Investigating Neuronal Network Dynamics Supporting Memory in the Human Brain

Thesis

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Abstract

Abstract to write here

Contents

List of Abbreviations

depth EEG depth electroencephalography

ECoG electrocorticography

EMD empirical mode decomposition

ERP event-related potential

fMRI functional magnetic resonance imaging

HHSA holo-Hilbert spectral analysis

IED interictal epileptiform discharge

ISOMAP isometric mapping

LFP local field potential

MEG magnetoencephalography

MTL medial temporal lobe

PAC phase-amplitude coupling

PPC pairwise-phase consistency

REM rapid eye movement

SWR sharp-wave ripple

SWS slow-wave sleep

tmEMD tailored masked EMD

UMAP uniform manifold approximation and projection

Introduction

Theta oscillations in mammals

Rodents

Memory

What about theta oscillations in humans?

Direct recording of hippocampal activity using depth electroencephalography (depth EEG)

Some history of depth EEG, methodological considerations and differences between electrode types. Then describe our setup, and how to identify electrode position.

1 Evaluating Memory in Humans

I Associative Memory in Humans

I.1 Short-Term and Long-Term Memory

I.2 Inference Tasks in Cognitive Psychology

I.3 The Role of the Hippocampus in Inference Behaviour

I.3.a Animal Studies

I.3.b Human Lesion Studies

I.3.c Indirect Recordings of Brain Electrical Activity in Humans (fMRI, MEG)

I.3.d Direct Recordings of Brain Electrical Activity in Humans

II Investigating Inference using a Social Community Task

II.1 Behavioural Paradigm

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II.2.a Simple and Complex Tasks

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III Quantifying Behavioural Performance

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IV.1 Inter-Individual Variability in Memory Performance

IV.2 The Hippocampus Is Central for Inference Performance

IV.3 Limitations and Considerations

2 Neural activity in the online human hippocampus is paced by a 2-Hz rhythm

I Hippocampal 2-Hz tracks mnemonic engagement

I.1 Prominent 2-Hz bursts structure hippocampal LFPs

I.1.a Using tmEMD to detect slow oscillations

Description of the usual EMD. Why it fails when not optimized especially in the context of important inter-subject variability. Then tailored masked EMD with optimization of consistency and mode mixing. IMF PSDs across contacts => frequency range of the detected oscillations. Here also present wavelet spectrograms so the reader can understand how these two methods compare. How EMD captures non-linearities in the signal (phase-frequency plots) => hippocampal 2-Hz is particularly non-linear.

I.1.b Hippocampal 2-Hz oscillations are transient

Detection of IMF cycles. Detection of discrete oscillatory bursts. Show multiple examples of 2-Hz bursts across contacts and subjects, particularly in contacts clear from IEDs. Quantification of bursts duration.

I.1.c Local referencing reduces detection of slow oscillations

Local referencing on micro and bipolar referencing on macro => This is why we will be using CAR throughout the manuscript

I.1.d Slow-oscillation amplitude and IEDs rate

Detection of IEDs (methods). IEDs are transient, non-oscillatory events. IEDs rate increases at rest. 1- and 2-Hz oscillations are more prominent in contacts clear from IEDs.

I.1.e Phase reversal of hippocampal 2-Hz oscillations

Echo to the introduction where we will have presented how the dipole is structured between layers, in humans and rodents. Show maybe one laminar recording from rodents. Then show phase reversal with cycle-triggered average of LFPs.

I.2 Hippocampal 2-Hz is selectively evoked in the memory task

I.2.a Hippocampal 2-Hz power increase with task engagement

Methods: one-over-f fitting. Results: Example contact; estimation plots with various controls; linear mixed-effects models. This is all using contacts free of interictal discharges (reader will understand why because we explained in the previous subsection). Burst duration is also higher in learning and recalling.

I.2.b Hippocampal 2-Hz bursts are evoked by mnemonic cues

I.2.b.i event-related potentials (ERPs) are modulated by mnemonic engagement

ERPs change throughout the task in the hippocampus.

I.2.b.ii Evoked oscillations follow ERPs deflection

Evoked 1-, 2- and 6-Hz amplitudes relate to mnemonic engagement. Correlation between evoked ERPs deflection and 2-Hz amplitude.

I.2.c Hippocampal 2-Hz oscillations are not evoked by motor activity

Methods: Stepping sessions. Results: three example contacts (PSDs) with clear 2-Hz in learning but not during stepping. Statistics on these three subjects.

Note to myself: I could as well add a small control here, using viewing and post-viewing sessions when the participants hit the space bar (second image). Paired analysis by comparing the evoked amplitude after the first (no motor activity) and the second (motor activity) image seen in a row. It may be confounded by the short term memory effect but we dont expect this to elicit a massive 2-Hz.

II Hippocampal neuronal activity is preferentially modulated at 2-Hz

II.1 Hippocampal neurons are paced at 2-Hz

II.1.a Basic firing properties of hippocampal neurons reveal 2-Hz rhythmicity

Methods: spike sorting and quality control. Results : firing rate distributions show that slow firing neurons constituted the biggest part of our dataset. Waveform classification: mainly broad spikes. So this looks more like pyramidal neurons. Autocorrelograms at 2-Hz. Inter-spike intervals at 500 ms.

II.1.b Hippocampal neurons prefer 2-Hz oscillations

Methods: pairwise-phase consistency (PPC) and phase randomization. Results: cycle-triggered average of population rate to illustrate co-modulation at 2-Hz. Example spike-phase distribution reveals preference at 2-Hz. Quantification of spike-phase coupling using PPC.

II.2 Hippocampal gamma oscillations are preferentially modulated at 2-Hz

II.2.a Gamma activity correlates with spiking activity

Methods: Detection of gamma activity (60-160 Hz). Results: Illustration of the correlation (CAR and bipolar referencing). Correlation with local VS distal gamma.

II.2.b Hippocampal gamma activity is preferentially coupled to 2-Hz phase

Methods: phase-amplitude coupling (PAC) with the modulation index and phase randomization. Results: cycle-triggered average of gamma activity to illustrate co-modulation at 2-Hz (with spikes). Example gamma-phase distribution reveals preference at 2-Hz. Quantification of phase-amplitude coupling using PAC. Control with leave one recording day out shows that the effect is not driven by one recording day. Gamma from the anterior and posterior hippocampi prefer 2-Hz (no gradient).

II.2.c Holo-Hilbert amplitude modulation analysis confirms prevailing 2-Hz hippocampal modulation of gamma activity

Methods: holo-Hilbert spectral analysis (HHSA) with illustration. Results: 2-Hz modulation prevails in the human hippocampus. 7-Hz oscillations dominated the mouse hippocampus.

III Hippocampal 2-Hz synchronizes neuronal activity across MTL regions

III.1 2-Hz oscillations are preferentially observed in the MTL

III.1.a 2-Hz power dominates in the MTL and particularly in the hippocampus

Cycle-triggered average of LFPs show that 2-Hz oscillations propagate in the MTL. PSDs across the MTL and non-MTL contacts free of IEDs. 2-Hz vs 6-Hz power ratio.

III.1.b Prominent 6-8Hz oscillations in the non-MTL were detected using tmEMD

IMF PSDs in the MTL and non-MTL with example of detected 6-8-Hz bursts in the non-MTL.

III.1.c 2-Hz oscillations are not directly evoked by mnemonic cues outside the hippocampus

III.1.c.i ERPs deflections in MTL and non-MTL regions

ERPs become bigger with familiarity only in the hippocampus.

III.1.c.ii ERPs deflection does not correlate with evoked 2-Hz bursts outside the hippocampus

Measure evoked 1-, 2- and 6-Hz in other MTL and non-MTL regions. The measure of ERP deflections is adjusted to each region to match visual input. Correlation between ERP deflection and evoked 1-, 2- 6-Hz oscillations.

III.2 MTL neurons are paced at 2-Hz

III.2.a Basic firing properties of MTL neurons reveal 2-Hz rhythmicity

Results : Autocorrelograms at 2-Hz. Inter-spike intervals at 500 ms in the MTL. Example neuron in the non-MTL to show we can easily find 6-Hz rhythmicity in the non-MTL.

III.2.b MTL neurons prefer 2-Hz oscillations in the hippocampus

Results: cycle-triggered average of population rate in the EC and HPC to illustrate co-modulation at 2-Hz in these two example structures. Example spike-phase distribution reveals preference at 2-Hz of EC neurons. Quantification of spike-phase coupling using PPC in the MTL. Linear mixed-effects models showing that MTL gamma is better modulated at 2-Hz than non-MTL gamma.

III.3 Hippocampal 2-Hz synchronizes MTL gamma oscillations

Methods: distal PAC. Results: cycle-triggered average of gamma activity in the MTL. Illustration of phase-amplitude coupling across the MTL. MTL gamma activity is preferentially coupled to hippocampal 2-Hz phase = quantification of MTL preference for 2-Hz oscillations. Phase synchronization is higher during learning and recalling than viewing sessions.

3 Neural activity in the offline human hippocampus

I Hippocampal physiology across sleep stages

I.1 Hippocampal 2-Hz features REM sleep but not SWS

Methods: describe polysomnography. Example of 2-Hz bursts. 2-Hz power across sleep stages. Maybe: propagation of 2-Hz oscillations in the rest of the MTL (hypothesis of the ponto-geniculo oscillations PGO)?

I.2 Hippocampal ripples feature SWS and rest sessions

I.2.a Detection of hippocampal ripples

Methods: two-step algorithm used to detect ripples. Show the templates, and the quality control used to identify reliable ripples without manual intervention.

I.2.b Basic properties of the ripples

Show raw examples as well as ripple-triggered averages of LFPs and spectrograms. Distribution of ripple frequency centers around 70 Hz. Ripples ride on a sharp-wave. Ripples can be detected on the local tetrodes as well.

I.2.c Ripples properties across sleep stages

Ripple rate is higher in SWS and N1 than wake and REM. Ripples detected in rest are comparable to N1. Ripples basic properties are stable between pre- and post-learning rests.

I.2.d Hippocampal neurons are modulated by ripples

Trigger average (and quantification!) of the modulation of hippocampal single neurons around sharp wave ripples. Single examples and summary heatmap.

I.2.e Ripples propate to the MTL

Ripple-triggered averages of the LFPs and ripple band in other regions (MTL and non-MTL). The propagation is more consistent in the MTL than the non-MTL.

II Neuronal coactivity motifs in 2-Hz bursts reactivate in post-learning hippocampal ripples

II.1 Measuring reactivation using neuronal coactivity motifs

II.1.a 2-Hz bursts coactivity motifs reactivate in post-learning ripples

Methods: building coactivity matrices and measuring reactivation with MTL single-neurons. In-bursts vs out-of-bursts. 1-, 2- vs 6-Hz bursts (exclusion).

II.1.b Reactivtion is relevant for behavioural performance

Learning but not viewing coactivity motifs reactivate. All controls related to learning vs viewing (firing rate, shuffled cell ID, out-of-ripples, single subjects). Best better reactivate than worst recalled associations.

II.2 Measuring reactivation using gamma coactivity motifs

II.2.a Gamma coactivity motifs are physiologically meaningful measures

Previous figure S18: shuffling contact IDs breaks the matrices. Intra-regional coactivity is higher than inter-regional coactivity. Correlation with 2-Hz phase amplitude coupling matrices (with illustration). Idem with ripple coactivity.

II.2.b Gamma coactivity motifs are rigid

All negative results on gamma coactivity, using the exact same analytical framework as with single-neurons. The aim here is to report this negative result, and echo the work done with gamma correlations in the visual field (other lab).

4 Discussion