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Peer Review

Review of: "The Role of Feedforward and Feedback Inhibition in Modulating Theta-Gamma Cross-Frequency Interactions"

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Review in brief

The authors propose a detailed investigation of the different roles of feed-forward and feedback theta rhythmic spiking bursts in modulating gamma-band bursts at the local level within cortical column circuit models. The results proposed rely on solid theoretical modeling, which I find well designed. Improving the clarity of the text and of results presentation would lead to a better the assessment of their robustness.

Thanks to its relevance for the field, I would be glad to revise an updated version of the manuscript.

Summary

The authors resort to two alternative models of cortical cells interaction (Interneuron Network Gamma, ING, and Pyramidal ING, PING), respectively associated to feed forward inhibition and feed-back inhibition, inducing fast-to-slow interactions vs slow-to-fast interactions. The cell types modeled are Pyramidal Cell (PC) and Basket Cell (BC), interconnected via excitatory (AMPA, NMDA) or inhibitory ($GABA_A$) synapses, modulating the directionality of feed forward and feedback interactions. The authors introduce theta-band oscillations in the range of 4-8 Hz, and gamma-band oscillations in a very wide range spanning 30-150 Hz. Through the study of theta-gamma interactions, the authors assess the possibility of flexibly switching directionality between the two rhythmic interactions as assessed via amplitude-to-phase coupling and mutual information analyses.

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Conceptual Remarks

Methods: Theta-gamma generation in the θ-ING and θ-PING motifs

The authors report "*Each cycle contains 10000 spikes, distributed according to a second Gaussian*". It is not clear what is distributed according to a second Gaussian. Is it their spiking time? or any other feature?

Methods: Cross-Frequency-Coupling

The statement "*This method involves first filtering the signal at both f_{high} and f_{low}*" needs further elaboration. What filtering method is used? What are f_{high} and f_{low}? What is the pass/transition band width used? Is the band pass filter using any specific windowing method to compensate for spectral leakage? Is the filter used causal?

In the following, the text refers to the "*analytic signal's amplitude*", not specifying whether this refers to the quadratic sum of the real signal $x(t)$ and of its Hilbert transform $\hat{x}(t)$, i.e., $a(t) = \sqrt{x(t)^2 + \hat{x}(t)^2}$.

In the same section, the text refers to "*the Comodulogram class from the pactools Python library created by [29]*", which is not introducing Phase Amplitude Coupling (PAC) and not even hinting at the methods behind its computation.

Methods: Cross-Frequency-Directionality

First of all, I understand that it "*does provide insights into potential temporal relationships between them*", referring to slow and fast signal components, yet it is not a direct measure, as phase difference may not always imply that one signal "*leads*" the other. A linear dependence between phase difference and frequency describes how the phase shifts with frequency, but it does not inherently describe the directionality (or causality) between the signals. Directionality typically refers to the spatial or temporal relationship where one signal influences or propagates towards the other. While this can be safely assumed in the model, it must be taken with caution when applied to Hippocampus data. In real data, if the phase difference is frequency-dependent in a linear way, this could be a result of a system's properties, such as dispersion or filtering effects, but not necessarily indicate that one signal has a directional influence over the other.

Also, about the notation, I have quite some remarks. The authors first denote the Fourier transform of signals "*x*" and "*y*" as "*X*" and "*Y*", then they specify that "the series are then split into N smaller segments". But aren't the signals already discrete? The discrete Fourier transform is already made of digitized samples in frequency bins, so they would be better defined as $X(f_i)$, $Y(f_i)$, $f_i \in [0, F_s/2], i = 1, \ldots, N$.

This would drastically improve also subsequent definitions, currently bland: In $C(f)$, where summation indices i are not shown, thus not correctly reported for X and Y; even more so in $PSI(f_i)$, where summation index is not reported and the argument refers to f_j, with j undefined (presumably $\sum_{f_j \in [f_i - \beta/2, f_i + \beta/2]} C^*(f_j) C(f_j + \Delta f)$, with *, β and Δf to be defined). Also, in the same section, the specification "*In cross-frequency analysis, the PSI is adapted by when y is not a signal independent from x, but rather the amplitude of x filtered around a high frequency, f_{high}*" is really not comprehensible, and f_{high} is still not defined.

Lastly, in this section, the authors "*normalise the CFC so that it takes values between 0 and 1, thus creating a mask*", which is probably understandable, but it would be appreciated to specify if the normalization is a min-to-max re-ranging, or if it is a peak normalization, or else, eventually also giving further hints into why is this considered a mask.

Methods: Mutual Information

For the way it is stated, it is not clear why would the variables x and y be continuous random variables, nor what is their physical meaning. If they are time series obtained through convolution with exponential kernel, as defined in previous section ("*From spikes to continuous timeseries*"), it would make sense to consider them as continuous. Yet, they are processed as binned samples via the "*Scikit-learn*" module, thus possibly suggesting to use the finite summation form instead of the theoretical double integral version, and that keeping in mind that probability mass functions, thus MI, are estimated, rather than calculated.

Nomenclature and results presentation

The objectives of the investigation shall be more clearly defined. Starting at "*fast activity*" in the abstract, to "*brain oscillations*" in the summary, and "*mammalian brains exhibit oscillatory activity*" in the Introduction, the authors should better define what is intended as "*activity*" and as "*oscillations*". Neural activity is a broadly used term that may refer to many things, like extracellular spikes, local field potentials, or cellular membrane potential. Also, it is important to clarify if there is a difference between what is empirically measured in Hippocampus data and what is assumed in the ING/PING models. Also, there has to be a clear definition of "*brain oscillations*". I assumed that, as it is generally the case, and as by the main Figures, the authors refer to periodic bursts of (extracellular) spiking activity giving rise to rhythmic oscillations in the average firing rate tuned to different frequency bands, of which theta and gamma are considered of interest for the submitted work.

All figures. Colorbars shall indicate what they refer to (e.g., CFC, CFD).

Figure 1. The acronyms PC and BC are used in the caption before they are introduced in the text. Besides the indication CFC/CFD in the colorbar, there also needs to be indicated in the legend which panels refer to CFC and CFD, *"(a) Cross-Frequency Coupling (CFC, top right) and Cross-Frequency Directionality (CFD, bottom right)".*

Figure 2. "*(c-d) Theta-phase spiking profiles*" it is not clear what is the physical meaning of the y-axis. Is it time series obtained by convoluting spike events to exponential kernels? Is it the equivalent of a firing rate? It should be more clear why is it called "*profiles*" and it has [a.u.].

And most of all, I could not understand the meaning of "*each spike is associated with the theta phase of the synaptic current measured at the distal dendrites of PCs*". A single spike is not associated to a phase, but the firing rate or its time series obtained by the convolution with some kernel is.

Also, the contour lines showing CFD above 95th percentiles can be barely seen, they would probably more salient in gray.

Figure 3. The caption could have mentioned why the first two BC panels from the top (v.) only show one blue line, and it is eventually because the BCs are not affected by changes in synaptic coupling strengths.

Also, it is not fully clear what "*the orientation of the coloured arrow indicates whether the firing rate increases, decreases, or remains the same as the corresponding synaptic weight increases*" is supposed to mean. Is a flat, rightwards directed arrow meaning no increase? but rightwards shift? and what about upwards/rightwards directed arrows? Increase and shift? So they indicate both change in rate and shift in phase?

Figure 4. Are panels in (b) always reflecting weights in rightmost column of (a) where corresponding stars are? If yes, I suggest reporting this in the caption.

If I understand correctly, the blue shaded rectangles stand for transitions in theta-gamma directionality shifting from theta-to-gamma (θ-PING) to gamma-to-theta (θ-ING), as indicated by CFD sign, but the transition happens across panels, not within panels. If so, there would also be a full blue star panel with gamma-to-theta directionality. As it is now, is not so easy to grasp the change in directionality and that this change occurs across panels.

Lastly, the authors state "*Note how increasing feedforward inhibition advances the firing of BCs*". Does this refert to "inducing phase anticipation in the firing rate of BCs"?

Figure 5. It is not clear how are C2 and C3 characterized. Are they they equivalent of stars transitioning from blue to red? is the change due to change in weight between theta and BC? If so, it should be clearly

stated in the caption.

It could be nice to show in the diagram (b) where are the variables out taken.

Results

The authors state "*Overall, these results rule out a spurious contribution of theta harmonics or wave shape to the sign of CFD*". It would have been nice to hint at which would be the expected alternative results in that case, and why is the evidence so clearly discarding such eventuality.

In the following paragraph, it is not clear what the authors mean with "*we assigned to each PC and BC spike the theta phase associated to the synaptic current of the theta input in the distal dendrite of the PC*". The wording needs to be improved. One does not possibly assign a theta phase to a spike, and it is not clear what is that done for.

Discussion

Overall, I find that this work provides substantial advancement in the understanding of rhythmic bursts of action potentials across cellular populations.

I found interesting the application to Hippocampus data, where the circuitry proposed a neat simplification, which is not easy to extend to the cortex, where cell types have larger variation, with diverse putative functional roles.

I found fascinating to connect such findings to the evidence for the existence of "smooth cells" and "pyramidal cells" in a canonical microcircuit propagation in motif in the neocortex[1][2][3], and broader inter-areal spectral segregation theories[4][5], previously attempted to combine[6][7][8].

Minor remarks

The text bluntly reports multiple times references (e.g. "*adapt a model from the work of [30]*") which does not read well at all. I would suggest using more standard format including the authors and date with reference (e.g. "*we adapt a model from the work of Neymotin et al., 2011[30]*").

I would suggest refraining from using "*demonstrates*", while it is better accepted for the modelling part, it is less so for the data analyses, for which I would suggest using "*to show*".

References

1. ^ Rodney J. Douglas, Kevan A.C. Martin, David Whitteridge. (1989). A Canonical Microcircuit for Neocortex. Neural Computation, vol. 1 (4), 480-488. doi:10.1162/neco.1989.1.4.480.
2. ^ Sacha B. Nelson. (2002). Cortical Microcircuits. Neuron, vol. 36 (1), 19-27. doi:10.1016/s0896-6273(02)00944-3.
3. ^ Andre M. Bastos, W. Martin Usrey, Rick A. Adams, George R. Mangun, et al. (2012). Canonical Microcircuits for Predictive Coding. Neuron, vol. 76 (4), 695-711. doi:10.1016/j.neuron.2012.10.038.
4. ^ André Moraes Bastos, Julien Vezoli, Conrado Arturo Bosman, Jan-Mathijs Schoffelen, et al. (2015). Visual Areas Exert Feedforward and Feedback Influences through Distinct Frequency Channels. Neuron, vol. 85 (2), 390-401. doi:10.1016/j.neuron.2014.12.018.
5. ^ Timo van Kerkoerle, Matthew W. Self, Bruno Dagnino, Marie-Alice Gariel-Mathis, et al. (2014). Alpha and gamma oscillations characterize feedback and feedforward processing in monkey visual cortex. Proc. Natl. Acad. Sci. U.S.A., vol. 111 (40), 14332-14341. doi:10.1073/pnas.1402773111.
6. ^ Rodney J. Douglas, Kevan A.C. Martin. (2004). NEURONAL CIRCUITS OF THE NEOCORTEX. Annu. Rev. Neurosci., vol. 27 (1), 419-451. doi:10.1146/annurev.neuro.27.070203.144152.
7. ^ Stewart Shipp. (2007). Structure and function of the cerebral cortex. Current Biology, vol. 17 (12), R443-R449. doi:10.1016/j.cub.2007.03.044.
8. ^ Demetrio Ferro, Jochem van Kempen, Michael Boyd, Stefano Panzeri, et al. (2021). Directed information exchange between cortical layers in macaque V1 and V4 and its modulation by selective attention. Proc. Natl. Acad. Sci. U.S.A., vol. 118 (12). doi:10.1073/pnas.2022097118.

Declarations

Potential competing interests: No potential competing interests to declare.