Qeios

Peer Review

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

Bernard A. Pailthorpe[1]

1. Physics, Brain Dynamics Group, University of Sydney, Sydney, Australia

Review to Qeios: Chalkiadakis et al.

(v1 26/2/25)

This is a professional, well prepared manuscript. The topic, relating to Theta-Gamma CrossFrequency Interactions, is of interest in the contemporary neuroscience literature. The research is sound and references an extensive background literature. The writing is clear and proceeds logically. However there are some gaps, as discussed below. Thus minor revisions would improve the paper.

Abstract should be labelled as such.

The aims, to understand directionality of multi frequency coupling, are worthy and partially fulfilled by the methods employed – more on that below.

In discussing the aims, refs 29, 30 are mentioned: the first introduces the unusual concept of a “phase frequency”, that was already employed in Fig.1 (cf. discussion of Figures, below). This f /phase appears to be a phase difference between oscillators at two differing frequencies - the authors would understand this in detail, but it is not clear from the text as is. Authors should introduce and explain these concepts early on, to aid the reader in understanding the methods and results.

The models O-ING and O-PING are first introduced in Fig. 1, without explanation, and then only discussed later (p6) – this is confusing. A few sentences are needed, say on page 3 before Fig 1, to briefly introduce these models and to guide the reader.

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Overall, the blending of methods from physical sciences with biological data is a good approach that is likely to lead to new insights.

With a range of minor revisions, discussed below, this work is worthy of publication.

Methods:

The precise model used in this simulation study is hard to discern from the text as is. Network motifs, of presumably 2 neurons, are depicted in Figs 1b(i) & 1c(i), but not described adequately in the text. The NEURON software is referenced, but note that this is a soma/axon level model of a single neuron. Reference to ING models [your refs 21, 31-33] describe network of many neurons, some randomly connected. The further discussion that "our model was adapted from previous works modeling the hippocampus CA3 area by [30] ", for this reader, that only confused things more. That work studied a randomly connected network of 800 Py plus 200 BC neurons. More clarity is needed on what the precise model is.

What is described well is inputs to, and features of, the model – currents, effects of modulating by chemicals, etc. Eventually (p10) it emerges that "Each simulation included 200 PCs and 40 BCs." That was hard to find and should be clearer and listed in a model description up front in the Methods section. Its also hard to reconcile this with the motifs in Fig. 1. In summary, fragments of the model description are scattered through this section - they should be aggregated into a single paragraph, with details discussed later, as needed.

The text refers the reader to a 2024 PhD thesis for a "comprehensive description of the model"; that is not sufficient, and the thesis may be hard to access? For this paper to be selfcontained a paragraph should be devoted to describing the actual model underlying the results, possibly with a related diagram. And/or a compact paragraph, up front, describing key features of the model would also help.

A key feature of the model is that the theta input is generated externally, rather than by another intrinsic oscillator. The reality of that assumption is not assessed? Neural masses (NM) exhibit oscillation frequencies dependent on their internal characteristics (time constants, etc.) and their connectivity to other neural masses. Feedforward and feedback links and their weights drive the oscillations, so that frequency and phase shifts emerge. This may be a little difference to a fixed external drive. Have the authors compared their simple model to a more complete model, where a NM(theta) interacts with a NM(gamma), so that the two oscillations mutually stimulate and influence each other? The simple model has utility; even so, it would be helpful to know its limitations?

This work uses the computed coherence of the two signals in the Cross Frequency Coherence framework to infer directionality of coupling of the two oscillators. It has been tested [ref 29] but it's still unclear how statistically robust it is - might it be a special case? Finding causation amongst correlation is an ongoing challenge. Cf. methods to Infer directionality: Grainger causality (discussed in ref 29) and transfer entropy (book by T Bossomeir)

Results:

A range of simulation conditions and resultant CFC and CFD predictions are presented, with much detail, and then compared with multiple experiments (mouse, rat, human). This is impressive and likely interesting to a neuroscience audience. It will take time to digest and assess that – likely in the years after publication, rather than in this review (if it is to be timely).

At a first reading of this mss. it was unclear if it was simulating single neurons or ensembles of neurons – cf. comments on Methods. More clarity on what is being simulated would make the Results easier to digest and assess.

Other:

Note other relevant work. Two classes of neuronal network models generate gamma band oscillations and bursts: Leaky Integrate and Fire (LIF) models, and extended Neural Mass (NM) models. LIF [1, ref below] models typically employ 80% excitable model neurons plus 20% inhibitory, typically randomly connected. The resultant power spectral density spans alpha to gamma bands, depending on the neuron and network parameters. NM models [2] are well established in studying neural oscillations, such as EEG, and interacting anatomical areas. They include excitatory and inhibitory neural populations with feedforward and feedback interactions. An extension, to include an extra fast inhibitory population, generate gamma bursts [3,4] and describes well EEG observations. Your new work complements those studies, especially in highlighting the role of inhibition. Clarifying any uncertainties of the model used in the present manuscript will help reconcile your results with these other studies.

Figures:

The figures are very dense and crowded – the reader needs to magnify them to see what they are about, and then to read captions, etc. Consider breaking them up into multiple figures. Likewise the captions are very dense and hard to read. This makes reading the paper more difficult: have mercy on the reader. In Fig 1a ii-vii there are three variable plotted, one being represented by the color. I am

guessing that the color scale represents CFD, with scale indicated by the colorbar? – that is not stated or explained in the caption or the text. Note that the same colorbars in Fig 5 of ref 29 are labelled CFC and CFD – doing that for your Fig 1 would be helpful. I couldn't follow f/ ampl vs. f/ phase (as the y-x axes)? More explanation (eg. in the context of ref 29) would help.

Minor details, or corrections:

The mss. is largely free of minor errors.

Nb. "modelling" has 2 l's.

The reference list is little hard to read, since it appears to be all italics. Common practice is to use a regular type face for author list, journal, vol, year; with maybe italics reserved only for the title. Sometimes volume(issue) is underlined.

Each reference begins with a superscript character[s] ("^" or "a,b,c..."): it is unclear what this means, or what message is conveyed? - possibly omit; or explain the intent.

Extra Refs.

1. Mazzoni, A., Panzeri, S., Logothetis, N. K., and Brunel, N. (2008). Encoding of naturalistic stimuli by local field potential spectra in networks of excitatory and inhibitory neurons. PLoS Comp. Biol. 4: e1000239. doi: 10.1371/journal.pcbi.1000239.

2. Jansen, B. H., and Rit, V. G. (1995). Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. Biol. Cybern. 73, 357–366. doi: 10.1007/BF00199471.

3. Wendling F, Bartolomei F, J. J. Bellanger JJ, Chauvel P. (2002). Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. Eur. J. Neuroscience, 15, 1499-1508. doi:10.1046/j.1460-9568.2002.01985.x

4. Zavaglia, M., Astolfi, L., Fabio Babiloni, F., and Ursino, M. A. (2006).

neural mass model for the simulation of cortical activity estimated from high resolution EEG during cognitive or motor tasks. J. Neurosci. Methods 157, 317–329. doi: 10.1016/j.jneumeth.2006.04.022.

Declarations

Potential competing interests: No potential competing interests to declare.