

# Oscillatory Patterns in Behavioral Responses during a Memory Task

**M ter Wal (M.J.terWal@bham.ac.uk)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

**J Linde Domingo (JXL495@student.bham.ac.uk)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

**J Lifanov (JXL1118@student.bham.ac.uk)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

**F Roux (FredericRouxw@googlemail.com)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

**L Kolibius (LDK898@student.bham.ac.uk)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

**D Rollings (David.Rollings@uhb.nhs.uk)**

Queen Elizabeth Hospital Birmingham, Edgbaston, B15 2GW, Birmingham, UK

**V Sawlani (Vijay.Sawlani@uhb.nhs.uk)**

Queen Elizabeth Hospital Birmingham, Edgbaston, B15 2GW, Birmingham, UK

**R Chelvarajah (Ramesh.Chelvarajah@uhb.nhs.uk)**

Queen Elizabeth Hospital Birmingham, Edgbaston, B15 2GW, Birmingham, UK

**B Staresina (B.Staresina@bham.ac.uk)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

**S Hanslmayr (S.Hanslmayr@bham.ac.uk)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

**M Wimber (M.Wimber@bham.ac.uk)**

University of Birmingham, Edgbaston, B15 2TT, Birmingham, UK

## Abstract:

Computational models propose that memory formation (encoding) and memory retrieval occur at opposite phases of the hippocampal theta rhythm. Such phase locking would predict that memory processes are, effectively, rhythmic themselves. Here, we ask whether rhythmicity of encoding and retrieval is detectable at the level of behavior. We analyzed the behavioral response times from different phases of a memory task and compared them to responses from a visual task. We report that memory-dependent task phases produced detectable oscillations in responses across trials, while memory-independent responses were not oscillatory. Oscillation frequencies centered in the theta frequency range (2-5Hz), in line with previous findings in humans. In addition, we show that the memory task induced phase locking in the same frequency range in hippocampal (intracranial) EEG recordings, providing a mechanistic underpinning for the oscillation in behavioral responses.

**Keywords:** episodic memory; theta oscillations; behavior; rhythmic sampling; intracranial EEG.

## Memory processes are rhythmic

When we make new memories or remember existing ones, information is sent within and between the hippocampus and cortical areas that are involved in sensory and associative processing. Many studies in rodents, but also in humans, have shown that the theta rhythm in the hippocampus is linked to successful storage of new and retrieval of old memories (see Colgin, 2016 for a review). One potential role for this theta rhythm is the separation, in time, of the information stream within the hippocampus from



information coming from the cortex, preventing new information from interfering with stored memories, while still allowing for new experiences to be encoded (Hasselmo, Bodelón, & Wyble, 2002).

Recent findings support the notion that the encoding and retrieval information streams are locked to the theta rhythm, particularly in area CA1 of the hippocampus. Several groups report that during encoding, gamma oscillations originating in Entorhinal Cortex appear in CA1 only around the trough of the theta cycle. Similarly, during retrieval, slow gamma oscillations from CA3 consistently occur before the peak of the theta oscillation (Amemiya & Redish, 2018; Fernández-Ruiz et al., 2017; Lopes-dos-Santos et al., 2018). Spiking activity of both inhibitory and excitatory neurons in EC, CA1 and CA3 show phase locking to the theta rhythm (Douchamps, Jeewajee, Blundell, Burgess, & Lever, 2013; Fernández-Ruiz et al., 2017). In addition, in a human study, when EEG signals recorded during encoding and retrieval of items were decoded with a classifier, a modulation of performance by hippocampal theta phase was observed, with optimal encoding and retrieval of items occurring at opposite theta phases (Kerren, Linde-Domingo, Hanslmayr, & Wimber, 2018). Furthermore, theta phase-locked optogenetic suppression of CA1 activity in mice led to improved task performance for the process associated with the opposite theta phase, i.e. retrieval performance improved when encoding information was suppressed and vice versa (Siegle & Wilson, 2014).

Rhythmic scanning of information has been proposed to be a more general characteristic of competing information in the brain. During visual and auditory attention tasks, sampling of the to-be-attended stimulus was alternated with sampling of other parts of the input space at a frequency of 4Hz (Fiebelkorn, Saalman, & Kastner, 2013; Helfrich et al., 2018). Intriguingly, this 4Hz rhythm did not just appear in electrophysiological signals from the relevant brain areas, but also in the behavioral responses of the monkeys and humans performing the task (Fiebelkorn, Pinski, & Kastner, 2018). With encoding and retrieval information streams in hippocampus restricted to certain phases of the theta rhythm, access to stored information can itself appear as a rhythmic process. We therefore pose the question: does rhythmic scanning of to-be encoding and retrieved information appear as oscillations in the behavioral responses during a memory task?

### Associative memory task

To address our question, we analyzed the behavioral responses recorded during seven variations of an associative memory task, including the dataset described in (Linde-Domingo, Treder, Kerrén, & Wimber, 2019), in which subjects were asked to make

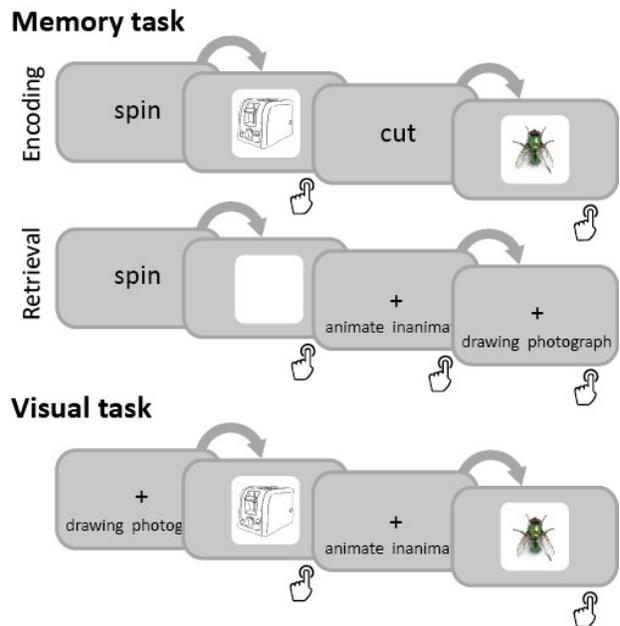


Figure 1: Task sequence and layout.

associations between action verbs and objects (Fig. 1, top). Subjects pressed a button when the association was made. After performing a distractor task, the subjects were cued with the verbs and instructed to press a button as soon as they remembered the associated object (Fig. 1, middle). Note that this setup with ‘association-made’ and ‘association-retrieved’ button presses allows us to look at the timing of these processes in relative isolation, e.g. without visual processing. The subject then answered one or two questions about the retrieved object. A part of the subjects was shown the catch question before the retrieval cue was presented. In total, 176 subjects performed the memory task. A separate group of 48 subjects instead performed a visual task (Fig. 1 bottom), where the same catch questions were answered while the objects were shown on the screen.

### The Oscillation score

To assess the frequency content of the behavioral responses from the two tasks, we collapsed button presses from all trials onto a single response trace (Fig. 2A). For each subject, we then computed the Oscillation score (O-score) for this response trace. The O-score measures the height of the highest peak in the spectrum of the response trace relative to the average spectral power (Muresan, Jurjut, Moca, Singer, & Nikolic, 2008). We Z-scored the O-score against a subject-specific reference distribution, which was produced by randomly redrawing the response times while maintaining the

overall structure of the data. We computed the O-score separately for every phase of the memory task (encoding, retrieval, catch questions) and for the visual task.

### Oscillations in memory-related responses

In the memory task, O-scores for both the encoding phase and the two versions of the retrieval task phases were significant for the majority of subjects and in a second-level analysis (Fig. 2B). Intriguingly, we did not observe significant oscillations in the answers to the catch questions when those questions succeeded the point of memory recall, even though the data were obtained from the same subjects. Neither did we find evidence for oscillations in the visual task, suggesting that the observed oscillations are the result of memory processing and are not induced by task events or sensory processing of the cues or objects.

For the memory dependent processes, individual peak frequencies of the oscillations clustered around low theta frequencies (2-5Hz, Fig. 2C), as well as frequencies that we hypothesize to be harmonics of the low theta frequency band. Further analyses revealed that only correct trials showed locking to the oscillation, while incorrect trials were uniformly distributed across phases. These results suggest that the rhythmicity of memory encoding and retrieval that has been reported in models and electrophysiological data can also be detected in behavioral responses.

### Phase locking in (i)EEG supports behavior

To detect oscillations in behavioral data, i.e. across trials, requires the presence of a rhythm with a stable phase relationship relative to one or more events in the trial. Without such a stable phase structure across trials, responses could still be phase locked within a trial, but this locking would average out across trials. The significant O-scores that we report for memory-dependent responses therefore suggest that the task induces periods of phase locking in the ongoing theta rhythm. Visually induced phase resets are commonly observed in cortical recordings and are generally broadband, but few studies have assessed the effect on the memory-related theta rhythm (Mormann et al., 2005; Williams & Givens, 2003).

To test our prediction, we analyzed two datasets: 1) EEG recorded in 24 healthy subjects and 2) intracranial EEG recorded in hippocampus using Behnke-Fried electrodes in 7 epilepsy patients. We report that both datasets support the existence of phase locking in the relevant theta frequency band. Phase locking is strongest after stimulus onset during the encoding phase and after cue onset during the retrieval phase and extends in time until the response. Our

electrophysiological data therefore support our behavioral results and provide a potential mechanistic link between rhythmicity in behavior across trials and hippocampal theta oscillations.

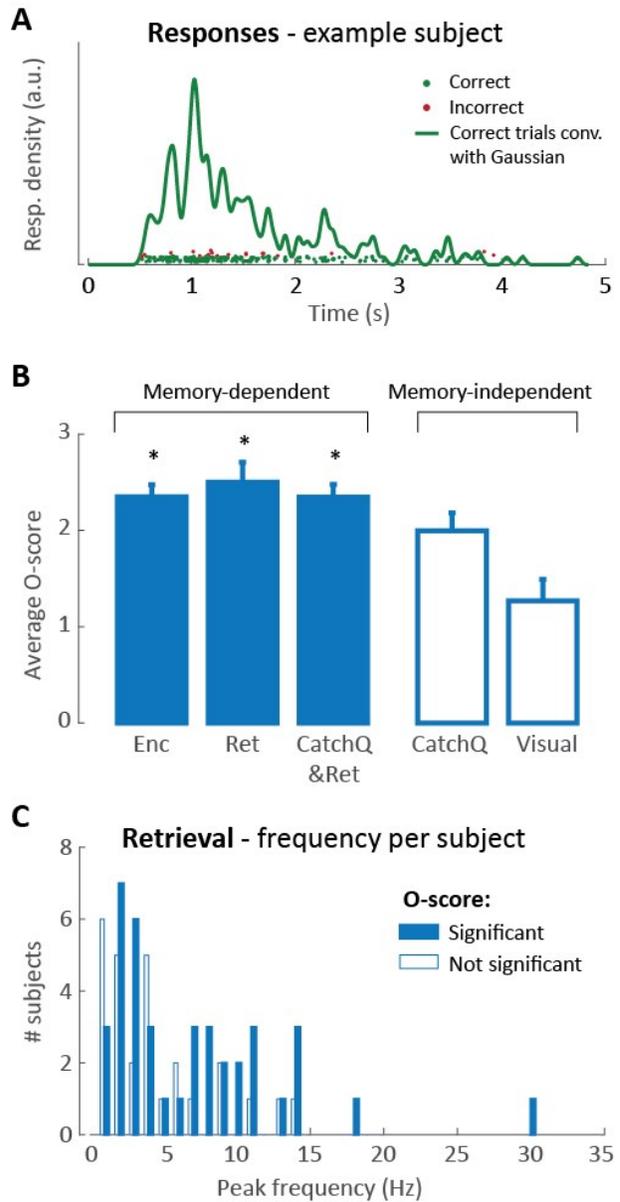


Figure 2. A: Response trace for an example subject, with dots representing individual button presses. The curve was obtained by convolving the correct responses with a Gaussian kernel with  $\sigma = 50\text{ms}$ ; B: Average Z-scored Oscillation Scores per task phase; C: Histogram of peak frequencies for the retrieval phase for subjects with significant (closed bars) and not-significant O-scores (open bars).

## Acknowledgments

This work is supported by European Research Council Starting Grant ERC-2016-STG-715714 (STREAM).

## References

- Amemiya, S., & Redish, A. D. (2018). Hippocampal Theta-Gamma Coupling Reflects State-Dependent Information Processing in Decision Making. *Cell Reports*, 22(12), 3328–3338. <https://doi.org/10.1016/j.celrep.2018.02.091>
- Colgin, L. L. (2016). Rhythms of the hippocampal network. *Nature Reviews Neuroscience*, 17(4), 239–249. <https://doi.org/10.1038/nrn.2016.21>
- Douchamps, V., Jeewajee, A., Blundell, P., Burgess, N., & Lever, C. (2013). Evidence for Encoding versus Retrieval Scheduling in the Hippocampus by Theta Phase and Acetylcholine. *Journal of Neuroscience*, 33(20), 8689–8704. <https://doi.org/10.1523/JNEUROSCI.4483-12.2013>
- Fernández-Ruiz, A., Oliva, A., Nagy, G. A., Maurer, A. P., Berényi, A., & Buzsáki, G. (2017). Entorhinal-CA3 Dual-Input Control of Spike Timing in the Hippocampus by Theta-Gamma Coupling. *Neuron*, 93(5), 1213–1226.e5. <https://doi.org/10.1016/j.neuron.2017.02.017>
- Fiebelkorn, I. C., Pinsk, M. A., & Kastner, S. (2018). A Dynamic Interplay within the Frontoparietal Network Underlies Rhythmic Spatial Attention. *Neuron*, 99(4), 842–853.e8. <https://doi.org/10.1016/j.neuron.2018.07.038>
- Fiebelkorn, I. C., Saalman, Y. B., & Kastner, S. (2013). Rhythmic sampling within and between objects despite sustained attention at a cued location. *Current Biology*, 23(24), 2553–2558. <https://doi.org/10.1016/j.cub.2013.10.063>
- Hasselmo, M. E., Bodelón, C., & Wyble, B. P. (2002). A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Computation*, 14(4), 793–817.
- Helfrich, R. F., Fiebelkorn, I. C., Szczepanski, S. M., Lin, J. J., Parvizi, J., Knight, R. T., & Kastner, S. (2018). Neural Mechanisms of Sustained Attention Are Rhythmic. *Neuron*, 99(4), 854–865.e5. <https://doi.org/10.1016/j.neuron.2018.07.032>
- Kerren, C., Linde-Domingo, J., Hanslmayr, S., & Wimber, M. (2018). An Optimal Oscillatory Phase for Pattern Reactivation During Memory Retrieval. *Current Biology*, 28, 1–10. <https://doi.org/10.1016/j.cub.2018.08.065>
- Linde-Domingo, J., Treder, M. S., Kerrén, C., & Wimber, M. (2019). Evidence that neural information flow is reversed between object perception and object reconstruction from memory. *Nature Communications*, 10(1). <https://doi.org/10.1038/s41467-018-08080-2>
- Lopes-dos-Santos, V., van de Ven, G. M., Morley, A., Trouche, S., Campo-Urriza, N., & Dupret, D. (2018). Parsing Hippocampal Theta Oscillations by Nested Spectral Components during Spatial Exploration and Memory-Guided Behavior. *Neuron*, 940–952. <https://doi.org/10.1016/j.neuron.2018.09.031>
- Mormann, F., Fell, J., Axmacher, N., Weber, B., Lehnertz, K., Elger, C. E., & Fernández, G. (2005). Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. *Hippocampus*, 15(7), 890–900. <https://doi.org/10.1002/hipo.20117>
- Muresan, R. C., Jurjut, O. F., Moca, V. V., Singer, W., & Nikolic, D. (2008). The Oscillation Score: An Efficient Method for Estimating Oscillation Strength in Neuronal Activity. *Journal of Neurophysiology*, 99, 1333–1353. <https://doi.org/10.1152/jn.00772.2007>
- Siegle, J. H., & Wilson, M. A. (2014). Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. *ELife*, 3, 1–18. <https://doi.org/10.7554/elife.03061>
- Williams, J. M., & Givens, B. (2003). Stimulation-induced reset of hippocampal theta in the freely performing rat. *Hippocampus*, 13(1), 109–116. <https://doi.org/10.1002/hipo.10082>