Boundary and Event Cells Modulate Gamma Frequencies in Theta-Gamma Phase Amplitude Coupling to Encode Details in the Working Memory

Research Proposal

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Why do you remember what you ate for breakfast, but not which pajamas you ate it in? Recent research has identified two types of working memory cells: boundary and event cells. Boundary cells respond around small or large points of change in visual content (soft or hard boundaries) during encoding if the content is made available for recall. The magnitude of boundary cell responses during encoding predicts the strength of the memory. Event cells are related to the memory of time, firing after a hard boundary at a consistent phase of the theta band during encoding. Event cell phase locking to theta occurs when temporal order, or sequence, is encoded for recall (Zheng, 2022).

Studies in *rats* have robustly identified a type of memory cell, a place cell, active during *recall* when traversing a known environment. Place cells that fire close in time represent a place field, or the memory of one location, noted by a single gamma wave crest. The crest occurs at the same point on the theta phase as the memory is active, and the time difference between gamma crest locations on theta directly represents their spatial separation (Lisman, 2008, **Fig.1D**).

The dynamic and function of boundary and event cells mirror that of place cells. Both cell populations peak in activity upon the detection of a notable change in scenery (Zheng, 2022; Lisman, 2008). Theta precession (see Lisman et al.) during the recall of sequential observation is seen in both rats and humans (Reddy, 2021). With place cell firing directly related to gamma, it should be noted that improvements in the working memory of *humans* have been seen when gamma peaks on theta's falling phase just after a crest (Jones, 2020, **Fig.1A**). In addition, the theta-gamma relationship can be seen as phase-amplitude coupling (PAC, **Fig.1**). Older adults with impaired working memory function lacked the theta component of theta-gamma PAC; HD-tACS activation of theta improved PAC and working memory significantly (Reinhart, 2019).

The similarities between human memory cells and place cells and the relevance of theta precession and theta-gamma PAC to their functioning led me to hypothesize that, boundary and event cells encode visuals and sequences from the working memory by modulating gamma in theta-gamma PAC. To test my hypothesis, I propose the following.

Young adult subjects will be measured through electroencephalography (EEG) while doing the task. A slide show will consist of 10 images each shown for 750ms, 6 to 9 being of similar look and content (i.e. warm colored animals), and the rest being stand-out images of notably different looks and content that will be sandwiched by two of the similar images. Next, the subject will be asked standard screening questions for 15000ms. Finally, a timer is started and the subject will recite the slide images and any details in order to the researcher, who records responses and response time from start. This should be repeated 5-10 times per subject. EEG data will be processed with the state space

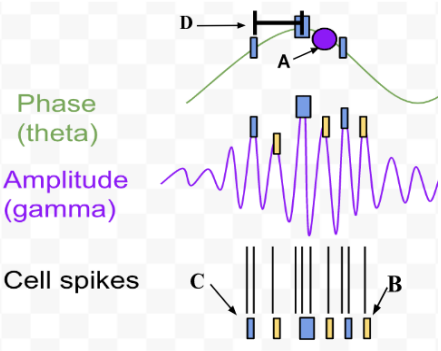

Fig.1- Diagram of Predicted Recall Process From Working Memory Encoding **A** Theta-gamma PAC at the falling side of theta post peak. **B** Boundary cell responses that encoded content. **C** Boundary cell responses that elicited event cell activity, encoding content and time/ sequence. **D** Distance relative to time and space between events.

method, a method of PAC analysis designed to address areas of error in previous methods (Soulat, 2022), MatLab, and SPSS. Theta and gamma will be extracted and time locked. The task setup includes similar and stand-out images, replicating the soft and hard boundaries noted in Zheng's study, so recall performance can be attributed to boundary/ event cells.

Subject responses and corresponding EEG data will be separated into three categories: recalled images correctly in order, recalled images out of order, and no recalled images. If one subject has multiple recordings in the no-recall category (ideal), average them together. For images recalled in the correct order: (1) gamma should be viewed during the encoding phase about 150-250 ms after the first image's presentation. If peaks are consistently observed 150-250ms after recalled images or details, then these peaks likely represent boundary cell activity specific to that image or detail. If the number of peaks reflects the number of recalled items, then working memory loads may be determined by the number of gamma peaks per theta over the time of encoding. (2) If 50-150 ms after the boundary cell response a gamma peak is phase-locked to theta, then boundary cell activation strength in the parahippocampal gyrus may have elicited event cell activity (**Fig.1C)** in the hippocampus. If such a peak exists, I predict it will occur near the presentation of a stand-out image. The space between peaks phase-locked to theta should be investigated in relation to temporal order. For images recalled out of order, only perform analysis 1. If a peak only occurs 150-250ms post-presentation of recalled images, then this peak may represent boundary cell responses that failed to reach a certain amplitude (**Fig.1B)**, preventing the signal from reaching event cells in the hippocampus.

Comparing encoding and recall data can confirm theta precession of the events encoded by gamma exists during recall. If a peak thought to mark successful encoding appears around the same slope point of opposite magnitude soon after the image is recalled, then this process may represent the reversal of information flow seen in recall theta precession. Memory strength will be analyzed in the context of response times during recall. For each image after the first, subtract the time of the previous response(s). If the strongest memories (shortest recall time) display overall gamma activity peaking on the falling side of theta just after its crest, then PAC at this location is most ideal for memory strength, explaining why this is noted in working memory improvement. Other amma peak locations should also be explored.

The final part of the analysis will investigate amplitude thresholds. Data from subjects with a no-recall trial will be subtracted from their data in the other category(ies). I predict that subtracting the activity of encoding failure from success will reveal approximate gamma amplitude thresholds needed for an image to be encoded and/or sequenced.

The study does not come without possible limitations. It should be noted that the attribution of activity to boundary and event cells assumes Zheng's findings are consistently accurate, as EEG recordings cannot directly measure the activity of these cells. Secondly, theta and gamma activity could be a secondary result of other frequency bands, such as alpha. Finally, a number of outcomes not proposed here may appear to be significant and should not be ignored.

Works Cited

Jones, K. T., Johnson, E. L., & Berryhill, M. E. (2020). Frontoparietal theta-gamma interactions track working memory enhancement with training and tDCS. *NeuroImage*, *211*, 116615. https://doi.org/10.1016/j.neuroimage.2020.116615

Lisman, J., & Buzsaki, G. (2008). A Neural Coding Scheme Formed by the Combined Function of Gamma and Theta Oscillations. *Schizophrenia Bulletin*, *34*(5), 974–980. https://doi.org/10.1093/schbul/sbn060

Reddy, L., Self, M. W., Zoefel, B., Poncet, M., Possel, J. K., Peters, J. C., Baayen, J. C., Idema, S., VanRullen, R., & Roelfsema, P. R. (2021). Theta-phase dependent neuronal coding during sequence learning in human single neurons. *Nature Communications*, *12*(1), Article 1. https://doi.org/10.1038/s41467-021-25150-0

Reinhart, R. M. G., & Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. *Nature Neuroscience*, *22*(5), 820–827. https://doi.org/10.1038/s41593-019-0371-x

Soulat, H., Stephen, E. P., Beck, A. M., & Purdon, P. L. (2022). State space methods for phase amplitude coupling analysis. *Scientific Reports*, *12*(1), Article 1. https://doi.org/10.1038/s41598-022-18475-3

Zheng, J., Schjetnan, A. G. P., Yebra, M., Gomes, B. A., Mosher, C. P., Kalia, S. K., Valiante, T. A., Mamelak, A. N., Kreiman, G., & Rutishauser, U. (2022). Neurons detect cognitive boundaries to structure episodic memories in humans. *Nature Neuroscience*, *25*(3), 358–368. https://doi.org/10.1038/s41593-022-01020-w