Trends in Neurosciences

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Spotlight

Mechanisms and implications of gamma oscillation plasticity

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A recent study by Hadler and colleagues uncovered a novel form of plasticity of gamma oscillations in an *ex vivo* hippocampal slice preparation which they term 'gamma potentiation'. We discuss the potential cellular mechanisms of this form of plasticity and its functional and translational implications.

Two of the most studied neurophysiological features of neural circuits are synaptic plasticity and neuronal oscillations. Plasticity is the mechanism through which brain circuits adapt to new information and experience, whereas oscillations are viewed as the 'pace-makers' that provide the temporal window to synchronise activity across different brain regions to allow efficient computations to take place. Neuronal oscillations are rhythmic patterns of electrical activity that are detected extracellularly [e.g., via local field potential (LFP) recordings or electroencephalography (EEG)] and occur across a range of frequencies, with certain frequency 'bands' associated with particular brain functions. Interplay between plasticity and oscillations has long been hypothesized. A recent study by Hadler *et al.* reveals specific facets of the link between the two phenomena, and presents evidence for activity-driven strengthening of gamma band oscillations in the hippocampus [1]. This offers a useful macroscopic measure of synaptic plasticity and raises the question of whether this form oscillation plasticity may have specific functions.

The hippocampus is widely studied for its role in memory and for exhibiting oscillatory behaviour in several different frequency bands. Theta oscillations (~4–10 Hz in rodents) are associated with spatial navigation or decision-making whereas gamma oscillations (~30–80 Hz) are observed in multiple brain regions and are associated with periods of high cognitive load. GABAergic inhibitory interneurons make up a minority of hippocampal neurons but support the generation of different neuronal oscillations, and parvalbumin (PV)-expressing interneurons play a key role in driving many, although not all, types of gamma oscillation (reviewed in [2]). Although there is ongoing debate about whether neuronal oscillations actively shape brain activity or are simply epiphenomenal, they provide a physiological proxy for particular behavioural phenotypes [3] and are emerging as a useful biomarker for a range of brain disorders including dementia [4]. Given the view that oscillations facilitate temporally precise long-range communication between brain regions, the common assumption tends to be that oscillations associated with a particular brain state are relatively stable across substantial periods of time.

Using an *ex vivo* hippocampal slice preparation, Hadler *et al.* evoked persistent gamma oscillations by bath application of kainic acid (KA) [1]. Oscillations were detected and assessed via extracellular recordings in CA3. The authors found that the oscillations persisted for around 30 minutes after washout of KA, as would be expected. Their key finding, however, was that subsequent reapplication of KA either 1 or 3 h after the initial period consistently evoked another period of persistent gamma oscillations, but this occurred at higher power (i.e., stronger amplitude) than the first epoch. The authors termed this plasticity of oscillation power 'gamma potentiation' [1]. Importantly, during gamma potentiation, a change to the power of gamma oscillations occurred but without any change to the peak frequency of the oscillation.

Gamma potentiation was found to be both activity-dependent and mediated by calcium-permeable AMPA (CP-AMPA) receptors in the study. Further investigation, using multiple approaches including neuron subtype-specific neurotransmitter receptor knockout mice, revealed that gamma potentiation is driven via PV-expressing GABAergic neurons with the involvement of mGluR1 and mGluR5 metabotropic glutamate receptor signalling via PKA and PKC pathways. Further evidence for this mechanism was inferred from chemogenetic inhibition using metabotropic DREADD (designer receptor exclusively activated by designer drugs) tools specifically in PV interneurons. This was sufficient to block gamma potentiation, while chemogenetic activation of PV interneurons with excitatory DREADDs was able to rescue gamma potentiation even in the presence of mGluR antagonists [1]. Supported by computational modelling, it was concluded that gamma potentiation is probably driven by plasticity of the pyramidal cell to PV interneuron synapse [1]. This mechanism is well supported by other studies: for example, a study from 2014 found that long-term potentiation of mossy fibre inputs onto dentate gyrus PV interneurons was dependent on both mGluR1 and mGluR5 and calcium entry via CP-AMPA receptors [5]. The study by Hadler and colleagues demonstrates that this mechanism is also present in CA3.

What further mechanisms may underlie gamma plasticity? There are two mechanisms through which a neuron can express CP-AMPA receptors: lack of Q–R editing of the GluA2 subunit, or not having a GluA2 subunit at all; PV interneurons in general have fewer GluA2-containing subunits and are enriched for AMPA receptors that contain the GluA4 subunit (reviewed in [2]). Hadler and colleagues found that gamma potentiation is activity-dependent: the immediate early protein NPTX2 (also called Narp) is released by presynaptic excitatory neurons in response to synaptic

activity and regulates the homeostatic scaling of excitatory synapses onto PV-expressing interneurons (reviewed in [2]). In earlier work it was found that NPTX2 and other neuronal pentraxins are essential for the expression of GluA4-expressing AMPA receptors on PV interneurons and that loss of pentraxins could substantially impair gamma oscillations both *ex vivo* and *in vivo,* and drive deficits in spatial memory [6]. It was also found that NPTX2 is reduced in the brains and cerebrospinal fluid (CSF) of individuals with either Alzheimer's disease [7] or schizophrenia [8]. Relevant to the present study, deleting *Nptx2* from an amyloidopathy mouse model further exacerbated deficits in gamma oscillations [7] and, similarly, loss of *Nptx2* from wild-type mice made them more susceptible to behavioural impairments driven by social isolation accompanied by perturbed gamma oscillations [8].

Evoking persistent gamma oscillations in an *ex vivo* slice is a rather artificial system, and an important question concerns whether this mechanism is present in normal physiological conditions *in vivo*. Whether it does occur *in vivo* and, if so, whether it could persist over a long period remain open questions. Although Hadler and colleagues observed a form of plasticity in the gamma oscillation, the change occurred only in power, reflecting recruitment of more neurons into the oscillation, with no change in frequency. This suggests that the 'pacing' of oscillations is not plastic, at least in this context, which would be logical for a phenomenon that is associated with the long-range synchrony of brain activity.

What are the practical implications of the form of gamma plasticity uncovered by Hadler and colleagues? Gamma potentiation may provide a useful *ex vivo* neurophysiological assay for detecting and attempting to ameliorate deficits in hippocampal network function in animal models relevant to dementia and schizophrenia, such as those mentioned in the preceding text [6,7], which are often particularly sensitive to PV interneuron function. However, might gamma plasticity be more than merely a biomarker of synaptic plasticity, and actually play a functional role in modulating brain activity? A recent study [9] found that plasticity of visual cortex responses depended on the power of oscillations in the low-gamma band (the measure that was altered in the study by Hadler *et al.*) and not on differences in neuronal firing rate, showing that gamma oscillations can regulate plasticity even if their fundamental rhythmicity may be stable. One of the few studies to determine whether the electrical field generated by oscillations can influence neuronal activity did indeed find that this was the case [10], albeit in a reduced *ex vivo* slice preparation. The use of transcranial magnetic stimulation shows that electrical fields could influence brain activity *in vivo*, but whether the endogenous field generated by oscillations influences brain activity remains an open and contentious question. Although this question is not yet settled, the notion that rhythmic network activity in general, and oscillation plasticity in particular, might play a causal role in brain function is an intriguing issue that will provide fertile ground for future research.

Declaration of interests

The authors declare no competing interests.

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References

1. Hadler, M.D. *et al.* (2024) Gamma oscillation plasticity is mediated via parvalbumin interneurons. *Sci. Adv.* 10, eadj7427
2. Pelkey, K.A. *et al.* (2017) Hippocampal GABAergic inhibitory interneurons. *Physiol. Rev.* 97, 1619–1747
3. Craig, M.T. and McBain, C.J. (2015) Navigating the circuitry of the brain's GPS system: future challenges for neurophysiologists. *Hippocampus* 25, 736–743
4. Witton, J. *et al.* (2023) Sleep-based neuronal oscillations as a physiological biomarker for Alzheimer's disease: is night time the right time? *Neural Regen. Res.* 19, 1417–1418
5. Hainmüller, T. *et al.* (2014) Joint CP-AMPA and group I mGlu receptor activation is required for synaptic plasticity in dentate gyrus fast-spiking interneurons. *Proc. Natl. Acad. Sci. U. S. A.* 111, 13211–13216
6. Pelkey, K.A. *et al.* (2015) Pentraxins coordinate excitatory synapse maturation and circuit integration of parvalbumin interneurons. *Neuron* 85, 1257–1272
7. Xiao, M.-F. *et al.* (2017) NPTX2 and cognitive dysfunction in Alzheimer's disease. *Elife* 6, e23798
8. Xiao, M.-F. *et al.* (2021) A biomarker-authenticated model of schizophrenia implicating NPTX2 loss of function. *Sci. Adv.* 7, eabf6935
9. Galuske, R.A.W. *et al.* (2019) Relation between gamma oscillations and neuronal plasticity in the visual cortex. *Proc. Natl. Acad. Sci. U. S. A.* 116, 23317–23325
10. Fröhlich, F. and McCormick, D.A. (2010) Endogenous electric fields may guide neocortical network activity. *Neuron* 67, 129–143