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Commentary

Commentary on the Pinotsis and Friston Neural Fields DCM and the Cadonic and Albensi Oscillations and NMDA Receptors Articles

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1. Introduction

It is a pleasure to discuss our article in relation to the other two on the topic of gamma oscillations in the last issue. Due to the different approaches of each article, we will focus on only one at a time in relation to how our proposed theoretical model fits with the points made. This paper-specific discussion is followed by suggestions for future research tied to all three articles.

2. Relationship to Pinotsis and Friston paper

2.1. Relationship of gamma oscillations to underlying microstructure

Pinotsis and Friston [1] provided an interesting paper on the combination of neural population models and dynamic causal modeling that provides evidence to distinguish among alternative hypotheses regarding cortical excitability and the microstructure underlying gamma oscillations. Their detailed model provides an opportunity to compare how our proposed dynamic column model provides a more detailed understanding of the microstructure of the cortex that is consistent with their analyses. In relation to their discussion of gamma oscillations and lateral connections, the basic assumption is that in local populations there is an excitatory center and an inhibitory surround. Although this assumption is an accurate statement in relation to the inhibitory surround, the Dimensional Systems Model (DSM) that we described leads to a more elaborate understanding for the excitatory center of the receptive field [2].

When a stimulus is first processed or a new column is formed in learning, there is initially expected to be more excitatory activity in the column than there will be later with repeated stimulation. The three or four pyramidal cell (PC) motifs with high interconnectivity in the boundary

minicolumns of the column are expected to be the initial ones to activate via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (2 to 10 ms duration) leading to activation of the AMPARs of the interconnected PCs and interneurons. With the activation of the other three and four PC motifs inside the column in line with the boundary ones, there is increased excitatory activity throughout the column followed by the pervasive gamma-aminobutyric acid (GABA) inhibition inside and outside the column resulting from parvalbumin-expressing (PV) interneuron involvement during the gamma oscillatory activity. Although the N-methyl-D-aspartate (NMDA) receptors (100 to 400 ms duration) next become predominant on both PCs and the PV and somatostatin-expressing (SOM) interneurons, the excitatory aspect is expected to occur in the boundary minicolumns only via vasoactive intestinal polypeptide-expressing (VIP) interneuron disinhibitory control. At that time, the interior PCs are inhibited. During reentrant signaling [3,4] only the PCs in the outer minicolumns are disinhibited via VIP interneurons while both interior and exterior minicolumns are inhibited via neuroglial cell GABA release. We further suggested that the outer minicolumns are synchronized and become phase locked with outer minicolumns of other columns in the circuit across all frequency ranges.

With repeated stimulation, both the inhibitory effect of neuroglial cells and the interior PCs falling out of synchrony from the outer minicolumns' PCs theoretically allows the localization of synchronized activity (i.e., signal) to be in the outer minicolumns only. Within a weak pyramidal interneuron gamma (PING) model, lack of PC activation of interior minicolumns results in failure to activate the PV interneurons and gamma oscillatory activity decreases. Thus, the outer minicolumns maintain gamma synchrony with sufficient PC activation, but overall gamma frequency oscillations across the entire column lessen. With decreased cellular activity in a column, measures of metabolic activity are expected to decrease as well. Such a pattern fits well with a biologically efficient system with short-term higher energy expenditure during column formation (i.e., new learning and early memory), but less long-term energy costs following consolidation (i.e., long term memory).This pattern of decreased activity is also consistent with studies showing repetition suppression in the cortex [5]. An interesting extension of their findings would be to examine data from a study on repetition suppression to examine whether their modeling techniques would yield evidence consistent with the more detailed microstructure described in the DSM theory.

A second point of discussion on the relationship to microarchitecture come from page 27, where Pinotsis and Friston note that for both conductance and convolution models as the strength of inhibition increases, activity becomes progressively faster. However, our column model suggests the cause and effect are reversed. With increased neural firing, the release of GABA increases and accounts for the increase in inhibition. They note a discrepancy of the two models in which convolution models show decreases in gamma power while conductance models show the opposite effect. Our model suggests the boundary minicolumns more likely fit the conductance pattern while the interior minicolumns fit the convolution pattern. Additionally, initial column activation would show a general conductance pattern during the AMPAR duration, but during subsequent NMDAR involvement the conductance pattern would be in the outer minicolumns only.

2.2. Understanding contrast effects on gamma oscillations

In their Bayesian Model Comparison tied to cross spectral density features under different levels of contrast, the results best support a combination model. That includes recurrent connections of neuronal populations, horizontal connections between excitatory and inhibitory pools of neurons,

and spatial dispersion of horizontal connections. Based on that best model, they next examined parameter estimates and note, "these results suggest that the largest contrast modulations are observed in (log scale parameter) estimates of connections to and from the superficial pyramidal cells" (p 32).

First, the finding that superficial PCs' connections account for the largest gain modulations is consistent with our theory because, the layer2/3 PCs are those that have the close horizontal connections involved in activating high-order columns and are logically the ones that best account for such modulations. While this is a point of consistency with the data, we also think that our theory can provide an explanation for the empirical finding of differences in the size of the area of activation for differing contrast levels.

The data were based on a task (which we assume was trained as an operant response based on contingent reward) in which a monkey first fixated its gaze and later released a lever when it detected a color change at fixation. Pinotsis and Friston focused on the bottom-up sensory level. However, it is important to keep in mind that each receptive column, both lower-order and higher-order, has its respective action column. In the case that the monkey was trained to depress a lever, other higher-order external action columns (and one highest-order action column for all inputs) were formed based on input from the color action columns, the frontal eye field action columns, and the action columns involved in the premotor area of the operant response (in addition to the medially located internal columns associated with the reward conditions and transitional regions between the internal and external areas, such as the supplementary motor area and the anterior insula). The relevance of the highest order external action column and its lower order action color columns is that we believe they are involved in the larger response area during low contrast because they exert a top-down influence on the receptive columns.

In color perception, input from the V1columns activates higher-order columns in V4. In the task of discriminating color contrast, there are multiple lower-order columns shared by higher-order ones. The point at which a new single higher-order column activates versus the one previously activated is dependent on new lower-order columns activating and previous lower-order columns deactivating. Higher-order columns share lower-order columns because color information would be represented across multiple lower-order columns. Two differentiable color contrasts would be represented by two different higher-order V4 columns. In high contrast, few or no lower-order columns are shared and a new higher-order column activates. However, more similar colors would be expected to share more lower-order columns (i.e., a distributed lower-order representation). For high contrast, the smaller area of activation is due to few lower-order columns activating in a bottom-up fashion. High contrast leads to fast activation of the associated action column of the newly activated high contrast column and quick lever release. The low contrast condition involves more shared lower-order columns and the larger area being activated. These conditions require higher-order action columns to activate a number of lower-order action columns which in turn activate each of the associated receptive columns. In essence, there is a progressive pattern of isolating the specific lower-order receptive columns that are actually activated and deactivating each higher-order column not being fed by all lower-order columns. If an actual higher-order receptive column is identified (i.e., there is a contrast), the associated action column activates and the operant response ensues. This process of interactive activation has some similarities to models of perception in which top-down and bottom-up activation interact to drive perception [6].

3. Relationship to the Cadonic and Albensi article

Cadonic and Albensi [7] provided an overview of oscillatory activity, tying this into neural systems. They next discuss NMDARs, noting the support for their involvement in synaptic plasticity and memory. They provided information on pathological activation of NMDARs (both hyperactivity and hypoactivity) that has been tied to disorders, including Alzheimer's and schizophrenia. They conclude by noting that the brain activity oscillations are a relatively new area of research that has provided an added dimension in memory and cognition, with the interplay of NMDARs being an additional dimension.

Of the numerous points made by Cadonic and Albensi, we will comment on one our theory may explain. Hyperactivity of NMDARs leading to excitotoxic processes and cell death (p 59) likely results in the death of both PCs and interneurons involved in dynamic column consolidation, as well as the late loss of minicolumns in Alzheimer's disease. Early damage occurs with hippocampal neurons and theoretically leads to disruption of the pacemaker functions and would be expected to disrupt the consolidation of parallel columnar circuits. Notably, this damage would have no effect on dynamic column formation in the medial temporal perirhinal and entorhinal cortex based on the same stimulus input, only in the failure to consolidate the new columns.

An example is list learning in which the patient can immediately repeat the list and show short term improvement over several trials. Reentrant processes involving adjoining columns and the thalamus can provide sufficient short-termmemory performance. However, the lack of the long-term potentiation in hippocampal cells discussed by the authors removes the "driver" (p 58) of memory encoding at the level of new medial temporal cortical columns and there is disrupted long-term memory. This account is a reasonable explanation of problems in delayed recall of verbal materials in early Alzheimer's with relatively intact short-term memory. If the excitotoxic process leads to cell death at the columnar level, it is a logical cause of later minicolumn loss associated with the disorder. At that point, short term memory would also be affected because the cells involved with dynamic column formation of the new association memories in the medial temporal lobe have been lost. With progression, the problems in executive functions are theoretically related to loss of minicolumns comprising the action columns in the frontal lobes.

We hope the discussed applications of dynamic columns based on the DSM theory are helpful in developing a better understanding of the theory. By taking the information provided by the other authors and providing explanations based on our theoretical model, we hope this encourages other researchers to see how well it explains results from their studies. Although we readily acknowledge our theoretical model is far from conclusive, we believe the level at which it is described can lead to a number of testable hypotheses. It is of note that others [8] are also suggesting that transient dynamics in balanced excitation and inhibition is a generic organizational principle in the cerebral cortex. All modeling studies work under a number of assumptions, and the current theory provides a basis for how the current assumptions may be modified to see if fit and prediction improve. If the dynamic column is the cortical bit, neuroscientists can concentrate on this level in relation to the current and developing technologies tied to the EU Human Brain Project and the US BRAIN Program. In the short run, we expect some interesting discussions and debate will result from the new theory. In the long run and in keeping with the stated goals of AIMS Neuroscience, perhaps new neuroscience theory can provide direction for ongoing projects to allow a faster arrival at the goal of understanding the human brain.

Conflict of Interest

The authors declare to have no conflict of interest.

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