Neuronal resonance in the theta (4-10 Hz) frequency range is modulated by dynamic changes in the input resistance

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Abstract

Most neurons of the mammalian brain display intrinsic resonance with frequency selectivity (f_R) for inputs within the theta-range (4-10 Hz). Variations in network oscillation along this range depend on the animal behavior; however, whether neurons can dynamically tune their f_R has not been addressed. Using slice electrophysiology, dynamic clamping and computer modeling we studied three types of cortical neurons, finding that the input resistance (R_{in}) inversely sets f_R into the theta range, following a power law. We demonstrate that physiological changes in R_{in} modulate f_R and response phase, serving as a mechanism that instantaneously tunes oscillatory responses. Moreover, these modulations are translated into spiking regimes, modifying spike frequency and timing. Since synaptic inputs reduce R_{in} , this modulation provides a mean for adjusting the frequency and timing of firing of individual neurons in interplay with the network fluctuations. This might be a widespread property among resonant neurons.

Introduction

Theta frequency oscillations (4-10 Hz) are observed in different brain regions associated to active sensory sampling, navigation and learning processes (Kay, 2005; Lisman & Buzsáki, 2008; Mizuseki *et al.*, 2009; Ranade *et al.*, 2013). These oscillations reflect synchronized neuronal activity spreading across different networks and support a neural code based on the frequency and timing of neural firing (Lisman and Jensen, 2013; Wilson *et al.*, 2015).

Theta activity is displayed by several brain regions and varies with time according to the behavioral state of the animal, increasing or decreasing its frequency, depending on the animal behavior (Kay, 2005; Geisler *et al.*, 2007; Ranade *et al.*, 2013; Bender *et al.*, 2015). This observation is in accordance to the emergent idea that neurons can modify their responsiveness relative to the network state (Destexhe *et al.*, 2003; Ratté *et al.*, 2013). For instance, neurons can switch their behavior to favor or hamper neural synchrony (Prescott *et al.*, 2008; Kirst *et al.*, 2017; Vera *et al.*, 2017). Thus, it is expected that variations in the frequency of the network oscillations would demand flexibility of the intrinsic activity of the neurons, in order to follow such ongoing dynamic changes.

Many cortical neurons resonate, displaying an enhanced voltage response in the theta range, strengthening input signal processing and transmission at those frequencies (Hutcheon *et al.*, 1996a; Ulrich, 2002; Hu *et al.*, 2002; Erchova *et al.*, 2004; Vera *et al.*, 2014). This intrinsic property relies on the presence of the hyperpolarization-activated cationic current (I_h) (Biel *et al.*, 2009) and/or the muscarine-sensitive current (I_M) (Shah *et al.*, 2002), that selectively reduce the low frequency (<10 Hz) voltage responses due to their slow activation/deactivation kinetics (Hutcheon and Yarom, 2000; Izhikevich, 2002).

This property can be phenomenologically described by an inductor (Mauro, 1961) that reduces not only the impedance, but also the phase-lag, which is the frequency-dependent delay of the voltage response with respect to an oscillatory stimulus. The phase-lag approaches zero at particular frequencies in the theta range (Narayanan & Johnston, 2008; Rotstein, 2014), thus functioning as a mechanism to synchronize synaptic inputs (Vaidya & Johnston, 2013).

The frequency at which the maximal impedance is observed is called resonance frequency (f_R), and is set by a combination of passive and active intrinsic membrane properties (Hutcheon & Yarom, 2000). *In vitro* experiments have shown that most resonant neurons in the

mammalian brain display f_R s between 2 and 10 Hz: isocortex (Gutfreund *et al.*, 1995; Hutcheon *et al.*, 1996a), thalamus (Puil *et al.*, 1994), hippocampus (Hu *et al.*, 2002), entorhinal cortex (Erchova *et al.*, 2004; Giocomo *et al.*, 2007), amygdala (Pape & Driesang, 1998; Vera *et al.*, 2014) and olfactory bulb (Hu *et al.*, 2016). However, it is not clear whether the differences in f_R represent variations in the resonant mechanism or are due to different experimental conditions. Previous investigations have shown that f_R can increase due to a rise in the amplitude of the I_h current, caused by the induction of long term synaptic potentiation (Narayanan & Johnston, 2007). A dynamic change in f_R is also observed during membrane depolarization (Gutfreund *et al.*, 1995; Hutcheon *et al.*, 1996a and b), however, this process has not been observed in all resonant cells (Erchova *et al.*, 2004).

One relevant parameter involved in setting f_R is the passive membrane resistance (R_m , the reciprocal of the leak conductance), that together with the membrane capacitance (C_m) sets the cut-off frequency of the low-pass filter that determines the frequency response ($f_{c_m}=1/2\pi\tau_m$, where $\tau_m=C_m*R_m$) (Hutcheon & Yarom, 2000). The presence of I_h or I_M endows resonant neurons with a high-pass filter whose cut-off frequency depends on the kinetic properties of the conductances (Hutcheon & Yarom, 2000). The combination of these two filters produces a bell-shape impedance profile that defines the frequency selectivity into the theta range, with f_R corresponding to the peak of the resulting band-pass filter (Hutcheon & Yarom, 2000). Thus, it can be expected that changes in R_m will modify the steepness of the low-pass filter, therefore shifting f_R . Moreover, changes in R_m also modify the membrane time constant, drastically altering the timing of neuronal responses (Destexhe *et al.*, 2003; Broicher *et al.*, 2012) and probably modifying the phase-lag at theta frequencies.

Measurement of R_m is hampered by the presence of I_h or I_M , whose voltage- and time-dependent activation deviate the voltage behavior from the purely passive response. Instead, we used a current pulse to measure what we refer to as input resistance (R_{in}) of a neuron, which at frequencies near zero is directly related to the total membrane conductance at steady state.

We predict that neurons with different R_{in} s would display different f_R s. Moreover, sources of R_{in} variations such as voltage-dependent and independent, as well as synaptic conductances could modify it, generating variations in the f_R and the kinetics of the responses. Whether this R_{in} dependence is relevant in setting f_R and the phase-lag of the responses in theta range has not been evaluated.

We characterized how f_R and the phase-lag depend on R_{in} in three different cortical neurons types that share the same resonant mechanism, but differ in their R_{in} range: stellate neurons from layer II of the entorhinal cortex (SL)(Erchova *et al.*, 2004), CA1 pyramidal neurons from the hippocampus (HP)(Hu *et al.*, 2002) and layer II resonant neurons of the cortical amygdala (AM)(Vera *et al.*, 2014). To evaluate frequency selectivity upon changes in R_{in} , we considered, i) the natural differences in R_{in} among cell types, ii) changes in R_{in} due to activation/deactivation of voltage-sensitive conductances upon membrane depolarization, and iii) changes in R_{in} caused by introducing virtual passive conductances by means of dynamic clamp (Dorval *et al.*, 2001).

We found that neurons exhibit a frequency selectivity that is determined by R_{in} according to a power law distribution, setting f_R values within the theta range. Moreover, variation in R_{in} alters the phase-lag curves at frequencies below 15 Hz. The relationship between f_R and R_{in} is robust for different cortical neurons, as well as for R_{in} variations within individual cells. This modulation is observed in both subthreshold and spiking regimes, modifying spike frequency and timing.

Methods

Ethical approval

Animal care and experimental procedures were approved by the Bio-Ethical Committee of the Faculty of Sciences, University of Chile, according to the ethical rules of the Biosafety Policy Manual of the National Fund for Development of Science and Technology (FONDECYT).

Slice preparation

Male Sprague Dawley rats (18 to 30 days-old) were deeply anesthetized with isoflurane, decapitated and their brain was rapidly removed and transferred to an ice-cold dissection solution containing (in mM): 206 sucrose, 2.8 KCl, 1 MgCl₂, 2 MgSO₄, 1 CaCl₂, 26 NaHCO₃, 1.12 NaH₂PO₄, 10 glucose and 0.4 ascorbic acid (equilibrated with 95% O₂ and 5% CO₂), pH 7.3. Slices (400 μm) containing the region of interest were obtained with a vibratome (Vibratome Sectioning System 102, Pelco) using standard disposable stainless steel razor blades (www.personna.com). For the anterior nucleus of the cortical amygdala we used coronal slices targeting the region between bregma -2.2 and -3.3 (Sanhueza & Bacigalupo, 2005; Vera *et al.*, 2014). For hippocampal neurons we used septotemporal slices targeting the dorsal hippocampus (Vera *et al.*, 2017), and for stellate cell we used horizontal slices to target the dorsomedial entorhinal cortex (Giocomo *et al.*, 2007). Slices were placed in a holding chamber with standard artificial cerebro-spinal fluid (ACSF) and were left to recover at least 1 h at 30°C before using them for recording.

Electrophysiological recordings

Whole cell patch-clamp recordings were conducted under visual guidance by an upright microscope (Nikon Eclipse E600FN) equipped with DIC optics. Patch pipettes (3.5–4.5 MΩ) were fabricated of borosilicate glass (0.8 - 1.10 x 100 mm; Kimble Glass Inc) using a horizontal puller (Flaming/Brown P- 97, Sutter Instrument Co). Current-clamp recordings were made with an EPC-10 patch-clamp amplifier (Heka, Heidelberg, Germany), data were filtered at 5 kHz and acquired at 40 kHz using the Patch Master software from Heka. All experiments were performed in the presence of 10 μM CNQX and 100 μM PTX, to block AMPA-R and GABA_A-R mediated currents.

Recording solutions (in mM):

Artificial cerebro-spinal solution (ACSF) contained (in mM): 124 NaCl, 2.8 KCl, 1.25 NaH₂PO₄, 26 NaHCO₃, 10 Glucose, 2 MgCl₂, 2 CaCl₂ and 0.4 ascorbic acid (equilibrated with 95% O₂ and 5% CO₂), pH 7.3 and 290 mOsm.

Internal pipette solution contained (in mM): 123 K-Gluconate, 10 KCl, 4 Glucose, 1 EGTA, 10 HEPES, 2 Na₂ATP, 0.2 Na₃GTP, 10 phosphocreatine-Na, 1 MgCl₂, 0.1 CaCl₂, pH 7.35 and 290 mOsm. This composition was based on previous works reporting stability of intrinsic excitability parameters (Xu *et al.*, 2005; Kaczorowski *et al.*, 2011), and was corroborated in investigations related to intrinsic frequency preference (Vera *et al.*, 2014, 2017). We measured the liquid junction potential (LJP) between pipette solution and ACSF (~13 mV) according to the procedure described by Neher (Neher, 1992) and used this to correct the data in offline analyses.

ZAP stimulation and data analysis

The ZAP (impedance amplitude profile) stimulus consisted in a pseudo-sinusoidal current of constant amplitude and linearly increasing frequency from 0 to 20 Hz in 10 s (ZAP stimuli). The protocol was repeated 8 to 10 times in every neuron and the membrane voltage waves were averaged for the impedance analysis. The impedance profile ($Z(f)$) and phase-lag ($\Phi(f)$) curves were obtained from the ratio of the Fast Fourier Transforms (FFT) of the output (voltage) and input (current) waves ($Z(f) = \text{FFT}[V(t)] / \text{FFT}[I(t)]$). The impedance is a complex quantity ($Z(f) = Z_{\text{Real}} + iZ_{\text{Imaginary}}$), where the real part (Z_{Real}) is the resistance and the imaginary part ($Z_{\text{Imaginary}}$), the reactance. For each given frequency, the complex impedance can be plotted as a vector whose magnitude and phase ($\Phi(f)$; angle with the real axis) are respectively given by the following expressions:

$$|Z|(f) = \sqrt{Z_{\text{Real}}^2(f) + Z_{\text{Imaginary}}^2(f)} \quad (1)$$

$$\Phi(f) = \tan^{-1} \left(\frac{Z_{\text{Imaginary}}(f)}{Z_{\text{Real}}(f)} \right) \quad (2)$$

Throughout the text the term *impedance* is used to refer to the magnitude of the impedance vector, unless otherwise stated. The impedance phase corresponds to the phase shift

of the voltage wave relative to the current wave. Frequencies below 0.2 Hz were not plotted in the impedance and phase profiles graphs, to avoid low frequency distortions.

Quantification of the resonance

Resonance is defined as the band-pass filter property of the impedance profile (Hutcheon & Yarom, 2000). The resonance strength is usually quantified as the ratio between the maximal impedance (i.e. the impedance at the resonance frequency, $|Z(f_R)|$) and the impedance at 0.5 Hz ($|Z(0.5)|$). This ratio is termed Q , and indicates the sharpness of the impedance curve around the resonance frequency. For a more precise determination of Q , the experimental data were fitted with a polynomial curve between 0.2 and 15 Hz and the peak value was calculated.

Dynamic clamp experiments

For the dynamic-clamp experiments, the current-clamp amplifier was driven by an analog signal from a dual core desktop computer running the Real-Time Experimental Interface, RTXI (Dorval et al., 2001), using an update frequency of 25 KHz.

The somatic conductance was altered by simulating a constant conductance via the dynamic clamp. The leak current was computed according to the following equation:

$$I_{Leak} = G_{Leak}(V_m - E_{Leak}) \quad (3)$$

where G_{Leak} is the evaluated leak conductance, V_m is the online recorded membrane potential and E_{Leak} is the reversal potential (set to -70 mV). To evaluate a decrease in R_{in} , $G_{Leak} > 0$; for an increase in R_{in} , $G_{Leak} < 0$.

We show dynamic currents (I_{DynC}) as the external current that was injected to neurons, following the standard convention that positive currents are depolarizing and negative currents are hyperpolarizing. Therefore,

$$I_{DynC} = -I_{Leak} \quad (4)$$

Computer simulations

We developed a minimal point process and conductance-based model following the Hodgkin-Huxley formalism (Hodgkin & Huxley, 1952). The model included a membrane capacitance (C_m), a passive leak current (I_{Leak}), the hyperpolarization-activated h current, I_h

(Richardson et al., 2003) and an external stimulating current, I_{ZAP} . The model did not include a firing mechanism (fast sodium and potassium conductances).

The equation describing the evolution of the membrane potential (V) in time is

$$C_m \frac{dV}{dt} = I_{ZAP} - I_{Leak} - I_h \quad (5)$$

where C_m is the membrane capacitance and I_{ZAP} is the externally applied current. The intrinsic ionic currents in Eq. 1 are described by the following equations:

$$I_{Leak} = G_{Leak}(V - E_{Leak}) \quad (6)$$

$$I_h = G_h f(V - E_h) \quad (7)$$

where G_{Leak} and G_h are the maximal conductances of the corresponding currents and E_{Leak} (-65 mV) and E_h (-40 mV) are the reversal potentials of I_{Leak} and I_h , respectively. f is the state variable of I_h (Spain *et al.*, 1987). For simplicity, in our minimal model we only used the fast component of I_h , which is related to theta resonance and accounts for ~80% of the total current (Spain *et al.*, 1987).

The dynamics of the state variable f is ruled by the following equation:

$$\frac{df}{dt} = \frac{f_{\infty}(V) - f}{\tau_f(V)} \quad (8)$$

where τ_f is the time constant and f_{∞} is the steady-state value of f , calculated according to:

$$f_{\infty} = \frac{1}{1 + e^{(V+78)/7}} \quad (9)$$

τ_f was set to 0.05 s, similar to the fast component described by Spain et al. (Spain *et al.*, 1987), to match the exact f_R range observed in our experiments.

We reproduced each cell type using the membrane capacitance estimated from voltage-clamp recordings (50 ms, 5 mV pulse) and the maximal conductances were tuned to obtain similar voltage responses at -80 mV (Table 1, Fig. 5). When exploring the effect of G_{Leak} , we varied its value from 1 to 80 nS.

Simulations were performed using Igor Pro 6.37 software with an integration time step of 10 μ s. The code for reproducing the computer simulations described in this paper is available upon request to authors.

Statistical analysis

The statistical analysis was performed in GraphPad Prism 6.07 (GraphPad Software, Inc, USA). Group data is presented as the mean $\pm$ standard error. We used different parametric tests for data with normal distribution (as Z_{Max} , resting potential or R_{in}). When the data structure was a

Table 1. Parameters used in (C_m , G_h and G_{Leak}) and obtained from (R_{in} , f_R , Φ_{6Hz} and Φ_{IR}) simulated neurons.

Model cell	C_m (pF)	G_h (nS)	G_{Leak} (nS)	R_{in} (M Ω)	f_R (Hz)	Φ_{6Hz} (deg)	Φ_{IR} (deg)
SL	160	$0.06 \cdot C_m$	$0.1 \cdot C_m$	30	8.9	-1.5	-10.6
HP	120	$0.025 \cdot C_m$	$0.08 \cdot C_m$	66	6.1	-13.5	-14.8
AM	80	$0.013 \cdot C_m$	$0.04 \cdot C_m$	190	3.9	-31.5	-17.5

single variable (Z_{Max} , R_{in} , f_R) measured at the same membrane potential and compared between different cell types (Fig. 1) or was coming from the same cell type but comparing different membrane potentials (Fig. 2), we used one-way ANOVA with matched samples and Tukey's multiple comparison tests. When the comparison of variables was between two conditions in the same cell (Fig. 3), we used paired Student's t-test. To evaluate differences in firing probability as a function of stimulation frequency after reducing R_{in} (Fig. 4), we used two-way repeated measures ANOVA with Holm-Šidák's multiple comparison tests. The statistical significance of the linear relation between f_R and R_{in} (Figs. 1 and 2) was evaluated with a Student test. Statistical tests were two-tailed and we used $\alpha=0.05$ as critic value.

Results

The preferred frequency and phase-lag of cortical neurons are correlated with the input resistance.

To investigate the connection of R_{in} with f_R and the phase-lag, we conducted whole cell recordings in three well described types of cortical neurons that share the same subthreshold resonant mechanism: entorhinal cortex layer II stellate (SL) neurons (Erchova *et al.*, 2004), hippocampal CA1 pyramidal neurons (HP) (Hu *et al.*, 2002) and cortical amygdala layer II resonant neurons (Vera *et al.*, 2014). Figure 1a shows the voltage responses of representative neurons of each type to hyperpolarizing and depolarizing square current pulses. The responses to both stimuli polarities start with a sag at the onset of the pulse, produced by the slow (tens of milliseconds) activation or deactivation of the inward I_h , respectively (Biel *et al.*, 2009). At the end of the pulse, there is a transient rebound with similar kinetics (Biel *et al.*, 2009). Further depolarization induced trains of action potentials with some frequency accommodation, presumably due to I_h deactivation and the activation of the muscarine sensitive potassium current (I_M) (Lawrence *et al.*, 2006). These similarities in voltage responses and firing pattern corroborate that these neurons possess similar electrophysiological behaviors (Hu *et al.*, 2002; Erchova *et al.*, 2004; Vera *et al.*, 2014).

R_{in} was measured with 250 ms hyperpolarizing pulses adjusted to produce a ~5 mV maximal deflection from -80 mV. R_{in} values of the three types of neurons ranged from 10 to 400 M Ω , where SL neurons are more abundant in the lower (mean = ~26 M Ω), HPs in the intermediate (mean = ~65 M Ω) and AMs in the highest R_{in} sub-ranges (mean = ~200 M Ω ; Fig.1b, Table 2). Our observations corroborate that the three cell types are suited for investigating how R_{in} influences their f_R and phase-lag.

To quantify and compare the resonant properties of these neurons we recorded their voltage responses to oscillatory stimulation. We applied ZAP (impedance amplitude profile) stimuli (Puil *et al.*, 1986), consisting of a 10 s oscillatory current of constant amplitude and linearly incremental frequencies, from 0 to 20 Hz. The membrane potential was manually adjusted to ~-80 mV in order to set a similar level of activation of I_h and the stimulus amplitude was adjusted to produce a comparable voltage deflection of ~5 mV peak to peak at its onset (ranging from 10 to 50 pA). As expected (Hutcheon & Yarom, 2000), the voltage response in all

Figure 1. Frequency preference of resonant cell types (peak impedance and --lag) correlates with their R_{in} . Impedance analysis performed in stellate neurons from layer II entorhinal cortex (SL, $n=12$), pyramidal cells from CA1 hippocampus (HP, $n=31$) and resonant neurons from the anterior cortical amygdala (AM, $n=25$). **a** Representative voltage response of SL (red), HP (blue) and AM (red) neurons. Current pulses were -150,-50,+100,+150 pA for SL, -200,-100,+50,+100 pA for HP and -100, -50, +50, +100 pA for AM. **b** Input resistance of SL, HP and AM neurons measured at -80 mV with a hyperpolarizing squared pulse. **c** Representative voltage responses of each cell type stimulated with the ZAP protocol (grey traces, see Methods). Peak voltage responses are shown with arrows. **d** Impedance profile curves from each cell types (dark and light colors depict mean and SEM, respectively); the inset shows normalized curves from 0.8 to 1 (y axes) and from 0 to 14 Hz (x axes). Arrows shows the peak of each curve. **e** Population peak impedance measured from impedance curves. **f** Population f_R measured from impedance profile curves. **g** Phase-lag curves, dark and light colors depict mean and SEM, respectively. **h** Quantification of phase-lag at 6 Hz (Φ_{6Hz}). **i** Scatter plots of f_R vs. R_{in} with data from all recorded neurons ($n=68$); **j** Scatter plot of f_R vs. R_{in} transformed to $\log(f_R)$ vs. $\log(R_{in})$. **k** Scatter plot of Φ_{6Hz} vs. R_{in} . One way ANOVA, * = $P < 0.05$, ** = $P < 0.01$ and *** = $P < 0.001$.

Table 2. Electrophysiological parameters for stellate (SL), hippocampal (HP) and cortical amygdala (AM) neurons characterized at hyperpolarized potential. Mean $\pm$ SEM. Pairs for statistical comparison: 1 SL-HP, 2 SL-AM and 3 HP-AM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

	V_m (mV)	Z_{Max} (M Ω)	f_R (Hz)	Q	Φ_{6Hz} (deg)	Φ_{fR} (deg)	R_{in} (M Ω)	n
SL	-79.6 ± 0.4	48 ± 6.1	8.7 ± 0.4	1.62 ± 0.05	-0.7 ± 1.5	-12.4 ± 0.6	26.5 ± 3.2	12
HP	-80.0 ± 0.6	78 ± 5.0	6.5 ± 0.3	1.23 ± 0.02	-12.6 ± 0.1	-13.9 ± 0.6	64.8 ± 4.4	31
AM	-80.6 ± 0.3	220 ± 16.2	4.1 ± 0.3	1.15 ± 0.02	-17.5 ± 0.8	-8.4 ± 0.7	200.9 ± 13.4	25
Statistics	ns	1(ns),2****,3****	1****,2****,3****	1****,2****,3(ns)	1****,2****,3*	1(ns),2**,3****	1*,2****,3****	

tested cells displayed a maximal amplitude in the theta range (arrows) and the low and high frequencies of their responses were attenuated (Fig. 1c).

The average impedance profiles of the three groups of neurons were clearly different. Their characteristic shapes resemble band-pass filters with peaks in the theta range (Fig. 1d), but their average maximal impedances (Z_{Max}) and f_R s were obviously dissimilar: the average Z_{Max} was ~ 50 M Ω for SL, ~ 80 M Ω for HP and ~ 220 M Ω for AM neurons (Table 2, Fig. 1e) and their respective impedance curves are displaced in the frequency range, as can be better appreciated in the normalized impedance profiles (Fig. 1d, inset). The f_R s derived from the impedance curves was higher in SL (8.7 ± 0.4 Hz, $n = 12$) compared to HP (6.5 ± 0.3 Hz; $n = 31$) and AM neurons (4.1 ± 0.3 Hz, $n = 25$; $P < 0.001$ for all paired comparisons; Table 2, Fig. 1f). The resonance strength among the different cell populations, evaluated using the Q value (see Methods), was higher in the SL neurons, than the HP and the AM neurons (Table 2).

The time dependence of the voltage response was analyzed with phase-lag curves that quantify the delay of the output voltage wave relative to the current stimulus as a function of frequency. The negative phase-lag values reflect a delay of the voltage response and the mean of the positive values an advance, which may provide important insights of the temporal processing of oscillatory stimuli (Rotstein, 2014). The analysis of phase-lag curves showed that the response is faster (i.e., shorter lag) at frequencies within and below the theta range (0-8 Hz) for SL in comparison to HP and AM neurons (Fig. 1g). We quantified the phase-lag of each cell at two relevant frequencies: at the middle of theta range (6 Hz, Φ_{6Hz}) and at the f_R of each particular neuron (Φ_{fR}). The Φ_{6Hz} values were markedly different between the three groups: -0.7 ± 1.5 deg, -12.5 ± 1.0 deg and -17.5 ± 2.0 deg for SL, HP and AM neurons, respectively (Fig. 1h, Table 2, $P < 0.001$ in all paired comparisons). By transforming these lag values from degrees to time (where 360 deg are 166.7 ms in a single oscillation at 6 Hz) we obtain a phase-lag of -0.3 ms, -

5.8 ms and -8.1 ms, for SL, HP and AM neurons, respectively ($P < 0.05$ for each pair, see values in Table 2), presenting a difference in the temporal response that might be relevant for spike timing and coding in these cell types. When phase-lag is compared at the f_R of each neuron the three cell types display less variability than at 6 Hz, with values grouped in the narrow range of 8-14 deg. The quantification shows similar phase-lags in SL and HP cells, with a reduced lag in AM neurons (-12.4 ± 0.6 deg, -13.9 ± 0.6 deg and -8.4 ± 0.7 deg for SL, HP and AM neurons, respectively. $P < 0.001$, 1 way ANOVA; see paired statistics in Table 2).

For a more detailed examination of the f_R and R_{in} relationship, we built a scatter plot with the values from all recorded cells. We found that f_R increased as R_{in} decreased, exhibiting a negative correlation. Low- R_{in} cells show the highest f_R s and the lowest f_R s were observed in the high- R_{in} cells (Fig. 1i). The R_{in} range covered by the three cell types is associated with a continuum variation of f_R s from about 2 to 10 Hz, matching the theta range. Since the distribution of the data in the scatter plot seems to represent a multiplicative relationship between f_R and R_{in} , we transformed the data to logarithmic values (Kass *et al.*, 2014). The scatter plot of $\log(f_R)$ - $\log(R_{in})$ pairs yields a linear relation characterized by a Pearson's correlation coefficient of -0.82 and a slope of -0.39 ($n = 68$, $P < 0.001$), suggesting a power law between f_R and R_{in} (Fig. 1j).

We also explored the correlation between $\Phi_{6\text{Hz}}$ and R_{in} pooling the data from all cells in a scatter plot. $\Phi_{6\text{Hz}}$ is also correlated with R_{in} , dominating the values around zero lag for lower R_{in} cells, while for higher R_{in} the phase values can reach ~ -40 deg (Fig. 1k).

This comparative analysis revealed a co-variation between the resonant parameters (f_R and $\Phi_{6\text{Hz}}$) and the magnitude of R_{in} at -80 mV. It is noteworthy that, despite all the factors that could influence R_{in} in neurons from distinct brain regions (like the magnitude and distribution of membrane conductances, dendritic and somatic morphologies, etc.), it is still possible to find such a high degree of correlation with the resonance. This result shows that the R_{in} of the neurons is associated with a particular setting of resonance, producing cell-type specific f_R s along the theta range and different phase-lag, even though all cells tested possess the same active resonant mechanism.

Neurons modify the frequency preference and phase-lag during depolarization-driven increase in R_{in}

To investigate to what extent the variation in R_{in} was associated with modifications in f_R and phase-lag, we changed R_{in} by manipulating the activation levels of the voltage-sensitive conductances with current injection, an operation that does not modify the cell passive properties. Steady-state depolarization of the cortical neurons from -80 mV to near threshold potentials produced a reduction of I_h due to deactivation (Hutcheon *et al.*, 1996a; Hu *et al.*, 2002; Biel *et al.*, 2009) and the activation of the persistent Na^+ current, I_{NaP} , above -70 mV (Crill, 1996; Vera *et al.*, 2014, 2017; Ceballos *et al.*, 2017). Both modifications produce a voltage-dependent rise in R_{in} that has been observed previously in resonant neurons (Gutfreund *et al.*, 1995; Hutcheon *et al.*, 1996a), and characterized in detail more recently (Surges *et al.*, 2004; Economo *et al.*, 2014; Yamada-hanff & Bean, 2015; Ceballos *et al.*, 2017); we will refer to it as “depolarization-driven increase in R_{in} ”. We manually adjusted the membrane potential to -80, -70 and -60 mV by current injection and applied the ZAP stimuli at each potential, exploring R_{in} and resonance in SL and AM neurons. We did not include HP neurons in this experiment because they present a U-shaped voltage dependence of the resonance, lacking frequency preference between -70 and -65 mV (Hu *et al.*, 2002; Vera *et al.*, 2017).

The shape of the voltage responses to ZAP stimuli changed with depolarization, revealing an increased filtering at high frequencies and an early peak of the voltage response, manifesting a reduction in the f_R (Fig. 2a). R_{in} increased with depolarization from 26 to 65 M Ω in SL neurons and from 167 to 290 M Ω in AM neurons, with an equivalent increase in peak impedance (traces in Fig. 2b,f, and values in Table 3). This wide variation in R_{in} allowed a good comparison of this variable with the f_R and phase-lag. We confirmed that the increase in R_{in} was accompanied by a reduction in f_R from 8.7 to 6 Hz in SL neurons (Fig. 2c), and from 3.6 to 2.7 Hz in AM neurons (Fig. 2g, Table 3). The depolarization was also accompanied by a modification in the phase-lag profiles of both cell types, shifting the curves downward and leftward, with the consequent increment in lag as a function of frequency (Fig. 2d, h). The overall change in the phase-lag curves produced a considerable increase of $\Phi_{6\text{Hz}}$ in SL and AM neurons (-0.75 to -25.8 deg and -17.0 to -34.8 deg, respectively; Fig. 2e, i, Table 3). However, when quantified at f_R , the phase-lag showed a smaller range of variations under depolarization, increasing Φ_{f_R} from -12 to -20 deg in

Figure 2. Depolarization-driven increase in R_{in} correlates with reductions in f_R and increments in phase-lag. Paired measurement of resonant properties in SL ($n=11$) and AM ($n=8$) neurons recorded at hyperpolarized (Hyp), resting (Res) and depolarized (Dep) membrane potential (see Table 3), to evaluate the effect of depolarization. **a** Representative voltage response of a SL neuron to a ZAP stimulus. The amplitude of the sinusoidal current (gray trace) was adjusted in order to maintain voltage oscillations near 5 mV (in this example, 40, 20 and 5 pA for -80, -70 and -60 mV, respectively). **b** Impedance profile curves of SL neurons (mean $\pm$ SEM). **c** Quantification of f_R as a function of membrane potential for SL neurons. **d** Phase-lag curves for SL neurons (mean $\pm$ SEM). **e** Quantification of phase-lag at 6 Hz in SL neurons. **f** Impedance profiles of AM neurons (mean $\pm$ SEM). **g** Quantification of f_R as a function of membrane potential for AM neurons. **h** Phase-lag curves for AM neurons (mean $\pm$ SEM). **i** Quantification of phase-lag at 6 Hz (Φ_{6Hz}) in AM neurons. **j** Scatter plot of f_R vs. R_{in} with the pooled data from SL and AM neurons. Colors indicate the voltage range of SL (circles, $n=3 \times 11$) and AM (triangles, $n=3 \times 8$) neurons. **k** Scatter plot of the same data of (j) transformed to logarithmic value. Labels are identical as (j). **l** Scatter plot of Φ_{6Hz} vs. R_{in} from the pooled data of SL and AM neurons. Labels are identical as (j). All neurons were recorded at three voltage ranges. One way ANOVA, $*$ = $P<0.05$, $**$ = $P<0.01$ and $***$ = $P<0.001$ and $****$ = $P<0.0001$.

SL neurons ($P<0.001$, 1 way ANOVA), while in AM neurons it stayed near -8 deg without significant changes ($P=0.16$, 1 way ANOVA; see details in Table 3).

To explore the changes in f_R and phase-lag associated to the depolarization-driven increase in R_{in} , we built scatter plots with the pooled data of f_R and Φ_{6Hz} vs. R_{in} from SL and AM neurons. R_{in} ranged from 10 to $\sim 100 M\Omega$ in SL neurons and from 100 to $\sim 350 M\Omega$ in AM neurons, filling the R_{in} range from 10 to 350 $M\Omega$ almost completely (Fig. 2j). f_R s inversely

Table 3. Intrinsic electrophysiological parameters for stellate (SL) and cortical amygdala neurons (AM) characterized at hyperpolarized (Hyp), near-resting (Res) and depolarized (Dep) potentials. Mean $\pm$ sem. Pairs for statistical comparison: 1 Hyp-Res, 2 Hyp-Dep and 3 Res-Dep. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

	V_m (mV)	R_{in} (M Ω)	Z_{max} (M Ω)	f_R (Hz)	Q	Φ_{6Hz} (deg)	Φ_{fR} (deg)	n
SL	Hyp	-79.6 $\pm$ 0.4	26.5 $\pm$ 2.9	47.9 $\pm$ 5.7	8.7 $\pm$ 0.4	1.62 $\pm$ 0.04	-0.7 $\pm$ 1.4	11
	Res	-68.6 $\pm$ 0.8	36.2 $\pm$ 6.1	56.7 $\pm$ 9.0	7.5 $\pm$ 0.5	1.49 $\pm$ 0.06	-11.4 $\pm$ 2.3	11
	Dep	-61.6 $\pm$ 0.4	65.5 $\pm$ 10.3	106.1 $\pm$ 18.1	6.0 $\pm$ 0.5	1.43 $\pm$ 0.12	-25.8 $\pm$ 4.5	11
Statistics		1**,2***,3**	1*,2***,3***	1****,2***,3*	1*,2**,3(ns)	1****,2***,3*	1**,2**,3*	
AM	Hyp	-80.6 $\pm$ 1.8	167.5 $\pm$ 13.9	182.2 $\pm$ 17.3	3.6 $\pm$ 0.3	1.16 $\pm$ 0.04	-17.0 $\pm$ 3.7	8
	Res	-75.8 $\pm$ 1.8	200.3 $\pm$ 20.3	226.7 $\pm$ 23.5	3.2 $\pm$ 0.3	1.17 $\pm$ 0.03	-23.7 $\pm$ 4.1	8
	Dep	-63.6 $\pm$ 1.1	290 $\pm$ 35.8	312.7 $\pm$ 44.5	2.7 $\pm$ 0.3	1.22 $\pm$ 0.06	-34.8 $\pm$ 4.4	8
Statistics		1*,2**,3*	1**,2*,3*	2*,3*	ns	1*,2**,3*	ns	

correlate with R_{in} , spanning the entire theta range when both data sets are taken together. The distribution of f_R starts at 12 Hz for low- R_{in} SL neurons recorded at hyperpolarized potentials and decreases continuously to $\sim$ 2 Hz for high- R_{in} AM neurons recorded at depolarized potentials (Fig 2j). The distribution of f_R and R_{in} values, strongly suggest a multiplicative relationship, as described above (Fig. 1). The log-log graph exhibits an even higher linear correlation, with a Pearson's coefficient of -0.92 and a slope of -0.43 (Fig. 2k, $P < 0.001$). These results agree with the R_{in} - f_R relationship between different cell types, and show that individual neurons are able to modify their f_R in coherence with changes in R_{in} .

The scatter plot of Φ_{6Hz} against R_{in} shows that cells increment their phase-lag during the depolarization-driven increase in R_{in} , with both cell types spanning the whole range of 0 to -50 deg (Fig. 2l). This increase is dictated by linear correlations of different slope for each cell type (Pearson coefficient of -0.91 and -0.71 and slope of -0.45 deg/M Ω and -0.11 deg/M Ω for SL and AM neurons, respectively). Interestingly, despite having different R_{in} ranges and phase-lag curves, both cell types can vary their Φ_{6Hz} along a similar range.

The question that arises is whether R_{in} effectively has a causal role in the modulation of resonance. In single cells, f_R is proportional to the level of activation of I_h (Narayanan & Johnston, 2007), therefore it is expected that depolarization will deactivate a fraction of I_h and reduce f_R . Here, by definition, R_{in} includes both, the passive and active electrophysiological properties; a decrease in I_h with depolarization will also cause an increment in R_{in} which, according to our results, will also be accompanied by a reduction of f_R . Therefore, is not clear

whether the changes observed in f_R under the depolarization-driven increase in R_{in} (Fig. 2) are due to changes in I_h , R_{in} or both, impeding a clean evaluation of the f_R - R_{in} relation.

To evaluate the causal role of f_R modifications governed by R_{in} , we designed a protocol to control R_{in} while keeping unaltered the contribution of the voltage-dependent conductances involved in resonance. The observation that f_R and phase-lag are modified when a neuron undergoes changes in R_{in} with depolarization opens the possibility that other sources of R_{in} variations, like synaptic activity, can operate as modulators of resonance. Both questions will be addressed in the following series of experiments.

Modulation of the frequency preference and phase-lag by controlled changes in the input resistance

To explore additional evidence that physiological changes in R_{in} can by themselves modulate the resonance we used the dynamic-clamp technique, to add or subtract virtual membrane conductances to the recorded neuron (Dorval et al., 2001). This virtual conductance is used to stimulate the cell, mimicking the opening (reducing R_{in}) or closing (incrementing R_{in}) of ion channels, thus closely representing a physiological condition, unlike the oversimplified traditional procedure of injecting current (Dorval et al., 2001). We performed these experiments in HP neurons at -80 mV, because at this voltage their R_{in} values (~ 70 M Ω) are associated to f_R s and phase-lags at the middle of the dynamic range, facilitating the detection of positive and negative changes (see Fig. 1).

To recreate a steady reduction ($-R_{in}$) or increase ($+R_{in}$) in R_{in} we injected a dynamic current calculated as a constant leak conductance, G_{Leak} , of positive or negative value, respectively (Fig. 3a,b. For more details see Methods). By manipulating the somatic conductance we aimed to reduce or increase the R_{in} of HP neurons in order to match the average values of SL and AM cells, as examples of low and high R_{in} cells, respectively. Using this criterion, we generated a $-R_{in}$ condition with an average reduction of $\sim 45\%$ (from 63.8 ± 5.4 M Ω to 35.4 ± 4.8 M Ω ; $G_{Leak} = 16.6 \pm 2.9$ nS, $n=10$, $P < 0.05$) and a $\sim 100\%$ increment for a $+R_{in}$ condition (from 71.7 ± 4.7 M Ω to 151.8 ± 16.7 M Ω ; $G_{Leak} = -6.1 \pm 0.8$ nS, $P < 0.05$, Fig. 3c). R_{in} values of both control groups were not different ($P = 0.13$). These results demonstrate that our experimental procedure enabled us to change R_{in} over a wide physiological range in different cell types. We manually adjusted the membrane potential to -80 mV and recorded the voltage responses to ZAP

Figure 3. Changes in input resistance modulate frequency preference of CA1 hippocampal neurons.

a The manipulation of R_{in} was performed by means of the dynamic-clamp, as shown in the scheme. The neuron R_{in} was decreased ($-R_{in}$) or increased ($+R_{in}$) injecting a virtual negative ($+G_{Leak}$) or positive ($-G_{Leak}$) somatic conductance as an external dynamic current (I_{DynC}). **b** Dynamic-clamp experiment showing the attenuation ($-R_{in}$) or amplification ($+R_{in}$) of voltage responses revealed by the same 0.4 s and 50 pA hyperpolarizing pulse (gray). At $-R_{in}$ condition, I_{DynC} acquires negative sign (blue trace), hyperpolarizing the neuron and attenuating voltage response. At $+R_{in}$, I_{DynC} is positive (red trace), depolarizes the cells and amplifies the voltage deflections. **c** Quantification of R_{in} manipulations as pairs, Control ($-Ctrl$) vs. $-R_{in}$, Control ($+Ctrl$) vs. $+R_{in}$. R_{in} was measured with a squared pulse (as in b), but the amplitude was adjusted to evoke a ~ 4 mV voltage deflection in all conditions. The rationale to guide the magnitude of R_{in} change was to attain a reduction of 50% ($G_{Leak} = 16.6 \pm 2.9$ nS, $n=10$) or an increase in $\sim 100\%$ ($G_{Leak} = -6.1 \pm 0.8$ nS, $n=10$). **d** Representative experiment showing oscillatory responses at different R_{in} values; for simplicity we show an experiment in which both conditions were explored in the same cell. ZAP stimulation was applied at control (black), $-R_{in}$ (blue) or $+R_{in}$ (red) conditions. I_{DynC} is the dynamic current injected by the dynamic-clamp. **e** Impedance profile curves (mean $\pm$ SEM) for $-R_{in}$ and $+R_{in}$ conditions, with their respective curves in the control condition. Note the difference in the scale in the impedance axes. The inset shows normalized curves. **f** Peak impedance for $-R_{in}$ and $+R_{in}$ conditions. **g** f_R for $-R_{in}$ and $+R_{in}$ conditions. **h** Ratio of $\Delta \log(f_R)$ and $\Delta \log(R_{in})$ for $-R_{in}$ and $+R_{in}$ conditions. **i** Phase-lag curves for $-R_{in}$ and $+R_{in}$ conditions, with their respective curves at control condition. **j** Phase-lag at 6 Hz (Φ_{6Hz}) for $-R_{in}$ and $+R_{in}$ conditions. **k** $\Delta \Phi_{6Hz} / \Delta R_{in}$ for $-R_{in}$ and $+R_{in}$ conditions. ** = $P < 0.01$, Paired Student T test.

stimuli (Fig. 3d, black traces). Then, we reduced ($-R_{in}$, blue traces) or increased ($+R_{in}$, red traces) R_{in} with the dynamic clamp and recorded the voltage responses to oscillatory stimulation at the new level of somatic conductance. In 4 out of 16 experiments we explored both conditions in the same cell, while in the other experiments we recorded only one of the two conditions and their respective controls. To keep constant the contribution of active properties at different R_{in} values, we measured resonance systematically by adjusting the amplitude of the ZAP current to produce ~ 5 mV peak-to-peak oscillations (measured at 4 Hz, Fig. 3d). As expected, the manipulation of the somatic conductance was accompanied by changes in the impedance profile. In the $-R_{in}$ condition the impedance curve fell, decreasing in 50% at Z_{Max} (from 90 ± 10.2 M Ω to 44.1 ± 6.2 M Ω). In contrast, in the $+R_{in}$ condition the impedance curves raised (Fig. 3e), reaching $\sim 150\%$ growth at Z_{Max} (from 89.4 ± 5.1 M Ω to 221.6 ± 29.7 M Ω , Fig. 3f. $P < 0.01$).

The changes in peak impedance were accompanied by modifications in f_R . In agreement with the results presented above, the reduction of R_{in} involved an increase in f_R of ~ 1 Hz (from 6.3 ± 0.4 to 7.3 ± 0.4 Hz, Fig. 3g), while an increase in R_{in} was associated to a f_R decrease of ~ 1.3 Hz (6.5 ± 0.4 Hz vs. 5.2 ± 0.3 Hz, Fig. 3g, $P < 0.01$). To evaluate the degree of the resonance modulation, we calculated the ratio of the changes in the logarithms of f_R and R_{in} ($\Delta \log(f_R)/\Delta \log(R_{in})$) in each condition, obtaining values of -0.29 ± 0.09 and -0.31 ± 0.03 for $-R_{in}$ and $+R_{in}$ conditions, respectively (Fig. 3h). These values are similar to the slopes of the linear regression obtained for $\log(f_R)$ - $\log(R_{in})$ when the source of R_{in} variation was the heterogeneity of SL, HP and AM neurons (Fig. 1k), or the depolarization-driven increase in R_{in} in SL and AM neurons (Fig. 2k). This demonstrates that by modifying R_{in} through changing only the passive somatic conductance it is possible to induce comparable variations in the frequency preference of the neurons.

R_{in} manipulation also modified the phase-lag curve. The reduction of R_{in} produced a frequency-dependent reduction in phase-lag that was traduced into a $\sim 50\%$ drop in Φ_{6Hz} (from -12.8 ± 1.7 deg to -6.8 ± 1.3 deg, Fig. 3i,j). For $+R_{in}$ the phase-lag increased, displaying a slower response at frequencies above 2 Hz (Fig. 3i), with a $\sim 130\%$ increase in lag (Φ_{6Hz} changes from -11.7 ± 1.3 deg to -26.9 ± 2.3 deg; Fig. 3j. $P < 0.005$). These variations give a rate of change in Φ_{6Hz} ($\Delta \Phi_{6Hz}/\Delta R_{in}$) of -0.18 ± 0.04 deg/M Ω and -0.31 ± 0.05 deg/M Ω in $-R_{in}$ and $+R_{in}$ conditions, respectively (Fig. 3i), between the values obtained for SL and AM neurons (Fig. 2l).

Taken together, these results indicate that by modifying exclusively the passive somatic conductance involved in setting R_{in} it is possible to modulate resonance in the same ranges observed in figures 1 and 2, supporting a causal role of R_{in} in setting and modulating the frequency preference and the phase-lag. Moreover, these observations suggest that individual neurons may adjust the frequency preference and the temporal response when R_{in} varies, as it occurs upon intense synaptic input.

Subthreshold modulation of the frequency preference and phase-lag is translated into changes in the frequency and timing of spikes

A critical question is whether the subthreshold modulation of the frequency preference is translated into a spiking regime, influencing neural activity. We tested this possibility by applying ZAP stimuli at perithreshold potentials and evaluating if changes in R_{in} modified the spike firing probability and timing. These experiments were conducted in AM neurons because their high R_{in} and low f_R conditions offer a wide range to reduce R_{in} and facilitates the detection of increases in firing frequency.

As in the previous experimental set, here we decremented R_{in} by recreating a constant leak conductance with the dynamic-clamp. As expected, this manipulation decreased the voltage responses, with the consequent reduction in the excitability of the cell, but without altering its ability to fire action potentials (Fig. 4a). In these experiments we set the $-R_{in}$ condition by lowering R_{in} in ~25 % (from $211 \pm 27 \text{ M}\Omega$ to $163 \pm 21 \text{ M}\Omega$, with $G_{Leak} = 1.8 \pm 0.46 \text{ nS}$, $n=8$. Fig. 4a). The neurons were depolarized to -60 mV and the amplitude of the oscillatory current was adjusted to reveal the preferential firing frequency. The stimuli consisted of a series of sinusoidal current pulses of constant amplitude with discrete increments in the frequency between 0.5 and 14 Hz (Fig. 4b, blue traces). A representative example of an AM neuron response is shown in Fig. 4b. (black trace). As expected, this neuron fired at frequencies of ~2-4 Hz, with no action potentials at higher or lower frequencies. Interestingly, in the $-R_{in}$ condition the neuron changed its firing preference (red trace) to higher frequencies (6-8 Hz), with no action potentials in lower range (2-4 Hz; Fig. 4c). To quantify the change in firing probability, we computed the cumulative firing probability (cumulative probability density function, CPDF) vs. stimulus frequency (Fig. 4d; see Methods) for all recorded neurons. These curves of the firing probability as a function of frequency show the distribution of selective firing frequencies from zero to one

(Fig. 4d). AM neurons display a CPDF that rises from 0 at 2 Hz and reach a fractional probability of 1 at 8 Hz, limiting the firing probability to that frequency range (Fig. 4d). However, in the $-R_{in}$ condition the CPDF rises with a small probability at 2 Hz and saturates at 10 Hz, presenting lower firing probabilities than the control curve between 2 and 6 Hz (Fig. 4d, $P < 0.015$). These differences indicate a displacement in the firing probability towards higher frequencies when R_{in} is reduced. The comparison of the frequencies at which the CPDF curves reach a probability of 0.5 ($F_{p0.5}$) reveals that the reduction of R_{in} produces a ~ 2 Hz rightward shift in the firing probability curve (from 3.8 ± 0.7 Hz to 6.0 ± 0.8 Hz; $P < 0.01$, $n=8$, Fig. 4e). To discard that this firing modulation could have been generated by other factors that may also produce a reduction in R_{in} and not by the R_{in} change directly, we compared the spike threshold, the voltage at which a spike is generated (perithreshold potential) and the peak of the hyperpolarization induced with the ZAP protocol (hyperpolarized potentials) for each spike fired in both conditions (control and $-R_{in}$, Fig. 4f). Neither of these parameters was different, suggesting that the voltage trajectory during oscillations and the activation of voltage-sensitive conductances was equivalent in control and $-R_{in}$ conditions. Therefore, the changes in firing frequency can be attributed exclusively to the changes in f_R induced by the increase in somatic conductance. To evaluate if the modulation of the phase-lag influenced the timing of spikes fired, we quantified the phase-shift of each spike. We examined the delay of each spike relative to the peak of the sinusoidal current in control and $-R_{in}$ conditions (see Methods). When the oscillatory current reached ~ 4 -8 Hz, the AM neurons fired action potentials with average delays of -13 to -18 deg, the same range observed for the subthreshold phase-lag (Fig. 4g, black traces). We found that in the $-R_{in}$ condition the neurons consistently fired action potentials with a reduced delay, at all tested frequencies (Fig. 4g, h). Note that at 4 Hz the reduction in the delay even caused that the spikes were fired earlier than the peaks of oscillatory current (Fig. 4g, h; vertical dotted line indicates the peak of oscillatory current used as the reference 0 deg). This reduction in the phase-shift is traduced into an average phase advance in spiking in 22, 18 and 13 deg for 4, 6 and 8 Hz, respectively (Fig. 4i, top trace). In the time domain, this manipulation gives an average advance in spike timing of 15.4, 8.4 and 4.6 ms for 4, 6 and 8 Hz, respectively (Fig. 4i, bottom trace). This result supports the notion that the modulation of the phase-lag associated to changes in R_{in} at subthreshold potentials is also manifested in the spiking regime.

A resonant current and a leak conductance are sufficient to account for the setting and modulation of the frequency preference and temporal response

We used computer simulations to evaluate if a minimal conductance-based model containing only the hyperpolarization-activated conductance (G_h), a passive leak conductance (G_{Leak} , the reciprocal of R_m) and a membrane capacitance (C_m), can account for our experimental observations.

We first aimed to reproduce the differences in resonant properties of SL, HP and AM cells. Our strategy was to set the value of C_m according to experimental measurements and then adjust the magnitudes of G_h and G_{Leak} for each cell type to reproduce the average behavior observed under ZAP stimulation at -80 mV (i.e., R_{in} , f_R and phase. Fig. 5a, dotted box). Using this minimal model, it was possible to reproduce the characteristic voltage response of each cell type (Fig. 5a, dotted box. See details in Methods). Moreover, varying C_m , G_h and G_{Leak} within physiological values, it was possible to reproduce an f_R value inside the theta range and a proper phase-lag, in a way that mimics the experimental results. We then used the three model neurons to explore the effect of R_{in} variations caused by changes in the passive conductance G_{Leak} . As in our dynamic-clamp experiments (Fig. 3), we explored a reduction ($-R_{in}$) or an increase ($+R_{in}$) of the input resistance by manipulating G_{Leak} gradually between 1 and 90 nS. This manipulation varied the R_{in} of the model cells over the whole range, from 10 to 310 M Ω . Each simulated neuron changed their frequency preference and phase-lag as a result of G_{Leak} modifications. The reduction of R_{in} produced an increase in f_R and a reduction in Φ_{6Hz} in the three cell types, with opposite effects when R_{in} is increased (Fig. 5a, arrows indicate the f_R). Moreover, the f_R vs. R_{in} relationship obtained for each simulated cell type displays the same power-law distribution observed in our experimental data (Fig. 5b, filled circles show values at G_{Leak} control value, representing the average behavior of each cell type as in Table 2). Note that these simulations represent the range of modulation of a single neuron when R_{in} was varied with slight increments in G_{Leak} . In agreement with the experimental measurement, the $\log(f_R)$ - $\log(R_{in})$ plot yields nearly linear curves in the three model cells, described by a linear fit with slopes of -0.29 and -0.31 for the SL and HP models, respectively (Fig. 5c). In the case of the AM model, the log-log curve presents two regions of different slopes, of -0.25 below 2.0 Hz (similar to the HP model) and -0.57 above 2.0 Hz (Fig. 5c, dotted line above green line).

Figure 5. Minimal computer model reproduce the setting and modulation of frequency preference and phase-lag according to R_{in} range.

a. A representative SL, HP and AM neurons were simulated using a minimal resonant model (see Methods). Starting with a G_{Leak} that reproduced the average f_R , R_{in} and Phase-lag of each cell type (i.e. control conditions, dotted box), we explored voltage responses ranging G_{Leak} from ~ 1 nS ($+R_{in}$) to 80 nS ($-R_{in}$) while maintaining constant I_h and C_m (4 conditions are shown for each cell type, R_{in} and G_{Leak} are reported at the top-left of each voltage trace). The impedance profiles are shown at the bottom plot, with the darker curve corresponding to the control condition. Grey lines show the f_R at control condition, while arrows show the f_R at each voltage trace. The amplitude of oscillatory current was adjusted to produce voltage responses of ~ 2 mV peak-to-peak while DC current was injected to hyperpolarize to -80 mV. **b.** Scatter plot of f_R vs. R_{in} obtained with the exploration of G_{Leak} in the three cell types (colored lines), with filled circles showing values at control condition. Empty figures show experimental data. **c.** Same as b but plotting $\log(f_R)$ vs. $\log(R_{in})$. Dotted black lines are the linear fit of each curve, with a slope of -0.29 (SL), -0.31 (HP) and -0.57 (AM, note this fit is between 2.2 and 2.5. See main text). **d.** Scatter plot of $\Phi_{6\text{Hz}}$ vs. R_{in} obtained from G_{Leak} exploration (colored lines), empty figures are experimental data. The inset shows a zoom to visualize SL response.

The exploration of different R_{in} values in our model cells also reproduced the modification of the phase-lag, increasing the $\Phi_{6\text{Hz}}$ proportionally to R_{in} , with a distribution that matches the experimental values (Fig. 5d). The rate of change was different for each model neuron, with slopes of -0.09, -0.25 and -0.17 deg/M Ω for SL, HP and AM models, respectively (Fig. 5d, dotted lines).

Overall, the computer simulations demonstrate that only one resonant conductance (in this case the h current) is sufficient to provide a mechanism of frequency preference that is set and dynamically modulated by the magnitude of the membrane conductance.

To illustrate the mechanism by which R_{in} influences the f_R and phase-lag of neurons, we used a conductance-based model to qualitatively analyze the independent contribution of the low-pass and high-pass filters in setting the f_R and the phase-lag of the response after a R_{in} change. Figure 6a shows the decomposition of a resonant impedance profile into 4 components: i) the low-pass filter produced by R_m and C_m (blue), ii) the high-pass filter produced by the resonant current (I_h , black), iii) the resultant band-pass filter (dark orange) and iv) the impedance of the trivial case in which only R_m is considered (i.e., in the absence of C_m and inductive current) as the inverse of total membrane conductance (gray). This resistive impedance sets the value of the membrane resistance ($R_m = \sim 90 \text{ M}\Omega$) with slight frequency dependence, determining the maximal values for the impedance at both, the low and high-pass filters. Therefore, the band-pass filter that accounts for the frequency preference in the theta range results from the meeting point of the low and high-pass filters, defining a set-point for f_R (red circle).

The simplest scenario to describe mechanistically the modulation of the f_R and the phase-lag of the response is the variation of R_{in} due to changes in a leak conductance (as in Figs. 3 and 5). A reduction in G_{Leak} (increase in R_m and thus in R_{in}) raises the maximal impedance for both, low and high-pass filters (+ R_{in} condition, Fig. 6, green arrows). Since the steepness of the low-pass filter is set by its cut-off frequency ($f_c = 1/2\pi * R_m * C_m$), the increase in R_m reduces this value and increases its steepness (blue circle and green arrow). On the other hand, the cut-off frequency of the high-pass filter is independent of R_m , thus its frequency dependence remains constant while its maximal impedance is updated to the new value of R_m . The modifications in the low-pass filter (increase in maximal value and steepness) displace this filter towards low frequencies, shifting the meeting point with the high-pass filter towards low frequencies and reducing f_R (Fig. 6a). In case of a reduction of R_{in} by an increase in G_{Leak} , the modifications occur

Figure 6. Mechanism behind the modulation of frequency preference and phase-lag by changes in R_{in} .

a. Independent impedance analysis of resistive (grey), high-pass (black), low-pass (blue) and band-pass filters (dark yellow) of a resonant neuron. A model cell consisting in a capacitance (100 pF), a leak conductance ($G_{Leak}=10$ nS) and an h conductance ($G_h=3$ nS) was used to investigate the impedance profile of each component. Each simulation was performed maintaining the cell at -80 mV and stimulating with the ZAP current (0-20 Hz in 10 s interval) producing a maximal peak-to-peak response of 2 mV. **b.** Phase-lag curves obtained from the impedance analysis described in a. Arrows indicate the direction of curve changes when R_{in} is increased (+ R_{in} , green) or reduced (- R_{in} , red).

in the other direction. The increases in G_{Leak} reduce R_m (and R_{in}) and rises the cut-off frequency of the low-pass filter, reducing its steepness, displacing the meeting point with the high-pass filter towards higher frequencies and increasing f_R (Fig. 6a, - R_{in} condition red arrows).

In the case of the phase response, the observation of the resistive, capacitive and inductive components separately allows an easier understanding of the role of total conductance in the control of the temporal properties of the response (Fig. 6b). The phase response associated to the low-pass filter (R_m and C_m) shows a monotonic increase in lag along the frequencies of interest (Fig. 6d, blue). In contrast, the phase response of the high-pass filter shows positive lead with a peak near 3 Hz, which gradually descends and turns to negative lags around 10 Hz (black). When the complete model is evaluated, the phase-response is the sum of the other two curves (high and low-pass), displaying a positive phase lead below 3 Hz due to the inductive effect, and a shift to negative lags at higher frequencies (dark orange trace). Following the previous example, a reduction in G_{Leak} increases R_m (and R_{in}) with a consequent increase in the phase-lag due to the low-pass filter (Fig. 6b, green arrows and bottom gray curve). Since the phase response of the high-pass filter is not altered, the sum of both curves yields a phase response with higher lag, increasing the lag at 6 Hz (dotted arrow). When G_{Leak} is raised, the low-pass filter reduces the lag, with a consequent reduction in the lag of the final curve (red arrows). This dependence of the phase-lag curve on R_m explains the modulation of the phase observed experimentally.

Taken together, these results show that the f_R and phase-lag of neurons are dynamic parameters that vary according to R_{in} , serving as a tuning mechanism to modulate the frequency preference inside theta range, and to adjust the timing of action potential generation into a millisecond scale.

Discussion

In the present study we investigated the role of the input resistance in setting the frequency of preference and phase-lag upon oscillatory stimulation in cortical neurons. We found that the input resistance determines the f_R following a power law, in which R_{in} in the physiological range sets the f_R s spanning the theta frequency range. Moreover, the phase-lag of the responses critically depends on R_{in} . This dependence on R_{in} has two major implications: 1) Cell types within different R_{in} ranges will display distinct frequency preference and phase-lag, following a stereotyped scheme, and 2) Changes in R_{in} , as those expected to occur instantaneously in physiological conditions, modulate the frequency preference and phase-lag along the theta range. Additionally, we show that this modulation can be translated into a firing regime, modifying the spike firing frequency and timing in a way that might be relevant for the network activity (Lisman and Jensen, 2013; Ratté et al., 2013).

R_{in} sets and modulates the preferred frequency of cortical neurons

The conclusions summarized above are based on experimental measurements and computer simulations. The first evidence is derived from a comparative analysis across different resonant cell types that allowed us to characterize, under the same experimental conditions, their resonance properties along the range of R_{in} normally observed in cortical neurons. This comparison revealed a power law tendency between f_R and R_{in} , with R_{in} values spanning the whole theta range. When transformed into a log-log plot, the data from the three cell types present a linear relationship, thus offering a simple way to describe and quantify the f_R - R_{in} link. Therefore, we propose that resonant neurons with different ranges of R_{in} will show different set-points for f_R in the theta range, a value that can be described by a simple mathematical relationship.

A second line of evidence confirmed that variations in the R_{in} of individual neurons are accompanied by modifications in their frequency preference and temporal responses (Fig. 2). Considering the increase in R_{in} that occurs when the neurons are depolarized (Surges *et al.*, 2004; Economo *et al.*, 2014; Yamada-hanff & Bean, 2015; Ceballos *et al.*, 2017), we measured the voltage response of SL and AM neurons at three different R_{in} values. The variation of f_R with respect to R_{in} exhibited an even higher degree of correlation. The slope of the log-log linear

distribution of R_{in} and f_R was in close agreement with the value obtained for different cell types (Fig. 1). This result shows that the R_{in} - f_R relationship also applies for R_{in} variations in individual neurons within physiological ranges and that these changes may dynamically modulate the f_R along the theta range.

To confirm the causal role of R_{in} in this modulation we changed the R_{in} by modifying only its passive component, increasing or decreasing somatic conductance by means of dynamic-clamp (Dorval *et al.*, 2001). This technique makes possible to maintain unchanged the active and preexistent passive components and observe the resulting voltage response. In this unique experimental condition, we reproduced the changes in f_R due to variations in R_{in} . Moreover, we further corroborate with computer simulations the strength of the R_{in} - f_R relationship, and show that the presence of one resonant current (in this case I_h) and a leak conductance are sufficient to fully reproduce the modulation of f_R and phase-lag associated to changes in R_{in} (Fig. 5).

Additionally, the use of computational models allowed us to evaluate the entire possible range of f_R modulation as a function of R_{in} . We found that a single neuron can change its f_R along most of the theta range, regardless of the cell type. Considering the constraints of these minimal models, it is expected that the diverse set of voltage and ligand-gated ion channels present in real membranes would expand the range of f_R modulation along the whole theta range. It can be noted, for example, that the neurons duplicate R_{in} relative to hyperpolarized values near the spike threshold (due to the depolarization-driven increase in R_{in}). Besides, the contribution of the active membrane properties and morphology (size and shape) of neuron will provide a structural constrain to set R_{in} into a defined range at resting conditions. Moreover, considering the complex cell morphology and the heterogeneous expression of the ion channels implicated in the resonance (responsible of I_h and I_{NaP}), it is possible that R_{in} changes can occur independently in different sites of the same neuron. This would produce an even more complex scenario, where f_R would be modulated differentially in separate compartments of the neurons according to the local variations in membrane conductance.

It is important to mention that our experiments were performed under conditions that favored the stability of the recordings (-80 mV and reduced voltage oscillations), rather than maximizing the magnitude of the modulation. For example, as explained below, it is expected that at perithreshold potentials the modulation of the resonance will be higher, since the peak impedance can reach above 100 M Ω (Surges *et al.*, 2004; Economo *et al.*, 2014; Yamada-hanff

& Bean, 2015; Ceballos *et al.*, 2017; Vera *et al.*, 2017) even in SL neurons (Table 3), providing a wider dynamic range to vary R_{in} and modulate f_R and phase-lag.

R_{in} sets and modulates subthreshold phase-lag

In contrast to the importance usually assigned to f_R , the role of the phase-lag in processing the oscillatory inputs has received less attention (Hutcheon *et al.*, 1996a; Hutcheon and Yarom, 2000; Richardson *et al.*, 2003). What makes the modulation of the phase-lag in resonant neurons interesting is that it introduces a novel aspect of the frequency preference, since the timing of the spikes generated selective at the f_R could be adjusted. The dependence of f_R and phase-lag on R_{in} implies that both parameters vary together, with higher f_R being associated with lower lag. Subthreshold phase-lag has been shown to depend on I_h in CA1 pyramidal neurons, and the proximal to distal gradient of the I_h conductance along the dendrites controls the magnitude of the phase-lag (Narayanan & Johnston, 2008). The increased G_h conductance at distal sites reduces the phase-lag of distal inputs, compensating for the delay associated to dendritic filtering and producing temporal synchrony between distal and proximal inputs (Vaidya & Johnston, 2013). One of the most interesting aspects of the resonance is that during an oscillatory activity the inductive properties of the membrane allow a zero or even a positive phase lead at a specific frequencies (Narayanan & Johnston, 2008; Rotstein, 2014).

Here we show that the modulation of the phase-lag in the subthreshold response is preserved in the spiking regime as a modulation in the delay of the spikes fired when the voltage goes suprathreshold, influencing directly the timing of the neuronal responses (Fig. 4). The proper control of spike timing is vital for the generation of synchronized activity between different brain circuits (Fuhrmann *et al.*, 2002), suggesting a novel mechanism to precisely adjust the spike timing in the millisecond scale. According to theories of neural coding based on nested theta-gamma activity and neural synchrony, the control of the spike timing is crucial to properly coding and decoding neuronal information (Lisman and Jensen, 2013). Therefore, it can be speculated that neurons exploit the R_{in} -Phase-lag relationship to adjust their temporal responsiveness in order to properly engage in coherent activity. Until now, a detailed measurement of phase-lag in cortical neurons as a function of R_{in} and voltage had not been done. Our comparative study allowed the characterization of the subthreshold phase-lag curves for the

different cell types and to measure their variation under R_{in} changes, finding that maximal differences in phase-lag curves among the three cases occur in the theta range.

The phase response of the three cell types was very different when compared at 6 Hz, $\Phi_{6\text{Hz}}$ was close to 0 deg for SL neurons, increasing substantially in HP and AM neurons. These marked differences in the phase responses are reduced when compared at the f_R of each cell. This similarity of Φ_{f_R} among cells with different phase-lag curves is the result of an opposite effect of R_{in} changes on f_R and phase-lag. While a R_{in} reduction increases f_R and displaces Φ_{f_R} toward more negative values of lag (the lag increases with frequency), it reduces the amplitude of the new phase-lag curve (low R_{in} implies a reduced lag) in a way that compensates for phase-lag measured at f_R , thus keeping relatively similar values (Tables 1, 2 and 3). Given this compensatory effect, it is reasonable to think that cortical neurons that oscillate near their f_R will share similar phase-lags. Therefore, resonant neurons promote a constant delay in the transmission of electrical activity regardless of their individual f_R s. Whether this intriguing phenomenon has some role in the processing of oscillatory activity has to be investigated.

Modulation of the resonance is translated into spiking regime

Here we confirmed that subthreshold frequency preference is a property that can be translated into a selective firing at the preferred frequency, as previously described for neocortical neurons (Hutcheon *et al.*, 1996a; Ulrich, 2002), SL neurons (Erchova *et al.*, 2004), HP neurons (in this case relying on I_M as a resonant current) (Vera *et al.*, 2017) and AM neurons (Vera *et al.*, 2014). More importantly, our results reveal that the modulation of f_R and phase-lag is preserved during the spiking regime, generating a dynamic tuning of both, the firing frequency and the spike timing. Since this tuning mechanism relies on the modulation of basic electrophysiological properties (i.e. the subthreshold frequency preference and phase-lag), it is reasonable to propose that this is a general property exhibited by most cortical neurons.

Intrinsic changes in R_{in} : Self-generated modulation of resonance

The mechanism that we describe here points to the cell impedance as a key factor in the set-point of the frequency preference and phase-lag. Since R_{in} will vary in cortical neurons expressing subthreshold voltage-dependent conductances (like I_h , I_M or I_{NaP}) (Surges *et al.*, 2004; Yamada-hanff & Bean, 2015; Ceballos *et al.*, 2017; Vera *et al.*, 2017), their resonant properties

will depend on the membrane potential. At hyperpolarized potentials, I_h will be fully activated, reaching a maximum in the steady-state conductance and a consequent minimum R_{in} . At this point, the neurons will express their intrinsic highest values of f_R and lowest phase-lag (fastest response). At depolarized potentials (above -70 mV), I_h deactivation will reduce the steady-state conductance, increasing the impedance, shifting f_R to lower values and increasing the phase-lag. Above -70 mV I_{NaP} activates, producing a significant increase in R_{in} (Ceballos *et al.*, 2017; Vera *et al.*, 2017), and above -60 mV I_M begins to activate with a consequent reduction in R_{in} . Given this combined effect of I_h deactivation and I_{NaP} and I_M activation, the neurons are able to increase in 100% or more their R_{in} , thus significantly reducing f_R and increasing Φ_{6Hz} . In this context, I_{NaP} might play a pivotal role in tuning of the frequency preference and temporal neuron response, raising the perithreshold R_{in} and increasing the range for f_R and phase-lag modulation.

Changes in R_{in} due to synaptic inputs: Extrinsic control of the frequency preference

In addition to R_{in} changes resulting of intrinsic modifications, a major source of R_{in} variation are synaptic inputs. Regardless of their excitatory or inhibitory nature, the activation of post-synaptic receptors increases the membrane conductance with a consequent reduction in R_{in} . Moreover, it has been postulated that neurons that are part of active circuits *in vivo* receive a plethora of uncorrelated excitatory and inhibitory synaptic inputs that gives origin to drastic R_{in} variations, that can drop to 10% of the values observed *in vitro* (reviewed in Destexhe *et al.*, 2003). According to our results, such R_{in} variations during intense synaptic activity would change the f_R in ~ 2 Hz and reduce Φ_{6Hz} , causing a shift of the output wave of more than 6 ms. Importantly, this mechanism of modulation enables upstream neurons of the network to strongly influence the frequency preference and temporal response of their target cells, controlling their f_R and phase-lag through differential levels of synaptic activity.

Therefore, the f_R of a cortical neuron in a specific moment is set along the theta range according to its R_{in} , which in turn is dynamically adjusted by the interaction between the intrinsic and synaptic properties. The same occurs with the phase-lag. Whether cortical circuits effectively implement this mechanism of f_R modulation to promote oscillatory activity in the theta range requires further investigation.

The dynamic adjustment of the frequency preference and phase-lag may contribute to engage cortical neurons with the time-varying theta activity of the network, providing a robust cellular mechanism to promote coordinated neuronal activity across separate brain regions.

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