ) was 3%; gap junctions were not incorporated. Each κ–g_{syn}–I_μ plot shown is the average of five sets of simulations. **A** | Rasterplot illustrating synchronization in a network with delays, fast conductances and shunting inhibition during a 500-ms simulation epoch. Each dot represents an action potential. Note that the network synchronizes rapidly. **B** | Schematic illustration of the arrangement of κ–g_{syn}–I_μ plots in **C**. **C** | κ–g_{syn}–I_μ plots for various conditions, including the original W–B model. The height of the peaks corresponds to the degree of synchrony in the network, whereas the area covered by the peaks indicates the stability of oscillations against changes in g_{syn} and I_μ. The average firing frequency of the neurons is represented by a superimposed colour code; red and orange correspond to the gamma frequency band. Arrow indicates parameter settings for the rasterplot in **A**. Whereas changing a single parameter (delay, synaptic decay time constant or synaptic reversal potential) relative to the W–B model has little effect on synchrony, a combination of changes (delays + fast conductances + hyperpolarizing or shunting inhibition) substantially boosts coherence. Data are from P.J., I.V. and M.B, unpublished observations. The plots for the original W–B model (**Ca**) and the model with delays, fast conductances and hyperpolarizing inhibition (**Cf**) closely reproduce published data obtained under similar conditions[65,75].

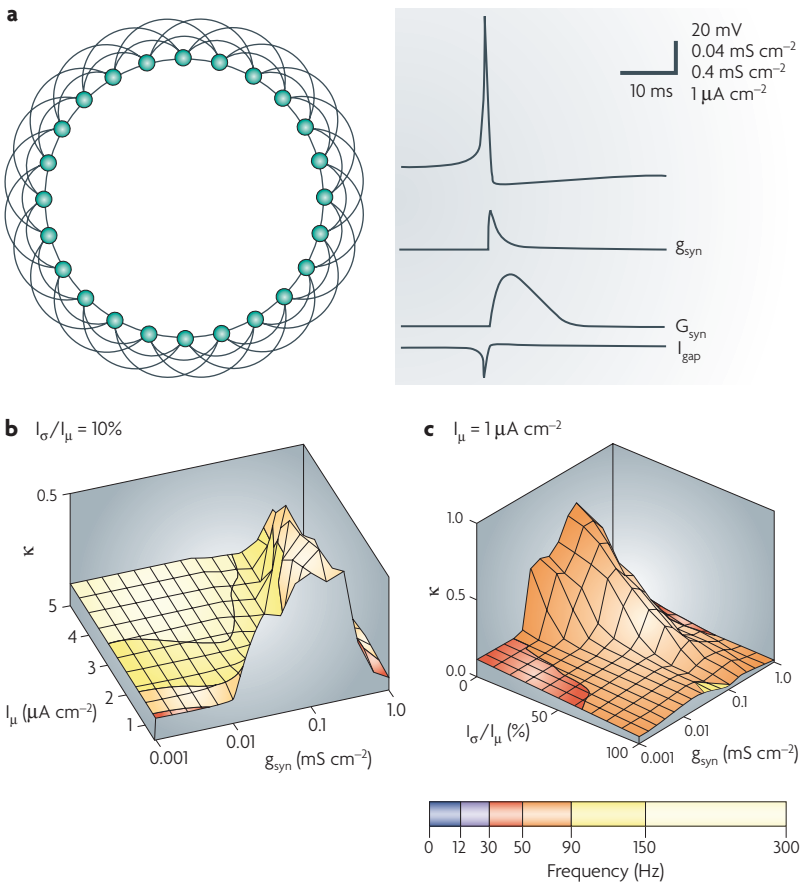

Figure 5 | **'Realistic' interneuron network models with fast, strong and shunting inhibitory synapses as well as gap junctions are optimal gamma frequency oscillators.** Illustration of synchronization properties of an interneuron network model, including network structure, fast, strong and shunting inhibitory synapses, and gap junctions. **a** | Two hundred neurons were arranged on a virtual ring. Traces on the right show, from top to bottom, simulated presynaptic action potential, unitary $GABA_A$ (GABA type A) receptor-mediated conductance (g_{syn}), compound $GABA_A$ receptor-mediated conductance in a fully synchronized network (G_{syn}), and current flowing through a single gap junction (I_{gap}). **b** | Coherence (κ) is plotted against unitary synaptic peak conductance g_{syn} and mean tonic excitatory drive I_μ. In the κ–g_{syn}–I_μ plot, the height of the peak corresponds to the degree of synchrony in the network, whereas the area covered by the peak indicates the stability of oscillations against changes in g_{syn} and I_μ. In this set of simulations, the coefficient of variation in the tonic excitatory drive (I_σ/I_μ) was 10%. **c** | κ is plotted against the coefficient of variation I_σ/I_μ (left axis) and g_{syn} (right axis). Unlike the original Wang–Buzsáki model[65], the 'realistic' network model generates synchronized oscillations with up to 70% heterogeneity. In this set of simulations, I_μ was 1 µA cm^{-2}. In **b** and **c**, average firing frequency of neurons is indicated by the colour code. Note that the peaks in both plots coincide with the gamma frequency range; red and orange correspond to the gamma frequency band. Panels **a**–**c** reproduced, with permission, from REF. 68 © (2006) Elsevier Science.

Synaptic depression
If GABA synapses are stimulated repetitively, the amplitude of the IPSCs often decreases. This phenomenon is known as paired-pulse depression (for a pair of stimuli) or multiple-pulse depression (for a train of stimuli). The opposite of depression is facilitation.

glutamatergic synapses on interneurons in both the CA3 and CA1 region (~fourfold higher than at neighbouring synapses on principal neurons)[106].

In conclusion, basket cells show two molecularly and functionally distinct mechanisms of fast excitation, one from other basket cells through gap junctions, and another from principal neurons by fast and strong glutamatergic synapses. The two forms of excitation can act synergistically, allowing interneuron networks to act as synchrony detectors[103].

Models incorporating fast excitation

How do the two forms of phasic excitation, mediated by gap junctions and glutamatergic synapses, affect synchronization in interneuron network models? In the absence of chemical synapses, gap junctions can lead to synchronized activity in network models if the tonic excitatory drive is homogeneous[61,107]. However, unrealistically high conductance and connectivity are required in the presence of a heterogeneous drive (I.V., M.B. and P.J., unpublished observations). By contrast, if gap junctions are included in combination with inhibitory synapses, synchrony is enhanced at plausible values of gap junction conductance and connectivity[33,75,76,107,108]. Unlike other parameters, such as the kinetics of synaptic conductance and delay, gap junctions selectively enhance coherence, but leave network frequency largely unchanged[76,108].

Modelling has shown that the propagation of both suprathreshold and subthreshold electrical events (including after hyperpolarizations) is important for the synchronizing effect of gap junctions[33]. Transmission of suprathreshold components of action potentials across gap junctions generates an immediate depolarization in a coupled neuron, synchronizing spike initiation. Furthermore, propagation of subthreshold voltages through gap junctions constitutes a homogenization mechanism for interspike interval voltage trajectories and, therefore, firing rates in the network[108]. So, gap junctions between interneurons can stabilize coherent gamma oscillations, although they are neither necessary nor sufficient for their generation.

Similarly, how does fast excitation by glutamatergic synapses affect synchronization in interneuron network models? A full incorporation of excitation introduces several additional free parameters into the model, which need to be constrained by anatomical and functional experimental data. A two-population model of principal neurons (PNs) and interneurons (INs) contains four types of chemical synapse (IN–IN, PN–IN, IN–PN and PN–PN synapses). In addition, electrical synapses (for example, IN–IN and presumably PN–PN synapses via axo-axonic gap junctions[93,109]) have to be considered. Although the full model is extremely complex, two limiting cases have been defined. In the first case, in which only chemical IN–IN and IN–PN synapses are present, the behaviour of the PN–IN network approaches that of the pure interneuron network. In the second case, in which only PN–IN and IN–PN synapses are included, the behaviour of the PN–IN network approaches that of a modified interneuron network, in which short-delay, monosynaptic inhibitory connections (IN–IN) are replaced by long-delay, disynaptic inhibitory connections (PN–IN–PN)[67,110]. Under these circumstances, long delays reduce network frequency[67,76,110].

How does the full PN–IN network model behave between these extreme scenarios? Although information is limited, the available modelling results indicate that the oscillatory properties often reflect a compromise between the limiting cases[110]. Furthermore, two specific functions of PN–IN synapses have been pinpointed. First, excitatory PN–IN synapses increase the synchrony of firing of interneurons in an extended network model;

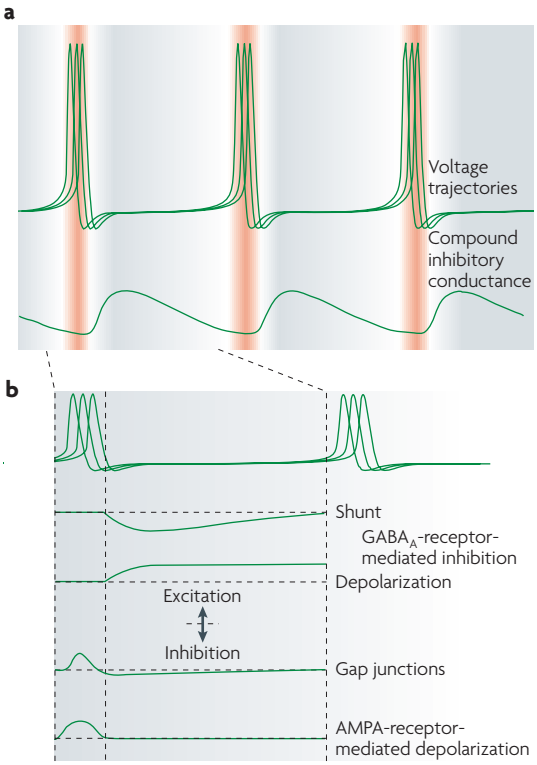

Figure 6 | **Several synaptic mechanisms underlie synchronization in interneuron networks during gamma oscillations.** Schematic summary of the contribution of different synaptic mechanisms to synchronization in oscillating interneuron networks. **a** | Voltage trajectories in three representative neurons and mean $GABA_A$ (GABA type A)-receptor-mediated compound inhibitory conductance in an oscillating interneuron network[68]. Temporal windows of high excitability (red) and low excitability (grey) follow in an alternating manner. **b** | Expanded view of one oscillation cycle, plotted together with the corresponding effects of $GABA_A$-receptor-mediated shunt, $GABA_A$-receptor-mediated depolarization, gap junction coupling, and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-receptor-mediated depolarization (positive values, excitatory effect; negative values, inhibitory effect; arbitrary scaling in vertical direction). Note that the $GABA_A$-receptor-mediated shunt defines windows of low excitability, whereas the other three mechanisms define windows of high excitability.

however, the effect is less pronounced with shunting than with hyperpolarizing inhibition at IN–IN synapses (I.V., M.B. and P.J., unpublished observations). This suggests that the excitation at PN–IN synapses and the depolarizing phase of shunting inhibition at IN–IN synapses have equivalent functions in the generation of gamma oscillations. Second, excitatory PN–IN synapses help to convert local synchrony into global (long range) synchrony. In Traub's model of PN–IN networks, they do so by triggering spike doublets in interneurons[28,111].

In summary, both gap junctions and PN–IN synapses promote synchronization (FIG. 6). Gap junctions between interneurons selectively increase coherence, whereas PN–IN synapses both increase coherence and reduce network frequency. The full PN–IN network model might describe *in vitro* gamma activity that depends on phasic excitation, such as mAChR-dependent gamma activity in CA3 (REFS 18,19) and *in vivo* gamma activity under conditions of elevated and synchronized principal cell activity. Intriguingly, the full PN–IN network model can reproduce the activity pattern that is seen in interneurons (high frequency and high coherence) and principal cells (low frequency and low coherence; I.V., M.B. and P.J., unpublished observations) during gamma oscillations *in vitro* and *in vivo*. However, additional theoretical studies will be needed to understand the complex interactions between different types of neuron in the full network.

Perspectives

Both experimental and theoretical evidence indicate that specialized synaptic properties support the generation of gamma oscillations by networks of interneurons. However, although our understanding of oscillatory activity in the brain has advanced substantially, several fundamental questions remain unanswered. How does interneuron diversity, such as the presence of cholecystokinin-expressing basket cells and dendrite-inhibiting interneurons, affect oscillatory activity[54,112,113]? What are the primary synaptic interactions in oscillating networks *in vivo* and *in vitro* (for example, IN–IN versus PN–IN–PN)? Which *in vitro* model of gamma oscillations is the 'right' one? Or, alternatively, are all *in vitro* models relevant *in vivo* as various mechanisms are used in a region- and state-dependent manner? Can the mechanisms of oscillations be extrapolated from the hippocampus to other brain regions? And, finally, what is the functional role of gamma oscillations in information processing in neuronal networks?

Although these questions are challenging, new strategies might provide the answers. First, high-resolution whole-cell patch-clamp recordings in the behaving rat will be useful[114]. Such measurements might resolve the inhibitory and excitatory synaptic events in both interneurons and principal cells during gamma oscillations. Second, the combination of electrophysiological and optical techniques with genetic approaches will be essential, permitting the activation, inhibition and functional modification of subsets of neurons *in vitro* and *in vivo*[115]. This strategy could be used to assess the contribution of specific interneuron subtypes to gamma oscillations. Third, simultaneous recording from a large number of individual neurons, for example, with electrode arrays, voltage-sensitive dyes or calcium indicators, will be informative[116]. This approach might be applied to probe the spatiotemporal characteristics of the synchronization process. Finally, we will have to put the pieces of the puzzle together in a synthetic manner. This must be done using a combined experimental–computational approach, based on analysis of synaptic function and connectivity, and detailed modelling of cortico-hippocampal oscillator circuits and their interactions[117]. Such an interactive experimental–computational approach, although demanding, will be a crucial test of whether we understand the dynamic behaviour of complex oscillating networks.

Gramicidin perforated-patch recording
Non-invasive whole-cell recording, in which the antibiotic gramicidin is used to obtain electrical access to the intracellular compartment. Gramicidin pores are impermeable to chloride. Therefore, the reversal potential of $GABA_A$-receptor-mediated synaptic currents can be measured without perturbation.

EPSP
Membrane depolarization of the postsynaptic neuron following excitatory input, usually measured under current clamp conditions.

EPSC
Electric current, representing ion flow across a membrane, measured under voltage-clamp conditions.

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