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A future for neuronal oscillation research

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Abstract

Neuronal oscillations represent the most obvious feature of electrical activity in the brain. They are linked in general with global brain state (awake, asleep, etc.) and specifically with organisation of neuronal outputs during sensory perception and cognitive processing. Oscillations can be generated by individual neurons on the basis of interaction between inputs and intrinsic conductances but are far more commonly seen at the local network level in populations of interconnected neurons with diverse arrays of functional properties. It is at this level that the brain's rich and diverse library of oscillatory time constants serve to temporally organise large-scale neural activity patterns. The discipline is relatively mature at the microscopic (cell, local network) level – although novel discoveries are still commonplace – but requires a far greater understanding of mesoscopic and macroscopic brain dynamics than we currently hold. Without this, extrapolation from the temporal properties of neurons and their communication strategies up to whole brain function will remain largely theoretical. However, recent advances in large-scale neuronal population recordings and more direct, higher fidelity, non-invasive measurement of whole brain function suggest much progress is just around the corner.

Keywords

Alpha, beta, coherence, cognition, cross-frequency coupling, delta, electroencephalogram, filtering, neuron, population, resonance, synapse, theta

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Introduction

Perhaps, the most obvious pattern visible in recordings from neural tissue is one of rhythmicity – a periodic fluctuation in electrical activity at frequencies ranging from fractions of 1 Hz up to a few hundreds of Hertz. Such a fundamental feature of brain activity has attracted much attention for over 100 years. But what underlies this rhythmicity? This brief review will consider the main evidence that exposes a broad range of mechanisms – from single neuronal membrane conductance complements leading to resonance, through to highly specific patterns of neuronal connectivity at the local network level and on to the temporal organisation of brain-wide responses to sensory input.

Arguably, the most important (and as yet not fully answered) question this raises is why does neural tissue behave in this way? Taken as a whole, evidence points to brain rhythms being an inescapable consequence of the array of time constants governing threshold and sub-threshold neuronal responses and the chemical and electrical synapses permitting intercommunication between population of co-active neurons. This temporal component of neuronal activity may have little observable influence on rapid, transient events such as central reflex activation. However, when sensory inputs are protracted and actions upon those inputs laborious and sequential, it results in iterative, periodic changes in activity instead of continuous activity. This has been suggested, in theory, to reduce the information content of neuronal representations. However, in massively parallel systems like the brain coding information by phase, within sets of neuronal oscillations, is tremendously efficient and powerful (McLelland and Paulsen, 2009). In fact, the spatial and temporal structure of neuronal activity, taken together, constitutes the best substrate for the functional 'engram' proposed by Lashley over 70 years ago to be the most fundamental signature of cognitive processing.

A (very) brief history of neuronal oscillation research

The early history of neuronal oscillations is inexorably linked to pioneering work that led to the discovery of the electroencephalogram (EEG) – the non-invasive recording of the brain's electrical activity from the scalp. Caton reported slow oscillatory activity (<6 Hz) from the cortical surface of laboratory animals as far back as 1875 using galvanometric recording techniques (what would now be called electrocorticography (ECoG) rather than EEG). In doing so, he became the first person to quantify neuronal oscillations and relate them to the general behavioural

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state by comparing oscillations in sleep and wakefulness. This attracted a lot of attention, culminating in the first non-invasive recordings of oscillations from human scalp by Berger. As technology improved so did the frequency bandwidth, allowing reasonable signal: noise recordings of frequencies up to ca. 50 Hz by the late 1930s (Gloor, 1969). It was these higher frequencies which appeared to relate neuronal oscillations directly to representations of sensory information in a modality-specific fashion (Adrian, 1942). During this period, a number of important tenets emerged. Dietsch demonstrated the existence of 'state-dependent', discrete frequency bands in the Fourier transform of raw EEG signals (Dietsch, 1932) – the beginnings of the classical EEG sub-bands we still refer to today (theta, alpha, beta, gamma, etc.). In addition, armed with only a small amount of knowledge of individual neuronal electrophysiology, it became clear that these signals arose from the temporally coordinated (synchronous) activity of large populations of neurons: The beginnings of the idea of neuronal oscillations representing some mechanism that allowed the concerted, temporally aligned activity of vast numbers of nerve cells and thus implicating 'time' as a dimension used by the brain to perform cognitively relevant tasks (Jasper and Andrews, 1938).

But what was synchronising the population activity? For this we need to move away from early cortical surface or scalp EEG recordings to those taken at depth from specific brain structures. Resulting local field potentials provide a relatively local picture of neuronal outputs and a slightly wider picture of neuronal inputs (up to a few millimetres). In recordings from hippocampus, Green and Arduini (1954) were arguably the first to characterise theta rhythms in the hippocampus: A discovery which ultimately led to one of the most important observations in the history of neuronal oscillation research. In the 1970s, O'Keefe and Dostrovsky (1971) demonstrated that this theta oscillation held within it patterns of neuronal spiking that were directly related to the animal's place in the environment (see Figure 1). This discovery led to much work linking neuronal oscillations, not just to the general state of arousal and sensory input as originally shown, but to the process of generating a representation of the outside world spatiotemporally coded in the activities of populations of neurons.

This concept of neuronal spike timing coding for sensory representations was taken further by the work of Wolf Singer and colleagues on the visual system (Gray and Singer, 1989). By recording the response of primary visual cortical neurons to simple visual stimuli, they noted that neurons responding to different features of the same sensory object did so synchronously and iteratively at gamma frequency. In contrast, those neurons responding to background features fired out of phase with their partners. This further accentuated the idea that the brain uses relative timing (phase-coding) to segregate related and unrelated aspects of the sensorium.

From the early work on visual sensory gamma oscillations, later more reductionist studies uncovered a mechanism for the temporal control of neuronal outputs at the local population level. In vitro models of gamma rhythms demonstrated that spike timing probability was iteratively and rhythmically modulated at gamma frequency by a form of relaxation oscillator made up of synchronous outputs from mutually interconnected populations of interneurons (Whittington et al., 1995) (Figure 1). Coupling between local networks oscillating in such a manner, using the near-ubiquitous excitatory projection motifs in the cortex, also allowed longer-range synchrony of oscillating neurons independent from finite axonal conduction delays (Traub et al., 1996).

In addition to revealing the mechanism underlying at least some forms of rhythmic temporal code in the cortex, the corpus of work on gamma rhythms was perhaps the first demonstration of the incredible usefulness of biologically realistic computational modelling in unravelling the complexities of physiological brain dynamics. This approach had been used effective previously in understanding epileptiform population events (Traub and Wong, 1982) but is now proving tremendously useful in providing both conceptual frameworks and predictions to help understand increasingly large and complex neurophysiological datasets.

The current conceptual framework

The original work on population synchrony using oscillations was expanded and refined by Fries (2005) to form the 'communication by coherence (CTC)' hypothesis. Put simplistically, the idea is anatomically and functionally distinct brain areas can work in concert by sharing information, in the form of neuronal outputs, via specific phase relationships within one or many ongoing oscillatory frequency bands. The resulting temporal organisation of neuronal outputs carries information about the nature of sensory stimuli presented (e.g. Siegel et al., 2009). This is not a million miles away from the original ideas proposed over 70 years ago (see above), but armed with the current wealth of neurophysiological knowledge it now allows for a direct relationship between global brain and local neuronal activity to be quantified.

It is clear that populations of neurons in very small regions (maybe as small as a single cortical column) can generate multiple frequencies of oscillation both concurrently and selectively depending on neuromodulatory state (Table 1). At its most basic, the CTC hypothesis implies that communication between brain regions occurs optimally if those regions all share a single frequency – a little like two people trying to communicate via two-way radio: impossible unless the same carrier frequency and mode of modulation is used. However, just as there is no canonical cortical circuit, neither is there a single mechanism for generating many cortical oscillations. The same brain area can be seen to generate different frequencies under different conditions and different brain areas can generate the same (spectrally identical) frequency under different conditions. This generates a huge degree of complexity and facilitates the routing of information through the brain in a manner dependent on relative activity levels and neuromodulatory cues in a richly diverse and controllable manner (Kirst et al., 2016).

Dynamic routing of information in the brain via neuronal oscillations can now be readily recorded non-invasively at the global level using magnetoencephalography (MEG) data and functional connectivity metrics and more locally using ever increasing large, concurrent individual unit recordings (see Figure 1(b)). Fundamentally, the process of routing is dependent on the basic mechanisms that give rise to oscillations in the first place (Kopell et al., 2010). Rhythm generation depends on the interplay between intrinsic and both chemical and electrical synaptic conductances. Different rhythms have different dependencies on the time constants ascribed to each of these

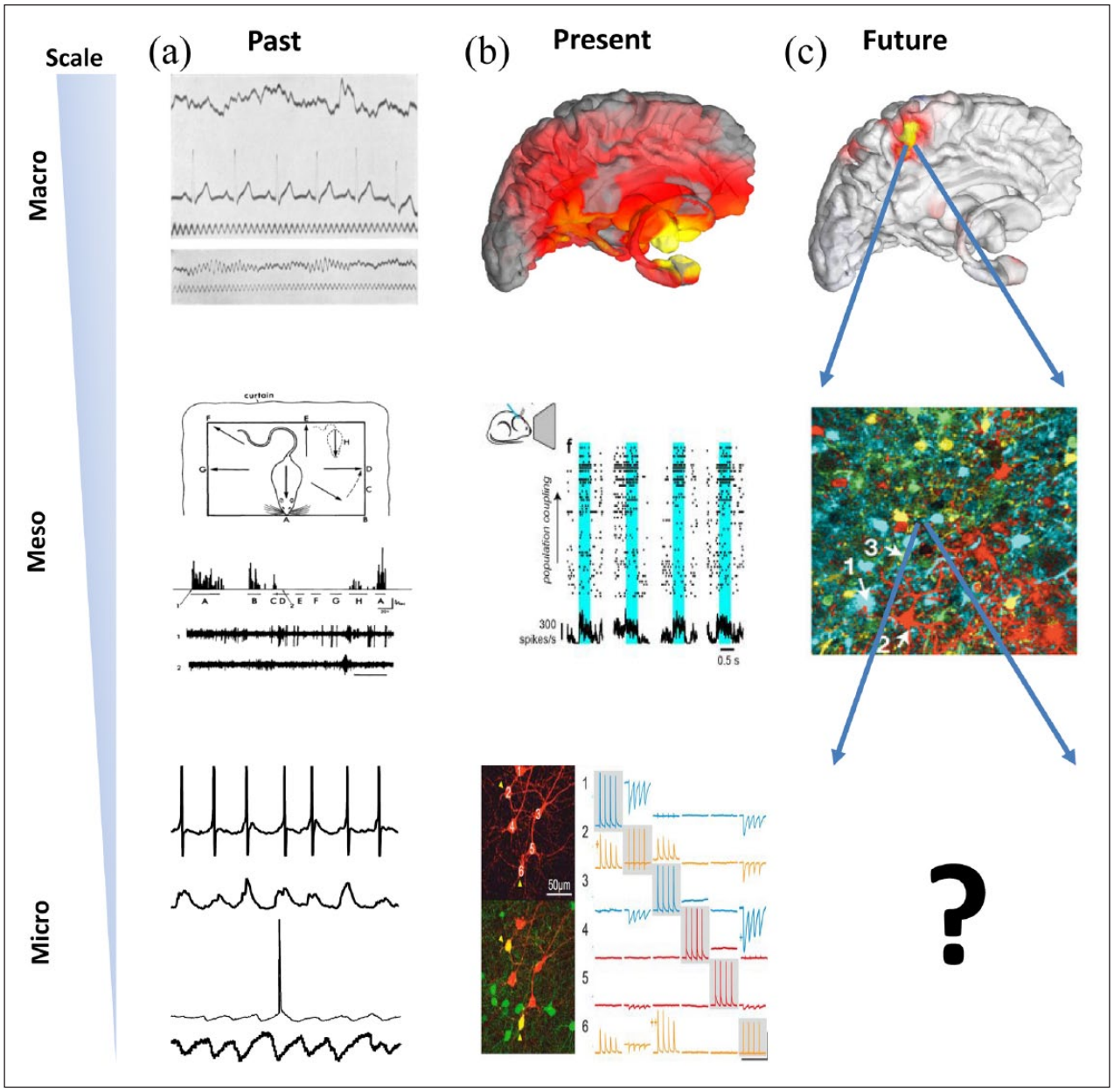

Figure 1. Recording methods used to understand neuronal oscillation mechanism and function. (a) Past – EEG dominated the early history of oscillation research. Top panel reproduces part of one of Hans Berger's original report figures. Middle panel shows the first demonstration of a link between the output of neurons, controlled by oscillations, and sensory input as recorded in vivo from hippocampus of behaving rats (O'Keefe and Dostrovsky, 1971). Bottom panel illustrates intracellular recordings from rat hippocampal neurons during an experimental model of gamma rhythms (authors' own data from 1998). (b) Present – Upper panel: EEG technology is very much still in use but for research purposes has been surpassed by MEG combined with beamforming routines to construct many multiples of concurrent recording sites non-invasively in human brain. Panel shows authors' own data illustrating the causal influence of thalamus on neocortical delta rhythms during sleep. Middle panel shows data illustrating the rich diversity of neuronal outputs in vivo in populations stimulated optogenetically (Okun et al., 2015). Bottom panel shows data from the current state of the art multi-patch technology allowing concurrent recordings from up to eight identified neurons used to quantify both multiple neuronal outputs and, more importantly, the network origins of synaptic inputs that cause them (Böhm et al., 2015). (c) Future – the largest technical problem facing oscillation research is the inability to record from many multiple neurons concurrently and non-invasively in humans. While individual regions can be functionally identified with ease (top panel), we still cannot interrogate the local networks, and their global interactions in this manner. In experimental preparations, optical recording shows the best promise so far. However, they require direct optical access to the cortex and genetic manipulation of neurons to allow a readout of changes in intracellular calcium levels (GCaMP6 as illustrated in the middle panel (Chen et al., 2013)). What is required is a near-real time, massively parallel, direct measure of neuronal inputs and outputs in humans. Where the technology to do this will come from is unknown, but there are a number of promising avenues (see text).

Table 1. Multiple oscillations, multiple mechanisms.

Frequency band	Origin	Mechanism (area, neuron subtype)
Ultra-slow (<0.2 Hz)	Neocortex, periallocortex	Kainate receptors/K_{ATP} (mEC, superficial pyramids)
Delta (0.5–4 Hz)	Neocortex, thalamus	NMDA/$GABA_B$ (parietal cortex, L5 IB, NG) $I_{T(window)}$, I_{leak}, I_h (Thalamus, TC)
Theta (5–9 Hz)	Ubiquitous in cortex, subcortical structures (e.g. MS/DBB, IO), cerebellum	mGluR, mAchR, dendrite-targeting synaptic inhibition (hippocampus/neocortex, som+ interneurons)
Alpha (9–12 Hz)	neocortex, thalamus	NR2C/D, Kv10.2 (V1, L4 pyramidal neurons), gj, mAchR (TC)
Beta1 (13–20 Hz)	Neocortex	NMDA, I_h, fast and slow synaptic inhibition (parietal ctx, L2/3 RS, L5 IB – concatenation of gamma and beta2, see text)
Beta2 (21–29 Hz)	Neocortex, hippocampus	Kainate receptors, gj, m-current (parietal cortex, L5 IB) nAchR, gj, synaptic inhibition (1° auditory cortex, L5 RS, LTS)
Gamma1 (30–50 Hz)	Cortex, cerebellum, hippocampus, nRT	Glutamatergic excitation, cholinergic neuromodulation/fast synaptic inhibition (with/without gj depending on phasic/tonic interneuron excitation) (hippocampus, pyramids, PV+ interneurons) (Neocortex L2/3, RS, FRB, PV+ interneurons)
Gamma2 (50–90 Hz)	Neocortex, periallocortex	NR2C/D, fast inhibition (1° auditory cortex, stellate cells, PV+ interneurons)
VFO/HFO (100–250 Hz)	Cortex, cerebellum, hippocampus, subcortical structures (incl. OB)	Gj between axons (hippocampus, L2/3 neocortex, pyramidal neurons)

IB: layer 5 intrinsically bursting neuron; NG: neurogliaform neuron; TC: thalamocortical neuron; som+: somatostatin immunopositive; RS: regular spiking neuron; LTS: low-threshold spiking neuron; FRB: fast rhythmic bursting neuron; gj: gap junction; PV+: parvalbumin immunopositive neuron.
A cursory list of the classical EEG bands and sub-bands where a mechanism or mechanisms have been elucidated. The frequency banding is derived from predominantly in vitro mechanistic studies and, for the most part, corresponds well with original EEG spectral definitions. Where mechanistic differences are precedented within or across bands, the mechanistically led frequency divisions are stated (Kopell et al., 2010). In stating the origin, we refer to studies which clearly identify a local generator; this does not mean any particular rhythm is *only* recordable in the above areas.

properties but, with the exception of very fast oscillations generated by gap junctional coupling, the basic phenomenon at work is one of selective filtering. Membrane potential resonances in individual neurons dictate the input–output characteristics of that cell in a stereotyped manner (Hutcheon and Yarom, 2000). Imparting resonance in local circuits (such as with shared inhibition in gamma rhythms (see above)) provides a substrate for auto-adaptive filtering which can effectively sort signal from noise and even decide which signal to respond to in a use-dependent fashion (Akam and Kullmann, 2010). It is becoming increasingly obvious that the brain possesses many such filters and has modified their response characteristics depending on the role of the regions they are present in. For example, a very rigid filter at beta frequencies is seen in parietal cortex generated in a manner that does not involve chemical synaptic transmission (Roopun et al., 2008). In contrast, in prefrontal areas where activity across many different regions of the brain converges, heterogeneous intrinsic neuronal properties combine with homogeneous inhibitory synaptic connections to provide a very loose filter for inputs (Adams et al., 2017).

While useful, filtering in a single-frequency band is highly limiting in terms of computational flexibility. But individual neurons possess a multiplicity of membrane resonances depending on which cell compartment is studied. Likewise, individual laminae in cortex have multiple, different network resonances. Interactions between different cellular and network resonant frequencies, and the mechanisms that underlie them can have dramatic effects on the timing (phase) of neuronal population outputs (Roopun et al., 2008). This provides huge theoretical scope for interplay between rhythms, with multiple examples of oscillation interactions readily recordable from neural tissue. The most obvious multiple frequency behaviour shown by the brain is 'nesting' – the amplitude modulation of one frequency according to the phase of a lower frequency. This can occur across multiple frequency bands during sensory tasks. Cross-frequency coupling is also seen, where two different frequencies of oscillation can coexist with periodic phase alignment implying that the two separate rhythm generators are functionally coupled. Perhaps, the most comprehensively understood pattern of cross-frequency interactions involves that seen between gamma and beta rhythms in parietal cortex: during activation of this brain area, both gamma and beta rhythms are seen in superficial and deep laminae, respectively. No stable phase relationship exists between the deep and superficial neurons. However, after a period of excitation, a slower beta frequency activity persists in a synaptic plasticity-dependent manner with both deep and superficial layer neurons showing a stable, fixed phase relationship. Experiments revealed the origin of this behaviour to be a form of concatenation of the original superficial and deep gamma and beta rhythms, that is, two separate frequencies interlaced (Roopun et al., 2008).

Taken as a whole, the brain has a rich array of filtering strategies at individual frequencies, and multiple, combinatorial motifs for linking temporally distributing neuronal activity across many different frequency bands. This temporal framework permits multiplexing of multiple concurrent data-streams (by phase and/or spectrally), selection of subsets of population activity by salience and combinatorial processes based on synaptic plasticity. Were this all to happen on an individual neuron-by-neuron level the computational scope of a structure with 100 billion such processing elements is mind-boggling. However, this does not appear to be the case. Many neurons anatomically local to each other appear to act in concert – without this fundamental property

of brain activity, no EEG rhythms would be recordable at all (Jasper and Andrews, 1938). In addition, the relationship between outputs of a single neuron and its local neighbours is seen to be remarkably stereotyped and invariant to sensory stimulus (Okun et al., 2015). And yet individual neurons such as the cerebellar granule cell hold in their input and output characteristics a huge range of locomotor patterns (Powell et al., 2015). These observations strongly suggest a modular functional organisation to cortex, with each module representing many thousands of local neurons. The relative outputs from such local populations, under temporal control from neuronal oscillations, would then be ideally placed to take advantage of the non-linear properties inherent in temporal summation of synaptic inputs to target areas (Ainsworth et al., 2012).

Comments on possible future directions

The reductionist approach to understanding neuronal oscillations is relatively mature. Where progress is needed is in translating the fine dynamic structure of neuronal interactions in a distributed population into a universal framework for sensory processing, cognition, affectation and motor output. Furthermore, neuronal oscillation recordings effectively link behaviourally relevant brain dynamics to molecular factors controlling excitability and connectivity. Thus, in the long term, the field needs to work towards neuron-level recordings non-invasively in the most behaviourally complex organism known – ourselves.

This goal is a long way distant. Currently, technology such as combined EEG/MEG approaches coupled with powerful analytical models has increased the spatial resolution sufficiently to interrogate regions as small as those influencing invasive local field potential recordings (ca. 1 mm) and can, at least post hoc, separate activity in superficial and deep cortical layers (Bonaiuto et al., 2018; Troebinger et al., 2014). But this still constitutes average activity of many hundreds of thousands of neurons. Combining detailed, fine spatial-scale dynamical measurements with detailed, biologically realistic computational models hold much promise. In this way, neuron-level mechanisms revealed from reductionist approaches – used to construct the models – can be applied to human brain-wide data sets. However, there are inevitable species barriers to overcome in addition to interpretational problems caused by incomplete characterisation of any particular oscillatory signature. Not least of the problems inherent in this approach is that of computational tractability. Huge resources would be needed.

In the short-term, perhaps the most promising approach to concurrently recording from large numbers of neurons in situ is the continuing development electrode microarrays (Jun et al., 2017) and of optical techniques. Although invasive and requiring genetic manipulation – thus not suitable for human subjects – optical markers for changes in intracellular calcium levels are a reasonable surrogate for direct electrical recordings when dealing with oscillations at the lower end of the EEG spectrum (Chen et al., 2013). Currently, temporal resolution is slow when recording from many neurons, and the relationship between neuronal inputs and outputs is complex, but continued improvements would have tremendous value. In the longer-term, the hunt for a truly non-invasive, neuron-level recording strategy lies with the development of novel imaging techniques. Employment of spin hyperpolarisation has been shown to increase magnetic resonance imaging (MRI) signal: noise by over four orders of magnitude (Adams et al., 2009). This alone should increase spatial and temporal resolution of fMRI recordings. However, it also opens the door to a more direct functional imaging approach: spin hyperpolarisation is exquisitely sensitive to electric fields, suggesting that the immense local potential gradient fluctuations at an active neuronal membrane surface could allow the possibility of direct measurements of neuronal inputs and outputs remotely.

In combining what we currently know with where the gaps in our knowledge are blatant, one thing is clear: there is still a long way to go before we understand enough about how large numbers of functionally disparate, interconnected neurons generate and use dynamics to control concerted, whole brain activity. Without this, we still remain a long way from fully understanding how our brains use ‘time’ to make us who we are.

Declaration of conflicting interests

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