

Mechanisms of neuronal rhythmogenesis by synchronization in the rodent medial septum



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A thesis submitted for the degree of *Doctor of Philosophy*

Budapest, 2025

*“Qui autem sperant in Domino mutabunt fortitudinem adsumunt pinnas sicut Aquilae
current et non laborabunt ambulabunt et non deficient.”*

Abstract

Episodic learning and memory retrieval are dependent on hippocampal theta oscillation, thought to rely on the GABAergic network of the medial septum (MS). To test how this network achieves theta synchrony, we recorded MS neurons and hippocampal local field potential simultaneously in anesthetized and awake mice and rats. We show that MS pacemakers synchronize their individual rhythmicity frequencies, akin to coupled pendulum clocks as observed by Huygens. We optogenetically identified them as parvalbumin-expressing GABAergic neurons, while MS glutamatergic neurons provide tonic excitation sufficient to induce theta. In accordance, waxing and waning tonic excitation is sufficient to toggle between theta and non-theta states in a network model of single-compartment inhibitory pacemaker neurons. These results provide experimental and theoretical support to a frequency-synchronization mechanism for pacing hippocampal theta, which may serve as an inspirational prototype for synchronization processes in the central nervous system from Nematoda to Arthropoda to Chordate and Vertebrate phyla.

Acknowledgements

First and foremost, I would like to express my gratitude to the God, the Creator and Provider. From Him we come; from Him we receive new life. He gives meaning and purpose to our existence. Seeking His ways is our trust, resting in His love is our peace. He orders the circumstances of our lives and opens opportunities by His grace. I regard this work as a gift from Him and mark it with His name as a seal.

I am aware that today, PhD training has become more accessible and, consequently, its perceived value has changed. Yet, I think that in everyday life, there are many situations where degree holders may be tempted to set themselves higher in their hearts than others. Therefore, I consider it important to express that my aim with this training was not the acquisition of the ‘dr.’ title. Should I be awarded it, I do not intend to use it for personal purposes or to change my documents because of a change of name. I pray that this temptation may never take root in my heart at any level.

I owe the greatest thanks to my former supervisor, Balázs Hangya. In these 10 years, I have learned a lot from him about conducting high-quality scientific research. Although I did not complete my PhD as his student, he undertook a thorough review of my dissertation without interest and provided me with useful suggestions. I thank him for his trust and patience.

I also extend my thanks to my supervisor, István Ulbert, for his confidence, encouragement and flexibility in supporting my PhD studies.

I am grateful to the research participants listed in the *“My contributions”* section. I also thank the faculty and staff of the Faculty of Information Technology at Pázmány Péter Catholic University for the twelve years I spent here, as well as my classmates for their support throughout my studies.

Finally, I am grateful to my wife, who has been complementing my life since 2019, standing by me in difficult situations. I also express my heartfelt thanks to my family, who raised me, and to all those who have selflessly supported me since childhood.

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Abbreviations

6-OHDA: 6-hydroxydopamine
AAC: axo-axonic/ chandelier cells
AAV: adeno-associated virus
Ach: acetylcholine
AComA: Anterior Communicating Artery
AD: Alzheimer's Disease
ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADHD: Attention-Deficit/ Hyperactivity Disorder
AIC: Akaike Information Criterion
AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP: action potential
A-P: anterior-posterior
ASD: Autism Spectrum Disorder
ASM: anti-seizure medication
BBS: Binding-by-synchrony
BDNF: Brain-derived Neurotrophic Factor
BF: Basal Forebrain
BIC: Bayesian Information Criterion
BOLD: blood oxygen level dependent contrast phenomena
BRF: Brainstem Reticular Formation
CA1-3: Cornu Ammonis 1-3
CaBP: calbindin (positive neurons)
CBT: Cognitive Behavior Therapy
CCI: Chronic Constriction Injury (model)
ChAT: choline acetyltransferase
CCK: neuropeptide cholecystokinin (positive neurons)
CLS: Complementary Learning Systems
CR: calretinin (positive neurons)
CT: computed tomography
CTC: Communication-Through-Coherence
CTE: chronic traumatic encephalopathy
DBS: Deep Brain Stimulation
DG: Dentate Gyrus
Dil: 1,1'-Diocetadecyl-3,3',3'-Tetramethylindocarbocyanine Perchlorate
DISC1: Disrupted-in-schizophrenia 1
DLPFC: Dorsolateral Prefrontal Cortex
DMN: Default Mode Network

DR: Dorsal Raphe
 DRE: Drug-resistant Epilepsy
 DREADDs: designer receptors exclusively activated by designer drugs
 DSM-5: Diagnostic and Statistical Manual of Mental Disorders
 EC: Entorhinal Cortex
 ECoG: Electrocorticogram
 ECT: Electroconvulsive Therapy
 EEG: electroencephalogram
 fMRI: functional MRI
 FMT: frontal midline theta
 GABA: gamma aminobutyric acid
 GAD: glutamic acid decarboxylase
 GCaMP: genetically encoded calcium indicators
 GPCR: G protein-coupled receptor
 HCN/ hcn: hyperpolarization-activated cyclic nucleotide-gated channel
 hDBB: Horizontal limb of Diagonal Band
 HPC/ HP: Hippocampus proper/ hippocampus / hippocampal
 HPT: Hypothalamus
 ISI: interspike interval
 kd: d-type potassium channel
 kdr: delayed rectifier potassium channel
 LC: Locus Coeruleus
 LEC: Lateral Entorhinal Cortex
 LFP: local field potentials
 lml: lacunosum moleculare layer
 LTP: long- term potentiation
 M2: Secondary Motor Cortex
 MAM: methylazoxymethanol
 MDD: Major Depressive Disorder
 MEC: Medial Entorhinal Cortex
 MEG: magnetoencephalogram
 MIA: Maternal Immune Activation
 M-L: medio-lateral
 MMSE: Mini Mental State Examination
 mPFC: medial Prefrontal Cortex
 MR(N): Median Raphe Nucleus
 MRI: magnetic resonance imaging
 MS: Medial Septum
 MST: Magnetic Seizure Therapy

MTL: Medial Temporal Lobe
NAC: Nucleus Accumbens
nas: transient sodium channel
NBM: Nucleus Basalis of Meynert
NC: Neocortex
NGF: Nerve Growth Factor
NMDA: N-methyl-D-aspartate
NO: nitric oxide
NR: Nucleus Reuniens
NRI: norepinephrine reuptake inhibitor
NST: Nucleus of Solitary Tract
NVHL: Neonatal Ventral Hippocampal Lesion
OBX: Olfactory Bulbectomy (model)
OCD: Obsessive-compulsive disorder
O-LM: oriens- lacunosum moleculare neurons
OPETH: Online Peri-Event Time Histogram
PAC: phase-amplitude coupling
PB: Phosphate buffer
PC: principal cells
PD(D): Parkinson's Disease (Dementia)
PD-MCI: Parkinson's Disease Mild Cognitive Impairment
PET: positron emission tomography
PFA: para-formaldehyde
PO: Nucleus Pontis Oralis
PPC: pairwise-phase consistency
PTD: post-traumatic dementia
PTSD: post-traumatic stress disorder
PV: parvalbumin (positive neurons)
REM: rapid eye movement
RPO: Reticularis Pontis Oralis
RSA: rhythmical slow activity
rTMS: Repetitive Transcranial Magnetic Stimulation
SALT: Stimulus-associated spike latency test
sl: stratum lucidum
slm: stratum lacunosum moleculare
SN: Substantia Nigra
SNRI: serotonin-norepinephrine reuptake inhibitor
so: stratum oriens
sp: stratum pyramidale

SPECT: single-photon emission computed tomography
sr: stratum radiatum
srl: stratum radiatum layer
SSRI: serotonin reuptake inhibitor
SST: somatostatin (positive neurons)
STA: Spike-triggered average
STN: Subthalamic Nucleus
STS: Spike-triggered average spectrum
SUM: Supramammillary Nucleus
SWR: sharp wave ripples
tACS: transcranial alternating current stimulation
TBI: Theta-burst Index
TBI: Traumatic Brain Injury
TBS: tris-buffered saline
tDCS: transcranial direct current stimulation
TH: Thalamus
TLE: Temporal Lobe Epilepsy
TNS: Trigeminal Nerve Stimulation
tRNS: transcranial random noise stimulation
tSC: theta Spectral Component
tUS: transcranial ultrasound stimulation
(t)VNS: (transcutaneous) Vagus Nerve Stimulation
vDBB: Vertical limb of Diagonal Band
VGluT: vesicle glutamate transporter
VIP: vasoactive intestinal peptide hormone (positive neurons)
VP: Ventral Pallidum
VTA: ventral tegmental area

Chemical compounds

192- IgG saporine: inside the cell inhibit protein synthesis and lead to cell death selectively in cholinergic cells.

Amphetamine: dopamine enhancers, used in the treatment of attention deficit hyperactivity disorder. Used in drug induced model of schizophrenia.

Apomorphine: dopamine enhancers, used in drug induced model of schizophrenia.

Atropine: muscarinic agonist.

Bicuculline: competitive antagonists of GABA_A receptors.

Carbachol: muscarinic agonist

Catecholamine: monoamine neurotransmitter. Including: dopamine, norepinephrine, epinephrine neurons.

Curare: anesthetic and disinhibits principal cells by blocking GABAergic inhibition

Diazepam: GABA_A receptor targeting anesthetic.

Diethyl ether: general anesthetic.

Donepezil: Acetylcholinesterase inhibitor.

Isoflurane: general anesthetic.

Ketamine: non-competitive NMDA receptor antagonist (similar to PCP). Anaesthetics/ induces psychosis.

Lidocaine: local anesthetic.

Memantine: NMDA antagonist- dopamine agonist.

MK-801 (Dizocilpine): a pore blocker of the NMDA receptor, used in drug induced model of schizophrenia.

Muscimol: a potent and selective orthosteric agonist for the GABA_A receptor and displays sedative-hypnotic, depressant and hallucinogenic psychoactivity.

Neuromelanin: dark pigment found in the brain which is structurally related to melanin. Neuromelanin is found in large quantities in catecholaminergic cells.

Orexin-saporine: used for the selective lesion of GABAergic cells.

Pentobarbital: GABA_A receptor targeting anesthetic.

Phencyclidine: dissociative anesthetic, used in animal model of schizophrenia.

Procaine: local anaesthetic.

Propofol: GABA_A receptor targeting anesthetic.

Reboxetine: norepinephrine reuptake inhibitor. Antidepressant.

Rotigotine: non-selective dopamine agonist.

Scopolamine: antimuscarinic drug.

SSRI, SNRI, NRI: Selective serotonin and norepinephrine reuptake inhibitors, second-generation antidepressants.

Tetrodotoxin: potent neurotoxin.

Urethane (ethyl carbamate): anesthetic for animals.

Xanomeline- trospium chloride: muscarinic acetylcholine receptor agonist, new antipsychotic drug.

1 Motivation and Topics overview

Exploratory behaviors are accompanied by a 4-12 Hz theta oscillation in the hippocampus of rodents, carnivores, and primates, including humans (Buzsáki, [2002](#); Buzsáki & Moser, [2013](#); Kahana et al., [1999](#); Rutishauser et al., [2010](#)). This theta oscillation provides a temporal reference signal for hippocampal networks, which is crucial for episodic learning and memory retrieval (Buzsáki, [2006](#)). GABAergic neurons of the medial septum have been identified as putative pacemakers of hippocampal theta rhythms (T. F. Freund & Antal, [1988](#); Hangya et al., [2009](#); Petsche et al., [1962](#); Yoder & Pang, [2005](#)). However, the mode of theta-frequency synchronization within the septal GABAergic network has not been tested experimentally.

Theoretical studies proposed that individual pacemaker neurons may oscillate at different frequencies and synchronize in the frequency domain upon increased depolarizing input (Ujfalussy & Kiss, [2006](#); X.-J. Wang, [2002](#)), a mechanism termed “Huygens synchronization” in the physics of coupled oscillators (Oliveira & Melo, [2015](#); Ramirez et al., [2016](#)). Two influential models assumed the presence of two separate GABAergic populations that inhibit each other through a so-called ping-pong mechanism, either within the medial septal network (Cutsuridis & Poirazi, [2015](#); Ujfalussy & Kiss, [2006](#)) or involving the hippocampo-septal GABAergic projection neurons (X.-J. Wang, [2002](#)). Theta amplitude modulation through increased medial septal firing rates was proposed as a direct layer of control (Denham & Borisyuk, [2000](#); Oddie et al., [1996](#); Tokuda et al., [2019](#)), whereas a change in medial septal bursting patterns could also impact theta generation (Joshi et al., [2017](#); A. P. Simon et al., [2006](#); Sotty et al., [2003](#)). The role of the hyperpolarization-activated and cyclic nucleotide-gated channels was emphasized as part of the potential underlying ionic mechanisms (Kocsis & Li, [2004](#); Varga et al., [2008](#)). However, beside frequency synchronization, other mechanisms are also plausible, including synchronization in the phase domain without changes in oscillation frequency (Borhegyi et al., [2004](#); Ujfalussy & Kiss, [2006](#)). Additionally, little is known about the exact role of different medial septal cell types in theta generation (M. G. Lee et al., [1994](#); Robinson et al., [2016](#); Vandecasteele et al., [2014](#)).

Therefore, we investigated potential theta generation mechanisms experimentally by recording single neurons from the medial septum, with concurrent local field potentials from the hippocampus using multichannel silicon electrode arrays. To address the generality of results across theta oscillations observed in awake or anesthetized rodents (Kramis et al., [1975](#); Stewart & Fox,

[1989](#)), we obtained three data sets: from urethane-anesthetized rats, urethane-anesthetized mice and awake, drug-free mice. We found that hippocampal theta onset was accompanied by Huygens (frequency) synchronization of medial septal pacemaker neurons otherwise rhythmic at more distinct frequencies in the theta range. We confirmed the pacemaker role of PV-expressing GABAergic neurons (T. F. Freund & Antal, [1988](#); Hangya et al., [2009](#); Varga et al., [2008](#)) by optogenetic tagging (Kvitsiani et al., [2013](#); Lima et al., [2009](#)), whereas glutamatergic neurons showed strong firing rate increase during theta without much rhythmicity, suggesting they may contribute to the theta-associated increase of tonic drive to the pacemakers (Ford et al., [1989](#); Green & Arduini, [1954](#); Oddie et al., [1996](#); Vandecasteele et al., [2014](#); Yang et al., [2014](#)). Indeed, optogenetic stimulation of medial septal glutamatergic neurons induced theta oscillation in the CA1. These results were consistent with a circuit model of the medial septum in which a network of inhibitory neurons was capable of synchronizing and desynchronizing in the frequency domain upon changing levels of tonic excitatory input.

Thesis outline

The dissertation consists of three main sections: Introduction, Results and Discussion.

The Introduction begins with an anatomical overview to familiarize the reader with the target regions of this research: the hippocampus and the medial septum. This chapter covers their structure, cellular composition, and afferent and efferent connections. The anatomical overview is followed by a chapter reviewing nearly a century of research on hippocampal theta oscillations. This chapter introduces the major models, concepts and terminology of the field, as well as electrophysiological recording methods. As technical capabilities have advanced, an increasing number of findings and interpretations regarding the role of hippocampal theta have emerged. After providing a historical overview, I discuss three key aspects associated with hippocampal theta: its role in communication, memory, and information packaging.

As my research is primarily basic in nature, I consider it important to present an interdisciplinary field with significant translational potential. As part of the Introductory chapters, I provide an overview of oscillopathies. In addition to outlining innovative neuromodulation approaches, I argue for the development of strategies that specifically target the medial septum. I discuss each type of oscillopathy-related brain disorder individually, covering its symptoms, risk factors, current diagnostic and therapeutic options, animal models, anatomical substrates, and the functional

impairments of the affected neuromodulatory systems. I conclude this chapter with a summary of future research directions and translational limitations that should be considered.

Finally, to conclude the introduction, I briefly describe the physical phenomenon that gives my research its title: the Huygens synchronization.

In the Results section, I begin by outlining the rationale behind my experimental design, including the phenomena, models, methods and brain regions. I then present the experimental methods and the results that form the basis of my thesis, organized into three groups.

The first group starts with a detailed methodological description, including the recording conditions across three rodent models, preprocessing steps, hippocampal state detection and the identification of rhythmic neuronal activity. Next, I present the five identified cell groups and their synchronization, with particular emphasis on the Huygens-type synchronization of the 'putative pacemaker' group. Finally, I briefly describe the influence of septal rhythmicity groups on hippocampal supra-theta frequency components.

In the methodological description of the second group, I discuss the optogenetic viral injection surgeries, recording conditions, stimulation protocol and immunolabelling procedure. The results include the characterization of pacemaker-like behavior of PV+ cells, as well as theta oscillation induced by stimulation of glutamatergic cells.

For the third group, I describe the initial pacemaker model cell and its adaptation, the network modelling steps, and the exploration of the parameter space of the model. Finally, I demonstrate that the model successfully reproduces the key features of in vivo Huygens synchronization.

I begin the Discussion section with a detailed analysis that contextualizes my findings within the existing literature. This is followed by a chapter addressing the limitations of the study. In the 'Conclusions and Outlook' chapter, I outline potential future research directions and present the five main findings of this work, organized into three thesis groups.

Following the Discussion, I provide a detailed account of author contributions, information on the availability of the code used in this study, and a list of supplementary figures and data.

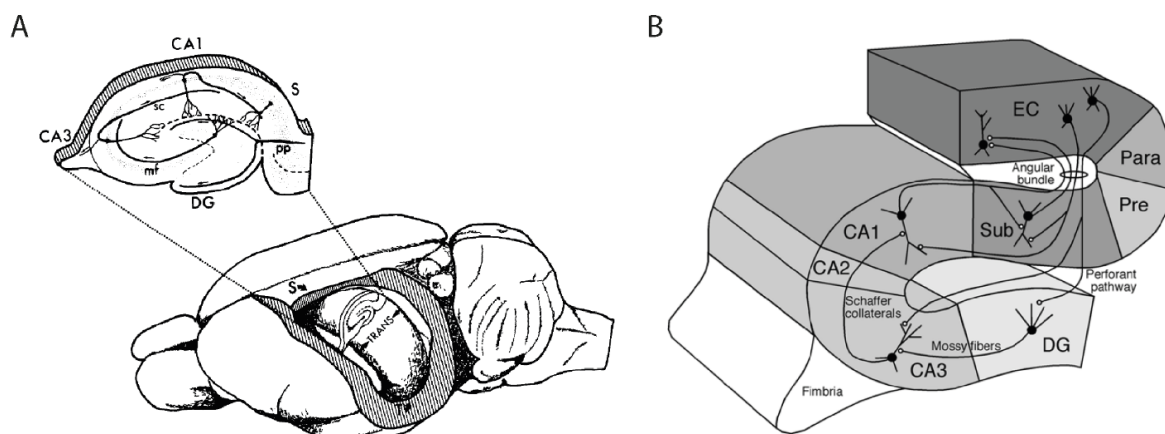
2 Anatomical overview

In this section, I introduce the anatomical structure of the hippocampus and the medial septum. I present the characteristic cell types, mentioning their connectivity, electrophysiology, receptors and some pieces of information about their proposed role in typical experimental paradigms or in disease pathology. Finally, I list the hippocampal and medial septal afferent and efferent connections. If otherwise not specified, details concern rodents, as our experimental animals were mice and rats.

2.1 Anatomy of the hippocampus

The hippocampal formation is part of the medial temporal lobe. It has a head (temporal pole), posterior to the amygdala, a body, and a tail (septal pole), which follows the upwardly curving lateral ventricle. Both cerebral hemispheres have a hippocampal formation, that are connected through the commissural system (commissure of fornix) ventral to the septum pellucidum and corpus callosum.

The hippocampal formation is comprised of the **hippocampus proper (HPC)**, **dentate gyrus (DG)** (separated by the hippocampal sulcus), subiculum, and other connected structures like the **entorhinal cortex (EC)**, presubiculum and parasubiculum (*Figure 1.*). The HPC includes the three parts of the hippocampus (**CA (Cornu Ammonis) 1-3**), which we separate based on cytoarchitectonic properties, like cell size and innervation.



1. Figure. Anatomy of the rat hippocampus. (A) "The hippocampus is an elongated, C-shaped structure with the long or septotemporal axis running from the septal nuclei rostrally (S) to the temporal cortex (T) ventrocaudally. The short or transverse axis (TRANS) is oriented perpendicular to the septotemporal axis. DG, dentate gyrus; mf, mossy fibers; pp, perforant path; SC, Schaffer collaterals." (D G Amaral & M P Witter, 1989, Figure 2). (B) "Neurons in layer II of the

entorhinal cortex project to the dentate gyrus and the CA3 field of the hippocampus proper via the perforant pathway. Neurons in layer III of the entorhinal cortex project to the CA1 field of the hippocampus and the subiculum via the perforant and alvear pathways. The granule cells of the dentate gyrus project to the CA3 field of the hippocampus via mossy fiber projections. Pyramidal neurons in the CA3 field of the hippocampus project to CA1 via Schaffer collaterals. Pyramidal cells in CA1 project to the subiculum. Both CA1 and the subiculum project back to the deep layers of the entorhinal cortex.” Figure is taken from (Per Andersen et al., 2007, Figure 3-1./A).

The HPC has a convergent-divergent organization: it receives highly processed, multimodal sensory information from a number of neocortical structures and in turn distributes integrated data to a large extent of its output structures.

The main processing circle of the HPC is the **trisynaptic loop**, which is a unidirectional excitatory pathway. As it has no direct feedback from successive elements of the loop, it is suitable to define the **proximo-distal axis** of the HPC. The major input of the HPC is the **perforant path** from the superficial EC layers (which have access to a number of neocortical regions) to DG granule cells. Subsequently, mossy fibers of these cells innervate the CA3 **principal cells’ (PC)** proximal apical dendrites and a great variety of interneurons. Thirdly, CA3 pyramidal cells send their Schaffer collaterals to the CA1 and CA2 PCs’ proximal and apical dendrites. The main output of HPC is constituted by the CA1 PC fibers to the subiculum and to EC deep layers. Additionally, CA1 is reciprocally connected with the amygdaloid complex and perirhinal, postrhinal cortices. The output fibers travel via the alveus and fimbria, continuing into the commissure of fornix.

Another HPC processing circuit starts with the **temporoammonic pathway**, which is a monosynaptic connection between the EC and CA1 PCs’ distal dendrites, including both excitatory and inhibitory components. This loop is topographically organized: proximal CA1 (closer to CA2) PCs receive and send input and output from the **medial entorhinal cortex (MEC)**, whereas distal PCs are connected to the **lateral entorhinal cortex (LEC)**. The CA3 and CA2 also have direct access to EC input through the collaterals of the perforant path.

The HPC is connected to several further brain regions that I review after the introduction of its anatomical structure.

The HPC has a laminar organization. Most superficially (dorsal at the septal portion), we find the **stratum oriens (so)**, containing the basal dendrites of the PCs and a number of inhibitory cells. Here, we find the CA3-CA3 **associational (recurrent) connections** and the **Schaffer collaterals** of CA3 pyramidal neurons to CA1. The axons of individual CA3 cells can spread to as much as two-thirds of the septotemporal extent of the CA1 of both hippocampi. Via this extensive connectivity, a PC can

interact with other neurons distributed throughout much of the ipsilateral and contralateral HPC. This immense potential for association is certainly linked to HPC function.

The 'so' is covered by a thin sheet of myelinated fibers called the **alveus**, carrying the EC–CA1 alvear (temporoammonic) pathway, the CA1–subiculum projection, and the CA1–EC projection. The alveus extends mediolaterally into a bundle called the **fimbria**, which is a flattened structure that contains approximately 900,000 axons in the rat. The **fornix** is the continuation of this bundle, extending to subcortical target structures. The exact transition between fimbria and fornix is difficult to define.

Below the 'so', the **stratum pyramidale** (sp) is located. The 'sp' contains the somata of PCs, densely packed in CA1, but more loosely in CA2 and CA3.

Only in the CA3 do we find a narrow acellular zone, the **stratum lucidum** (sl), which is occupied by the mossy fibers of DG granule cells innervating CA3 PCs.

The following layer is the **stratum radiatum** (sr), which contains PCs' apical dendrites, CA3-CA3 associational connections and the CA3-CA1 Schaffer collateral connections.

The last layer, the **stratum lacunosum moleculare** (slm) contains the branching segments of PCs apical dendrites and the perforant path collaterals.

The DG also has a laminar structure: in the polymorphic layer (closest to CA1) run the unmyelinated Mossy fibers, the stratum granulosum contains granule cell bodies and the stratum moleculare is occupied by granule cells' dendrites.

The subiculum starts at the distal CA1 border, where CA3 projections disappear. The 'sr' and 'slm' are replaced with the subicular deep and superficial plexiform molecular layers, respectively. The former receives CA1 innervation, the latter EC fibers. The PCs' bodies are in the pyramidal layer and the polymorphic cell layer contains PCs' axons.

The HPC is connected to various brain structures through the fimbria-fornix. The strongest subcortical innervation comes from the basal forebrain's medial septum (MS) through the **septo-hippocampal pathway**, which consists of the three major cell types of the MS (PV GABAergic, cholinergic and glutamatergic). These afferents target the DG, CA3 and CA1 terminating in the 'so' and 'sr'. In turn, the **hippocamposeptal projection** contains CA3 fibers, mainly exciting the lateral septal nucleus, and inhibitory projections to the MS.

Mainly, the CA3 receives neuromodulatory inputs from the brainstem: noradrenergic **locus coeruleus (LC)**, serotonergic **dorsal and median raphe (DR, MR)**; and the midbrain dopaminergic **ventral tegmental area (VTA)**. The CA2 receives input from the diencephalon: posterior **hypothalamus (HPT)**, mammillary bodies, supramammillary bodies and tuberomammillary nucleus) that distribute around the 'sp' and terminate on PCs. The **nucleus reuniens (NR)** of the **thalamus (TH)** sends excitatory input to the CA1 PCs and interneurons, terminating in the 'slm'.

Before I move on to the discussion of HPC cells, I first need to introduce the two competing activity patterns of HPC, in order to examine the neurons' electrophysiological activity.

During consummatory behavior, quiet sitting, grooming and slow-wave sleep the dominant HPC pattern is the slow, irregular wave activity, accompanied with **sharp wave ripples (SWR)**, which are short duration, 90-145 Hz ripples (Klausberger et al., [2003](#)) when large neuronal populations fire together in the hippocampal CA3 recurrent circuits, inducing transmembrane currents in the apical dendrites of CA1 pyramidal cells. In contrast, during exploration, orientation and paradoxical or **rapid eye movement (REM)** sleep, the dominant pattern is a highly regular, 4-10 Hz **theta oscillation**. Theta oscillation might carry higher frequency (**gamma**) components locked to different theta phases. These two oscillatory patterns reflect different network operations during different brain states (theta, non-theta), for example memory encoding and retrieval (Buzsáki, [1989](#)).

The hippocampal theta oscillation is typically recorded in the CA1 region, but also present in the CA3, dentate gyrus, subicular complex, entorhinal cortex, perirhinal cortex, cingulate cortex and amygdala. Several other subcortical structures, such as the dorsal raphe nucleus, ventral tegmental area, and anterior thalamic nuclei, are also phase-locked to hippocampal theta oscillations. In the attached regions theta dominates local field potentials, but also reflects subthreshold membrane potentials and strongly modulates cell firing.

Hippocampal theta has a characteristic phase versus depth profile, changing its polarity from the pyramidal layer to the stratum radiatum. Historically, hippocampal theta phase is referenced from the pyramidal layer, although it exhibits largest amplitude in the radiatum. In addition, this oscillation is described as a traveling wave along the septotemporal axis, modulating cell spiking and consequently establishing a topographically organized output as well (Lubenov & Siapas, [2009](#)).

Cell types of the hippocampus

The principal cell type of the HPC is the pyramidal or principal cell (PC) (*Figure 2.*). PCs express the vesicle glutamate transporter (VGLUT) and provide 90% of the whole neuron population. Their somata are located in the pyramidal layer. An average CA1 PC has 30000 synaptic inputs: inhibitory synapses on the cell body; oblique and basal dendrites receive excitatory CA3, local collaterals and amygdala input; apical dendrites receive glutamatergic EC and thalamic inputs.

Glutamatergic signaling is mediated via the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and only to a lesser extent through N-methyl-D-aspartate (NMDA) receptors.

PCs exhibit low average firing rate (< 1 Hz) and wide action potential (AP) shapes. Although most of them are silent during theta (Henze et al., [2000](#)), called **sparse coding**, their subthreshold voltage fluctuations may contribute to field theta amplitude. The active cells tend to fire around the negative peak of theta. PCs innervate the EC and LS. A specific group of principal cells, the **place cells** show spatial activity: they fire at certain areas of the given space. Their APs are phase locked to the theta oscillation. O'Keefe and Recce demonstrated in 1993 that place cells fire at more and more advanced phase of theta as the animal traverses through the given cell's place field, generally referred to as "**phase precession**" (O'Keefe & Recce, [1993](#)). This mechanism might contribute to the coding of physical distances. In the subiculum pyramidal neurons' activity was found to be correlated with the head direction of the animal.

Hippocampal interneurons (T. F. Freund, [2003](#); T. F. Freund & Katona, [2007](#); Jinno et al., [2007](#))

Interneurons express glutamic acid decarboxylase (GAD) and use gamma aminobutyric acid (GABA) as a main neurotransmitter. GABAergic cells act through the ionotropic GABA_A or the metabotropic GABA_B receptors. We can partition them based on the non-overlapping subgroups of calcium-binding protein expression: calbindin (CaBP), calretinin (CR), parvalbumin (PV); and other partly overlapping neuromarkers: neuropeptide cholecystokinin (CCK), signaling molecule somatostatin (SST), vasoactive intestinal peptide hormone (VIP), et cetera.

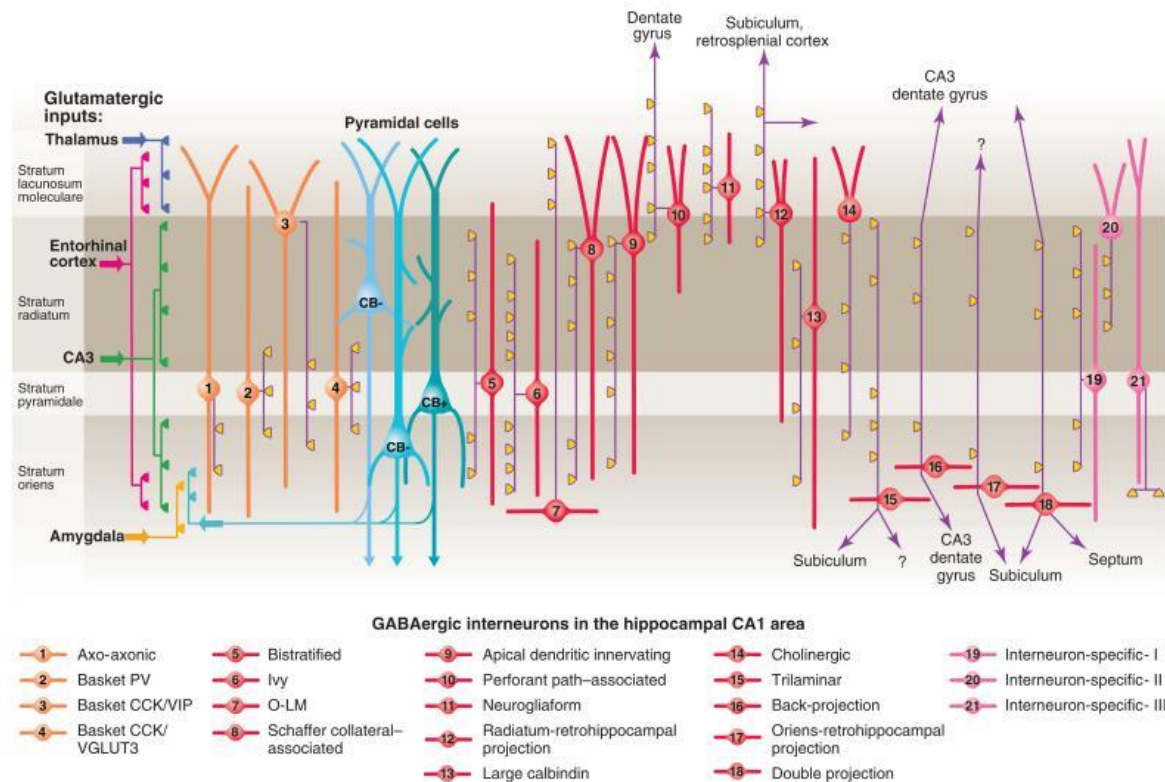
Grouping of GABAergic cells based on axonal target specificity and molecular expression profile (*Figure 2.*):

1. Perisomatic inhibitory cells take up information from their dendritic trees in the 'so', 'sr' and 'slm'. Besides their inhibitory innervation from intra and extra HPC sources, more than 2000 PCs form single synapses on them, reflecting a high convergence. On the other side they

innervate 1000-plus PCs, forming 2-10 synapse on each at the cell bodies, proximal dendrites or axon initial segments, making them highly effective controllers of PC activities.

- a. **PV basket cells** contain the Ca²⁺-binding protein parvalbumin. Their firing rates are maintained in response to a long depolarizing current pulse (non-accommodating). They typically locked to HPC theta peak (or descending phase) and preferentially fire counterphase with pyramidal cells. PVs activity can be modulated presynaptically either through the muscarinic M2 receptor or the mu opioid receptor, both of which reduce GABA release if activated. PVs tend to form non-plastic ensembles by connecting to 20-50 other PVs, and function as a precision clockwork for multiple brain oscillations. Selective AMPA knockout reduces phasic drive of PVs, disrupting temporal precision of their spikes and consequently reducing gamma power (Fuchs et al., [2007](#)). In the abnormal synchrony of epilepsy PVs are critically involved (Godoy et al., [2022](#)).
- b. **CCK basket cells** express the neuropeptide cholecystokinin. CCKs integrate over longer windows with accommodating firing rates (max fr. <40-50 Hz). They preferentially fire before and at the theta peak. CCKs also tend to form ensembles. They receive subcortical inputs, which may carry information about the emotional, motivational and physiological state of the animal. On the other hand, CCK malfunction is related to anxiety and mood disorders (Ballaz, [2017](#)). In contrast to the moderate tunability of the PV clock-like activity, CCK actions are highly modifiable in various ways (T. F. Freund, [2003](#)):
 - i. **postsynaptic actions:** CCKs form synapses rich in the alpha2-subunit-containing-GABA_A-receptors enabling anxiolytic benzodiazepines to upregulate inhibition. Additionally, CCK-B-receptors take up extracellularly released CCK.
 - ii. **presynaptic receptors:** CCK axons express CB1 cannabinoid receptors presynaptically, that can reduce GABA and CCK release. This homosynaptic depression is called depolarization induced suppression of inhibition ([DSI](#)). Upon activation, endogenous cannabinoids are released and diffused to nearby neurons, attenuating their activity as well. Furthermore, endocannabinoids may cooperate with nitric oxide ([NO](#)) a retrograde neurotransmitter controlling GABA release. Another form of presynaptic self-inhibition is mediated by GABA_B receptors. Lastly, estrogen alpha receptor mediates the reduction of the number of docked GABA vesicles, practically decreasing GABA release.
 - iii. **subcortical input:** First, CCKs are innervated by the serotonergic Median Raphe. Second, in contrast to PV cells, CCKs express the alpha7 nicotinic receptor. Consequently, the effect of **acetylcholine (ACh)** is excitation of CCKs and inhibition of PVs (through muscarinic M2 receptors).
 - iv. **local afferents:** While PVs are mostly locally driven by glutamatergic cells (up to 15000 synapses), forming ~15 time more synapses than GABA, CCKs receive only twice as much excitation (~5000 synapses), so the relative weight of local inhibition and subcortical input is larger for them. Interestingly, plasticity-related NMDA receptors are much denser on CCK

- cells than PV. Finally, CCKs are also innervated by calretinin-positive interneuron-selective interneurons.
- c. Axo-axonic/ chandelier cells' (**AAC**) somata are in the 'sp'. They innervate the axon initial segments of PCs, however, their inhibitory effect is not univocal (Tremblay et al., [2016](#)).
 2. Dendritic inhibitory cells target PC dendrites to adjust their excitatory drive. Their spikes occur mostly around the trough of theta, a quarter cycle following PV activity.
 - a. Bistratified cells' somata are in the 'sp' and their dendrites in the 'so' and 'sr'. They innervate basal and oblique dendrites, coaligned with CA3 glutamate input.
 - b. **O-LM** neurons connect the oriens layer with the lacunosum moleculare: their somata and dendrites are in the 'so', and they innervate PCs apical dendrites in the 'slm'. The 'so' contains the recurrent collaterals of PCs and the 'slm' the entorhinal cortex perforant path collaterals. Consequently, O-LM neurons are specific inhibitors of temporoammonic excitation (e.g. in case of multisensory context aversive stimulus association, (Müller & Remy, [2018](#)). Alternatively, O-LM cells can disinhibit CA1 PCs by inhibiting feed-forward interneurons in the 'sr'. In response to MS cholinergic input O-LM neurons also display fast nicotinic excitation. A specific marker of O-LM cells is their signaling molecule somatostatin content.
 - c. Neurogliaform cells' somata are in the 'slm' and innervate apical dendrites of PCs in the 'slm'.
 - d. Ivy cells' somata are in the 'sp' and innervate basal and oblique PC dendrites. Ivy cells express nitric oxide synthase and neuropeptide Y, through which they are likely to modulate glutamate release from terminals of CA3 PCs. Together with neurogliaform cells, they are a major source of nitric oxide, likely released by their exceptionally dense axons.
 3. The **interneuron selective interneurons** are distributed in all layer of the HPC and express CR. They selectively innervate other HPC interneurons.



2. Figure. Cell types of the hippocampal CA1. “Three types of pyramidal cell are accompanied by at least 21 classes of interneuron in the hippocampal CA1 area. The main termination of five glutamatergic inputs are indicated on the left. The somata and dendrites of interneurons innervating pyramidal cells (blue) are orange, and those innervating mainly other interneurons are pink. Axons are purple; the main synaptic terminations are yellow. Note the association of the output synapses of different interneuron types with the perisomatic region (left) and either the Schaffer collateral/commissural or the entorhinal pathway termination zones (right), respectively. VIP, vasoactive intestinal polypeptide; VGLUT, vesicular glutamate transporter; O-LM, oriens lacunosum moleculare.” Figure is taken from (Klausberger & Somogyi, 2008, Figure 1.)

In addition to theta phase related activity differences, these interneurons are also distinctly modulated during SWR and gamma. In the case of the former, basket and bistratified cells increase firing rate, AAC activity preceded SWRs and O-LM cells are suppressed. During gamma oscillation basket- and AAC cells fire in the ascending gamma phase (moderately coupled), bistratified cells are tightly coupled, but O-LM doesn't contribute.

From the list above it is quite clear that HPC interneurons imprint a spatiotemporal GABA conductance matrix onto PCs, that is dynamically changing in the function of the actual brain state. Since a particular PC is involved in numerous representations, hardwiring connection with inhibitory regulatory cells is unlikely. Instead, the exact effect of domain specific GABA inputs is more likely dependent on the state of the receiving PCs. This dynamic tuning of PCs enables for example to

gate incoming excitation in a winner-take-all manner or according to the recent history of the given dendrite.

Besides local interneurons, there are long-range interneurons as well. Hippocamposeptal SST GABAergic neurons innervate MS cholinergic and PV cells, even those that send direct projection to the HPC. They also send thick, myelinated axons to the subiculum and other retrohippocampal areas. Some GABAergic cells project only to the latter, parallel with glutamatergic CA1 PCs. Others innervate the subiculum, presubiculum and retrosplinal cortex. Collectively, these cortical long-range GABAergic projections could prime and reset activity in specific cells of the target areas before the information arrives via glutamatergic fibers from the PCs.

2.2 Anatomy of the medial septum

The septal region, located in the basal forebrain (BF), is a highly developed area in humans. It consists of the septum pellucidum, formed by fiber tracks and glia, and the septum verum (true septum) containing neurons as well. It is flanked by the lateral ventricles and roofed by the anterior portion of the corpus callosum.

The medial septum constitutes one subregion from the four anatomical septal groups: lateral, medial, posterior, ventral. Earlier, inadequate specification of the actual experimental regions led to the blending of septal areas in the literature, causing some controversies, rooting for example from different innervation of the lateral and medial nuclei. Regarding the cholinergic areas of the human basal forebrain the literature specifies Ch1, Ch2, Ch3 and Ch4 as the MS, vertical limb diagonal band (vDBB: projects to HPC), horizontal limb of DB (hDBB, projects to olfactory bulb), nucleus basalis of Meynert, respectively.

Now, I review the major cell types of the MS. Note, that these populations are not completely exclusive (the rate of overlap depends also on the given species) and so far, there is no consensus about the exact numbers and their proportions in the MS.

1. **Cholinergic** neurons express the enzyme choline acetyltransferase (ChAT). There are approximately 2000 cholinergic neurons in the rat MS (Gritti et al., [2006](#)). They are located mainly at the lateral zone of the MS. Excitation of the cholinergic cells slowly activates MS glutamatergic neurons. Cholinergic cells are slow firing, with wide AP and significant afterhyperpolarization. The cholinergic signaling is mediated through the ionotropic **nicotinic** and metabotropic **muscarinic** receptors, which can be expressed pre- or post-

synaptically. By the introduction of muscarinic agonists in vitro theta oscillations could be elicited and SWR abolished (Norimoto et al., [2012](#)), whereas muscarinic antagonist atropine eliminated slower theta. Similarly, in the presence of anti-muscarinic (scopolamine) or anti-nicotinic drugs the attention associated type theta disappeared from the HPC (Gu & Yakel, [2022](#)). Correspondingly, light activation of cholinergic cells increased the theta power during urethane anesthesia and suppressed SWRs (Vandecasteele et al., [2014](#)). In the light of the above, acetylcholine is thought to suppress oscillations in other frequencies than theta and is released during exploration and associative learning tasks. Cholinergic input in the HPC is also involved in the process of hippocampal place cell remapping in novel environments (Ikonen et al., [2002](#)).

2. There are approximately 15000 **GABAergic** cells in the rodent MS (Gritti et al., [2006](#)). They are fast firing, with narrow spikes and small afterhyperpolarization. PV+ GABAergic neurons are projecting ones (including to the HPC), located in the midline zone, and strongly overlap with the hyperpolarization-activated cyclic nucleotide-gated (**HCN**) channel expressing GABAergic cells (Varga et al., [2008](#)). PVs tend to fire burst of action potentials, phase locked to HPC theta, either to the trough or the peak (Borhegyi et al., [2004](#)). CR+ GABAergic cells don't project to the HPC, but send axons to other cortical areas (Kiss et al., [1997](#)).

The main role of the GABAergic neurons is to synchronize. They synchronize and entrain the HPC local inhibitory, mainly perisomatically innervating interneuron population to the theta rhythm. In this way, they rhythmically disinhibit the pyramidal neuron population. Optogenetic activation of the septo-hippocampal GABAergic neurons increases hippocampal theta oscillations, whereas optogenetic silencing of these neurons strongly reduces hippocampal theta (Gangadharan et al., [2016](#)).

3. **Glutamatergic cells** are excitatory neurons of the MS. There are approximately 39000 glutamatergic cells in the rodent MS (Gritti et al., [2006](#)). It is a morphologically diverse group with slow firing and cluster firing cells. Some glutamatergic neurons project to distinct areas (including the HPC), others are local neurons, including interneurons as well. The main projection targets of septo-hippocampal glutamatergic projections are GABAergic neurons in the 'so' (Müller & Remy, [2018](#)). Activation of glutamatergic neurons evoke strong and fast excitation of intermingled MS cholinergic, PV+ and GABAergic neurons. Interestingly, glutamatergic activity increase before locomotion initiation, and their rhythmic stimulation initiates movement (Fuhrmann et al., [2015a](#)). The local glutamatergic

network within the medial septum may provide the coupling of hippocampal theta oscillations to the running velocity.

The major output of the MS is the **septo-hippocampal** pathway via the fimbria/ fornix with contributions from the three major MS cell types (*Figure 3.*).

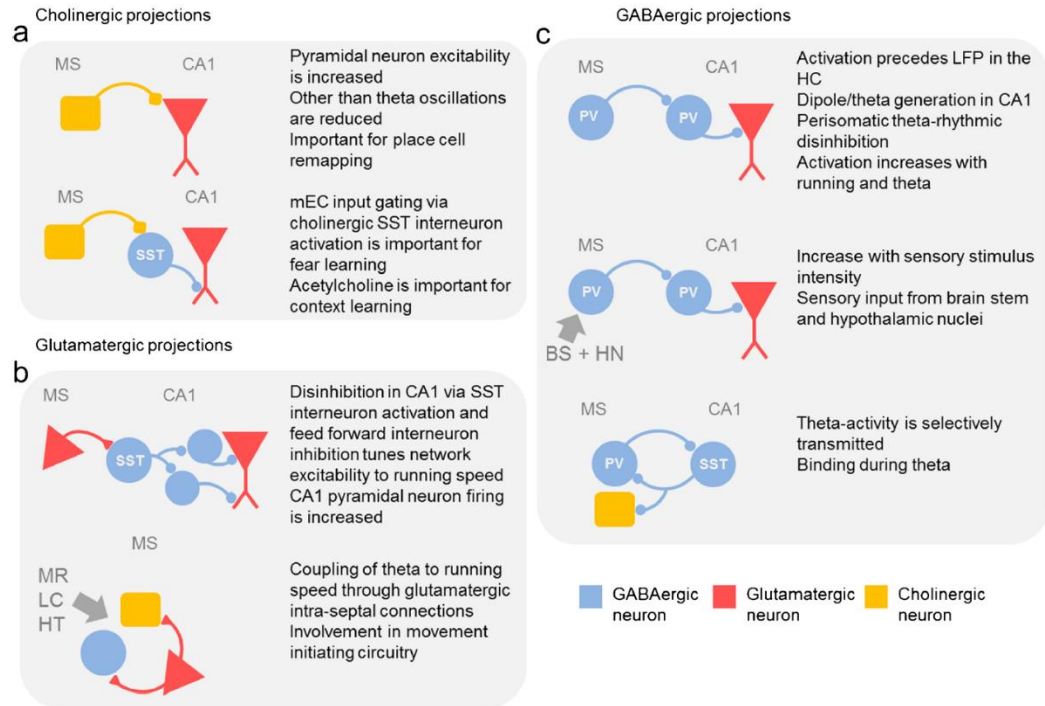
Cholinergic cells project to the dorsal HPC and MEC via the fornix and the ventral HPC and LEC via the fimbria. Primarily, they excite proximal dendrites and somata of PCs, and innervate SST O-LM cells, that in turn target PC distal dendrites in the 'so' inhibiting temporoammonic EC inputs and on the other hand control Schaffer collateral-PC communication in the 'sr'. MS cholinergic discharge highly correlates with HPC extracellular acetylcholine level, which is related to **volume transmission**.

PV-HCN expressing MS neurons provide theta rhythmic drive to the HPC PV neurons, to regularly liberate PCs through disinhibition.

Although less is known about projecting MS glutamatergic cells, 'so'/ alveus interneuron innervation is described in the CA1 (Freund Tamás & Buzsáki György, [1996](#)).

Altogether septal-hippocampal projections targeting PCs are 66% cholinergic, 27% GABAergic, in contrast to 67% GABAergic, 27% cholinergic, 12% glutamatergic innervation of HPC interneurons.

The **hippocampo-septal** feedback loop contains mainly 'so' SST GABAergic cells, active during SWRs, and some DG interneurons inhibiting MS glutamatergic cells.



3. Figure. Septo-hippocampal network interactions. "(a) Schematic drawing of cholinergic connections between the medial septum (MS) and the hippocampal CA1 sub-region and their summarized functional implications. SST somatostatin positive GABAergic neurons. (b) Schematic drawing of glutamatergic connections between the medial septum (MS) and the hippocampal CA1 sub-region, intra-septal glutamatergic connections and their summarized functional implications. MR median raphe nucleus, LC locus coeruleus. HT hypothalamus. (c) Schematic drawing of GABAergic connections between the medial septum (MS) and the hippocampal CA1 sub-region and vice versa and their summarized functional implications. BS brain stem nuclei, HN hypothalamic nuclei, PV parvalbumin-positive GABAergic neurons." Figure is taken from (Müller & Remy, 2018, Figure 2.)

The MS receives a large portion of ascending brainstem fibers through the **medial forebrain bundle**, including (Figure 4.):

- cholinergic fibers from the dorsolateral tegmental nucleus of Gudden (brainstem, involved in spatial navigation, orientation and REM sleep)
- adrenergic input from the locus coeruleus (pons, related to stress and panic)
- serotonergic fibers from the median raphe nuclei (midbrain, part of reticular formation, inhibit spinal pain sensation, thermoregulation, sleep-wake cycle, regulation of mood). Serotonergic fibers can desynchronize HPC EEG through MS GABAerg cells (Leranth & Vertes, 1999).
- noradrenergic innervation from the ventrolateral medulla (brainstem, controls blood pressure and breathing)
- reciprocal connection with the nucleus incertus (pons, can activate HPC theta)

Other afferents come from the

- histaminergic tuberomammillary nucleus (hypothalamus, controls circadian rhythm, maintains wakefulness). These neurons innervate GABAerg and cholinergic neurons in the MS.

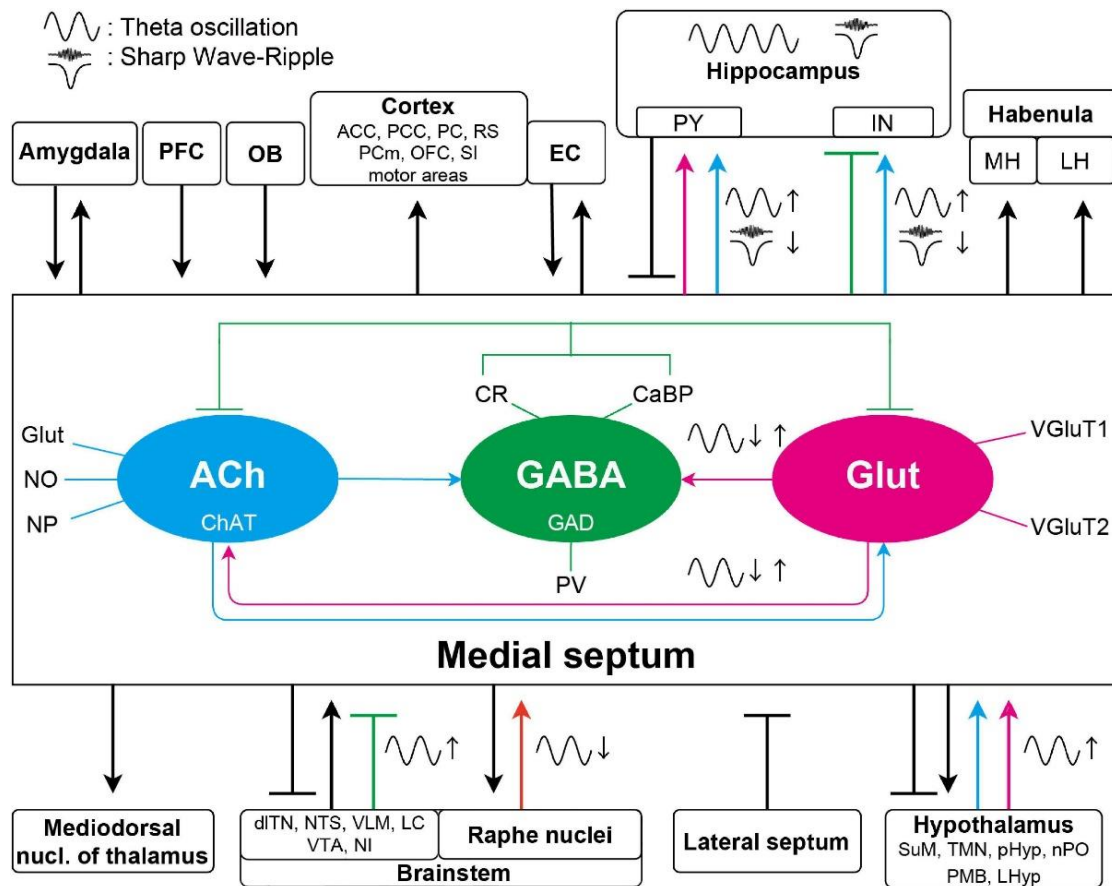
- posterior hypothalamus and Nucleus Pontis Oralis. Electrical stimulation of these areas evokes theta.
- supra mammillary nucleus (hypothalamus) send CR+/ glutamatergic fibers to the MS cholinergic cells. Interestingly, reticular excitation leads to theta burst of SUM neurons.
- lateral septum (related to reward, feeding, anxiety, fear, memory)
- and further afferents from the amygdala, thalamus and prefrontal cortex.

The MS efferents are topographically organized:

- the lateral part of the MS preferentially projects to the ventral parts of the subiculum, the HPC, the MEC and the LEC. On the other hand, the medial parts of the MS mainly project to the dorsal and ventral HPC, and the dorsal LEC.
- the lateral and intermediate MS connects to olfactory regions, amygdaloid nuclei and the LEC.

Furthermore, the MS sends

- GABAergic, cholinergic and glutamatergic fibers to the medial and lateral habenula. The GABAergic signaling here is under massive control by endocannabinoids, which is hypothesized to be involved in anxiety and depression. Glutamatergic fibers are involved in the induction of place aversion.
- Cholinergic neurons project to orexin/hypocretin neurons in the lateral hypothalamus.
- Glutamatergic fibers to preoptic area, involved in locomotion.
- A significant portion of the noncholinergic fibers project to the thalamus, the hypothalamus and the brainstem.
- A potential analgesic pathway travels through the raphe, to inhibit the dorsal horn of spinal cord involved in pain sensation.



4. Figure. Septal connections. "The three major neuronal populations maintain a delicate intraseptal network. The medial septal region receives a variety of afferents from the lateral septum, PFC, and forms bidirectional connection with amygdala, EC and a broad range of other neocortical areas, hypothalamus, and brainstem. Unidirectional, overwhelmingly cholinergic efferent fibers are innervating the thalamus and the lateral and medial habenula. For simplicity, specific neurotransmitters and the intraseptal origins or targets of the pathways are only marked in the septohippocampal connections. The medial septum is highly interconnected with the hippocampus as well. These pathways have significant roles in generation or regulation of different hippocampal oscillations. Colored arrows indicate important connections contributing to oscillations in the septo-hippocampal axis. Magenta arrows show glutamatergic, cyan cholinergic, green (blunt) GABAergic, and orange serotonergic innervations. Glutamatergic neurons in the medial septum more likely regulate other theta generating medial septal neuronal populations; however, roles of their projections to the hippocampus in oscillations are largely unknown. The GABAergic neurons have roles in theta generation by disinhibiting the hippocampal pyramidal neurons. The cholinergic connections are not only important in the theta generation, but they also suppress SPW-R generation although whether this suppression acts on the hippocampal pyramidal or interneurons remains elusive. ACC, anterior cingulate cortex; dITN, dorsolateral tegmental nucleus; EC, entorhinal cortex; IN, interneuron; LC, locus coeruleus; LH, lateral habenula; LHyp, lateral hypothalamus; MH, medial habenula; PCm, medial precentral cortex; NI, nucleus incertus; NTS, nucleus tractus solitarius; OB, olfactory bulb; OFC, orbitofrontal cortex; PCC, posterior cingulate region; PC, piriform cortex; pHyp, posterior hypothalamus; PFC, prefrontal cortex; PMB, posterior mammillary bodies; PY, pyramidal neuron; nPO, nucleus pontis oralis; RS, retrosplenial cortex; SI, substantia innominate; SuM, supramammillary nucleus; TMN, tuberomammillary nucleus; VLM, ventrolateral medulla; VTA, ventral tegmental area." Figure is taken from (Takeuchi et al., 2021, Figure 1.).

Anatomical components of the medial septal – hippocampal system and related structures can be seen on the online Alle Brain 3D Atlas on this link: <https://connectivity.brain-map.org/3d-viewer?v=1>.

3 Overview of the hippocampal theta oscillation

The following chapter will present a historical overview of the subject matter. The objective of this chapter is not to adhere strictly to the chronological sequence of publications. Instead, it aims to introduce the fundamental concepts, notations, and ideas pertinent to the subject by providing an overview of the relevant literature. The following section will present the tools most commonly used in the field, characteristic trends, and the historical limitations and pitfalls of the research. I will commence with the delineation of the technical advancements that have been made in the study of the topic. Subsequently, a more detailed examination of related electrophysiological research and the relevant models proposed over the years will be undertaken, with particular attention paid to the most significant publications.

Based on this, I will discuss topics such as type I and type II theta, relevant neurotransmitters and their receptors, the concept of phase precession, and hippocampal theta generators, among others. This chapter is intended as an introduction to the subject, and it is my hope that by the end of this section, the reader will have a comprehensive overview and appreciate the widespread use and integration of the topic and model system within the field.

3.1 Technical advances in hippocampal theta research

Since its discovery, the hippocampus (HPC) has been a subject of significant interest within the field of neuroscience research, with a multitude of studies conducted at the histological, electrophysiological, and behavioral levels. A number of its characteristics make it an appropriate and widely utilized **model system**. It is composed of a single compact cell layer with precisely organized inputs. Excitation of the principal computational circuit of the HPC, the trisynaptic loop, results in the sequential activation of its constituent substructures. The extrinsic and intrinsic fibers establish multiple pre-axon terminal (en passant) contacts with target neuronal dendrites, which are aligned orthogonally to the main dendritic axis. The high plasticity of HPC synapses renders it an appropriate subject for transplantation studies. Furthermore, its neurons can be effectively cultured, and both acute and cultured tissue slices have been observed to survive for prolonged periods in vitro.

Initially, it was considered to be part of the olfactory system; however, in 1947, Alf Brodal provided a summary and review of the existing research arguments for and against this view in a review

article (Brodal, [1947](#)), which led to the emergence of other theories. For example, James W. Papez's theory gained considerable traction, proposing that the HPC, as part of the Papez circuit, plays a pivotal role in establishing an internal emotional state through the integration of diverse sensory information (Papez, [1937](#)). The **lesion** results of Heinrich Klüver and Paul Bucy in monkeys, known as the Klüver-Bucy syndrome, also appeared to support this hypothesis (Klüver & Bucy, [1937](#)). Two decades later, it was demonstrated that the loss of fear and other behavioral alterations could be attributed to damage to the amygdala and its connections.

The Wernicke-Korsakov syndrome, which is caused by thiamin deficiency or punctate hemorrhages around the HPC, was first described at the end of the 19th century. Patients exhibiting symptoms of this condition demonstrated **deficits in memory** function, which correlated with softening of the HPC and surrounding structures. Following the surgeries of Scoville, the mnemonic function of the HPC received considerable attention from the scientific community. One of his patients, **H. M.**, underwent bilateral medial temporal lobectomy in an attempt to cure his epilepsy. As a consequence of the procedure, he developed severe anterograde amnesia (Scoville & Milner, [1957](#)). However, for an extended period, no lesion in an animal model that could mimic these syndromes. Instead, it opened the door to other possible HPC functions, such as involvement in exploratory behavior, which were controversial.

Subsequently, it was postulated that there might be more than one type of **memory**. Endel Tulving distinguished between **episodic memories**, which are situated in a **spatiotemporal** context, and semantic memories, which are more related to facts in a context-independent manner (Tulving, [1972](#)). Additionally, based on the concept proposed by Terry Winograd, Cohen and Squire delineated two categories of memory: declarative (which includes both episodic and semantic memories) and procedural (which encompasses skills) (Cohen & Squire, [1980](#)). This novel perspective resolved some of the inconsistencies that had previously been observed.

Meanwhile, due to the impact of Lawry and colleagues seminal work (Lowry et al., [1954](#)), **histochemistry** of the HPC gradually became well-known. His group introduced novel methodological improvements in tissue preparation and increased the accuracy of enzymatic measurements.

The advent of sophisticated recording techniques and innovative experimental testing paradigms in the 1960s and 1970s enabled researchers to investigate neuronal activity in **freely moving animals**. This led to the identification of various types of HPC neurons, including "**place cells**"

(O'Keefe & Dostrovsky, [1971](#)) and "**theta cells**" (Ranck, [1973](#)), which exhibited distinct patterns of activity correlated with the animal's behavior. Place cell firing is driven by environmental stimuli, which activate these neurons at their specific **place fields**. Upon relevant changes in sensory inputs, place cells can rapidly form distinct representations, called **remapping**, a process enabling them to store a large variety of experiences. The collective action of place cells forms an HPC internal **cognitive map** (O'Keefe & Lynn, [1978](#)), which enables the animal to navigate through the egocentric or allocentric world.

Another noteworthy finding by O'Keefe and Recce was the **phase precession** of place cells (O'Keefe & Recce, [1993](#)). Threshold depolarization of principal cells induced isolated, sporadic spikes around the pyramidal layer theta peak. However, if some coding neurons receive additional dendritic excitation, this may bring it to threshold earlier in theta cycle, resulting in the generation of earlier spikes. This phenomenon may potentially exert an inhibitory effect on non-coding neurons via feedback interneurons.

In recognition of O'Keefe's seminal contributions to the field, the 2014 Nobel Prize in Physiology or Medicine was bestowed upon him, along with May-Britt and Edvard Moser, the discoverers of entorhinal cortex (EC) **grid cells** (Hafting et al., [2005](#)). These neurons exhibit periodic hexagonal firing fields that cover the available space around the animal, enabling the storage and integration of information regarding locations, directions, and distances.

Other characteristic EC cell types are the "**border cells**", whose activities are modulated in accordance with the geometric boundaries of the environment (Trygve Solstad et al., [2008](#)), and **head direction cells**, which exhibit increased firing rates exclusively at specific directions of the animal's head.

The identification of these neurons has considerably enhanced our comprehension of the neural processes that underpin navigational abilities. Subsequent studies sought to elucidate the neural correlates of navigation-related topographical memory and episodic memory formation. For example, O'Keefe and colleagues discovered a significant degree of overlap between the neural networks involved in navigation and remembering the past or thinking about the future in humans (Burgess et al., [2002](#)). In 2013, Buzsáki and Moser put forth the proposition that the "mechanisms of memory and planning have evolved from mechanisms of navigation in the physical world," and that "the neuronal algorithms underlying navigation in real and mental space are fundamentally the same" (Buzsáki & Moser, [2013](#)).

In 1971, David Marr developed the first **computational model** of the HPC function, proposing that it supports the adaptation of action based on prior experiences (Marr, [1971](#)), a process often referred to as memory guided behavior. He described how elemental neurophysiological processes could perform certain basic mathematical procedures. For instance, inhibition exerted at a dendritic level causes relatively slight enhancement of the resting membrane potential, which can be interpreted as a subtraction. In contrast, perisomatic inhibition constitutes a considerably stronger change of the membrane potential, silencing most of the other synaptic drives, which is equivalent to mathematical division.

From the 1990s, technological advancements in **electrophysiology** (long term in vivo recordings with tetrodes and silicon probes (Fiáth et al., [2018](#); Henze et al., [2000](#)), have enabled for more detailed studies of brain oscillations at the cellular and network levels. The concurrent evolution of genetic tools and the creation of transgenic animals revolutionized electrophysiology. The use of **immunotoxins**, such as saporin, that enzymatically inactivates the target cell ribosomes, in conjugation with antibodies, let the experimenter to silence specific cell types, resulted in the first basal forebrain cholinergic immunolesioning model of Alzheimer's disease (Wiley et al., [1991](#)). Introduced in the mid-2000s, **optogenetics** enabled precise control of neuronal activity with light and study its causal role in behavior and cognition. The genetic code of an opsin (e.g.: light-activated channelrhodopsin) is inserted into the DNA of a carrier virus (e.g.: adeno-associated virus ([AAV](#))). Subsequently, genetic material is introduced into the target brain region, where neurons internalize it. The use of transgenic animals allows for the expression of the photosensitive opsin to be restricted to certain cell types, capitalizing on genetically engineered cell-type-specific expression of restriction endonucleases (e.g.: Cre-recombinase). While this technique is not yet applicable for use in humans, a recent paper reported promising interventions in human epileptic slices (Andrews et al., [2024](#)).

Chemogenetics, on the other hand, uses chemically engineered receptors unresponsive to native ligands and exogenous molecules that are specific for these receptors, to affect the activity of specific cells. The genetic code of the receptors is delivered to the area of interest via viral transduction. Most commonly, these engineered receptors are G protein-coupled receptors ([GPCRs](#)), specifically a subclass known as designer receptors exclusively activated by designer drugs ([DREADDs](#)). By circumventing some of the optogenetic challenges (e.g., spatial resolution limits due

to light scattering), and not least, its accessibility (no need for costly light equipment), chemogenetics started to gain increasing popularity.

Also introduced in the 2000s, genetically encoded calcium indicators ([GCaMP](#)) became a standard tool to study large neuronal circuits, even in real time. Genes of fluorescent indicators are introduced to transgenic animals with transfection. During action potentials Ca^{2+} ions flow into the cell and bind to fluorescent sensors, which either emit photons themselves or activate a fluorescent indicator. This activity can be monitored with microscopy with up to 100 Hz time resolution.

These techniques were subject to rapid development, thereby enabling the high-speed and large-scale examination of complex systems today in the present era.

In parallel with the advancement of experimental technology, there has been an exponential increase in computational power, which has enabled the automatic preprocessing of large datasets and the simulation of complex computational models. **In silico** experiments can simulate the joint effect of multiple variables that cannot otherwise be controlled simultaneously in vivo. Furthermore, the reduction in the number of animals required for a given research project is possible through the computer assisted selection of a few relevant experimental setups.

Beyond technological advancements, expanding literature, growing databases, open science, the establishment of scientific standards and multidisciplinary collaboration have largely contributed to the achievements of neuroscience.

Over the past two decades, research has concentrated on the interactions of brain rhythms, including **gamma** and theta oscillations, with the objective of elucidating their role in supporting complex cognitive functions. Studies have demonstrated that the coordination between theta and gamma rhythms is of paramount importance for tasks that require episodic memory, working memory, and spatial navigation (Colgin, [2013](#)).

The invention of genetically modified, drug-induced or developmental **animal models** of human neurological disorders has facilitated a more detailed study of neuropathology. A collection of validity criteria were established: face validity (resemblance to the human disease), construct validity (similar etiology to the human disease), and predictive validity (ability to predict therapeutic effectiveness) (Willner, [1984](#)). Contemporary research has focused on understanding how disruptions in brain oscillations are related to neurological and psychiatric conditions, such as

epilepsy and schizophrenia. Researchers have explored the potential for using, for example, theta rhythms as biomarkers for these conditions and as targets for therapeutic interventions.

Due to obvious ethical considerations human recordings were not available until the emergence of non-invasive **neuroimaging** techniques. Starting from 1927, cerebral angiography enabled the use of X-ray to image the blood vessels in the brain. As the sophistication of X-rays technology and computing algorithms advanced, the ability to process and visualize multiple cross-sectional recordings through CTs (computed tomography) became a reality.

In **nuclear medicine**, a radioactive tracer is introduced into the patient's bloodstream. During metabolic processes, the tracer attaches to glucose, resulting in the emission of a positron that can be monitored by a specific camera (PET, positron emission tomography). Conversely, SPECT (single-photon emission computed tomography) employs scanning gamma rays to measure blood flow in the brain.

Shortly after the proliferation of CTs for clinical applications, magnetic resonance imaging (MRI) was developed. It employs a strong magnetic field to induce coherent radiation (radio frequency signals) generated by hydrogen molecules. Building on the blood oxygen level dependent (BOLD) contrast phenomena, functional MRI (fMRI) revolutionized neuroimaging in the 1990s. This technique evaluates the hemodynamic response to energy use of brain cells.

Most recently, **intracranial human recordings** also became feasible, with parallel behavioral examination, for example during virtual navigation (Ekstrom et al., [2005](#)). As patients with various conditions (including brain tumors, hematomas, aneurysms, skull fractures, foreign objects and infections) undergo elective surgeries, intact brain functions are continuously monitored with the use of different tasks. For instance, Gattas et al. examined neocortical (NC) – HPC information flow during encoding, pattern completion and discrimination (Gattas et al., [2023](#)). Schonhaut et al. recorded 1854 single- and multi-units from the HPC and medial temporal lobe (MTL), simultaneously with HPC local field potentials (LFPs) in 28 neurosurgical patients who completed virtual navigation experiments (Schonhaut et al., [2024](#)).

Lastly, but equally significant, is the growing number of accumulating cases of accidental brain damage or pathological impairments in human subjects over the past century, which have provided invaluable insights into the function of theta oscillation, the HPC and the basal forebrain. Besides the aforementioned Wernicke-Korsakov syndrome and the case of patient H.M., other significant

clinical observations were made in human patients. A case study documented global anterograde and retrograde amnesia following the resection of a low-grade glioma, centered in the right diagonal band of Broca (M. K. Morris et al., [1992](#)). Another case study reported a patient with mild cognitive impairment induced by a rare septum pellucidum cyst who showed memory improvement following neuroendoscopic fenestration of the cyst (Chen et al., [2017](#)). The use of MRI and PET imaging has enabled the measurement of atrophy in different brain areas, which can be correlated with the clinical symptoms, such as the loss of cholinergic neurons and fibers in Alzheimer's and Parkinson's diseases.

3.2 Electrophysiology of the hippocampal theta, historical models

The subsequent paragraphs will present a historical overview of the major milestones in the research on HPC theta electrophysiology. This will be followed by an introduction to some of the most influential models of theta generators and a discussion of the various categorizations of theta types with regards to chemical agents.

As Buzsáki pointed out in his excellent review, it is essential to differentiate between current and rhythm generators (Buzsáki, [2002](#)). The former encompasses the elements responsible for producing the measured waves, while the latter is involved in regulating and adjusting oscillation patterns, including its frequency. This section will examine both generator types.

In 1938 Jung and Kornmüller identified a large amplitude sinusoidal slow-wave activity (4-7 Hz) in response to peripheral nerve stimulation in the rabbit, which they named theta (or RSA: rhythmical slow activity) (Richard Jung & A. E. Kornmüller, [1938](#)).

In 1954, Green and Arduini demonstrated that lesions in specific regions of the medial septum (MS) abolish theta rhythm completely (Green & Arduini, [1954](#)), while stimulation of the MS or brainstem reticular formation (BRF) could pronounce it. Eight years later, Petsche and colleagues showed that theta phase-locked bursting B-units of the MS remained rhythmically discharging when no theta was present in the HPC and that they were driven by inputs from the BRF (Petsche et al., [1962](#)). Although they acknowledged the HPC role in theta rhythm generation, they proposed that “the septum seems to be the place where the synchronization to theta is initiated.” Given the existing descriptions of the anatomical connections between the septum and the HPC, diencephalon, and mesencephalon, they identified the septum as a relay nucleus.

Two years later, Fujita and Sato reported strong phase connection of pyramidal intracellular- with extracellular theta in anaesthetized rabbits (Fujitai & Sato, [1964](#)). They proposed that measured theta rhythmic excitatory postsynaptic potentials are caused by grouped external impulses, originating probably from the septum. However, some years later this idea was rejected, based on the work of Andersen and colleagues on Na dependent prepotentials (Lanthorn et al., [1984](#)), which is the slow depolarization of pyramidal membranes that triggers burst of action potentials. Additionally, some research conducted during this period were compromised by the use of curare, a compound which both act as an anesthetic and disinhibits principal cells by blocking GABAergic inhibition.

Following the advent of microelectrode technology, enabling chronic recordings, a paper reported the discovery of two approximately 180-degree out-of-phase theta current generators, one in the CA1 and one in the dentate gyrus of rats (Jonathan Winson, [1974](#)). This finding was subsequently corroborated by the experiments of Bland and colleagues in the following year, conducted on rabbits (Bland et al., [1975](#)).

In 1975, Kramis and Bland conducted a series of experiments to test the effects of atropine (muscarinic agonist), diethyl ether (anesthetic), urethane (ethyl carbamate, anesthetic) and pentobarbital (sedative anesthetic) on HPC theta (Kramis et al., [1975](#)). The researchers identified **type I theta** activity (7-12 Hz in rabbits) in waking animals while walking, jumping or swimming (preparatory behavior). This theta was resistant to atropine administration and sensitive to urethane and could be elicited by peripheral (visual, auditory) stimulus. Later on, Buzsaki and his colleagues demonstrated that this theta can be abolished by EC lesion (Buzsaki et al., [1983](#), p. 198) and proposed that this glutamatergic pathway is affected by either the urethane-mediated presynaptic inhibition of glutamate release or by the NMDA receptor blocker ketamine.

On the other hand, **type II theta**, a 4-7 Hz oscillation was present during immobility, face-washing or licking (consummatory behavior). This oscillation was found to be atropine-sensitive, but urethane-resistant.

Additionally, the authors also found that hypothalamic stimulation evoked a 7-10 Hz theta and type I related behavior, which intensified with the strength of the stimulus, while the excitation of brainstem ascending cholinergic fibers evoked atropine-sensitive theta with a frequency of about 6 Hz.

While during urethane anesthesia, theta could be elicited by nociceptive stimulation, ethyl ether permitted only spontaneously occurring theta and sufficient doses of pentobarbital abolished all types of theta. The authors cited a paper by Gillespie (Gillespie, [1975](#)), in which it was demonstrated that atropine-resistant form of theta developed in 12-14 day rats, while atropine-sensitive theta appeared around the 20-22 day, proposing two distinct theta rhythm generator processes. The aforementioned results led to the dissemination of type I and II categorization of theta.

In 1977, Vertes and colleagues identified a group of nucleus reticularis pontis oralis (RPO) tonic movement-REM neurons that exhibited an increase in their firing rate selectively during theta-associated states of exploration and REM sleep (R. P. Vertes, [1977](#)). Moreover, from brainstem stimulation experiments, they identified three synchronizing pathways from RPO, and one desynchronization pathway from the serotonergic median raphe (MR), each of which traversed the diencephalon (R. Vertes, [1981](#)). In an attempt to find the theta-relevant structure in the diencephalon Kirk and McNaughton identified a group of rhythmic cells within the supramammillary nucleus (SUM) that remained rhythmic during local anesthetic procaine infusion to the MS, that abolished HPC theta (J. Kirk & Neil McNaughton, [1991](#)). According to the authors this indicates that intensity-to-frequency transduction occurred in the SUM.

In 1994, Bland and colleagues demonstrated that cholinergic agonist carbachol injection to the nucleus pontis oralis (PO) increased the discharge rate of MS theta-on cells, while following microinfusion of either anticholinergic atropine sulfate (muscarinic blocker) or procaine into the SUM, even electrical stimulation of the PO failed to induce HPC theta and suppressed rhythmic discharges of all MS theta-on cells tested (Bland et al., [1994](#)).

Although the medial entorhinal cortex (MEC) theta was described earlier, in the 1980s multiple pieces of evidence were presented to strengthen the MEC current generator role, yet still suggesting the MS as a pacemaker for all current generator systems (A. Alonso & Garcia-Austt, [1987](#)). For instance, Montoya and Sainsbury reported reduced amplitude HPC theta following bilateral lesion of the EC (Montoya & Sainsbury, [1985](#)).

Extending the seminal work of Petsche et al. (Petsche et al., [1962](#)), Gaztelo and Buno presented type 1 (theta coupled rhythmic, 74%), type 2 (theta coupled, non-rhythmic, 19%) and type 3 (non-coupled, non-rhythmic, 7%) cells of the MS (J.M Gaztelu & W Buño Jr., [1982](#)). Later, Vinogradova and Brazhnik (Brazhnik et al., [1985](#)); and Stewart and Fox (Stewart & Fox, [1989](#)) endeavor to ascertain the neurochemical (cholinergic or GABAergic) identity of these categories, i.e. sensitivity

to anticholinergics atropine or scopolamine. Other in vitro studies have associated membrane potential properties and action potential dynamics with MS cells, demonstrating a short afterhyperpolarization and longer bursts for non-cholinergic and a prolonged afterhyperpolarization with 2-3 spike bursts for cholinergic neurons (Brazhnik & Fox, [1997](#); Griffith, [1988](#)).

However, electrophysiological identifications of HPC neurons were controversial. Fox and colleagues recognized complex spike cells as principal cells and theta cells as interneurons generating HPC theta. Partially supporting their idea, Buzsaki identified short spike, high firing rate neurons as interneurons, being active at the positive peak of theta (Buzsaki et al., [1983](#)). On the other hand, Bland and others defined theta-on principal cells and septohippocampally disinhibited theta-off interneurons (Colom & Bland, [1987](#)).

In an effort to synthesize existing knowledge, Vertes and Kocsis developed a model describing the HPC as alternating between bursting and interburst modes, generating extracellular current fluxes that appear as theta waves (R. P. Vertes & Kocsis, [1997](#)). During the bursting mode (negative extracellular theta peak) MS cholinergic neurons drive principal cell firing and presynaptically inhibit HPC interneurons, while MS interneurons inhibit HPC interneurons. During the interburst mode (negative intracellular theta peak) relieved HPC interneurons rhythmically inhibit principal cells.

At the beginning of the 2000s, the “**classic**” model of CA1 pyramidal cell current generator was characterized by the temporal coupling of distal dendritic excitation (from the periformant path) and somatic inhibition (cholinergic MS input and rhythmically disinhibited basket cells). However, this model was unable to account for the principal cell firings (at theta peak in the stratum lacunosum moleculare) antiphasic to the strongest enthorinal cortex drive and the behavior-dependent dynamic theta phase relation of their activity. Furthermore, intrinsic resonance properties of pyramidal neurons and feedback hippocampo-septal connections were also not considered.

In 2002, Buzsaki suggested that septohippocampal cholinergic fibers may excite CA1 interneurons, while MS GABAergic cells impose phasic inhibition on these cells, which eventually results in pyramidal somatic outward currents of type II theta (Buzsáki, [2002](#)). In light of the findings of Lee et al (M. G. Lee et al., [1994](#)), Buzsaki speculated that the severe amplitude loss of theta after MS cholinergic neurotoxin lesion is due to the involvement of not just the muscarinic (M1, M2 receptors), but also the nicotinic receptor in theta regulation.

Alternatively, Buzsaki suggested type II theta rhythm generation in the CA3 recurrent collateral system, with a pivotal role for the Schaffer collaterals synapsing on pyramidal proximal dendrites. This idea is derived from Konopacki et al., who demonstrated that HPC slices bathed in carbachol generated short bursts of 4-15 Hz field oscillations, albeit only intermittently (Konopacki et al., [1987](#)). It is noteworthy that several years later, Goutagny and associates (Goutagny et al., [2009](#)) found that spontaneous theta rhythms emerge in vitro in an isolated rat HPC without the application of any drugs, although the amplitude was an order of magnitude smaller—approximately 0.1 mV compared to 1-2 mV in vivo. Moreover, they also observed CA1 theta if even the CA3 excitatory recurrent collateral system is removed. Furthermore, inactivation of the HPC between the septal and temporal pole resulted in the decoupling, but not the abolition, of theta oscillation. Besides the central role of the MS in sustained stable HPC theta generation, suggested by the MS lesioning/ cooling studies, or the temporal analysis of theta transitions in the MS versus HPC (Bland et al., [1999](#)), etc.), these results strongly indicated that the HPC cells possess inherent **resonance properties**.

4 Role of theta oscillation

While **neural oscillations** are linked to various cognitive functions, there is no direct mapping between specific rhythms and processes. Instead, oscillations in different frequency ranges may support different cognitive functions depending on the brain region. For example, it has been proposed that the theta rhythm likely involves the hippocampal-cortical network, whereas the alpha rhythm likely involves the thalamocortical network (Klimesch, [1999](#)). Although both are involved in mnemonic processes, the former is associated with learning and working- and episodic memory, whereas the latter is associated with selective attention and semantic memory. However, frontal midline theta ([FMT](#)), which appears in the parts of the default mode network, has been hypothesized as a mechanism for cognitive control (Gattas et al., [2023](#)), whereas hippocampal theta is primarily associated with spatial navigation and episodic memory processes. The gamma rhythm also operates in a region-dependent manner: on the one hand, cortical gamma primarily binds perceptual features into a coherent representation; on the other hand, hippocampal gamma associates perceptual and contextual information.

The hippocampal formation is part of the limbic system, which is responsible for behavioral and emotional regulation, including learning, memory formation, navigation, motivation, feeding, reproduction, the fight-or-flight response, and others. In particular, theta oscillation is examined thoroughly in relation to these functions.

Theta appears from the initial stages of sensory processing to later stages. As a highly regular oscillation, it is proposed to bring together the activity of sensory and memory activated neurons in time, thereby shaping behavioral output and plasticity. Examples of these operations include phase reset of the theta cycle by a conditioned sensory signal (Buzsaki et al., [1979](#)), theta phase locking of rhythmical voluntary movements (Buno & Velluti, [1977](#)), phase separation of memory encoding and retrieval (Hasselmo et al., [2002](#)), and synaptic plasticity of sequentially activated place neurons (Abbott et al., [2000](#)). Theta can also link to physiological rhythms, such as respiration rhythm (Grion et al., [2016](#)), cardiac rhythm (Pedemonte et al., [2003](#)), whisking, sniffing and step cycles in rats (Berg & Kleinfeld, [2003](#); Joshi & Somogyi, [2020](#); Macrides et al., [1982](#)), saccadic eye movements in non-human primates (Xie et al., [2022](#)), or modulated by the circadian rhythm (Munn et al., [2015](#)), sleep-wake cycle (e.g.: drowsiness and FMT: (Snipes et al., [2022](#)) and hormonal cycles (e.g.: menstrual cycle- (Becker et al., [1982](#))). The interplay of theta and other brain oscillations is

also studied in relation to various cognitive functions, including alpha-theta (Zhang et al., [2018](#)) and gamma-theta (Frieze et al., [2013](#)), whereas beta and delta oscillations are typically dominant during separate brain states.

The historical evolution of the proposed theta role followed the electrophysiological developments discussed in the preceding section. Early studies, especially those conducted on cats, indicated that theta rhythms were linked to the orienting reflex, memory, attention, and other cognitive processes. Notable contributions to this line of inquiry were made by researchers such as Grastyán and Adey, who proposed that theta rhythms are involved in attentional and motivational processes (Adey, [1967](#), [1977](#); Grastyán et al., [1959](#), [1966](#)). In contrast, Vanderwolf's work with rats led to the hypothesis that theta activity is related to motor behavior, specifically voluntary movements (Vanderwolf, [1968](#), [1969](#)), and appears during paradoxical (REM, rapid eye movement) sleep as well. His findings sparked a debate between researchers who studied theta in different species, particularly cats and rodents, leading to controversies regarding the generality of the motor behavior hypothesis.

In 1972, Landfield demonstrated a strong correlation between the magnitude of theta and the degree to which the rat remembered an electroconvulsive foot shock (Philip W. Landfield, [1972](#)), substantiating the central **mnemonic role** of this oscillation. Six years later Winson demonstrated severe spatial navigation capability loss in rats following medial septal lesion-induced theta removal (Winson, [1978](#)), similar to the case of patient H.M, which was discussed in the previous chapter (Scoville & Milner, [1957](#)). In 1989, Buzsáki introduced the famous **two-stage memory model**, according to which memory trace formation and consolidation were associated with theta rhythm and SWRs, respectively (Buzsáki, [1989](#)). A recent study indicated the importance of hippocampal (HPC) theta in the development of the memory circuits during postnatal periods (Reha et al., [2020](#)).

Such findings aligned with the theory that theta oscillations contribute to memory processes, possibly by supporting mechanisms like **long-term potentiation** (LTP). LTP, which enhances synaptic weights between neurons, was proposed as a key neural substrate for memory. The hippocampal theta was viewed as a natural tetanizer, depolarizing principal cells and thereby facilitating the opening of NMDA channels, which causes calcium influx initiating the cascade of molecular processes. More specifically, theta may bring together perforant path-mediated distal dendrite depolarization with the activation of Schaffer collaterals at its positive phase (in the radiatum), resulting in the modification of intrahippocampal associational pathways. In that way, the entrained

neuron group may be reactivated in the absence of entorhinal cortex (EC) input, e.g. during memory retrieval. In turn, negative peak entrainment may depotentiate or weaken synapsis (Hasselmo et al., [2002](#)).

In 1986, Larson and Lynch investigated LTP in rat CA1 slices (Larson et al., [1986](#)) and reported the theta frequency range priming effect of a single burst. The application of a priming burst extended the decay phase of excitatory postsynaptic potentials evoked by the subsequent burst, delivered 200 ms later. Primed burst stimulation effectively elicited LTP at the perforant path input to the dentate gyrus (Christie et al., [1995](#)), or in carbachol-induced theta in the CA1 radiatum (Huerta & Lisman, [1995](#)).

From the 1980s onwards, a growing body of evidence showed the importance of the order and optimal time lag between pre and postsynaptic cell activity with respect to plasticity. The **spike-timing-dependent-plasticity** described the involvement of **gamma/ SWR** frequency range operations in synaptic changes. The presynaptically released glutamate binds postsynaptic NMDA receptors after roughly 20 milliseconds, provided that the postsynaptic cell is depolarized in the meantime to remove the magnesium plug that blocks its NMDA receptor (Nyhus & Curran, [2010](#)).

4.1 Oscillations for communication

It is generally proposed that brain oscillations serve as flexible substrates for interregional communication. As the environment changes, so too do the cognitive demands. In some cases, this occurs rapidly, which would render anatomical changes (hard-wiring) in the brain too slow to keep pace with the necessary adaptations. A potential mechanism for transient and fast interaction of brain areas is through synchronization of their oscillations.

The Binding-by-synchrony (BBS) theory (C von der Malsburg & W Schneider, [1986](#)) posits that the neurons representing features (from different modalities) of an object are transiently coupled through synchronous firing. This hypothesis has been corroborated by multi-unit recording studies showing gamma synchronization of visual areas during contiguous visual input (C M Gray et al., [1989](#); Engel et al., [1989](#)).

In 2005, Fries et al. introduced the **Communication-Through-Coherence (CTC)** hypothesis based on human recordings (Fries, [2005](#)). They observed that the selection of a relevant attended stimulus from other competing but unattended stimuli occurred through the synchronization of motor cortex and spinal cord neurons. The authors suggested that rhythmic excitability fluctuations of

distinct brain areas open and close communication windows by affecting both the likelihood of a spike output and the sensitivity to a synaptic input (coincident postsynaptic potentials has greater impact on postsynaptic firing). For the establishment of selective communication three parameters are principal: the frequency of the coherent oscillations, the relative phase between them and the conduction delay of their connections.

According to Gattas et al., theta facilitates communication across brain regions (Gattas et al., [2023](#)). Its prolonged period allows for the accommodation of conduction velocity constraints over multi-synaptic communications. Accordingly, putative theta generator hippocampal interneurons are found to be highly connected, long-range projecting hub cells (Picardo et al., [2011](#)).

4.2 Memory model

In 1986, Teyler and DiScenna introduced their **memory indexing theory** (Teyler & Discenna, [1986](#)). According to this model, the neocortex (NC) transfers perceptual information to the HPC for the rapid creation of an index during the encoding process. In turn, the HPC teaches the NC experiences during offline periods, like sleeping. Published in 1995, O'Reilly came up with a model of the **Complementary Learning Systems** in this framework (CLS) (McClelland et al., [1995](#)), revisited and extended in (Randall C O'Reilly et al., [2014](#)). He proposed that while the HPC assigns distinct representations to stimuli regardless of their similarity (rapid learner), the NC compares overlapping representations for shared structures (incremental learner) during generalization to optimize capacity. However, if new information is consistent with existing schemas, the NC is also capable of rapid learning (Gattas et al., [2023](#)).

As discussed in the previous paragraphs, synchronization of brain regions is proposed to support memory encoding and retrieval. In general, theta power increase was associated with successful **encoding**, in case of correctly remembered words in humans (W. Klimesch et al., [1997](#)). Additionally, numerous studies reported theta phase-locking of cortical areas during successful memory encoding. For example, theta phase synchronization between frontal and posterior regions (including parietal and temporal cortex) during word encoding has been observed (Weiss & Rappelsberger, [2000](#)). In particular, close cortical-hippocampal theta rhythm coordinations were described: Siapas et al. reported that neurons in the medial prefrontal cortex (mPFC) phase-lock to the hippocampal theta during spatial working memory tasks in rats, and found a clear hippocampo-prefrontal directionality (Siapas et al., [2005](#)). Fujisawa observed stronger theta phase-locking of

choice predicting mPFC pyramidal neurons compared to unpredicted cells (Fujisawa & Buzsáki, [2011](#)). According to Rutishauser, in the medial temporal lobe neurons stronger phase-locking to locally recorded theta predicted stronger memory fixation in human subjects (Rutishauser et al., [2010](#)). Similarly, Schonhaut et al. reported phase-locking of the medial temporal lobe neurons to the hippocampal theta as a function of phase coupling of the two local field potentials in human fMRI studies (Schonhaut et al., [2024](#)).

If learning has occurred, previously co-firing cell assemblies are reactivated during **retrieval**, even when only a portion of the original cue is present. The cortical activity spreads to HPC and activates the entire memory representation, which in turn reactivates the cortex.

Electrocorticogram (ECoG) recordings in humans have revealed significant increases in 1–10 Hz pairwise-phase consistency (PPC) between the medial temporal lobe and prefrontal cortex during correct retrieval compared to incorrect retrieval (Watrous et al., [2013](#)). Similarly, human EEG experiments have shown greater phase-amplitude coupling (PAC) between frontal theta and fronto-temporal gamma oscillations for correctly remembered items compared to new items (Köster et al., [2018](#)). The role of theta-gamma coordination in successful retrievals has been extensively studied, including mPFC-CA1 coupling during correct choice trials in spatial working memory tasks (Jones & Wilson, [2005](#)), increased phase-locking of mPFC neurons to CA1 theta during correct trials (Hyman, [2010](#)) and enhanced mPFC-CA1 theta coherence following rule acquisition (Benchenane et al., [2010](#)). Beyond cortical areas, subcortical regions also synchronize with hippocampal theta during successful retrievals: increased HPC-striatum coherence during tone-direction selection in correct trials (DeCoteau et al., [2007](#)), HPC-amygdala theta coordination in fear memory processing (Seidenbecher et al., [2003](#)), and HPC-olfactory bulb synchronization during memory processing of non-aversive stimuli (L. M. Kay, [2005](#)). Conversely, reductions in theta coupling across brain regions have been linked to behavioral deficits in conditions like schizophrenia (Dickerson et al., [2010](#)). Notably, cognitive training during adolescence has been shown to prevent schizophrenia-related deficits and restore healthy theta synchrony between the left and right hippocampi (H. Lee et al., [2012](#)).

4.3 Theta for information packaging

Around the turn of the millennium, researchers began to conceptualize theta oscillations as temporal organizers for distinct informational units (**information quantum**), with each theta cycle

encoding discrete packets of information. This role is particularly evident in spatial navigation tasks. For example, Jezek and colleagues tested rats that were virtually 'teleported' between two boxes by altering environmental light cues (Jezek et al., [2011](#)). During periods of transient uncertainty ('flickering'), representations of the two boxes alternated, yet each theta cycle consistently encoded only a single location representation, as reflected by the activity of place cells.

In 2007, Foster introduced the concept of **theta sequences** (Foster & Wilson, [2007](#)). Since sequentially occurring place fields produce sequentially ordered spikes in their corresponding place cells, individual theta cycles encode compressed representations of space. Experiments by Gupta and colleagues further demonstrated that these theta sequences store discrete paths, with longer theta cycles corresponding to the encoding of longer path lengths (Gupta et al., [2012](#)).

In 2020, Kay and colleagues published a study investigating hypothetical experiences of a rat navigating a virtual maze (K. Kay et al., [2020](#)). Notably, they observed that potential future scenarios alternated at approximately 8 Hz. This cycling was found to generalize across representations of location and direction, leading the authors to describe this capability as 'generativity', a process potentially involved in planning, imagination, or decision-making. The study highlighted the dynamic and rapid nature of this process, which operates continuously, similar to how prey might instinctively flee from a predator.

5 Oscillopathies: a rationale behind this study

Understanding the synchronization mechanisms medial septal pacemaker neurons use to generate coordinated theta rhythms is important for understanding how the brain achieves temporal coordination of neural activity, a process essential for cognitive functions such as attention, memory, dynamic grouping, and awareness. Disruptions in synchronization are associated with specific cognitive deficits and implicated in various neurological and psychiatric disorders, collectively termed '**oscillopathies**'. Oscillopathies are considered significant contributors to the pathophysiology of these disorders (*Table 1.*). Although reduced neural synchronization can result from disconnection, it may also act as a causal factor. Regardless of whether oscillation abnormalities are a cause or consequence of symptoms, they hold clinical relevance as potential **biomarkers** or **therapeutic targets**. Beyond diagnosis there is also potential in **monitoring** disease progression and **evaluating** treatment efficacy.

1. Table. Table is taken from (Uhlhaas & Singer, [2006](#)).

Disorder	Neural synchrony	Cognitive dysfunctions	Anatomical connectivity	Neurotransmitters
Schizophrenia	consistent evidence for a reduction of local- and long-range synchronization	perception, executive processes, memory, attention, social cognition	evidence for reduced anatomical connectivity	glutamate, GABA, dopamine
Epilepsy	increase in local synchrony; evidence for a reduction in long-range synchronization	specific cognitive deficits in relationship to seizure focus	reduced connectivity between seizure focus and surrounding cortical areas	GABA, glutamate
Autism	reduced functional connectivity; preliminary evidence for impaired neural synchrony	perception, executive functions, social cognition, attention, memory	increased connectivity during early development, but possibly hypoconnectivity in mature cortex	GABA, glutamate, serotonin
Alzheimer's disease	reduced neural synchrony during resting state; evidence for reduced functional connectivity	working memory, perception, attention, executive processes	reduction in anatomical connectivity	acetylcholine, glutamate
Parkinson's disease	increase in neural synchrony in the basal ganglia, but also between subcortical-cortical structures	especially motor functioning, but also perception, working memory, attention, executive functions	unknown	dopamine

Identifying the neuronal correlates responsible for generating oscillatory activity is therefore crucial. Apparently, all major **neuromodulatory systems** are involved in this process. For instance, gamma oscillations depend on several key mechanisms: GABAergic neurons play a central role in primary generation and local synchronization; glutamatergic connections regulate the strength, duration, and long-range synchronization; and cholinergic modulation facilitates state-dependent high-frequency oscillations and associated response synchronization. However, further research is

needed to elucidate how GABAergic, glutamatergic, cholinergic, serotonergic, dopaminergic, and noradrenergic systems contribute to oscillogenesis and their interplay in oscillopathies.

The growing prevalence of age-related neurological disorders poses a significant challenge for global health systems. In 2020, over 57.4 million people worldwide were living with dementia - a number projected to nearly double every two decades, reaching 78 million by 2030 and 152.8 million by 2050 (alzint.org). Alzheimer's disease (AD) alone affects approximately 32 million people globally, while Parkinson's disease (PD) impacts 10 million individuals, with a substantial proportion developing dementia within ten years of diagnosis. The global **societal economic cost** of dementia was estimated at USD 1.313 trillion (including direct spending and caregiving expenses) in 2019 (Wimo et al., [2023](#)), and this figure continues to rise. Dementia thus represents one of the most pressing challenges for health and social care systems worldwide.

In addition to dementia and related neurodegenerative diseases, other cognitive and mental illnesses are also highly prevalent:

“Schizophrenia affects approximately 24 million people (globally)... Excess early mortality in schizophrenia is often due to physical illnesses, such as cardiovascular, metabolic, and infectious diseases” (WHO, 2022). A higher suicide rate is characteristic of patients with psychiatric conditions (schizophrenia, depression, etc.).

“Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally... The risk of premature death in people with epilepsy is up to three times higher than for the general population.” (WHO, 2024)

“Approximately 280 million people in the world have depression” (WHO, 2023).

However, the number of oscillopathy therapies is expanding, with prime potential in some **refractory** (pharmacological treatment-resistant) epilepsy, schizophrenia, PD, dystonia, depression, obsessive-compulsive disorders (OCD), etc.

In the following chapters, I will introduce advanced measures of brain synchrony, with an emphasis on the interplay of different frequency rhythms across brain regions. This will be followed by a review of studies highlighting the significant potential of medial septum (MS) research in interrogating and intervening in abnormal synchrony. A brief section will then outline current clinical neuromodulation techniques. Subsequently, disorders associated with oscillopathies will be discussed, focusing on observable biomarkers and both current and potential intervention

strategies. Finally, expectations surrounding technological advancements, the need for standardized interventions, and the future challenges of research -including the limitations of both animal models and human clinical studies- will be addressed.

5.1 Innovative methods and targets for neuromodulation

5.1.1 Advanced techniques to measure synchrony in humans

Prior to the 2000s, most research on the electrophysiological correlates of pathological brain states focused on analyzing power distributions across various frequency bands in resting-state electroencephalogram (EEG) activity. These studies largely neglected task- and performance-related investigations. Additionally, research often centered on abnormalities in averaged event-related potentials, which represent stimulus-driven evoked oscillations phase-locked to stimulus onset and are effectively quantified through stimulus-triggered averaging. However, induced oscillations, which are associated with cognitive processes, are self-paced and not strictly phase-locked to stimuli. Consequently, trial averaging tends to cancel out these oscillations, making their analysis more challenging.

While the amplitude of local field potentials (LFP), EEG, or magnetoencephalogram (MEG) signals correlates with the degree of neuronal synchrony, several confounding factors - such as dipole alignments, the fraction of active neurons, and the precision of neuronal responses - complicate the interpretation of synchrony based solely on amplitude measures. More recently, **phase synchronization** (precision) and **coherence** (the covariance of amplitude and consistency of phase relationships among oscillations) were advised to assess functional coupling between distributed neuronal populations at distinct electrode sites across different frequency bands. Although hemodynamic signals exhibit amplitude and latency covariations across brain regions, these signals are too slow to capture evoked and induced oscillations. However, they can still identify brain areas involved in cognitive tasks.

Recent research has also shifted focus toward the relationships between different frequency rhythms. Slow oscillations are believed to facilitate interareal communication by temporally organizing higher-frequency rhythms, which are essential for cognitive processes. However, in schizophrenia, for instance, cortico-cortical interactions are suppressed by increased cortico-thalamic interactions within the slow-frequency band. While decision-making, speech processing,

and other conscious behaviors require communication between higher-order brain structures, thalamic delta input abnormally disrupts cortical connectivity in affected patients. Normally, this interference promotes sleep or mind-wandering associated with activity in the default mode network (DMN), but excessive suppression can contribute to the “fractured mind” symptom of schizophrenia.

However, these alterations are hard to detect because delta, theta, and gamma band frequency powers vary across patients and states in schizophrenia. These inconsistencies arise from the dynamic pathology of the disorder as well as the effects of medications used for treatment. Region-specific EEG spectral analyses have not yielded a consensus because while spectral compositions may remain stable, different frequency components can **decouple** from one another.

One example of such decoupling was observed in an animal model of schizophrenia. In this model, the prefrontal-hippocampal pathway shifted from a theta-governed direct path to a delta-coordinated indirect path that involves the thalamus. This replacement of the normal "theta clock" with a slower delta rhythm may account for schizophrenic patients' prolonged temporal discrimination windows (Hunt et al., [2017](#)).

Importantly, both excessive synchrony and reduced synchrony can be detrimental to brain function. A precisely regulated balance between correlated and decorrelated activation patterns is essential for normal cognitive processes. Disruptions in this balance can lead to a range of impairments, including cognitive deficits, emotional dysregulation, and motor dysfunctions -such as those observed in epilepsy - highlighting the critical role of rhythmic coordination in maintaining healthy brain function.

5.1.2 The medial septum is a good target for interventions

As mentioned in the *"Technical advances in hippocampal theta research"* chapter, early research into brain function was often guided by the observation of hemorrhages in specific brain structures and the corresponding symptoms. In particular, disruptions in the circulation of the anterior communicating artery (ACoMA), which contributes to the blood supply of the basal forebrain (BF), were linked to amnesia in patients. This form of memory impairment affected anterograde memory, explicit episodic and semantic memory, as well as short- and long-term memory. The accumulation of cases and the improvement of imaging techniques provided invaluable insights into the specific functions of affected brain areas.

In the search for BF structures relevant to memory, lesions and volume measurements of the MS were found to correlate with the efficacy of memory formation and recall. The MS contributes to memory processes through mechanisms such as cholinergic neuromodulation and rhythm generation, which synchronize sensorimotor inputs with hippocampal (HPC) activity. The MS plays a critical role in generating oscillatory activity. Beyond its well-known importance in theta rhythm generation, some recent studies have reported MS involvement in generating supra-theta band oscillations, presenting a non-negligible therapeutic potential. This includes, for instance, high-amplitude gamma waves, implicated in seizure-induced automatism following temporal lobe seizures and schizophrenia-like symptoms after ketamine injection (Leung & Ma, [2022](#)). Conversely, inactivation or lesions within the septohippocampal-Nucleus Accumbens (NAC) system could reduce the dose of anesthetic required to suppress gamma oscillations and induce loss of consciousness in animals.

These findings highlight the therapeutic potential of MS stimulation. If disrupted oscillations are regulated by the MS, **patterned stimulation** could potentially compensate for or mitigate abnormal oscillatory activity, thereby modulating symptoms associated with oscillopathies (Takeuchi et al., [2021](#)). Emerging research has explored various intervention strategies targeting the MS for conditions such as dementia. These approaches include **pharmacological treatments** (e.g., dopamine-based therapies), **instrumental techniques** (e.g., Deep Brain Stimulation and Vagus Nerve Stimulation), and **behavioral interventions** (e.g., locomotor exercise and cognitive enhancement). A recent review summarized findings from animal studies that underscore the role of the MS in attention regulation, integration of reward signals, and processing locomotor signals, further supporting its therapeutic relevance (Tsanov, [2022](#)).

5.1.3 Brain stimulation techniques

Recent advancements in brain stimulation technologies have significantly expanded the therapeutic options for neurological and psychiatric disorders. These techniques can be broadly categorized into **non-invasive** and **invasive approaches**, each offering unique mechanisms and applications.

Non-Invasive Brain Stimulation Techniques

Non-invasive methods involve external modulation of brain activity without requiring surgical intervention. Key techniques include:

- **Electroconvulsive Therapy (ECT):** This method induces therapeutic seizures under anesthesia by delivering electrical currents to the brain. It is FDA-approved for treating depression and schizophrenia.
- **Repetitive Transcranial Magnetic Stimulation (rTMS):** Utilizing low-intensity magnetic pulses. rTMS stimulates specific brain regions and is FDA-cleared for treatment-resistant depression, OCD, migraines, anxiety with depression, and smoking dependence.
- **Transcutaneous Vagus Nerve Stimulation (tVNS):** A portable device delivers electrical stimulation through the skin to activate the vagus nerve, which communicates via the brainstem. This technique is FDA-approved for post-traumatic stress disorder (PTSD).
- **Trigeminal Nerve Stimulation (TNS):** This method targets the trigeminal nerve and is FDA-approved for Attention-Deficit/Hyperactivity Disorder (ADHD).
- **Sensory Stimulation:** This approach involves presenting stimuli across various sensory modalities, such as auditory, tactile, visual, or olfactory inputs.

Emerging non-invasive techniques include **transcranial alternating current stimulation (tACS)**, **transcranial direct current stimulation (tDCS)**, **transcranial random noise stimulation (tRNS)**, and **transcranial ultrasound stimulation (tUS)**.

Invasive Brain Stimulation Techniques

Invasive approaches involve surgical implantation of devices to deliver targeted electrical stimulation. Prominent techniques include:

- **Vagus Nerve Stimulation (VNS):** Unlike tVNS, this method requires an implanted device to stimulate the vagus nerve. VNS is FDA-approved for depression, refractory seizures, and motor deficits following chronic ischemic stroke (Micro Transponder Vivistim Paired VNS System). It is also under investigation for AD, PTSD, anxiety disorders, and pain management.
- **Magnetic Seizure Therapy (MST):** MST uses higher-frequency magnetic pulses than rTMS to induce seizures under anesthesia. It is being studied for depression, schizophrenia, and OCD.
- **Deep Brain Stimulation (DBS):** DBS involves implanting electrodes in specific brain regions to deliver continuous electrical pulses. It is FDA-approved for PD, OCD, and epilepsy. Clinical trials are exploring its use for chronic pain, major depression, AD, and drug addiction. Modern DBS systems incorporate advanced features such as directional leads and sensing-enabled devices to optimize stimulation parameters and reduce side effects. Lozano et al.

presents an extensive discussion on the therapeutic successes of DBS for treatment-resistant activity-related and affective disorders (Lozano et al., [2019](#)). The review emphasizes the efficacy of DBS in managing conditions such as tremors, dystonia, Parkinson's disease, chronic pain, and psychiatric disorders, including depression, bipolar disease, OCD, and Tourette's syndrome.

A comprehensive review by Belkacem et al. provides an in-depth analysis of the current state of **closed-loop brain-computer** interfaces, highlighting advancements and applications in the field (Jay Edelman et al., [2023](#)). The review includes key summaries, with Table 2 detailing closed loop brain stimulation studies and Table 3 offering examples of various stimulation setups, thereby providing a structured overview of methodologies and outcomes in this emerging area of research.

Despite their potential, challenges remain in optimizing these techniques for broader clinical use. Non-invasive methods often face limitations in spatial resolution and depth of stimulation. Conversely, invasive approaches carry surgical risks such as infection or hemorrhage. However, the rapid evolution of brain stimulation technologies underscores their transformative potential in healthcare. By addressing current limitations and expanding accessibility through innovations like portable devices or telemedicine integration, these techniques could revolutionize the management of neurological and psychiatric disorders.

5.2 Brain disorders characterized by oscillopathies

The following chapter comprises neurodegenerative and psychiatric diseases that result in sensory-motor issues or cognitive deficiencies associated with oscillopathies. The list is accompanied by a discussion of these disorders in terms of relevant symptoms, possible factors, diagnosis, current treatment, relevant animal models (see Takeuchi & Berényi, 2020 for a brief summary of phenomenological details and animal models), associated oscillopathies with anatomical substrates and neuromodulatory systems involved.

Furthermore, the potential applications of innovative techniques as either a treatment or a diagnostic tool will be reviewed. The interventions encompass pharmacological, electrical-, magnetic-, optical-, sonogenic- and sensory stimulation, or behavioral approaches, or a combination thereof.

5.2.1 Schizophrenia

Schizophrenia is a severe mental health condition that disrupts thought processes, emotions, and behavior. It is characterized by positive **symptoms**, such as delusions, hallucinations, and paranoia, as well as negative symptoms, including apathy, social withdrawal, affective flattening, and diminished motivation (American Psychiatric Association, 2013). Cognitive impairments are also a core feature of schizophrenia, affecting executive functioning, working memory, attention, and social cognition. These cognitive challenges often manifest as disorganized thinking and behavior. Patients may have difficulties in distinguishing relevant from irrelevant details, with hyperfocus on non-important sensory inputs and diminished recognition of emotional cues. Schizophrenia is often associated with mood disorders, anxiety disorders, substance use further complicating its clinical presentation.

The **etiology** of schizophrenia includes genetic predisposition and environmental factors. Genetic heritability is significant but not deterministic; environmental contributors such as prenatal infections, obstetric complications, psychosocial stressors, cannabis use during adolescence, and urban living have been implicated in increasing risk. The onset typically occurs in late adolescence or early adulthood. Despite extensive research, no objective diagnostic biomarkers have been identified to date, and current diagnosis relies on clinical observation of symptoms and psychiatric history using criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This process includes physical examinations, imaging studies to rule out other conditions, and mental health evaluations.

Treatment for schizophrenia is lifelong and focuses on symptom management rather than cure. Antipsychotic medications targeting dopamine and serotonin receptors are the cornerstone of therapy. Recently, novel agents such as xanomeline-trospium chloride have shown promise by targeting muscarinic receptors. Psychosocial interventions like cognitive behavior therapy (CBT) for psychosis are often employed alongside pharmacotherapy. In severe cases or treatment-resistant conditions ECT may be considered.

Animal models have been instrumental in advancing our understanding of schizophrenia's pathophysiology (Winship et al., [2019](#)). These models fall into three categories: developmental (e.g., Neonatal Ventral Hippocampal Lesion (NVHL), Maternal Immune Activation (MIA), methylazoxymethanol (MAM) model), drug-induced (e.g., dopamine enhancers like amphetamine

or NMDA receptor antagonists like ketamine), and genetic (e.g., disrupted-in-schizophrenia 1 ([DISC1](#)), Reelin mutations). Each model replicates specific aspects of the disorder and provides insights into its neurobiological underpinnings.

One prominent aspect of schizophrenia is the failure of neural **synchronization** across brain networks. Deficits in high-frequency oscillations (e.g., gamma rhythms) are linked to impairments in working memory, attention, and perceptual organization. Hyper-synchronization in primary sensory areas may contribute to hallucinations (Spencer et al., [2009](#)), while reduced coherence between the medial prefrontal cortex ([mPFC](#)) and HPC in the low-gamma band correlates with behavioral impairments (Dickerson et al., [2010](#)). Also reduced firing in a group of theta-modulated, gamma-entrained mPFC putative long-range neurons and subsequent reduction in cross-frequency coupling were observed (Dickerson et al., [2010](#)).

Structural abnormalities also play a critical role in schizophrenia's pathology. White matter anomalies indicate impaired long-range connectivity between brain regions, while increased local could account for the positive symptoms such as auditory hallucinations (Y. Chang et al., [2024](#); Hubl et al., [2004](#)). Dysregulation of key **neuromodulatory** systems further exacerbates these issues. For example:

- The **glutamatergic** system is implicated through NMDA receptor dysfunction; NMDA antagonists can induce psychosis by disrupting parvalbumin-positive ([PV](#)) GABAergic interneurons (Fujikawa et al., [2021](#)).
- **Dopaminergic** hyperactivity contributes to positive symptoms via ventral hippocampal activation of the ventral tegmental area ([VTA](#)) (Kätzel et al., [2020](#)).
- **GABAergic** dysfunction affects gamma rhythm generation through impaired interactions between principal cells and fast-spiking interneurons AMPA and GABAa receptor (Hunt et al., [2017](#)). Dysfunction in PV GABAergic interneurons has been also hypothesized for schizophrenia (Lewis & Moghaddam, [2006](#)).
- **Cholinergic** modulation via muscarinic and nicotinic receptor activation influences high-frequency cortical oscillations (Montani et al., [2021](#); Y. Wang et al., [2015](#)).

Two major hypotheses explain the physiological basis of schizophrenia's symptoms (Takeuchi et al., [2021](#)):

1. **The Glutamate Hypothesis:** NMDA receptor blockade disrupts PV interneuron function, leading to gamma rhythm abnormalities (Gonzalez-Burgos & Lewis, [2012](#)). Especially, the lack of NMDA signaling in fast-spiking PV cells has been shown to increase cortical baseline gamma activity and impair gamma induction (Carlén et al., [2012](#)). Pharmacological interventions targeting the MS can normalize enhanced hippocampal gamma, associated with hyperactive and psychotic symptoms (J. Ma et al., [2012](#)): Muscimol infusion inhibits

MS neurons and restores normal gamma oscillations. On the other side, orexin-saporin ablation of PV neurons also normalizes enhanced gamma oscillations.

2. **The Dopamine Hypothesis:** Hyperactivation of the ventral HPC pyramidal cells drives excessive dopaminergic activity in the VTA through pathways involving the NAC and ventral pallidum (VP) (Sonnenschein et al., [2020](#)). One possible explanation of the hyperresponsive dopamine system is related to the loss of regulatory PV cells (Grace & Gomes, [2019](#)). MS activation via NMDA infusion can normalize this dopaminergic overactivity.

Emerging therapeutic **interventions** aim to address these underlying mechanisms:

- **Deep Brain Stimulation:** Although Heath and colleagues conducted early experiments to cure psychiatric conditions (like schizophrenia) with brain stimulation., the legitimate development and application of DBS began with movement disorders (CE Mark approval for essential tremor and PD tremor in 1993, (Frey et al., [2022](#))), leading to its current evidence-based use in various conditions. DBS use for schizophrenia is quite recent (NCT02361554, Cascella et al., 2021). MS DBS suppress gamma increase induced by ketamine, and can normalize hyperlocomotion (Leung & Ma, [2022](#)).
- **Repetitive Transcranial Magnetic Stimulation:** Targeting the dorsolateral prefrontal cortex (DLPFC), rTMS can restore gamma oscillations and improve cognitive functions of patients with schizophrenia (Farzan et al., [2012](#)).
- **Cognitive Behavioral Therapy:** Early CBT interventions during adolescence may enhance phase synchrony across neural oscillations in delta, theta, and beta bands (H. Lee et al., [2012](#)). Timing is critical; younger patients with greater neuroplasticity may benefit more than older individuals.

5.2.2 Epilepsy

Epilepsy is a neurological disorder **characterized** by recurrent, unprovoked seizures caused by abnormal, excessive, and synchronized electrical discharges in the brain. These seizures can affect sensations, behaviors, awareness, and muscle movements. Epilepsy is often associated with psychological comorbidities such as anxiety and depression, which further impact the quality of life for affected individuals. Seizures are broadly categorized into focal (or partial) seizures, which originate in a specific brain region and may involve impaired awareness, and generalized seizures, which affect both hemispheres of the brain. Generalized seizures include tonic-clonic, myoclonic, and absence seizures. Additionally, some seizures are classified as unknown-onset. Temporal lobe epilepsy ([TLE](#)), one of the most refractory forms of epilepsy, is frequently linked to memory impairments.

The **causes** of epilepsy are diverse and include structural damage (e.g., trauma, stroke, tumors), metabolic abnormalities (e.g., fever, sleep deprivation), genetic predispositions, and infections. **Diagnosis** typically involves EEG to detect abnormal brain activity, imaging techniques such as MRI

or CT scans to identify structural abnormalities, and blood tests to rule out metabolic or infectious causes.

Treatment strategies for epilepsy vary depending on the type and underlying cause of the condition (<https://www.ilae.org/guidelines>). Pharmacological treatments with anti-seizure medications (**ASMs**) are the first line of therapy, controlling seizures in approximately 60–70% of patients. For drug-resistant epilepsy (**DRE**) alternative options include surgical interventions (e.g., resection of epileptogenic brain regions), neurostimulation techniques like VNS, and dietary therapies such as the ketogenic diet. Emerging therapies include closed-loop systems that detect abnormal brain activity and deliver targeted stimulation to prevent seizures.

Animal models have been instrumental in understanding epilepsy pathophysiology and testing therapeutic approaches (Y. Wang et al., [2022](#)). Common models include chemical induction methods (e.g., kainic acid, pilocarpine), electrical stimulation models (e.g., kindling), and genetic models such as GAERS and WAG rats for absence seizures. Other models are also established (closed head injury model, Audiogenic seizure model). These models replicate key features of human epilepsy, including spontaneous recurrent seizures and associated cognitive or behavioral impairments.

Epilepsy involves disruptions in neural oscillations that regulate brain function. For instance, absence seizures are characterized by low-frequency oscillations that impair higher cognitive functions (Kostopoulos, [2001](#)). **Synchronization imbalances** might also contribute to seizure generation. Both abnormal upregulation (enhanced local phase synchronization) or aberrant downregulation (Netoff & Schiff, [2002](#)) of synchronization may lead to seizures. Reduced long-range coupling between neuronal populations can isolate epileptic foci from network control mechanisms allowing pathological synchronizations. Seizure occurrence often follows circadian rhythms, HPC seizures more likely during drowsiness or light sleep (Stanley et al., [2013](#)).

Epilepsy is associated with an imbalance between excitatory and inhibitory **neurotransmitter** systems:

- **GABAergic System:** Chronic epilepsy reduces GABAergic neurons in the medial and lateral septum (García-Hernández et al., [2010](#); Garrido-Sanabria et al., [2007](#)). While GABAergic drugs can suppress convulsions (Treiman, [2001](#)), their effects are heterogeneous (Uhlhaas & Singer, [2006](#)).
- **Glutamatergic System:** Excitatory glutamatergic transmission contributes to seizure activity. In turn, chronic seizures modify neuronal and glial expression of glutamate

receptors and uptake transporters, further contributing to epileptogenesis (Barker-Haliski & White, [2015](#)).

- **Cholinergic System:** Cholinergic signaling via muscarinic receptors in the MS modulates anti-seizure effects through interactions with somatostatin-positive (SST) oriens-lacunosum-moleculare interneurons in the HPC (Takeuchi et al., [2021](#)).

Recent advancements highlight novel **therapeutic** strategies:

- The work of Colom et al. presented that both the theta generator (reduced amplitude) and pacemaker (increased frequency) systems are affected in epilepsy (Colom et al., [2006](#)). They observed the antiepileptic effect of theta, regardless of whether it was induced by carbachol (muscarinic agonist) or sensory stimulation. In other **animal models**, restoration of theta by sensory stimulation (Kitchigina & Butuzova, [2009](#)), septal electrical stimulation or cholinergic drugs infused into septum ameliorated seizures (R. S. Fisher, [2015](#)). On the other hand, septal inactivation abolishes postictal HPC gamma increase and behavioral hyperactivity (Leung & Ma, [2022](#)). Recently, a closed-loop optogenetic stimulation of thalamocortical neurons has been shown to terminate seizures following brain injury in a rat epilepsy model (Paz et al., [2013](#)).
- **Septal Stimulation:** Electrical or pharmacological activation of the MS can reduce epileptiform activity; however, improper stimulation may induce limbic seizures, necessitating precise closed-loop protocols (R. S. Fisher, [2015](#)).
- **Vagus Nerve Stimulation:** FDA-approved for refractory epilepsy since 1997, VNS improves seizure control while enhancing memory performance and attention (Cramer et al., [2001](#)).
- **Closed-Loop Systems:** Devices like the implanted NeuroPace® RNS® detect epileptiform activity and deliver targeted stimulation to prevent seizure propagation (Jarosiewicz & Morrell, [2021](#)).

5.2.3 Alzheimer's Disease

Alzheimer's disease is a chronic neurodegenerative disorder characterized by the progressive loss of neurons, leading to cognitive and behavioral impairments. The most common early **symptoms** include short-term memory loss, visuospatial difficulties, and executive dysfunction. As the disease progresses, patients may experience language problems, disorientation (e.g., getting lost), attention deficits, mood swings, loss of motivation. Additionally, there are pronounced deficits in tasks requiring interhemispheric information transfer, executive processing, and episodic memory (Uhlhaas & Singer, [2006](#)). The pathological hallmark of AD is the accumulation of malformed protein deposits: amyloid-beta plaques in the extracellular space and neurofibrillary tangles composed of tau proteins intracellularly. These aggregates disrupt normal cell function, leading to synaptic loss and irreversible neuronal degeneration. Secondary symptoms often include psychosis and behavioral disturbances.

AD arises from a combination of genetic predispositions and environmental risk **factors**. Contributing factors include head injury, clinical depression, and hypertension. **Diagnosis** is based

on a comprehensive evaluation that includes patient history, neurological exams, cognitive assessments (e.g., [ADAS-Cog](#), [MMSE](#)), medical imaging (e.g., MRI or PET scans), and cerebrospinal fluid or blood tests to detect biomarkers such as amyloid-beta or tau proteins.

While no **treatments** can halt or reverse the progression of AD, current therapies aim to temporarily alleviate symptoms and modify the disease trajectory. Pharmacological interventions include acetylcholinesterase inhibitors like donepezil to enhance cholinergic tone and memantine (an NMDA receptor antagonist) to regulate glutamatergic signaling. Non-pharmacological approaches such as a healthy diet, physical activity, and social engagement are recommended for reducing the risk of cognitive decline. Cognitive-behavioral therapy has also been explored as a supplemental tool to improve attentional components of memory formation (Carrion et al., [2018](#)).

Typical **animal models** are transgenic mouse models based on the amyloid and tau hypotheses; these models replicate specific aspects of AD but fail to fully capture the complexity of the human disease (Drummond & Wisniewski, [2017](#)). Examples include models targeting familial AD genetics or inducing protein aggregation (collection of models: <https://www.alzforum.org/research-models>).

AD is associated with distinct **oscillopathies**. A hallmark of AD is the increase in theta- and delta-band interactions, which co-occurs with a reduction in alpha- and beta-band activity (Maturana-Candelas et al., [2020](#)). Resting-state EEG reveals a slowing of the power spectrum at temporal areas (Meghdadi et al., [2021](#)). Notably, the region-specific reduction in alpha-band activity correlates with disease severity and cognitive deficits (Ranasinghe et al., [2014](#)). Additionally, reduced coherence in the alpha- and beta-bands during resting states and decreased synchronization in these bands during working memory tasks are observed (Pijnenburg et al., [2004](#)). These reductions in functional connectivity may represent one of the earliest functional markers of AD, outperforming behavioral performance or regional brain activation measures as diagnostic indicators (Bokde et al., [2006](#)).

Phase synchronization deficits are another critical feature of AD. The accumulation of AD-related proteins, such as amyloid-beta and tau, increases jitter in the timing of evoked action potentials in neocortical pyramidal cells, disrupting neural communication (Stern et al., [2004](#)). In rodent models of AD, disruptions in HPC and entorhinal cortex ([EC](#)) theta oscillations, gamma oscillations, and theta–gamma cross-frequency phase–amplitude coupling are commonly observed (Ahnaou et al., [2017](#)). Furthermore, delta wave disruptions during slow-wave sleep impair memory consolidation, highlighting the role of sleep-related oscillations in AD pathology (Y. F. Lee et al., [2020](#)).

Anatomically, the degeneration of white matter fiber tracts occurs. Amyloid-beta plaques and tau protein aggregates activate microglia, which subsequently release proinflammatory cytokines. These inflammatory mediators disrupt neural activity, impair synaptic plasticity, and result in the loss of synaptic connections (Vargas-Caballero et al., [2022](#)).

AD involves significant disruptions in **neuromodulatory** systems:

- **Cholinergic System:** Early degeneration of cholinergic projections from the BF to the cortex results in decreased cholinergic tone (Schmitz et al., [2018](#)). This decline correlates with cognitive impairment severity (Grothe et al., [2010](#)). Cholinergic signaling enhances hippocampal pyramidal cell firing related to **attention**. Donepezil is commonly used to enhance cholinergic tone (Howard et al., [2012](#)).
- **Dopaminergic System:** Dopaminergic pathways influence **motivational** salience coding via interactions with MS cholinergic neurons, that can code reward expectations (Hegedüs et al., [2023](#)). The MS receives reward signal from the hypothalamus, lateral septum and VTA. Although direct dopaminergic innervation of the MS by the VTA is extremely sparse, long-term depletion of VTA dopamine indirectly impairs cholinergic signaling in the MS, likely via downstream HPC or striatal circuits (Fitch et al., [2006](#); Szegő et al., [2011](#)). Dopamine-based therapies used in PD may have potential applications in AD (Mitchell et al., [2011](#); Naoto Watamura & Takaomi C Saido, [2024](#)).
- **Glutamatergic System:** Amyloid-beta plaques reduce NMDA receptor density and disrupt glutamatergic signaling (Snyder et al., [2005](#)). Optogenetic activation of glutamate receptors has shown promise in improving memory in animal models (K. W. Wang et al., [2019](#)).
- **GABAergic System:** Amyloid-beta peptides impair GABAergic signaling by disrupting PV and SST interneurons involved in theta-gamma signaling (Chung et al., [2020](#)). Optogenetic stimulation of MS PV neurons has been shown to rescue spatial memory deficits in rodent models (Etter et al., [2019](#)).

Potential **interventions** include:

- Indirect **activation of MS cholinergic neurons through dopaminergic pathways**, either pharmacologically or electrically, may hold therapeutic potential for enhancing motivation. Dopaminergic treatments, commonly employed for improving learning and memory in PD, could be adapted for AD. Current treatments for AD include donepezil (an acetylcholinesterase inhibitor) combined with memantine (primarily an NMDA antagonist but also a dopamine agonist with low affinity) (Howard et al., [2012](#)). There may be therapeutic promise in combining dopamine agonists such as rotigotine with TMS to restore synaptic plasticity. A clinical trial (NCT00306124) is currently investigating this approach in healthy adults.
Non-cholinergic MS cell stimulation may also influence motivation. For instance, non-selective MS stimulation, which activates interneurons, enhanced the spatial relevance of HPC place cell activity in rats (Mamad et al., [2015](#)).
- **Deep Brain Stimulation:**
 - o Clinical Evidence in PD and AD: Studies indicate that DBS targeting the BF in PD dementia patients improved memory, attention, and concentration (Freund et al., 2009, discussed below). Early-stage AD and PD dementia patients, characterized by

reduced cell loss and cholinergic neurodegeneration, may benefit more from DBS interventions.

- Nucleus Basalis of Meynert (NBM) DBS: A Phase I trial on six AD patients (Kuhn et al., [2015](#)) suggested that NBM DBS slowed disease progression, potentially by enhancing plasticity and stabilizing oscillations in memory-related circuits. Functional connectivity changes and increased glucose metabolism in the HPC were also reported (Gratwicke et al., [2020](#)).
- Fornix DBS: Long-term fornix DBS studies show promising results. Laxton et al. reported reduced cognitive decline (Laxton et al., [2010](#)), while Sankar documented increased HPC volume (Sankar et al., [2015](#)). Other studies found enhanced HPC connectivity and cerebral glucose metabolism, particularly in patients over 65 years of age, who performed better on cognitive tests (Lozano et al., [2016](#); G. S. Smith et al., [2012](#)).
- Further investigations into DBS for dementia are summarized in (Lv et al., [2018](#)), with detailed findings available in Table 1.
- Variability in DBS parameters (e.g., frequency, current intensity, duration) complicates outcome comparisons. A personalized DBS approach based on neuropsychological scores is under investigation in a clinical trial (NCT04856072).
- **Vagus Nerve Stimulation:**
 - Therapeutic Potential in AD: VNS has been proposed as a cognitive treatment for AD (C. H. Chang et al., [2018](#)). It promotes plasticity via both direct activation of BF cholinergic neurons and indirect pathways through the noradrenergic reticular system, such as the locus coeruleus (LC) to MS connection. In epilepsy patients, VNS has been shown to acutely improve memory performance and enhance visual attention, suggesting its potential applicability for AD (L. Sun et al., [2017](#)). Furthermore, tVNS has demonstrated efficacy in enhancing working memory task performance in healthy participants during offline stimulation (J.-B. Sun et al., [2021](#)).
 - Mechanistic Insights: VNS enhances HPC-dependent memory consolidation, visual attention, and working memory performance. It activates the nucleus of the solitary tract (NST) and LC, facilitating tonic (sleep-wake regulation) or phasic (attention related) norepinephrine release (Vargas-Caballero et al., [2022](#)). This modulation impacts both microglial anti-inflammatory profile and Brain Derived Neurotrophic Factor (BDGF) production; and astrocytes affecting glucose metabolism and neurotrophic support in the HPC (Feinstein et al., [2016](#)). However, abnormally high tonic LC activity may impair phasic norepinephrine release (Janitzky, [2020](#)).
 - Recent and current clinical trials for tVNS in AD are summarized in: [Vargas-Caballero et al., 2022/ Table 1.](#)
- **Gamma Frequency Entrainment:** Recent pilot studies (e.g., Chan et al., 2022) show that sensory stimulation at gamma frequency (40 Hz) may reduce AD pathology through mechanisms such as enhancing neural oscillations (Non-invasive Gamma ENtrainment Using Sensory stimulation (GENUS)).
- **Physical Activity** and Locomotion related to cognition: A six-month physical activity program improved cognitive test scores in healthy individuals (Lautenschlager et al., [2008](#)). Physical activity has been linked to increased muscarinic receptor density and cholinergic neuron count in the BF (Ang et al., [2006](#)). Particularly, the MS is involved in movement (Mocellin &

Mikulovic, [2021](#)) and optogenetic stimulation of its glutamatergic neurons induced locomotion. Locomotion influences MS glutamatergic and GABAergic activity, with theta rhythms in the HPC correlating with running speed and cognitive task performance. However, the underlying metabolic, hormonal, and cellular mechanisms require further exploration.

- **Cognitive Behavioral Therapy:** CBT may enhance cognitive function by modulating metabolic and hormonal factors, as well as promoting network-level neurotrophic effects. For instance, reduced nerve growth factor ([NGF](#)) levels in BF cholinergic neurons are a hallmark of AD (Salehi et al., [2004](#)). On the other hand, BDNF infusion in the right ventricle induced neurogenesis in the septal region (Pencea et al., [2001](#)). On the network level CBT may entrain septal circuits involved in the attentional components of memory formation (Mamad et al., [2015](#)).

5.2.4 Parkinson's Disease

PD is a neurodegenerative disorder primarily affecting motor systems. Common motor manifestations are tremors, bradykinesia (slowness of movement), rigidity, and balance issues. These **symptoms** typically develop gradually, with non-motor problems becoming more pronounced as the disease advances. Psychiatric complications, such as depression, sleep disturbances, psychosis, mood swings, and behavioral changes, are also frequently observed.

The pathophysiology of PD involves progressive degeneration of the nigrostriatal dopaminergic system, crucial for voluntary motor control. Although the underlying causes of neuronal death remain unclear, they are associated with the aggregation of alpha-synuclein into Lewy bodies within neurons.

Cognitive impairments in PD, such as (PD-[MCI](#)) and Parkinson's Disease Dementia ([PDD](#)), differ from AD. While PD-related cognitive deficits are often characterized by retrieval difficulties that improve with reminders or cues, AD-related impairments are primarily due to deficits in learning and storage mechanisms. Slowing of EEG rhythms, frontotemporal hypoperfusion, reduced functional connectivity in the default mode and attentional networks, and changes in prefrontal and basal-ganglia-cortical circuits often precede clinical symptoms and overt brain atrophy (Jellinger, [2024](#)).

The **etiology** of PD involves a complex interplay of genetic and environmental factors, including traumatic brain injury, medications, lifestyle, and pre-existing health conditions. PD diagnosis is primarily based on clinical signs and symptoms, particularly motor-related, as assessed during a neurological examination. Advanced imaging techniques, such as positron emission tomography ([PET](#)), can support the diagnosis. While PD typically affects individuals over the age of 60, it can also present as "early-onset PD" in those younger than 50.

DBS is an established **treatment** targeting structures such as the subthalamic nucleus ([STN](#)), the globus pallidus internus, and the thalamic ventral intermediate nucleus. The STN, in particular, exhibits oscillatory activity harmonically linked to tremor frequency (Timmermann et al., [2003](#)). Medication for PD dementia requires careful management to avoid interactions that exacerbate motor symptoms or induce psychotic symptoms.

Research on PD frequently employs **animal models**, including neurotoxin models and genetic models. Neurotoxins such as 6-hydroxydopamine ([6-OHDA](#)) and MPTP are used to simulate selective loss of nigrostriatal dopaminergic neurons.

In healthy individuals, motor-related neural **oscillations** display distinct patterns. Synchronized beta-band activity is prominent before movement preparation and during visuomotor coordination, with beta-rhythm inhibition and gamma-oscillation bursts marking movement initiation (Wessel, [2020](#)). During movement, synchronized gamma-band oscillations dominate (Tatti et al., [2022](#)). In contrast, PD patients exhibit increased long-range beta synchronization between subcortical and cortical motor regions and a failure of beta inhibition, potentially contributing to akinesia (Basha et al., [2023](#); Tinkhauser et al., [2018](#)).

The heterogeneity of cognitive phenotypes in PD suggests a shared neurodegenerative process impacting multiple functional neuronal networks and **neuromodulatory** systems. Dopaminergic neuron loss in the substantia nigra ([SN](#)) is a hallmark of PD (Kamath et al., [2022](#)). Although, DBS is an established treatment for PD, a recent study in mice reported that optogenetic stimulation of glutamatergic neurons in the secondary motor cortex ([M2](#)) increased striatal dopamine levels and evoked locomotor activity. The parallel administration of L-DOPA -a dopamine precursor primarily used to control bradykinetic symptoms- improved working memory performance (Magno et al., [2019](#)).

However, other processes precede the SN neurodegeneration. Even in the early stages of the disease, the noradrenergic locus coeruleus system becomes impaired, losing its potential anti-inflammatory and neuroprotective functions, affecting the efficacy of later pharmacological treatments (Paredes-Rodriguez et al., [2020](#)).

In addition, severe cholinergic deficits in the cerebral cortex have been demonstrated with in-vivo imaging. A recent MRI based study reported reduced structural integrity of the cholinergic basal forebrain Ch4- cortex pathways in PD patients with dementia (Slater et al., [2024](#)). Cholinesterase

inhibitors have been proposed as an effective treatment option (Emre, [2004](#)). Although interventions aimed at restoring cognitive functions in PD dementia patients are closely aligned with those used for AD, recent advancements highlight some further **therapeutic** strategies:

- Fan et al. demonstrated the feasibility of sonogenetics, a targeted ultrasound approach, as a therapeutic intervention to mitigate neurodegeneration in animal models of PD (Fan et al., [2021](#)). This technique represents a novel avenue for slowing disease progression.
- A case study involving a 71-year-old PD dementia patient utilized DBS targeting the STN to alleviate motor symptoms and the intermedial part of the NBM for cognitive enhancement (H.-J. Freund et al., [2009](#)). Targeting the NBM is particularly advantageous due to its clear visualization on MRI, high density of cholinergic cell bodies, and significant involvement in dementia. Improvements were observed in cognitive functions such as attention, concentration, and alertness, alongside enhanced personality features and social communication. These changes, reflecting general tuning effects, likely facilitated better utilization of remaining mental capacities. Although memory improved, it did not fully recover.
- A NBM DBS study by Gratwicke et al. involving six PD dementia patients reported no significant cognitive improvements but documented a reduction in complex visual hallucinations (Gratwicke et al., [2018](#)).

5.2.5 Depression

Depression encompasses a spectrum of severity, ranging from mild and moderate to severe forms. Major Depressive Disorder (MDD), the most severe type, is a prevalent and persistent psychiatric condition. It is characterized by extreme feelings of sadness and a low mood disproportionate to any apparent cause (American Psychiatric Association, 2013). Other symptoms include impaired concentration, excessive guilt or low self-worth, hopelessness about the future, and disrupted sleep patterns. Notably, other psychiatric conditions, such as bipolar disorder and borderline personality disorder, may share symptoms with depression, complicating diagnosis.

Intracranial electrophysiological recordings from epilepsy patients reveal that mood states can be decoded from oscillations in the limbic system, and symptoms could be alleviated with targeted interventions to abnormal oscillations (Sara Reardon, [2017](#)). Functional MRI studies have shown hyperconnectivity in the default mode network and the affective network, highlighting neural correlates of depressive states (Jacobs et al., [2014](#)).

Depression arises from an interplay of social, psychological, and biological **factors**. Stressful life events, physical inactivity, and harmful alcohol use are significant contributors. Depression is **diagnosed** when symptoms persist for most of the day, nearly every day, for at least two weeks. Blood or urine tests are often employed to rule out other underlying medical conditions.

Treatment for depression varies with severity. Psychological therapies are typically the first-line approach, particularly for mild cases. For moderate and severe depression, psychological treatments are often combined with antidepressant medications. Second-generation antidepressants include tricyclic antidepressants, selective serotonin reuptake inhibitors ([SSRIs](#)), serotonin-norepinephrine reuptake inhibitors ([SNRIs](#)), and norepinephrine reuptake inhibitors ([NRIs](#)). For treatment-resistant cases ECT may be recommended. VNS has been used for treatment-resistant depression since 2005, while TMS received FDA approval for MDD and OCD in 2008 and 2018, respectively. Behavioral therapies, particularly CBT, remain a cornerstone of psychological treatment for depression and have demonstrated effectiveness in related conditions such as PTSD (Leuchter et al., [2015](#)).

Animal models used to study depression include experience-based models (e.g., early life stress, chronic adult stress, and social stress paradigms), pharmacologic models (e.g., withdrawal from psychostimulant use), lesion models (olfactory bulbectomy ([OBX](#))), and genetic models (e.g., selective transgenic lines).

Oscillopathies associated with depression are suggested to predict the effectiveness of pharmacological treatments (Takeuchi & Berényi, [2020](#)). Studies have identified elevated alpha band activity in the temporoparietal region and increased theta band activity in frontal areas as significant markers (E. E. Smith et al., [2020](#)). Additionally, frontal alpha asymmetry, characterized by left hemispheric hypoactivity and right hemispheric hyperactivity, has been associated with mood dysregulation (Hecht, [2010](#)). Alterations in gamma band activity further highlight the role of oscillopathies, with decreased gamma activity noted during cognitive or emotional tasks (Y. Li et al., [2015](#)). However, increased gamma oscillations in the visual cortex (50–70 Hz) have been specifically linked to suicide attempts in depression, suggesting a unique pathological signature (Dai et al., [2024](#)). Pharmacological interventions, such as the norepinephrine reuptake inhibitor reboxetine, have shown the potential to modulate these oscillatory patterns by increasing theta and gamma power while enhancing hippocampal theta phase locking of medial septal units, indicating their role in restoring neural dynamics and improving clinical outcomes (Hajós et al., [2003](#)).

Neuromodulatory systems implicated in depression include the MS cholinergic system and the VTA dopaminergic system, both of which play roles in motivation and reward (Belujon & Grace, [2017](#); Dulawa & Janowsky, [2019](#)). MS cholinergic cell loss and dysfunction have been observed in the

olfactory bulbectomy model, underscoring their relevance in depressive pathophysiology (Hozumi et al., [2003](#)).

Potential interventions for depression encompass a range of pharmacological, neuromodulatory, and behavioral strategies, with emerging therapies providing novel insights into treatment mechanisms.

- Advances in **animal studies** using optogenetics and chemogenetics have provided significant insights into human depression research, as highlighted in a comprehensive review by Biselli et al. (Biselli et al., [2021](#)).
- **Dopamine-based treatments**, previously discussed for addressing motivational deficits in PD/ AD, may hold therapeutic value for MDD patients due to their shared underlying motivational impairments (Jeuring et al., [2023](#)).
- **Pharmacological innovations** include the administration of subanesthetic doses of ketamine (0.5 mg/kg), which enhances gamma oscillations in the human cortex, and has demonstrated rapid antidepressant effects (Shaw et al., [2015](#)).
- **Transcranial Direct Current Stimulation** paired with neurofeedback shows promise in alleviating depressive symptoms by targeting nerves in the left dorsolateral prefrontal cortex (Shiozawa et al., [2014](#); Yachou et al., [2025](#)).
- For treatment-resistant MDD, **DBS** targeting the medial forebrain bundle has shown efficacy (Dandekar et al., [2018](#)). Recent advancements, such as the closed-loop DBS system described by Scangos et al. (Scangos et al., [2021](#)), use multi-day intracranial electrophysiology of the amygdala to identify personalized biomarkers and optimize symptom-specific interventions in the ventral striatum. Another high-impact study reported efficacy of Subcallosal Cingulate Cortex stimulation guided by local field potentials used as biomarkers of the clinical state (Alagapan et al., [2023](#)).

5.2.6 Autism

Autism spectrum disorder ([ASD](#)) is a developmental brain disorder defined by the DSM-5 as comprising a dyad of impairments involving deficits in social interaction, encompassing both verbal and nonverbal communication, and restricted, repetitive patterns of behavior, interests, or activities. These behavioral characteristics are associated with abnormalities in the integration of cognitive mechanisms, where individuals with ASD may exhibit superior performance with unsegmented designs but impaired ability to integrate these into coherent representations in the block-design task. Additionally, recent research has highlighted anomalous sensory and perceptual function as a significant feature of ASD (D. M. Simon & Wallace, [2016](#)).

At the neurobiological level, both hyperexcitability with unstable cortical networks and hypoexcitability of glutamatergic cells have been observed, indicating a spectrum of excitatory-inhibitory imbalances (Uhlhaas & Singer, [2006](#)). Studies have reported altered ionotropic receptor

(AMPA, NMDA, GABA_A) densities in several brain regions of mouse models of ASD (Nardi et al., [2023](#)). Neuromodulatory systems implicated in ASD include the serotonergic, dopaminergic, cholinergic, and noradrenergic systems (Lam et al., [2006](#)). The regulation of these systems appears to vary across different brain regions, contributing to the heterogeneous manifestations of ASD. Dysfunctional integrative mechanisms in ASD are further linked to reduced neural synchronization and a pronounced reduction in functional connectivity, which may underpin the difficulties in integrating sensory, cognitive, and social information (Uhlhaas & Singer, [2006](#)).

5.2.7 Anxiety/ Fear

Dysregulated fear reactions can emerge from maladaptive processing of trauma-related memories, as observed in conditions such as post-traumatic stress disorder. The neural mechanisms underlying fear and anxiety involve specific oscillatory activities and their modulation by pharmacological and physiological interventions. Anxiolytic drugs have been shown to reduce theta frequency, while lesioning of MS cholinergic cells diminishes type 2 theta activity, which is associated with fear responses to predators and anticipatory fear, such as that elicited by food shocks (Korotkova et al., [2018](#); Woodnorth & Mcnaughton, [2002](#); Yoder & Pang, [2005](#)). Similarly, electrolytic lesioning or pharmacological inhibition of the MS, using agents such as tetrodotoxin, muscimol, or lidocaine, decreases anxiety, whereas chemogenetic activation of MS cholinergic cells is implicated in maintaining anxiety levels (Ashabi et al., [2011](#); Bannerman et al., [2004](#); Degroot et al., [2001](#); Degroot & Treit, [2004](#); Lamprea et al., [2010](#)).

The Median Raphe Nucleus ([MRN](#)) plays a complementary role in the modulation of theta activity, particularly type 2 theta. Activation of the MRN has been reported to suppress theta oscillations, thereby exerting anxiolytic effects, while MRN inhibition enhances theta activity and may result in anxiogenic outcomes (Hsiao et al., [2012](#), [2013](#)). State-dependent increases in theta and gamma oscillatory activity in the ventral HPC have been identified as potential biomarkers of impaired fear extinction, providing insight into the neural substrates of trauma-related disorders (Çalışkan & Stork, [2019](#)).

Emerging therapeutic interventions such as VNS have shown promise in modulating these neural circuits. A pilot study by George et al. demonstrated that VNS could restore normal oscillatory patterns and reduce anxiety, further supporting its potential as a treatment for dysregulated fear responses and anxiety disorders (George et al., [2008](#)).

5.2.8 Pain

When pain becomes chronic, as observed in neuropathic pain, it often persists despite treatment and is associated with complex neural adaptations. While chronic pain may correlate with slower processing speeds, cognitive impairments are not typically the most pronounced symptoms. However, substantial evidence supports the presence of oscillopathies and the involvement of the MS in pain modulation.

The MS plays a pivotal role in controlling exaggerated pain responses. Analgesic effects induced by electrical stimulation of the MS are hypothesized to involve activation of the descending pain inhibitory system. Early clinical findings by Heath and Mickle reported immediate relief of chronic pain in patients through septal stimulation, corroborated by Gol et al., who also documented pain relief via electrical stimulation of the septal area (Gol, [1967](#)).

The MS receives afferent inputs from nociceptive pathways, modulating theta rhythms in response to pain. These theta oscillations can be attenuated through electrical lesioning of the MS (Khanna, [1997](#)). Recent advances have elucidated more specific mechanisms of MS involvement in pain regulation. Selective inhibition of cholinergic neurons in the MS, which project to the rostral anterior cingulate cortex and hyperactive in chronic inflammatory states, has been shown to attenuate nociceptive behaviors in mouse models (Ariffin et al., [2018](#)). Conversely, MS neurons projecting to the ventral HPC are hypoactive in chronic pain conditions, and their stimulation has demonstrated analgesic effects. Notably, the administration of glutamate receptor antagonists attenuates peripheral hypersensitivity in chronic constriction injury (CCI) models, further emphasizing the critical role of MS and its projections in pain regulation (Ariffin et al., [2018](#)). Furthermore, inactivation or lesioning of the MS has been found to prolong the analgesic effects of general anesthesia (Leung et al., [2013](#)).

5.2.9 Traumatic Brain Injury and stroke

Traumatic Brain Injury (TBI) and stroke are recognized as contributing factors to the development of various brain diseases, but they also result in a range of secondary symptoms (National Institute of Neurological Disorders and Stroke). TBI can induce chronic traumatic encephalopathy (CTE), a condition that can manifest as cognitive impairments affecting thinking, understanding, and communication, as well as movement disorders, depression, confusion, and irritability. Another condition linked to TBI is post-traumatic dementia (PTD), which underscores the long-term

cognitive and behavioral consequences of such injuries. Notably, the functional connectivity of TBI-affected brains can be mapped and potentially improved through the application of TMS, which has shown promise in enhancing cognitive skills (Calderone et al., [2024](#)).

In the context of stroke, there is growing evidence pointing to stroke-induced alterations in hippocampal oscillatory activity and disrupted communication between brain networks as underlying mechanisms of post-stroke cognitive dysfunction. These changes emphasize the importance of understanding the neurophysiological consequences of stroke to develop targeted interventions. Comprehensive reviews, such as that by Sato et al. (Sato et al., [2022](#)), highlight the role of oscillatory disruptions and network connectivity impairments in shaping post-stroke outcomes, thereby providing critical insights into potential therapeutic approaches.

5.3 Emerging horizons in brain research and therapeutic innovations

Advances in the study of human brain diseases continue to enhance our understanding, largely through accumulating clinical cases and experimental research. However, findings from human studies are often inconclusive, necessitating rigorous approaches to improve reliability and applicability. Multicenter **studies** with double-blind, placebo-controlled, and randomized sham designs are crucial for addressing variability and ensuring robust conclusions. Patient group categorization should account for age and disease progression, with longitudinal follow-ups to track outcomes over time. However, ethical considerations, particularly regarding informed consent, remain a challenge given the cognitive and communication impairments and fluctuating decisional capacity of affected patients to participate in experimental studies.

There is a pressing need for **standardized** interventions, including clearly defined target brain areas, technologies, recording parameters, stimulation protocols (on-off time, intensity, frequency, pulse width), and treatment regimens (period, duration of sessions). Parameters optimized for cognitive modulation may differ from those routinely employed for other conditions like epilepsy or depression. Animal studies are important for the selection of initial parameters, such as adjusting the frequency of NBM-DBS to restore dementia (H.-J. Freund et al., [2009](#)). Nevertheless, systematic investigation should map synergistic effects of combined treatments.

Technological advancements are critical to overcoming current limitations. Intraoperative recording techniques require improvement to refine interventions. Treatments need greater reversibility; while pharmaceuticals often have systemic effects, localized and tunable stimulation offers a more customized approach. Adaptive closed-loop systems have the potential to reduce side effects and personalize treatments by responding to patient-specific states, such as seizure enhancement scenarios.

An insightful review by Frey et al. provides a comprehensive overview of anticipated advancements in DBS technology and its applications in the near future (Frey et al., [2022](#)): “Hardware advances such as longer-lasting batteries will reduce the frequency of battery replacement and segmented leads will facilitate improvements in the effectiveness of stimulation and have the potential to minimize stimulation side effects. Targeting advances such as specialized imaging sequences and “connectomics” will facilitate improved accuracy for lead positioning and trajectory planning. Software advances such as closed-loop stimulation and remote programming will enable DBS to be a more personalized and accessible technology”.

Innovations are expanding the scope of treatment and diagnostics. Developments include nanocognitive devices like the "endomycorrhizae-like interface" for dementia patients (Saniotis et al., [2018](#)), therapeutic sonogenetics for conditions like seizures, depression, and Parkinson’s disease (Leinenga et al., [2016](#)), and advanced spatiotemporal animal recording technologies such as real-time 3D visualization of synaptic plasticity at a single-neuron level in awake rats (Gonzalez et al., [2024](#)). Algorithmic enhancements are equally critical, focusing on signal-to-noise ratio maximization, stimulation artifact removal, and advanced analysis techniques to detect synchronization abnormalities, such as gamma-frequency coherence for functional connectivity and EEG phase synchronization changes for seizure prediction (Le Van Quyen et al., [2003](#)).

Early diagnostic tools are essential, particularly for diseases like Alzheimer’s, which are typically diagnosed late. Neuromelanin-sensitive MRI is a promising tool for identifying early pathological or functional changes in catecholamine neurons, potentially benefiting early interventions like VNS. Recent developments, such as a platform integrating hardware and algorithm libraries for real-time data processing and stimulation artifact removal with minimal feedback response time (Y. Li et al., [2024](#)), highlight the rapid translation of animal studies to clinical applications. While optogenetics is not yet available for human use in cognitive disorders, optogenetic-inspired approaches demonstrate significant promise for future research and treatment (Sahel et al., [2021](#)).

Optimized treatment parameters can be tailored to individual patients, enabling personalized therapy that is responsive in real-time through the use of physiological feedback biomarkers. Biofeedback techniques empower patients to voluntarily modulate aberrant neural activity by providing insight into their physiological states. Neurofeedback training, which delivers real-time feedback to facilitate the conscious modification of brain signals by users, has been applied in conditions such as ADHD, anxiety, depression, and PTSD, albeit with varying degrees of efficacy.

These advancements underscore the critical need for interdisciplinary efforts combining neuroscience, engineering, and clinical practice to develop precise, effective, and personalized interventions for brain disorders.

Challenges and considerations in translating research to practice

There are several limitations to consider when interpreting the findings and implications of the discussed research. Firstly, it is important to note that many of the observations were derived from studies conducted on rodent models. While these models provide valuable insights, they often face challenges in replicating the full spectrum of human diseases. Additionally, despite efforts to validate behavioral paradigms rigorously, testing complex cognitive functions in animal models remains limited. Consequently, translating these findings to clinical settings requires careful consideration. Another limitation arises from the ethical constraints inherent in human studies; clinical research often relies on epilepsy patients or samples, where network-level functions may already be altered, potentially confounding the results. Furthermore, as therapeutic advances progress, emerging issues demand attention, such as the potential for addiction to self-stimulation in cases of DBS for MDD. Lastly, neurodegeneration in humans currently shows limited reversibility under specific conditions, which means brain stimulation therapies are often restricted to supplementary roles, such as managing memory circuits rather than reversing degenerative processes.

6 The sympathy of clocks

An intriguing phenomenon known as the "sympathy of clocks," referring to the spontaneous synchronization of pendulum clocks, was first described by Christiaan Huygens (1629–1695) in a letter to the Belgian mathematician René-François de Sluse in 1665. Huygens was one of the most influential Dutch scientists of the 17th century, active in mathematics, mechanics, and optics, and is most famous for his fundamental contributions to the evolution of horology.

After the Age of Discovery, marine shipping presented a compelling need for the development of a precise navigation system. Although the latitude of naval vessels and merchant ships could be calculated from the angle between the Sun and the horizon and the angle sunrays make with the Earth's equator, finding longitude was difficult due to the complex and error-prone measurements of celestial body positions.

This problem of longitude also occupied Huygens' mind during this period. He reasoned that if sailors could keep track of the port's reference time, they might be able to calculate their longitude from the time difference between their local time and the reference time. Local solar time can be determined from the angle of the Sun. As a 360-degree rotation of the Earth takes 24 hours, the time difference between local and reference time can be converted into angles, which represent the longitudinal displacement of the ship.

Huygens made substantial advancements in the development of precise pendulum clock designs. These clocks included an escapement mechanism that compensated for energy loss due to dissipation (e.g., the drag force exerted by air). A weight was attached to a gear's hub, causing it to rotate as the falling weight pulled it down. The rotation was arrested from tooth to tooth by the escapement mechanism; otherwise, the falling weight would cause an acceleration in the ticking.

In 1665, Huygens sent his clocks on an experimental voyage aboard the ship of British Admiral Robert Holmes. To ensure the availability of the reference time, Holmes placed two pendulum clocks on board. These pendulums were suspended from a heavy beam to avoid disturbance. Although this experimental voyage did not yield a smashing success, Huygens continued to investigate the behavior of pendulum clocks. In his home setup, which consisted of two vertically held chairs, a horizontal coupling wooden bar, and two suspended pendulum clocks, he observed that after roughly half an hour, the clocks began to tick antiphase. Huygens investigated this synchronization and suggested that the imperceptible motion of the coupling structure (i.e., the

dynamics of bending and axial stretching) transmitted energy from one clock to the other. He summarized his research and shared a detailed description of a precise pendulum clock in “Horologium Oscillatorium” in 1673.

While Huygens predicted the existence of in-phase synchronization, later scientists discovered additional types of pendulum-like synchronization. Ramirez et al. summarized these findings and enhanced them with theoretical work and computer-assisted investigations of various limit behaviors (Ramirez et al., [2014](#)):

- **Quenching:** Lord Rayleigh (1842–1919) observed mutual synchronization in two nearly identical organ pipes in 1877. Even though the pipes were tuned to slightly different frequencies, they synchronized subtly, eventually producing only a faint whisper. The counteracting air vibration resulted in amplitude death.
- **Beating death:** In 1740, John Ellicott noted that one pendulum gradually ceased functioning after two hours in his setup. Although the escape mechanism was eliminated, the pendulum continued to oscillate at a small amplitude. Theoretically, it is possible for both clocks to stop functioning entirely.
- **Partial synchronization:** Sometimes, the pendula exhibit frequency synchronization, but not full in-phase or anti-phase; a constant phase difference remains between them.
- **Modulating or intermittent behavior:** Based on the simplified model of Huygens' experiment, Ramirez demonstrated modulatory coupling of the pendula. When the cross-sectional area of the vertical beams (chairs) of the coupling structure was reduced, the escapement mechanisms operated intermittently.

Some synchronization types are relatively sensitive to the initial conditions (the starting angles of the pendula), while others converge to a limit behavior from a broader spectrum of starting states. Ramirez identified the parameters in his nonlinear finite element model: the coupling strength (mass ratio of the pendula and the horizontal beam), damping coefficient (air resistance), and cross-sectional area of the vertical beams. He presented a coupling strength-damping relation that is also dependent on initial conditions: for small damping, in-phase synchronization was favored for weak coupling strength, while anti-phase synchronization was favored for strong coupling; for stronger damping, synchronization was exactly reversed. Regarding the influence of the escape mechanism, Ramirez observed that this cyclic energy reload did not significantly affect the limit behaviors.

7 Experimental design

The aim of this chapter is to justify the rationale behind the experimental choices made, including the identification of phenomena, models, methodologies, and specific brain areas. These aspects are crucial for addressing fundamental questions regarding theta rhythm generation and synchronization.

7.1 Phenomena

Oscillatory activities underlie numerous brain functions, coordinating information flow, segmenting neural processing, and dynamically linking distributed brain regions. Categorized by their frequency into delta (0.5–4 Hz), theta (4–12 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30–100 Hz) bands, these rhythms are believed to support distinct cognitive and behavioral functions.

Oscillations are not mere byproducts of neural activity. Brain rhythms are integral to neural computation and communication, enabling the temporal organization of neural ensembles. Investigating specific oscillations offers critical insights into how the brain orchestrates its vast networks to achieve complex functions.

Theta rhythm is the most regular oscillatory activity in the hippocampus, associated with exploratory behavior, learning, and memory. It serves as a temporal reference for hippocampal network activity (for a detailed description of its functions please refer to the *“Role of theta oscillation”* chapter). Despite nearly 90 years of extensive research and an ever-expanding body of literature, the precise dynamics of how medial septal neurons synchronize to generate theta rhythms remain unclear. The examination of such a phenomenon is critical in resolving discrepancies between theoretical constructs and experimental observations, particularly with regards to processes like Huygens synchronization, a foundational concept in coupled oscillator theory. A deeper understanding of theta mechanisms requires methods that selectively block theta rhythm generation with minimal side effects (e.g., loss of neuromodulatory inputs, changes in mean firing rates) to reveal causal links.

Studying theta rhythms could also shed light on fundamental brain processes and offer potential applications in treating neurological disorders such as schizophrenia, epilepsy and Alzheimer's disease (See *“Oscillopathies: a rationale behind this study”* below).

7.2 Models

7.2.1 Relevance of animal research

Animal research holds a pivotal role in neuroscience, offering detailed insights into neuromodulatory systems facilitating the development of new pharmacological strategies to enhance or restore neural synchronization. Modern experimental techniques enable the exploration of synchronization mechanisms in both wild-type and transgenic animals, supporting the identification of critical neuronal contributors and developing models of synchronization that can be validated across species.

Animal models of human diseases provide a valuable platform for analyzing abnormal synchronization patterns, identifying biomarkers, and refining diagnostic tools. The development of non-invasive and quantifiable recording methods, combined with sophisticated time-series analysis, offers great promise for tracking disease progression and assessing treatment efficacy, while reducing subjective interpretation and minimizing reliance on highly trained specialists. Additionally, animal research contributes to the identification of potential therapeutic tools targeting synchronization failures, such as deep brain stimulation or the exploration of GABAergic modulators for conditions like schizophrenia and autism.

7.2.2 Why rodents?

Rodents, especially rats and mice, are widely used in neurosciences, providing particularly useful models for studying brain function and neural dynamics. Much of the foundational neuroanatomical data in neuroscience has been derived from rodent studies, including detailed mappings of the hippocampal formation. Rodents play a prominent role in functional analyses of the hippocampus, making them an indispensable model for investigating oscillatory activities like theta rhythms. Their hippocampal theta oscillations are broadly comparable to those in humans, as they occur during exploratory behaviors, spatial navigation, and memory processing, providing a translational framework for understanding theta's role across species.

Rodents also provide excellent genetic and anatomical accessibility, enabling precise experimental manipulations. Techniques such as in vivo electrophysiology and optogenetics are well-established

in rodent models, providing powerful tools to dissect the contributions of specific neuronal populations and circuits to theta rhythm generation and synchronization.

Another advantage of rodents is their versatility in expressing theta oscillations. Theta is not only present during active wakefulness but also during REM sleep, indicating its essential role across behavioral states. Moreover, theta can be elicited under anesthesia in response to noxious stimuli.

Despite the utility of rodent models, notable differences exist between species, particularly in the expression of theta rhythms (see *“Limitation of the study”* chapter below). In mice and rats, theta oscillations manifest as a continuous rhythm during active behavior, whereas in humans, monkeys or bats, theta activity typically occurs in shorter bouts. This discrepancy may arise because experimental conditions in non-rodent species may not sufficiently engage the theta-generating neural circuitry. While rodent experiments often simulate naturalistic conditions that involve multimodal stimuli, such as foraging, simple virtual navigation intraoperative tasks in humane experiments may not fully engage the theta network. Supporting this view, Kahana et al. reported more frequent theta oscillations during navigation through complex virtual mazes compared to simpler tasks (Kahana et al., [1999](#)).

Another hypothesis is that continuous theta in rodents might be linked to rhythmic limbed locomotion, which is absent in bat or human experiments.

7.2.3 Why urethane anaesthetized and freely moving conditions?

Using both anesthetized and freely moving rodent models ensures that findings are not limited to a single physiological state, providing a more general understanding of theta rhythm generation and synchronization.

Anesthetized models offer a controlled environment for stable recordings, minimizing variability caused by behavioral factors. Urethane-induced anesthesia is particularly advantageous as it maintains robust and long-lasting oscillatory activity without requiring continuous administration, unlike other anesthetics such as isoflurane or barbiturates. Urethane preserves the functional connectivity between the medial septum and hippocampus, ensuring physiologically relevant theta rhythms are sustained throughout the experiment. Moreover, urethane has a minimal impact on cardiovascular and respiratory systems, thus providing a stable physiological baseline. Finally, the uniform and reproducible effects of urethane across experiments reduce inter-animal variability, enhancing the comparability and reliability of results.

In contrast, freely moving conditions are essential for investigating the functional relevance of theta rhythms during natural behaviors such as navigation and memory encoding. By combining anesthetized and freely moving models, we ensure that findings are robust across different physiological states and can generalize to both controlled and naturalistic scenarios.

7.2.4 Relevance of computer models

Computer models complement animal studies by allowing researchers to test hypotheses about network dynamics under controlled conditions. These models enable systematic manipulation of parameters like excitation levels, synaptic strength, or their variability among neurons to explore synchronization mechanisms that are difficult to isolate experimentally. Network simulations allowed us to study network dynamics under various conditions, confirming that frequency synchronization suffices for theta rhythm generation, independent of additional specialized mechanisms.

By combining in vivo and in silico approaches, we achieved a holistic understanding of synchronization mechanisms that extend beyond species-specific differences.

7.3 Techniques

To study theta rhythm generation and synchronization, we employed high temporal resolution methods capable of capturing millisecond scale changes. Electrophysiology provided direct recordings of neuronal activity and local field potentials, allowing observations of synchronization at both the single-cell and network levels. On the other hand, optogenetics enabled precise identification and manipulation of specific neuronal subtypes, such as parvalbumin-expressing neurons, helping to establish their roles in pacemaking and synchronization.

7.4 Target brain areas and signals

7.4.1 CA1 LFP

The hippocampal formation is particularly well-suited for field potential (LFP) studies due to its histological arrangement. The dense packing of the cell bodies, the roughly parallel position of the apical dendrites and their capacity for synchronous activation collectively contribute to the prominence and clarity of hippocampal field potentials.

Despite the similar cytoarchitecture and similar inputs of the CA1 and CA3 regions, the extracellular theta currents in the latter are considerably smaller than those in the former. This difference arises partly due to variations in the distal dendritic arbor sizes and the interference of mossy fibers induced excitatory currents with opposite phase perforant path and recurrent collateral generated currents.

7.4.2 Medial septal multiple single units

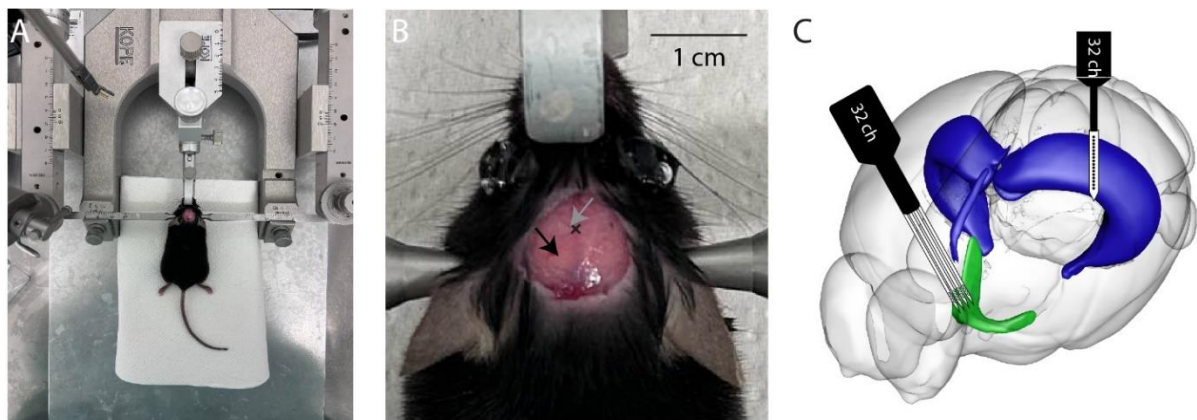
One of the earliest findings regarding hippocampal theta rhythm, discussed in *“Electrophysiology of the hippocampal theta, historical models”* chapter was that lesion of the medial septum abolish theta oscillations (Petsche 1962). The medial septum plays a central role in orchestrating oscillatory neuronal activities throughout the brain, contributing to functions such as sensory and emotional salience, locomotion, mood regulation, and the governance of learning and memory.

The hippocampus is the principal target of septal theta-generating circuits, and its local field potentials provide a direct measure of network oscillatory activity. Concurrent recordings of medial septal unit activity and hippocampal LFPs allowed us to correlate individual neuron dynamics with population-level rhythms, revealing mechanisms of frequency synchronization and phase relationships. This dual-focus approach established the medial septum's role as a pacemaker for hippocampal theta, aligning experimental observations with theoretical predictions.

8 Synchronization of septal rhythmic neurons- Thesis group I.

8.1 Surgery and electrophysiological recordings – Methods

Hippocampal theta oscillations have been investigated in both urethane-anesthetized and awake rodents (Borhegyi et al., [2004](#); Buzsáki, [2002](#); Klausberger & Somogyi, [2008](#); Kramis et al., [1975](#); Mikulovic et al., [2018](#); Stewart & Fox, [1989](#)). To explore the commonalities and differences across different theta model systems, we collected three independent data sets (*Figure 6*). We recorded multiple single neurons from the medial septum (MS) using silicon probes from anesthetized rats (n = 903 neurons from N = 7 rats; 416 and 636 neurons active during both theta and non-theta states or at least one of them, respectively), anesthetized mice (n = 1155 neurons from N = 11 mice; 617 and 950 active during both or at least one of the states) and awake mice (n = 312 neurons from N = 4 mice; 265 and 289 active during both or at least one of the states). Simultaneously, we recorded local field potentials (LFP) from all layers of the dorsal CA1 area of the hippocampus using linear silicon probe electrodes (*Figure 5*).



5. *Figure. Stereotaxic surgery in rodents (anaesthetized mouse). (A) Nose and ear bones are fixed by gently fitted metal bars. Now the three-dimensional coordinate system of the frame can be utilized in the stabilized skull. (Photo was taken by Vivien Pillár). (B) The intersection of the coronal and sagittal sutures is used as a reference landmark (Bregma, cross). Exact penetration sites of the electrodes (MS: grey arrow, HP: black arrow) are computed based on the detailed anatomical atlas of the mouse brain (Paxinos et al., [2001](#)). (C) Silicon probes are implanted in the MS (green) for single neuron recording and in the HPC (purple) for LFP recordings. Three-dimensional mouse brain adopted from (Bakker et al., [2015](#)).*

8.1.1 Acute rat recordings

Rats were anesthetized with an intraperitoneal injection of urethane (40%; dose, 0.37 ml/100 g). A homeothermic heating pad connected to a rectal probe held body temperature constant (36°C). The top of the head was shaved, the rat was placed in a stereotaxic frame (David Kopf Instruments, Tujunga, US), the skin and the connective tissue above the calvaria were removed and the skull was cleared. A craniotomy was opened over the medial septum and another one over the right hippocampus. A 32-channels linear silicon probe (A1x32-6mm-50-177; NeuroNexus Technologies, Ann Arbor, US) was lowered into the right CA1 (anterior-posterior (A-P): -4.5 mm and medial-lateral (M-L): 3 mm) and a 32-channels Buzsaki-type silicon probe (Buzsaki32; NeuroNexus Technologies, Ann Arbor, US) was lowered to the top of the medial septum (A-P: 0.4 mm and M-L: -1.6 mm, 15° angle in the coronal plane). The silicon probes were dipped in red fluorescent dye (1,1'-Diocetadecyl-3,3,3',3'-Tetramethylindocarbocyanine Perchlorate, Dil) before insertion to aid later histological reconstruction. The ground electrode was secured in the nuchal muscles.

Neural signals were acquired by two National Instruments PCI-6259 cards, amplified (2000 times) and digitized at 20 kHz. After allowing 30 minutes for the brain tissue around the electrode to stabilize, a 30-minute recording was conducted. Theta oscillation was induced by temporarily placing an insulated clip on the tail for 1 minute, repeated 3 times. After the recording, the septal probe was moved 100 µm ventrally, and the procedure was repeated. Recording sessions were conducted as long as theta oscillation could be detected via audio feedback; correct positioning of the probe in the MS was later confirmed by both histological reconstruction (*Figure 6*) and the presence of theta-rhythmic neurons in the recordings.

These experiments were carried out by Balazs Hangya (Lendület Laboratory of Systems Neuroscience, Institute of Experimental Medicine, 1083 Budapest, Hungary).

8.1.2 Acute mouse recordings

Implantations were performed under general anesthesia. Mice received an intraperitoneal injection of urethane (~1.3 mg/g). If necessary, an additional dose of urethane was injected intramuscularly to maintain the depth of the anesthesia during surgery and recordings. The body temperature of the animals was maintained during the experiments at 37 °C using a thermostatically regulated heating pad (Supertech, Pécs, Hungary). Mice were placed in a stereotaxic frame (David Kopf Instruments, Tujunga, US), then the skin and the connective tissue were removed from the top of

the skull. Next, two small circular craniotomies (1 mm diameter) were made on the skull with a dental drill, one for the recording probe inserted into the MS and one for the probe inserted into the hippocampus (CA1). Stereotaxic coordinates were used to determine the septal and hippocampal locations for recording (MS, A-P: 0.6 mm and M-L: 0.5 mm; CA1, A-P: -2.2 mm and M-L: 1.5 mm from the Bregma) (Paxinos et al., [2001](#)). For post-mortem histological verification of the recording location of the probes, the backside of the silicon shank was coated with red-fluorescent dye (Dil, D-282, ~10% in ethanol, Thermo Fischer Scientific, Waltham, US) before insertion (DiCarlo et al., [1996](#); Fiáth et al., [2019](#)). The septal probe was a high-density single-shank silicon probe with 128 square-shaped recording sites (Fiáth et al., [2018](#)). The 8-mm-long shank of the probe had a cross-section of 100 μm $\times$ 50 μm (width $\times$ thickness). The closely spaced recording sites (20 μm $\times$ 20 μm) were arranged in a 32 $\times$ 4 array with 2.5 μm spacing between the edge of electrodes. The probe was mounted on a motorized micromanipulator (Robot Stereotaxic, Neurostar, Tübingen, Germany) and inserted at a slow speed (2 $\mu\text{m}/\text{sec}$) into the brain tissue to increase the single unit yield by decreasing the tissue damage (Fiáth et al., [2019](#)). The probe was tilted at an angle of 8° from vertical in the coronal plane to have better access to the medial septum. Since the effective vertical recording area of the probe (~0.7 mm) was smaller than the dorsoventral extent of the MS (~1.5 mm), to obtain the spiking activity of as many septal neurons as possible, recordings were performed in three, slightly overlapping (~0.2 mm) depths. (Unit clusters recorded twice due this overlap, based on waveform similarity and autocorrelograms, were counted only once, see “*Overlapping septal clusters*” below and *Figure 7*.) The hippocampal probe was a linear silicon probe with 32 recording sites and with a shank thickness of 50 μm (A1x32-6mm-50-177, NeuroNexus Technologies, Ann Arbor, US). The recording sites of the device had a diameter of 15 μm and an interelectrode distance of 50 μm . The probe was attached to a manual micromanipulator, then inserted at a speed of ~10 $\mu\text{m}/\text{sec}$ to a dorsoventral depth of 2 mm. The two recording probes were connected to an electrophysiological recording system (RHD2000, Intan Technologies, Los Angeles, CA, USA) equipped with 32-channel and 64-channel headstages.

Wideband brain electrical activity (0.1 - 7500 Hz) was recorded on 160 channels with 16-bit resolution and at 20 kHz/channel sampling rate. A stainless-steel wire inserted into the neck muscle of the animal served as the reference and ground electrode during recordings. Room temperature physiological saline solution was regularly dropped into the craniotomy to prevent dehydration of the brain tissue. Recordings were conducted for 15 minutes each, consisting of 5 minutes baseline period, 5 minutes tail-pinch-induced theta oscillation, and 5 minutes recovery from stimulation.

These experiments were carried out by Richárd Fiáth (Institute of Cognitive Neuroscience and Psychology, Research Centre for Natural Sciences, 1117 Budapest, Hungary. And Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, 1083 Budapest, Hungary).

8.1.3 Chronic mouse recordings

Sst-IRES-Cre male mice of C57BL/6J genetic background underwent bilateral injection of AAV2/5-Ef1a-DIO-ChR2-YFP-WPRE (N = 2) or AAV5-Ef1a-DIO-SwiChRca-TS-EYFP-WPRE (N = 2) into the dorsal hippocampi (coordinates: A-P -2.1 and -2.5 mm and M-L $\pm$ 1.5 and 1.6 mm from Bregma with tip at DV -1.2 mm from brain surface; 2 $\times$ 150-200 nL on both sides) using standard surgery techniques. Silicon probes for multichannel electrophysiological recordings were implanted above the medial septum and into the dorsal hippocampus 40-83 days after the virus injection. The surgery was performed under isoflurane anesthesia induced by ketamine-xylazine (4:1) combination diluted 6x in Ringer's lactate solution (intraperitoneal injection, dose 0.01 ml/1g body weight). Mice were head-fixed in a stereotaxic frame (David Kopf Instruments, Tujunga, US) and their body temperature and respiratory rate were continuously monitored. After local disinfection (Betadine) and analgesia (10% Lidocaine-spray), the cranium was exposed and cleaned for application of adhesive agent (OptiBond XTR, Kerr Corporation, Orange, US). Craniotomies were performed for stereotaxis-guided implantation of a 32-channels linear type and a 32-channels, 4-shank Buzsáki-type silicon probe into the dorsal hippocampus (coordinates: A-P -2.5 mm and M-L + 2 mm from Bregma with tip at DV -2.1 mm from brain surface) and above the medial septum (A-P +0.9 mm and M-L +0.9 mm, at an angle of 12°, and with tip at DV -2.8 mm from brain surface), respectively. Both probes were mounted on a custom-made, adjustable micro-drive. The probes were coated with red fluorescent Dil for later histological confirmation of the recording site. After the recovery from the surgery, the tip of the septal probe was lowered in steps of 75-150 micrometers per day to reach the zone of cells with theta-modulated firing pattern. Within this zone, the probe was advanced in steps of 45 micrometers per day as long as the theta-modulated firing pattern was still present. In case of SwiChR-transfected animals, each shank of the septal probe was equipped with an optical fiber (50 micrometers core diameter, 0.22 NA) with tip positioned 75-100 micrometers above the uppermost recording site and glued by optical adhesive. In case of ChR2-transfected animals, one optical fiber (105 micrometers core diameter, 0.22 NA) was implanted to illuminate the fimbria, independently from the septal silicon probe. In one animal, a Buzsáki-type silicon probe was implanted into the hippocampus, instead of the linear probe. In this case, the probe was advanced

stepwise to reach the pyramidal layer of the dorsal hippocampus after the post-surgery recovery period. The craniotomies were sealed with artificial dura (Cambridge NeuroTech Ltd, Cambridge, UK). The probe-micro-drive assemblies were shielded by copper mesh preventing the contamination of the recordings by environmental electric noise. The mesh was covered by dental acrylate. Two stainless steel wires inserted above the cerebellum served as ground and reference for the electrophysiological recordings. Before finishing the surgery, Buprenorphine (dose: 0.045 µg/1g body weight) was injected subcutaneously. Recordings were started after a one-week-long post-surgery recovery and habituation to connectorization.

The electrophysiological activity was registered by a multiplexing data acquisition system (KJE-1001, Amplipex Ltd, Szeged, Hungary) at 20 kHz sampling rate. The position of the animal was tracked by a marker-based, high speed (120 frame/s) motion capture system and reconstructed in 3D (Motive, OptiTrack, NaturalPoint Inc, Corvallis, US). Recordings were conducted both in the animals' home cage (dominated by sleep) and while mice were placed on a linear track (dominated by active movement). Home cage and linear track recordings were concatenated for data analysis to include sufficient amount of time spent in theta and non-theta states. Thus, the majority of theta segments originated from movement epochs, while non-theta segments represented both quiet wakefulness and sleep. As the main focus was on general oscillatory mechanisms, these states were not subdivided further. The septal probe was lowered 45 micrometers after the recordings each day, through a total of 8-35 days of recording.

Optogenetic manipulations were carried out separately. Only the control recordings were analyzed in the present study. The Sst-IRES-Cre mouse line and the above AAV constructs were used in a large number of studies without reporting adverse phenotypic changes, and results of these studies were interpreted as general for mice and not specific for the particular strain (Adler et al., [2019](#); Cummings & Clem, [2020](#); Kim et al., [2015](#); Kvitsiani et al., [2013](#); Viney et al., [2018](#)). Therefore, we do not consider using this particular mouse line a significant limitation of our study.

These experiments were carried out by Andor Domonkos (Cerebral Cortex Research Group, Institute of Experimental Medicine, 1083 Budapest, Hungary).

8.1.4 Histological verification of the recording location

To detect the tracks of the silicon probes in the brain tissue, we used a histological procedure similar to that described previously (Borhegyi et al., [2004](#); Fiáth et al., [2018](#), [2019](#)). In brief, the animal was

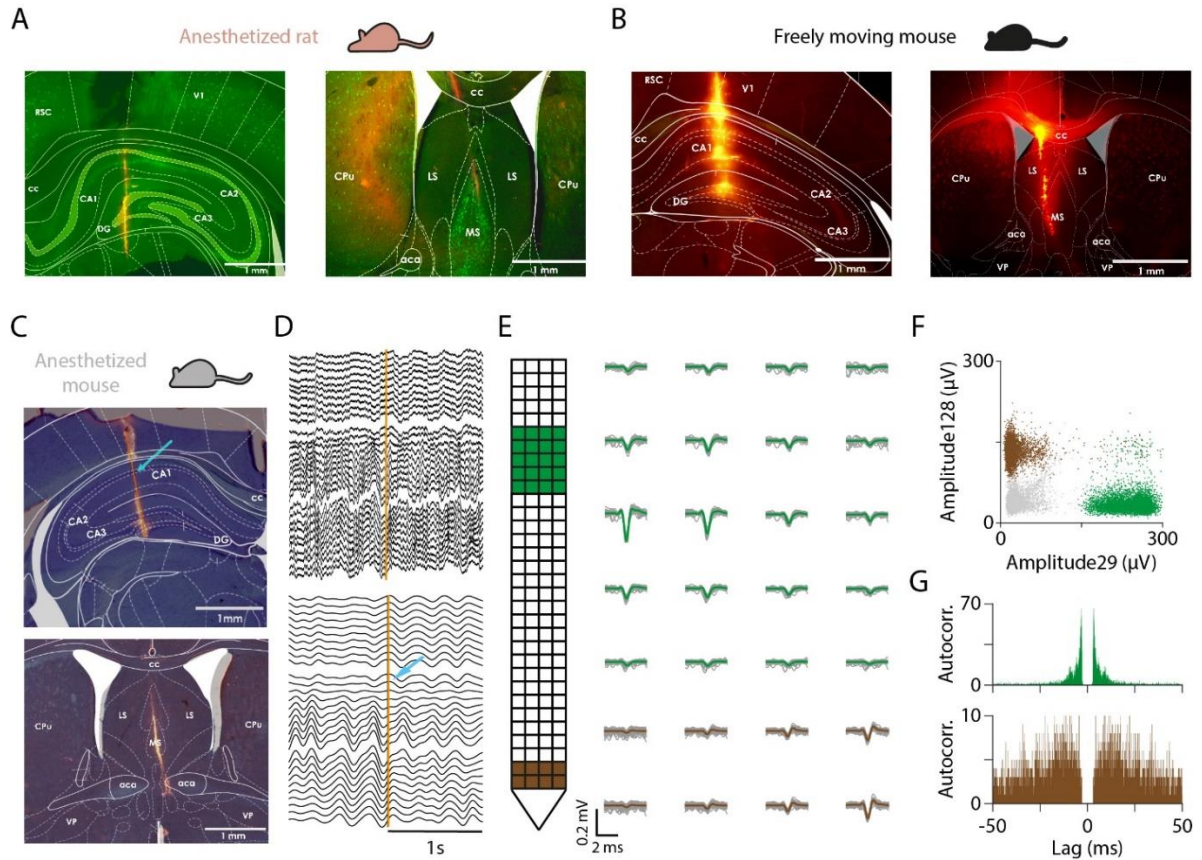
deeply anesthetized after the recordings, then transcardially perfused with physiological saline solution followed by a fixative solution containing 4% paraformaldehyde in 0.1 M phosphate buffer (PB, pH = 7.4). Next, the fixed brain was gently removed from the skull and stored at 4 °C in the fixative solution until processed further. Histological processing started by cutting 60- μ m-thick coronal sections with a vibratome (Leica VT1200, Leica Microsystems, Wetzlar, Germany). Then, the brain sections were washed in 0.1 M PB, mounted onto microscopic slides and air dried. To identify brain sections containing fluorescent marks of DiI corresponding to the probe track, the slides were examined under a light microscope (Leica DM2500, Leica Microsystems) equipped with a fluorescence LED illumination source (SFL4000, Leica; Zeiss, Oberkochen, Germany in case anesthetized rats) and with a digital camera (DP70 or DP73, Olympus, Tokyo, Japan). Relevant sections from the anesthetized mouse experiments were processed for cresyl violet (Nissl) staining, dehydrated in xylene and coverslipped with DePex (SERVA Electrophoresis, Heidelberg, Germany); sections from the anesthetized rat experiments were stained for choline-acetyltransferase (ChAT; mouse monoclonal anti-ChAT (Umbriaco et al., [1994](#))) to visualize the MS; no staining for sections from the awake mouse experiments was performed. Finally, to verify the recording location based on the stereotaxic mouse brain atlas (Paxinos et al., [2001](#)), sections containing the track of the silicon probe were photographed under the microscope.

8.1.5 Spike sorting of septal neurons

The mouse MS recordings were fed to the Kilosort software (Pachitariu et al., [2016](#)). Clustering was initialized with the desired number of clusters set to twice the number of channels. The Kilosort output was curated manually in the Phy template-gui graphical user interface module. We examined any potential violations of the refractory periods, slow electrode drifts, spatial distributions of action potential (AP) energies among neighboring channels, AP shapes and amplitudes and the principal components of the AP shapes. In case of noisy autocorrelograms and multiple subclusters in the principal components space, we considered manual splitting of the automatically assigned cluster. The high similarity of clusters as well as lack of co-firing ('mutual refractoriness') in crosscorrelograms could imply that two automatically determined clusters belonged to the same neuron, in which case the clusters were merged. Finally, we calculated objective cluster quality measures based on the interspike interval histograms and cluster isolation distances, to verify putative single neuron clusters. Kilosort execution time was reduced by running on an Nvidia Geforce GTX 1080 graphic card with the Matlab Parallel Computing Toolbox. The

anaesthetized rat recordings were clustered automatically in KlustaKwik (Rossant et al., 2016) (available at <http://github.com/klusta-team>) and curated manually based on auto- and crosscorrelograms similar to the mouse recordings, as described previously (Bartho et al., 2004).

Rat recordings were spike sorted by Péter Barthó (Sleep Oscillations Research Group, Research Centre for Natural Sciences, 1117 Budapest, Hungary).

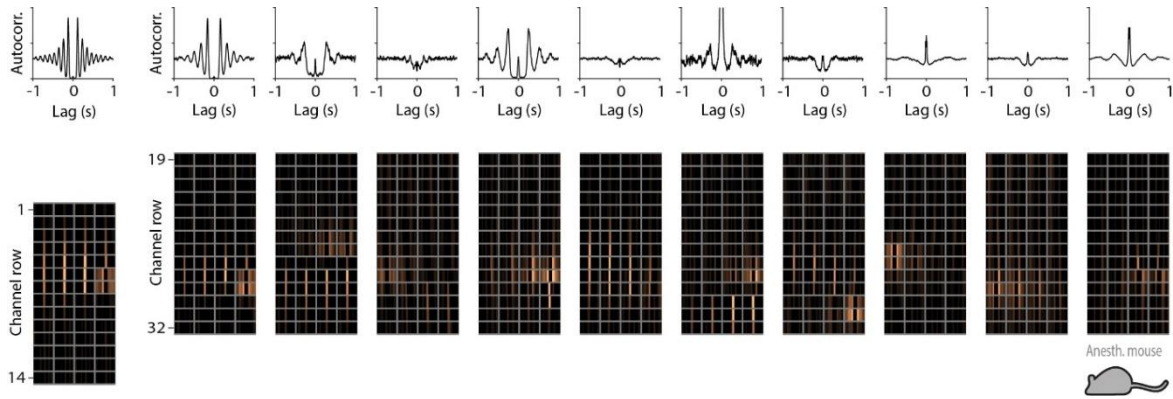


6. Figure. Dual recording of hippocampal local field potentials and single neuron activity from the medial septum of three rodent models of theta oscillation. (A) Histology of the silicon probe tracks in the HPC (left) and MS (right), rat brain slices. Characteristic abundance of cholinergic cells (ChAT staining – green) in the MS and fluorescent dye (Dil – red) from the probe surface (red). For abbreviations see “Abbreviations”. (B) Histology of chronic mouse recording. Dil (red). (C) Histology of anaesthetized mouse recordings. Nissl-staining of cell bodies and Dil (red). Top: HPC pyramidal layer coordinates on the linear probe (cyan arrow, see panel D). (D) Top: Raw 32-channel LFP recording from the HPC (two broken channels were removed). Bottom: LFP channels filtered in the theta band. Theta phase reversal, known to occur just below the pyramidal layer, is indicated by cyan arrow (corresponding to panel C). (E) MS single units were collected using a 128-channel silicon probe in anesthetized mice. Example spike waveforms for two neurons are shown for the channels marked on the schematic representation of the probe (green and brown, average waveforms; grey, 100 randomly selected individual spikes). (F) Amplitudes (peak-to-valley) on selected channels show clear separation of the example cells. (G) Autocorrelograms of the example neurons.

8.2 Identification of state dependent rhythmicity classes- Algorithm

8.2.1 Overlapping septal clusters

In case of acute mouse recordings, the size of the probe resulted in potential overlap between subsequent recordings. Therefore, putative overlapping units were excluded by using a semi-automated method (Figure 7). First, we calculated average spike waveforms for all clusters by averaging ± 2 ms windows around all individual spike times separately for all channels. Average waveforms were aligned to zero on each channel by subtracting their mean (across time). Next, the integral of the absolute value of mean waveforms were taken for all channels as a measure of channel magnitudes. Overlapping channels from consecutive recordings were 500 μ m from each other, resulting in an 88-channel displacement of the overlapping clusters due to the arrangement of the probe (4 channels in a row with 22.5 μ m longitudinal separation). If two clusters shared at least 9 out of their 16 top amplitude channels, we considered them duplication candidates. Mean waveform profiles and autocorrelations were compared visually by an expert experimenter for all pairs that had been marked as duplication candidates for final decision.

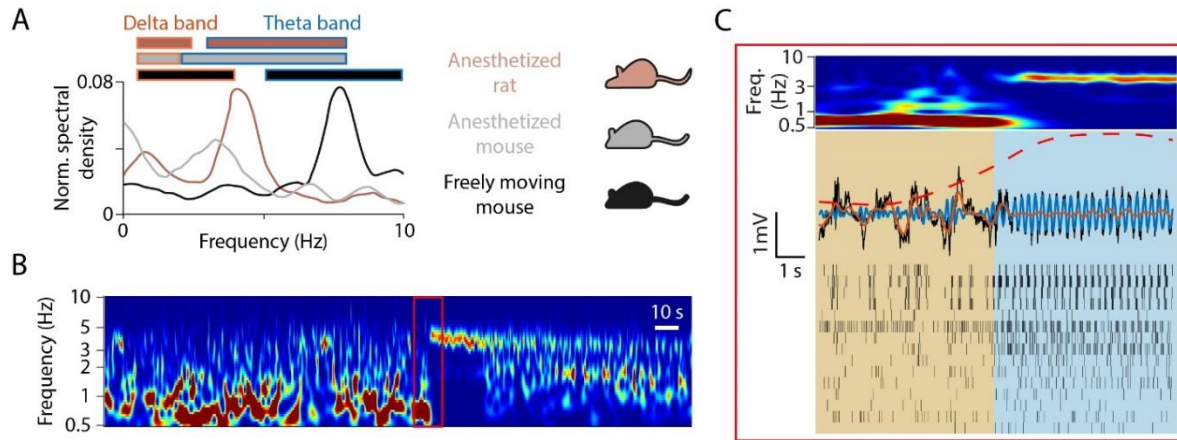


7. Figure. Identification of putative overlapping medial septal units across recordings. Left: Example cluster from the second recording session of an anesthetized mouse recording, after 500 μ m descent of the recording electrode array, corresponding to a displacement of 22 channel rows on the silicon probe. Top: autocorrelation; bottom: spatial waveform profile on the silicon probe. Right: Candidates for potentially overlapping units from the first recording session. We decided to exclude the example cluster in the left panel because of the high similarity to the first candidate in the right panel.

8.2.2 Hippocampal state detection

Pyramidal layer was detected from linear silicon probe recordings based on the documented phase reversal of hippocampal theta oscillation below the pyramidal layer and verified based on histological reconstruction (Figure 6D) (Buzsaki et al., 1986; Buzsáki, 2006; Green et al., 1960). Theta detection was performed on a single channel from the stratum radiatum (400 μ m below the

detected pyramidal layer in rats and 250 μm below the pyramidal layer in mice), since theta amplitude was largest in this layer, allowing the most robust detection (Buzsáki, [2002](#), [2006](#)) (*Figure 8*). In one chronically implanted mouse, a Buzsaki-type probe was used in the hippocampus; in this case, the deepest channel was used for LFP analysis, which appeared to be below the pyramidal layer based on theta phase reversal, thus providing phase values consistent with other recordings. The appropriate theta and delta frequency band boundaries were defined separately for the three different rodent models based on the Fourier spectra of the recordings (*Figure 8*), confirming the known observation of slower oscillations under urethane anesthesia (Borhegyi et al., [2004](#); Varga et al., [2008](#)). Our observations confirmed known spectral differences between urethane-anesthetized and awake rodents (frequency boundaries in anesthetized rats, delta, 0.5-2.5 Hz; theta, 3-8 Hz; in anesthetized mice, delta, 0.5-2 Hz, theta, 2-8 Hz; in awake mice, delta, 0.5-4 Hz, theta, 5-10; in optogenetic experiments, frequency boundaries were optimized for each mouse individually). Raw LFP traces were resampled at 1 kHz and bandpass filtered in the theta and delta bands using the built-in finite impulse response filter (fir1.m) with zero-phase-lag filtering (built-in filtfilt.m function). The filtered traces were Hilbert-transformed and the instantaneous amplitude and phase values were calculated as the magnitude and phase of the complex Hilbert-transform. A simple artifact removal was performed on the theta/delta ratio by clamping values exceeding 10-fold difference. Next, the theta/delta amplitude ratio was smoothed with a moving average (window size, 5 seconds for anesthetized and 3 seconds for awake recordings; the difference in window size was due to the observed faster and more frequent state transitions in awake recordings). Theta segments were defined where the theta/delta ratio exceeded an empirically defined threshold, optimized for each dataset separately (1 for anesthetized mouse and rat recordings, 2 for awake mouse recordings and 1.5 in the optogenetic experiments); all other segments were defined as non-theta (McNamara et al., [2014](#); Wikenheiser & Redish, [2013](#)) (*Figure 8C*). Brief interruptions of theta or non-theta segments were not considered state switches (<5 seconds in anesthetized and <3 seconds in awake recordings; the difference was due to the observed faster and more frequent state transitions in awake recordings). In some optogenetic tagging experiments (n = 8 recordings), only a part of the recording was analyzed due to electrical artifacts in other segments.



8. Figure. Hippocampal theta and non-theta states. (A) Theta and delta frequency band boundaries were determined based on Fourier spectra of HPC LFPs for each model separately (representative recordings), indicated by color-coded horizontal bars on top. (B) Representative HPC LFP wavelet spectrogram from an anesthetized rat recording. Non-theta - theta state transition (red box) is enlarged on panel C. (C) Top: Theta onset from panel B. Middle: Raw LFP (black), LFP filtered in the theta (blue) and delta frequency band (orange), and theta-delta power ratio (red dashed line). Bottom: Raster plot of individual units ($n = 15$) recorded from the MS concurrently. Note the change in network activity at theta onset.

8.2.3 Rhythmicity Indices of septal neurons

Theta- and delta-rhythmicity of MS neurons was judged based on rhythmicity indices derived from autocorrelograms. First, autocorrelation of the spike train was computed in a ± 3 seconds window at 1 ms resolution; the central peak corresponding to the total spike number was removed and the autocorrelogram was smoothed by a 20-ms moving average and normalized to an integral of 1. Next, theta and delta peaks were determined between time lags corresponding to theta and delta frequency bands. ‘Peak values’ were averaged from the autocorrelograms in the ± 20 ms neighborhoods of the peaks. ‘Baseline values’ were averaged from the ± 20 ms neighborhoods around the lags corresponding to half and one and a half times the peak location (assumed troughs). Finally, the difference between the peak and baseline values was normalized to the larger of the two, yielding a Theta Index and a Delta Index between -1 and 1:

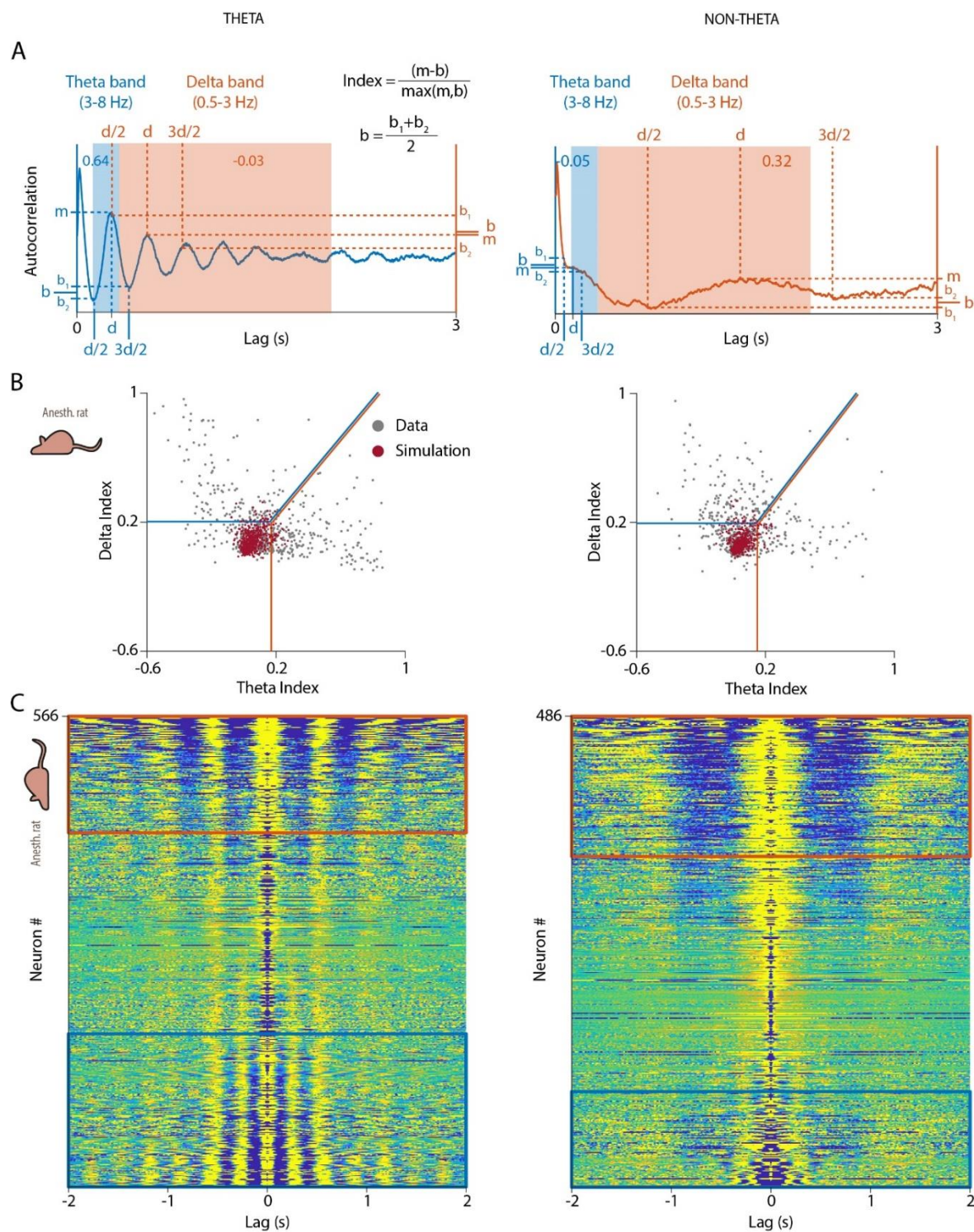
$$\text{Rhythmicity Index} = (\text{peak} - \text{baseline}) / \max(\text{peak}, \text{baseline})$$

Rhythmicity indices were calculated separately for hippocampal theta and non-theta segments (Figure 9A). Cells with insufficient number of spikes (< 2 spikes/autocorrelogram bin on average) were excluded from later analysis.

To assess statistical significance of rhythmicity in the theta and delta frequency bands, we simulated a dataset of neurons exhibiting spiking generated by a Poisson-process. We determined the λ

parameter of the Poisson-process individually for each simulated cell so that they matched the firing rate of an actual MS neuron. Rhythmicity Index was calculated for the simulated neurons using the same procedure as for the biological recordings, then Rhythmicity Index thresholds were determined corresponding to $p < 0.05$ significance levels based on this bootstrap null distribution (*Figure 9B*). Rhythmic modulation beyond these four significance thresholds (Theta and Delta Index during theta, and Theta and Delta index during non-theta) can be seen on the sorted image of the cells' autocorrelations (*Figure 9C*).

If both Rhythmicity Indices exceeded the threshold, rhythmicity was determined by the larger of the two Rhythmicity Indices (normalized to their respective thresholds) (*Figures 9B*).



9. Figure. Determining theta and delta rhythmicity of medial septal units. (A) Autocorrelations of spike trains were calculated for theta (left) and non-theta states (right) for each neuron. Theta Index was calculated by normalizing the theta-band peak (m at lag d) with the average of pre- and post-peak troughs (b , mean of b_1 and b_2 at lags $d/2$ and $3d/2$, respectively) for both states (blue numbers above the traces). Delta Index was calculated using a similar algorithm for the delta band (red numbers). (B) Theta and Delta Index was calculated for all recorded neurons during theta (left) and non-theta segments (right; grey, recordings from anesthetized rats are shown) and for simulated Poisson-neurons with matching firing rate (red). Significant rhythmicity was defined by the 0.05 percentile of the Theta and Delta Index

distributions of the Poisson-neurons (vertical and horizontal lines). If both indices exceeded the threshold, the larger of the two rhythmicity indices was considered (identity line). (C) Autocorrelograms (left, theta segments; right, non-theta segments) for all neurons with sufficient firing rate, sorted by the larger of the two rhythmicity indices: delta-rhythmic on top and theta-rhythmic on bottom; significantly delta- and theta-modulated neurons are above and below the respective colored lines (anaesthetized rat).

8.2.4 Hippocampal phase of septal spikes and phase-coupling

Selected LFP channels were filtered in the theta and delta frequency bands, as described above. The filtered signals were Hilbert-transformed, and the instantaneous phase values of the analytical signal were computed. Spike phases were determined by taking the instantaneous phase values corresponding to the spike times. To quantify phase-locking, mean phase and mean resultant length (measure of phase-locking strength) were calculated as the angle and magnitude of the first trigonometric moment of spike phases. Phase value distributions for individual neurons were visualized as phase histograms, and distributions over groups of neurons were visualized as polar plots, in which each neuron was represented by a vector pointing to its mean phase, with a length corresponding to its mean resultant length and color corresponding to its firing rate in greyscale.

A group of neurons classified in a certain way may preferentially align with distinct phases of the hippocampal oscillation. The distribution of mean phase values of individual neurons within a group can be described using multiple circular statistical models. These models were mixtures of one to five von Mises distributions (circular analog of the Gaussian distribution), corresponding to unimodal, bimodal, trimodal, etc. distributions on the circle (N. I. Fisher, [1993](#)). To assess which model described the data best, we performed model selection by calculating Akaike Information Criterion ([AIC](#)) and Bayesian Information Criterion ([BIC](#)) for these models. The model with the lowest value corresponded to the best fitting model (Akaike, [1973](#); Brewer et al., [2016](#); Konishi & Kitagawa, [2008](#)). The information criteria did not support models with more than three modes; therefore, we focus on the unimodal, bimodal and trimodal phase distributions below.

8.2.5 Statistical testing

We used non-parametric tests for comparing central tendencies of distributions: Mann-Whitney U-test for non-paired and Wilcoxon signed-rank test for paired samples. We report W^+ test statistic (ranksum for theta- > delta-related measures for theta-delta comparisons). Nonparametric tests are ideally suited when no assumptions on underlying distributions are made. We avoided statistical tests that require normal distribution of the underlying random variables, since statistical tests for normality may reject the null hypothesis of the Gaussian distribution of data, but the lack

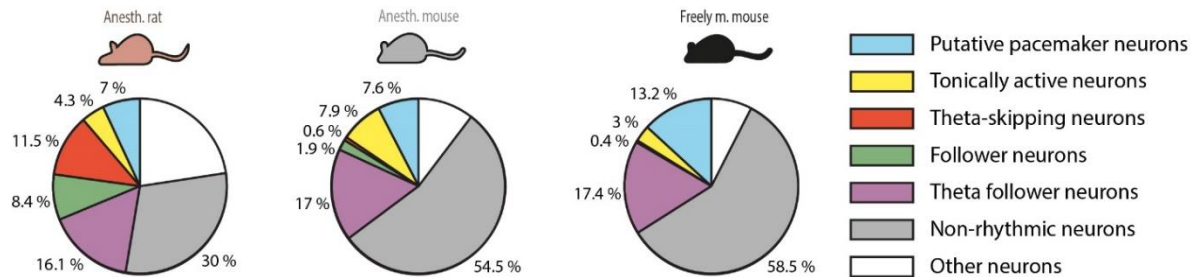
of significance does not prove normality, and their statistical power strongly depends on sample size. Additionally, firing rates are positive random variables known to deviate from normal distribution (Buzsáki & Mizuseki, [2014](#)). Significance was determined at $p < 0.05$ (*), $p < 0.01$ (**) and $p < 0.001$ (***), as also indicated in the figure legends.

We used non-parametric tests to compare firing rate changes between theta and non-theta states, to assess measures of pacemaker synchronization in both conditions, and to evaluate the effect of photo stimulation on theta/delta power ratios.

8.3 Rhythmic neuron classes of the medial septum

Above we described our unbiased method to identify functional MS neuron classes based on their rhythmic firing properties. Theta and delta rhythmicity indices were defined by the normalized autocorrelation peak in the respective frequency bands, and significant rhythmic activity was tested against bootstrap distributions generated from simulated Poisson neurons that were matched with MS neurons in their firing rates ($p < 0.05$, bootstrap test; *Figure 9*).

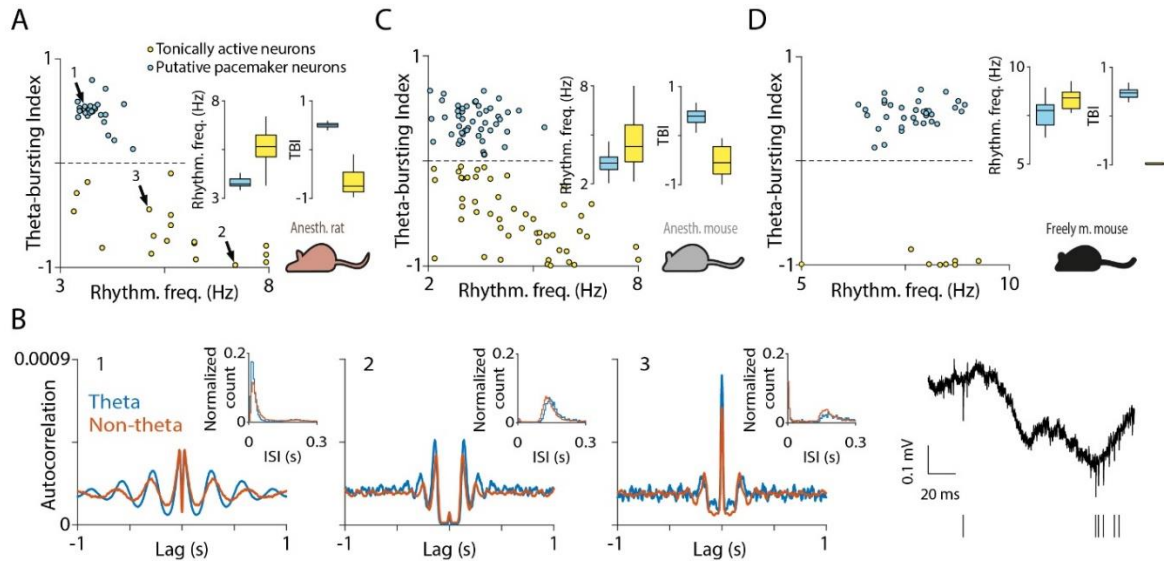
A neuron may exhibit theta-, delta- or non-rhythmic activity during the examined HPC state, which is either theta (dominated by theta oscillation) or non-theta (dominated by delta oscillation). Theoretically, any possible combinations of theta and non-theta state-dependent modulation is feasible resulting in 3x3 classes (*Table S1*). However, after excluding always non-rhythmic cells and accounting for a few false positive detections of unusual rhythmic modulations, primarily due to noisy autocorrelations, majority of the neurons fell into 4 defined rhythmicity classes: theta-theta (putative pacemaker neurons and tonically active neurons), theta-delta (follower neurons), theta-nothing (theta follower neurons) and delta/nothing- delta (theta-skipping neurons) (*Figure 10*).



10. Figure. Proportions of medial septal neurons in the different rhythmicity groups in anesthetized rats (left), anesthetized mice (middle) and freely moving mice (right).

When we looked more closely at the always theta-rhythmic class, we discovered a bursting and a non-bursting subpopulation, which also differed in the speed of theta rhythmic modulation. To

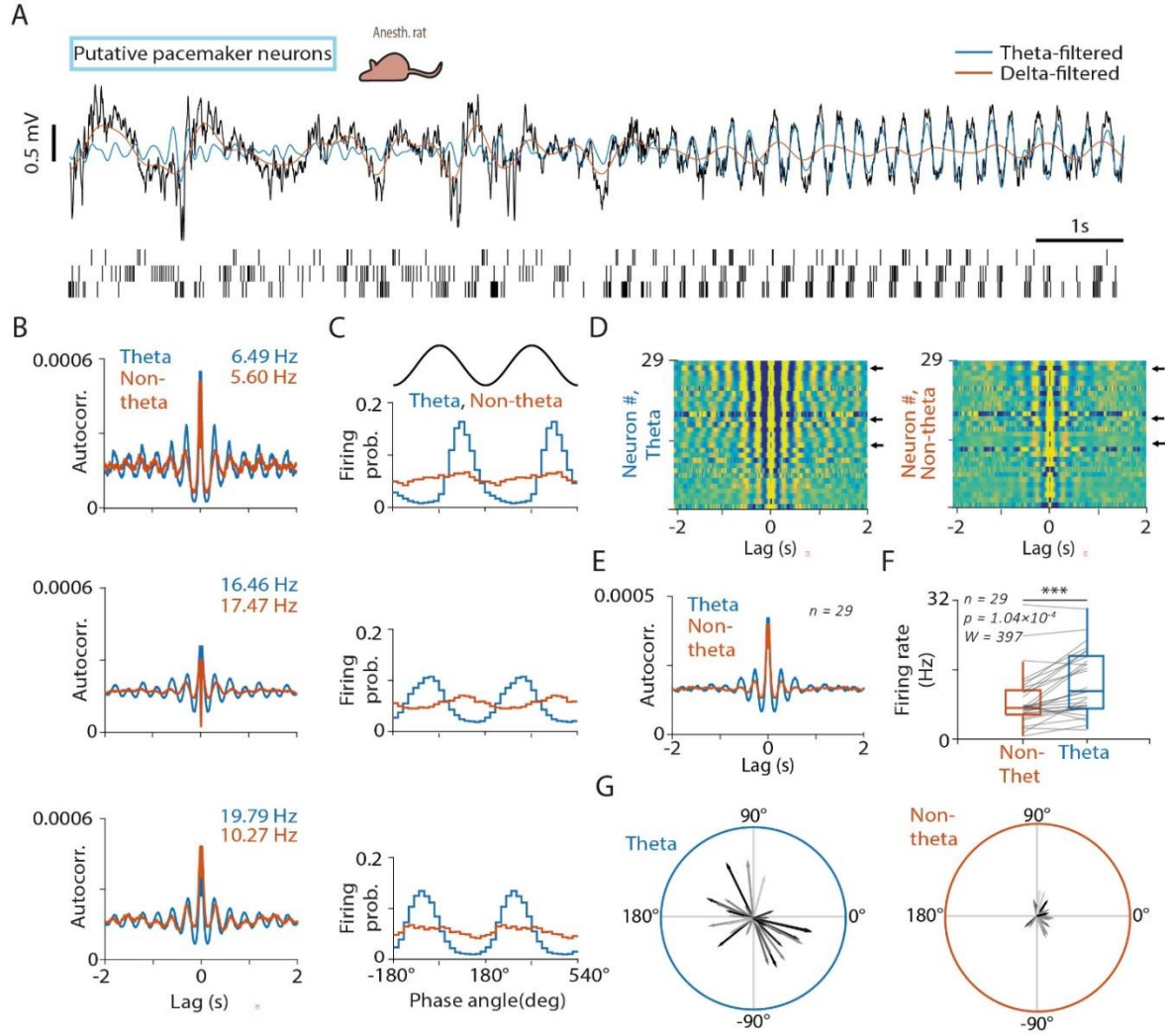
differentiate between them, a Theta-burst Index (TBI) was introduced, quantifying the characteristic long theta-bursts putative pacemakers fire during individual theta cycles (Borhegyi et al., 2004; Varga et al., 2008). Average autocorrelograms between lags corresponding to a pre-defined window spanning the intraburst interspike intervals (anesthetized rats, 20-40 ms; anesthetized mice, 20-50 ms and 20-40 ms in optogenetic tagging experiments, see below; freely moving mice, 10-30 ms) were normalized to the average autocorrelation, similar to the Rhythmicity Indices, providing a TBI between -1 and 1. The above windows were determined based on variations of theta frequencies across datasets. Using a traditional 20-50 ms window for all datasets altered the classification of only a few neurons and did not change the main results. Tonically active neurons were defined as those having a TBI <0 (Figure 11).



11. Figure. Separating theta-bursting and tonically active neurons. (A) Theta-bursting Index (see in text above) and rhythmicity frequency revealed a theta-rhythmic population that showed theta-bursting and a separate one that did not, in anesthetized rats. The former corresponded to putative pacemakers, while the latter formed the group of 'tonically active' neurons. (B) Left, autocorrelogram and interspike interval (ISI) histogram (inset) of three example neurons, marked by arrows in panel (A). Example 1 is a theta-bursting putative pacemaker; examples 2 and 3 are tonically active neurons. Right, raw data (top) and spike raster (bottom) of example 3. Note the fast-bursting phenotype, different from the slower theta-bursting observed in putative pacemakers. (C-D) The same distinction was observed in anesthetized (C) and freely moving mice (D). Box-whisker plots show median, interquartile range and non-outlier range.

Putative pacemaker neurons showed prominent theta oscillations in their autocorrelograms both when theta oscillation was present and when it was absent in the CA1 (Figure 12). These neurons exhibited strong phase locking to CA1 theta oscillation, but no strong phase relationship with hippocampal delta band activity during non-theta episodes. This constitutively theta-rhythmic bursting population, often considered as 'putative pacemaker neurons' of theta oscillation (Borhegyi et al., 2004; Ford et al., 1989; Hangya et al., 2009; Stewart & Fox, 1989; Varga et al., 2008),

was found in anesthetized rats ($n = 29/416$), anesthetized mice ($n = 47/617$) and freely moving mice ($n = 35/265$; note that these numbers represent conservative estimates based on significant rhythmicity; *Figure S1, Figure S2*).

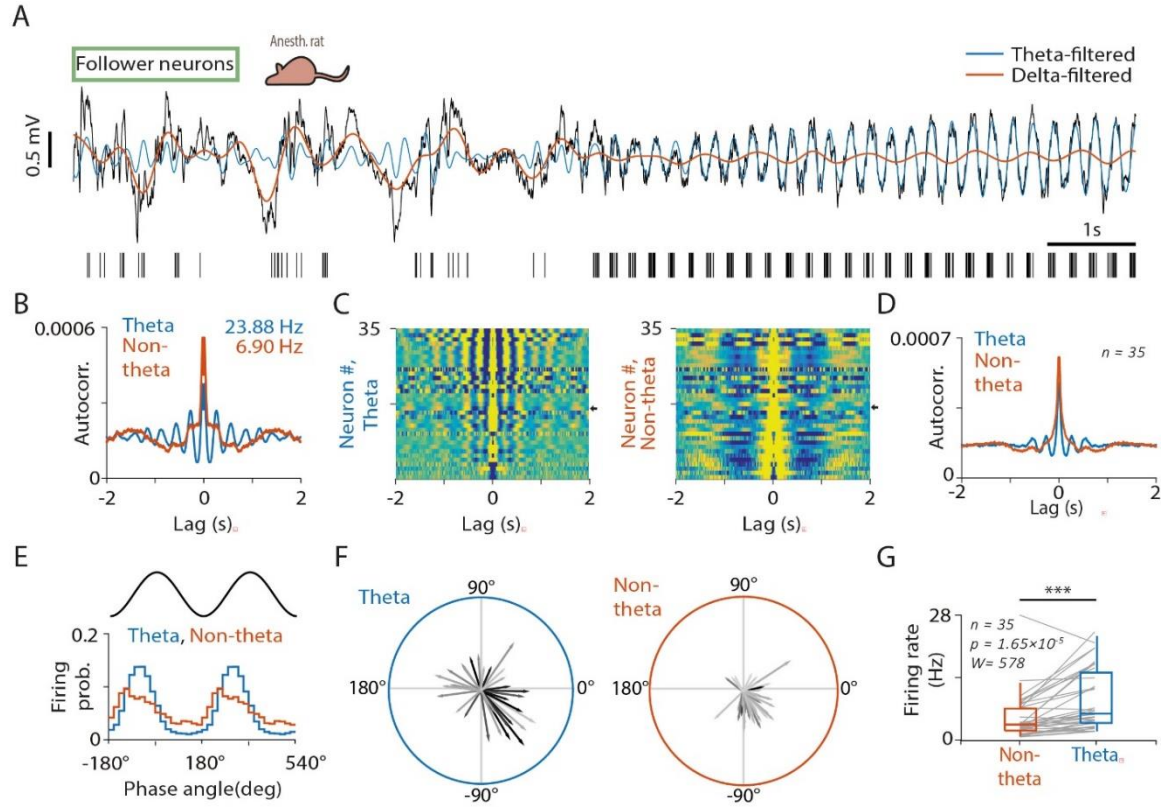


12. Figure. Putative pacemaker neurons of the anaesthetized rat. This group of neurons fired theta rhythmic bursts of action potentials, irrespective of the hippocampal state. (A) Top: Raw LFP (black) from the CA1 shows a delta-to-theta state transition. Bottom: spike raster of three examples of putative pacemaker neurons from the same recording session. (B) Theta and non-theta state autocorrelograms of the neurons from panel A. Numbers indicate average firing rates. (C) Phase histogram of the example neurons spikes (panel A) relative to HPC delta (orange) and theta (blue) oscillations in non-theta and theta states, respectively. Two oscillatory cycles are shown. (D) Autocorrelograms of all putative pacemaker neurons during theta (left) and non-theta (right) segments. Arrows indicate the example neurons (panel A). (E) Average autocorrelogram of all putative pacemaker neurons. (F) Firing rates of putative pacemaker neurons during non-theta and theta segments. Boxes and whiskers represent interquartile ranges and non-outlier ranges, respectively. Lines correspond to individual neurons. Firing rate was significantly higher during theta (Wilcoxon signed-rank test). (G) Phase-locking of all putative pacemaker neurons to HPC theta (left) and delta (delta) oscillations in polar coordinates. Angle: circular phase; length: mean vector length; greyscale corresponds to average firing rate (black, higher firing rate). Note that neurons formed two opposite phase clusters during theta (147.28° and 342.57° , see text), whereas phase-locking strength to delta oscillations was low.

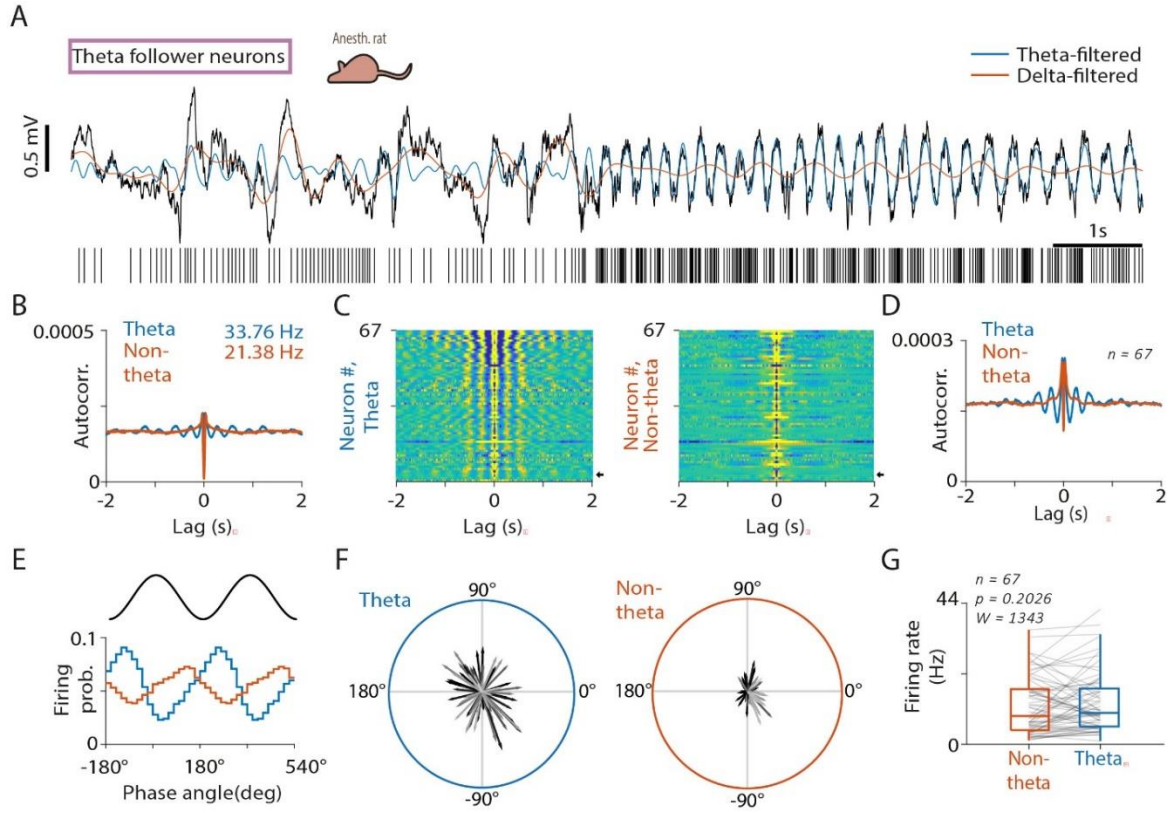
Among putative pacemakers we confirmed the presence of two separate clusters of neurons that showed anti-phase preference to hippocampal theta in anesthetized rats (AIC values for the unimodal, bimodal and trimodal distributions were 109.08, 103.19 and 108.98, respectively; BIC values were 111.81, 110.03 and 119.92, See *“Hippocampal phase of septal spikes and phase-coupling”*), as reported previously (Borhegyi et al., [2004](#); Varga et al., [2008](#)). This was further confirmed by a parametric bootstrap approach (N. I. Fisher, [1993](#)), which statistically tested whether a unimodal or a bimodal model can be rejected based on the data. The unimodal hypothesis was rejected at $p = 0.02$, while the bimodal hypothesis could not be rejected ($p = 0.91$). The mean phases of the best fitting mixture of two von Mises distributions were 147.28° and 342.57° (referenced to pyramidal layer theta).

Model selection results in mice favored either a unimodal (AIC in freely moving mice: 111.17, 113.11, 111.67; BIC in freely moving mice: 114.28, 120.89, 124.11; BIC in anesthetized mice, 171.09, 180.66, 175.92 for the unimodal, bimodal and trimodal distributions, respectively) or a more complex trimodal (AIC in anesthetized mice: 167.39, 171.41, 161.12 for the unimodal, bimodal and trimodal distributions, respectively) phase model.

A considerable MS population reflected (followed) the ongoing activity of the septo-hippocampal network. These neurons were theta-rhythmic during hippocampal theta oscillation but not when it was absent, often phase locked to both theta and delta band oscillations. In anesthetized rats, many of these neurons showed slow rhythmic activity at delta frequencies in the absence of hippocampal theta (*Figure 13; Figure 14*), while in mice, these follower neurons were mostly non-rhythmic or slow firing in non-theta states (**“theta follower neurons”**, *Figure S3, Figure S4; Figure S5; Table S1*). Some neurons exhibited follower activity only in the non-theta state, remaining non-rhythmic or silent during hippocampal theta.

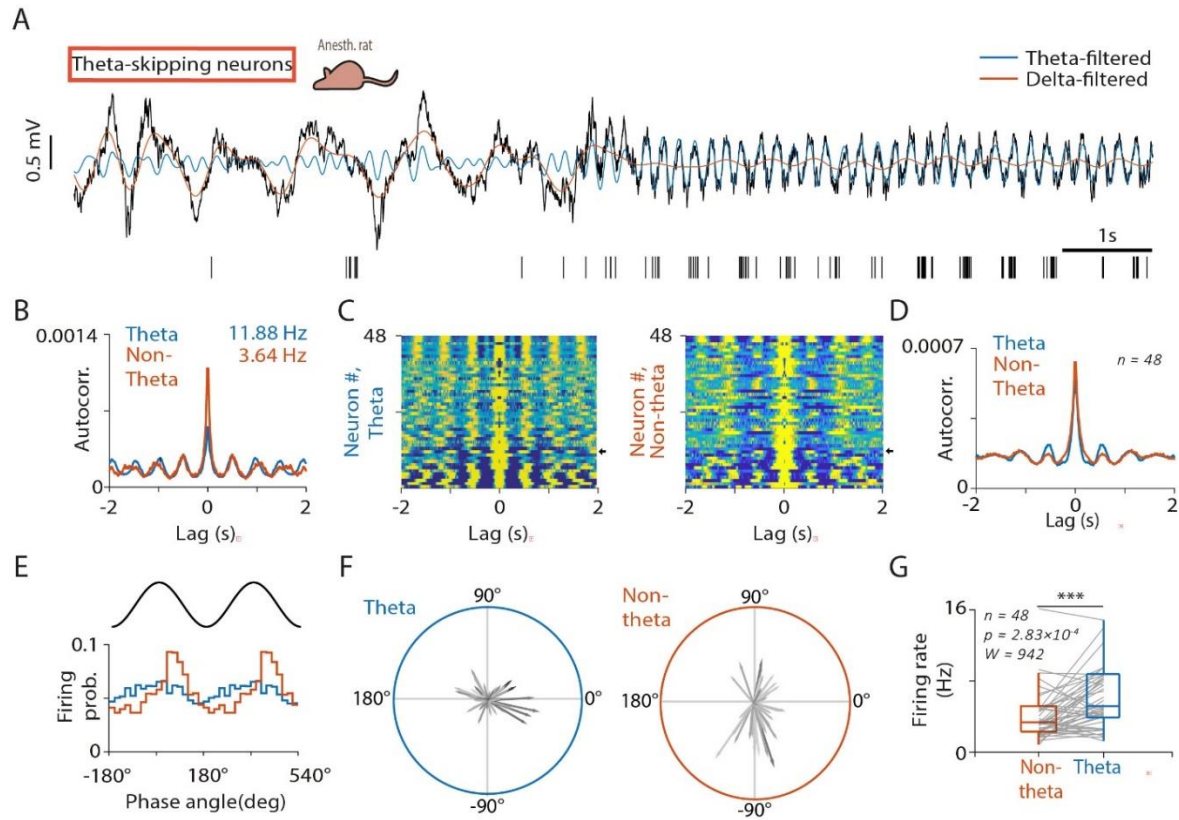


13. Figure. Follower neurons of the anaesthetized rat. This group showed delta-rhythmic activity during non-theta epochs and theta-rhythmic activity during theta epochs. (A) Top: Raw LFP (black) from the CA1 shows a delta-to-theta state transition. Bottom: spike raster of an example putative pacemaker neuron from the same recording session. (B) Theta and non-theta state autocorrelograms of the neuron from panel A. Numbers indicate average firing rates. (C) Autocorrelograms of all putative pacemaker neurons during theta (left) and non-theta (right) segments. Arrows indicate the example neuron (panel A). (D) Average autocorrelogram of all putative pacemaker neurons. (E) Phase histogram of the example neuron spikes (panel A) relative to HPC delta (orange) and theta (blue) oscillations in non-theta and theta states, respectively. Two oscillatory cycles are shown. (F) Phase-locking of all follower neurons to HPC theta (left) and delta (delta) oscillations in polar coordinates. Angle: circular phase; length: mean vector length; greyscale corresponds to average firing rate (black, higher firing rate). Many of these neurons were phase-locked to both HPC oscillations. (G) Firing rates of follower neurons during non-theta and theta segments. Boxes and whiskers represent interquartile ranges and non-outlier ranges, respectively. Lines correspond to individual neurons. Firing rate was significantly higher during theta (Wilcoxon signed-rank test). For two more example neurons see (Kocsis et al., 2022, Figure 3: B, F).



14. Figure. *Theta follower neurons of the anaesthetized rat. These neurons showed non-rhythmic activity during non-theta epochs and theta-rhythmic activity during theta epochs. Identical figure structure with Figure 13. Many of these neurons were phase locked to both HPC oscillations. No systematic firing rate change was found. For two more example neurons see (Kocsis et al., 2022, Figure S5: B, F).*

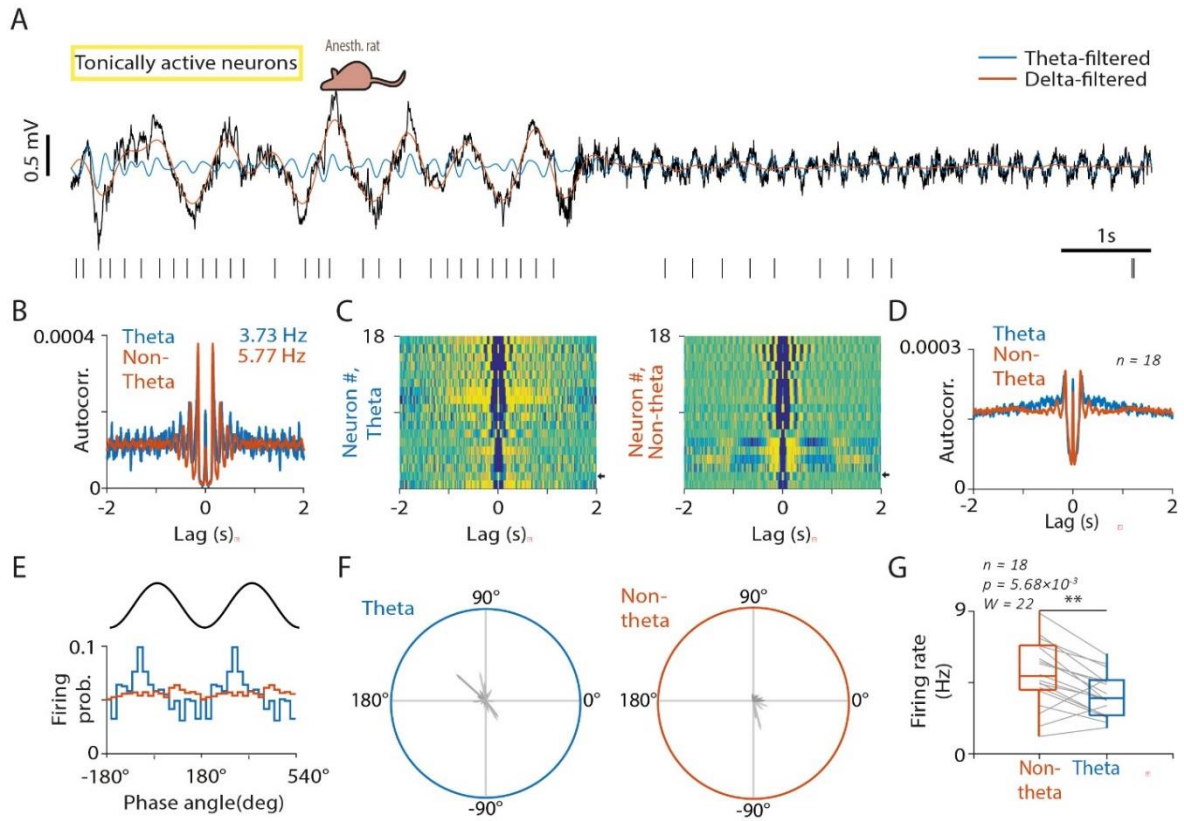
A subpopulation of MS neurons, identified previously as “**theta-skipping**”, showed slow rhythmic activity regardless of whether theta oscillation was present in CA1 (Figure 15). While some of these neurons doubled their rhythmic frequency at theta onset (but still in the delta range), many cells of this population maintained a constant slow rhythmicity, often firing regularly in every second theta cycle. Interestingly, while this group was rather prominent in anesthetized rats, these cells were only rarely found in mice, revealing species-specific differences in the MS theta generation network (anesthetized rats, 48/416; anesthetized mice, 4/617; freely moving mice, 1/265; Table S1).



15. Figure. Theta-skipping neurons of the anaesthetized rat. Identical figure structure with Figure 13. Many of these neurons were phase locked to HPC delta oscillations. Firing rate was significantly higher during theta. For two more example neurons see (Kocsis et al., 2022, Figure S9: B, F).

Finally, a group of MS cells showed regular rhythmic firing patterns resembling those of striatal cholinergic interneurons (Inokawa et al., 2010); therefore, we called this MS group “**tonically active neurons**” (Figure 16). Although these neurons fired rhythmically with a frequency in the theta band, they showed little to no overall phase locking to hippocampal activity, typically exhibiting rhythmicity at slightly higher frequencies than ongoing CA1 theta oscillation (based on autocorrelation peak, median $\pm$ standard error of the median, 5.68 ± 0.34 , 4.29 ± 0.41 and 8.40 ± 0.37 Hz during theta segments in anesthetized rats, anesthetized mice and freely moving mice, respectively). They did not show the long bursts with 20-50 ms interspike intervals (ISIs) known to be characteristic of the putative pacemaker group, but some of them occasionally fired short, fast bursts of action potentials ($ISI < 15$ ms; Figure 11). They were found in all three rodent theta models tested (anesthetized rats, 18/416; anesthetized mice, 49/617; freely moving mice, 8/265; Figure S6 and Figure S7). These neurons also showed a firing rate change during theta oscillation. Interestingly, however, while their firing rate decreased at theta onset in rats (15/18 neurons),

previously coined as a “theta-OFF” pattern (Ford et al., 1989), they exhibited a theta-associated firing rate increase in mice, both anesthetized (34/49 neurons) and awake (8/8 neurons; Table S1).



16. Figure. Tonic activity of neurons of the anaesthetized rat. Identical figure structure with Figure 13. These neurons did not show strong phase-locking to HPC oscillations. Firing rate was significantly higher during non-theta. For two more example neurons see (Kocsis et al., 2022, Figure S10: F, J).

Together with those cells that did not exhibit any rhythmic activity according to our conservative rhythmicity analysis, the above-described groups of MS neurons constitute the entire MS population (Figure 10; Table S2).

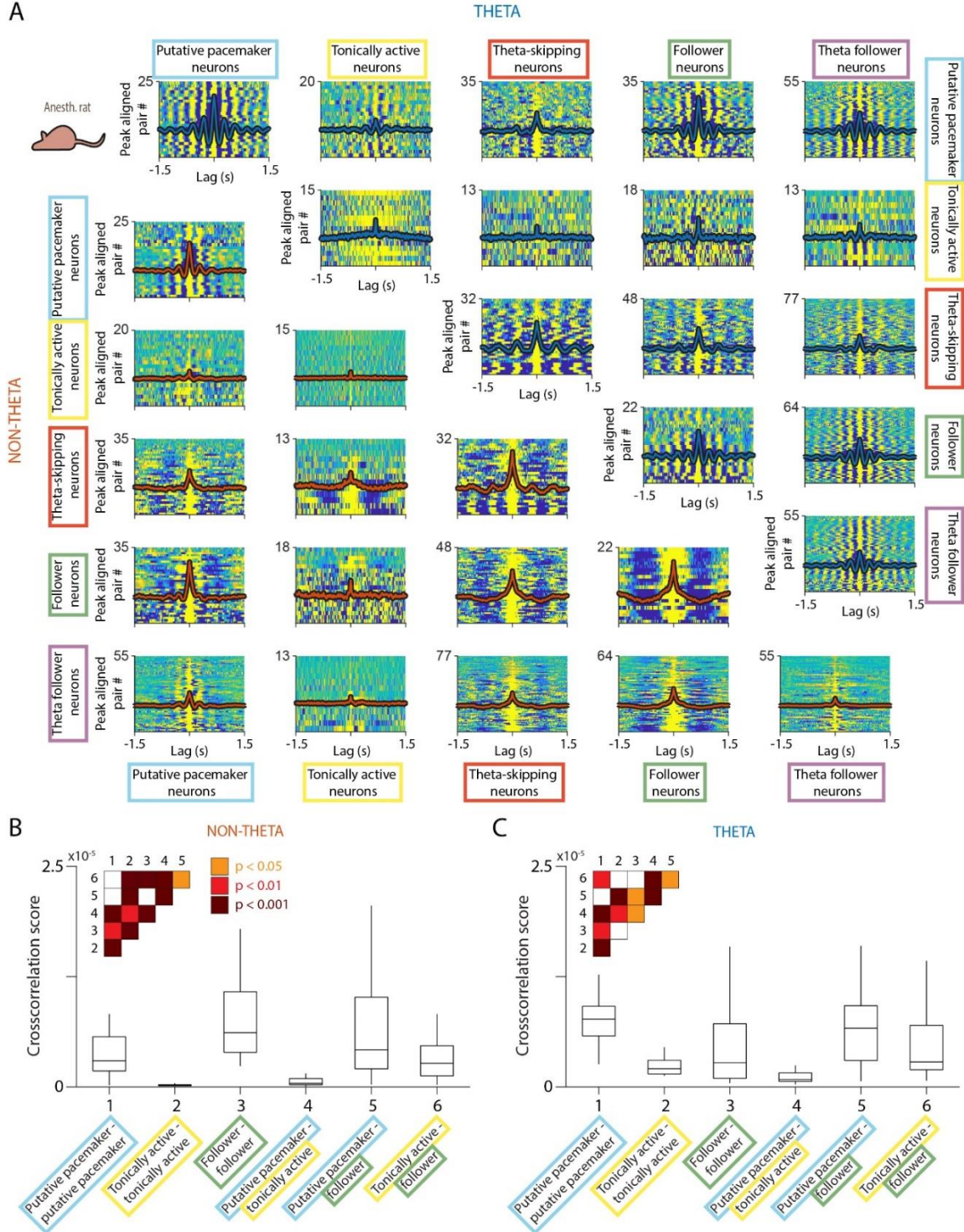
8.4 Synchronization of rhythmicity groups

To gain information on the neural synchronies between the above-described groups, we calculated pairwise crosscorrelations for pairs of MS cells ($n = 527$ pairs in anesthetized rats).

Crosscorrelations of simultaneously recorded pairs of MS neurons were calculated in ± 3 second windows at 1 ms resolution, smoothed by a 20-ms moving average and normalized to an integral of 1. Crosscorrelograms were aligned to their peaks between ± 1.5 seconds and averaged both within and across rhythmicity groups.

We quantified crosscorrelation strength by taking the squared integral of mean-subtracted individual crosscorrelograms and statistically compared crosscorrelation strength within and across the major rhythmicity groups in urethane-anesthetized rats.

We found that during non-theta segments, follower neurons showed strong synchrony within each other, but also with putative pacemaker neurons (*Figure 17*). This remained consistent across theta and non-theta segments, while the putative pacemaker neurons became the most synchronous group in theta state. Tonically active neurons showed lower levels of synchrony within each other and with putative pacemakers, while they expressed moderate correlations with follower neurons. Therefore, we reasoned that theta-rhythmic putative pacemaker and follower neurons likely participate in the MS theta generating mechanisms, unlike tonically active neurons.



17. Figure. Crosscorrelation within and between medial septal rhythmicity groups. (A) Crosscorrelations of all rhythmic cell pairs recorded in anesthetized rats were sorted by rhythmicity categories. Individual crosscorrelations are shown color coded (small values are blue) and average crosscorrelations are overlaid (red during non-theta, lower left triangle; blue during theta, upper right triangle). (B) Distributions of crosscorrelation scores (mean squared integral of the mean-subtracted crosscorrelograms) within and across rhythmicity groups during non-theta segments. Box-whisker plots show median, inter-quartile range and non-outlier range. The inset indicates statistically significant differences across the crosscorrelation score distributions (Mann-Whitney U-test). (C) Same as in panel B for theta segments.

8.5 Huygens synchronization of pacemaker cells

To test how putative pacemakers synchronize during theta segments, we calculated a number of parameters and performed comparisons during theta vs. non-theta episodes:

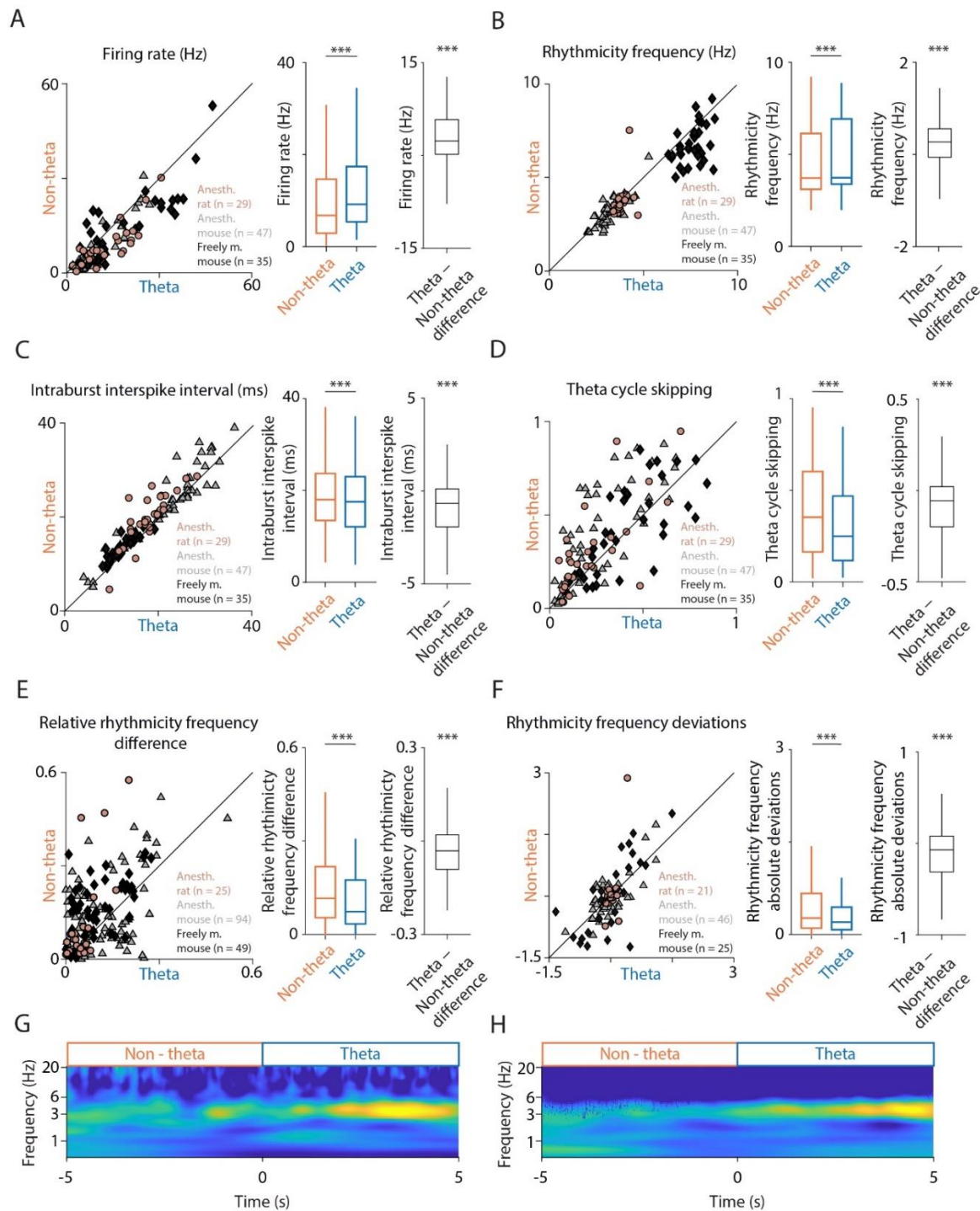
1. Tonic drive strength: First, firing rates were calculated as the ratio of spike number and total segment length. Second, rhythmicity frequencies were estimated from the peak locations of autocorrelograms, smoothed by a 20-ms moving average. We found, that during CA1 theta, putative pacemakers showed elevated firing rate and somewhat higher rhythmicity frequency, arguing for a stronger excitatory drive during theta (*Figure 18A-B*).
2. Bursts: Theta-bursts were defined by interspike intervals falling in the theta-burst windows defined for the TBI (see above in *“Rhythmic neuron classes of the medial septum”*) and average intraburst interspike intervals were computed. Interestingly, we only found moderate changes in burst parameters, suggesting that the bursting mechanisms of MS pacemakers are mostly intrinsic and show only slight modulation with changing network states (*Figure 18C*).
3. Theta-skipping: Since the change in burst parameters and rhythmicity frequency seemed too small to account for the observed elevated firing rate, we argued that putative pacemakers should be skipping more theta cycles during non-theta states. To estimate theta cycle skipping, an event vector was built from first spikes of bursts and single spikes. Theta cycle length was calculated for each neuron based on its rhythmicity frequency (see above at *“1. Tonic drive strength”*), and an edge vector was defined with uniform spacing according to theta cycle length. Events were binned by the edge vector and skipping was quantified as the ratio of empty to all cycles. Although the edge vector was only based on neuronal rhythmicity and thus could not account for individual cycle variabilities, this approach likely provides a good approximation of theta cycle skipping. Since we aimed to define this metric for both theta and non-theta segments, we had to move away from LFP-based cycle definitions for this analysis. We confirmed increased theta-cycle skipping during non-theta segments (*Figure 18D*).
4. Frequency synchronization: We analyzed the pairs of putative pacemakers further to address how the synchrony of these neurons changes during hippocampal theta oscillation. Based on theoretical work, we hypothesized that pacemaker neurons may synchronize their frequencies, thus increasing constructive interference across individual oscillators,

providing a stronger theta-rhythmic output toward the hippocampus (Ramirez et al., [2016](#); Ujfalussy & Kiss, [2006](#); X.-J. Wang, [2002](#); Willms et al., [2017](#)). This would imply that pairwise differences in the rhythmicity frequency of putative pacemakers decrease during theta oscillation compared with non-theta episodes. Difference in rhythmicity frequency was calculated between concurrently recorded pairs of putative pacemaker neurons and normalized to the greater of the two frequencies. This normalization of the relative frequency difference to the individual frequencies of the tested neurons ensures that a change in the individual theta frequencies could not account for this effect. Along these lines we found smaller differences in individual theta frequencies when hippocampal theta was present when we pooled all pacemaker pairs from the three data sets (*Figure 18E*). This difference was significant both for anesthetized rats and freely moving mice, and marginally significant when only anesthetized mice were considered (*Table S3*).

If differences across rhythmicity frequencies decrease during theta, one also expects rhythmicity frequencies across the putative pacemaker population to converge to a tighter distribution. We tested this by comparing the absolute deviation of rhythmicity frequencies from their mean during theta and non-theta segments. First, we took the difference of rhythmicity frequencies of individual putative pacemaker neurons and mean rhythmicity frequency of the recording session, to remove the variance stemming from differences in the exact theta frequency in each model (see *Figure 8*). Then we compared the absolute deviation from the mean across these normalized distributions by Wilcoxon signed rank test and found a larger spread in non-theta state (*Figure 18F*).

Additionally, we visualized the pacemaker synchronization process by calculating wavelet coherence among putative pacemaker pairs. Spike trains of the pacemaker neurons were convolved with a 50 ms Gaussian kernel to obtain continuous signals. Magnitude-squared wavelet coherence spectrograms of the signals were calculated around non-theta to theta transitions, where each of the segments were at least 7 second long, using the analytic Morlet wavelet. This analysis also indicated greater coherence in a narrow frequency band among putative pacemakers during theta (*Figure 18G-H*). Thus, these analyses confirmed our prediction that the theta-rhythmic population converges to a tighter rhythmicity frequency distribution after theta onset.

In conclusion, putative pacemakers appeared to receive stronger drive, skip fewer cycles and synchronize their bursts frequencies when hippocampal state is detected as theta, whereas burst parameters remained relatively stable across theta and non-theta segments.



18. Figure. Septal pacemakers synchronize their burst frequencies. (A) Firing rates of MS putative pacemakers were higher during theta oscillation than during non-theta segments. Left, scatter plot shows the firing rate of all putative pacemaker

neurons, color coded according to the rodent theta models. Middle and right, box-whisker plots showing statistics on pooled data ($***p < 0.001$; $p = 1.402 \times 10^{-9}$, $W = 5166$, $n = 111$, Wilcoxon signed-rank test). See Table S3 for statistics on the three datasets separately. All box-whisker plots show median, interquartile range and non-outlier range in this figure. (B) Left, scatter plot of rhythmicity frequency of putative pacemakers measured by the time lag of the first autocorrelation peak in the theta band. Middle and right, statistics on pooled data indicated higher rhythmicity frequency during hippocampal theta ($***p < 0.001$; $p = 2.64 \times 10^{-7}$, $W = 4857.5$, $n = 111$, Wilcoxon signed-rank test). (C) Left, scatter plot of average intraburst ISIs for putative pacemaker neurons. Middle and right, the moderate decrease of ISIs during theta oscillation indicates a slight elevation of intraburst frequency ($***p < 0.001$; $p = 7.336 \times 10^{-5}$, $W = 1275.5$, $n = 111$, Wilcoxon signed-rank test). (D) Left, scatter plot of the ratio of skipped theta cycles of putative pacemakers during non-theta and theta segments. Middle and right, statistics on pooled data indicated that putative pacemaker neurons skipped more theta cycles during non-theta segments ($***p < 0.001$; $p = 3.021 \times 10^{-6}$, $W = 1521$, $n = 111$, Wilcoxon signed-rank test). (E) Left, scatter plot of relative frequency difference of individual pacemaker neurons for simultaneously recorded pairs, normalized to the larger of the frequencies. Middle and right, statistics on pooled data indicated that individual pacemakers became more similar in frequency during theta oscillation ($***p < 0.001$; $p = 3.17 \times 10^{-6}$, $W = 4156$, $n = 168$, Wilcoxon signed-rank test). (F) Left, deviation from the session mean rhythmicity frequency during theta vs. non-theta segments for putative pacemaker neurons (sessions in which at least two putative pacemakers were co-recorded are included). Middle and right, statistics on pooled data indicated that the absolute deviation from the mean rhythmicity frequency was significantly larger during non-theta segments ($***p < 0.001$; $p = 4.189 \times 10^{-4}$, $W = 1233$, $n = 92$, Wilcoxon signed-rank test). (G) Mean wavelet coherence spectrogram of an example putative pacemaker neuron pair (spike trains were convolved with a 50-ms Gaussian window, from anesthetized rat) averaged around non-theta to theta transitions. (H) Mean wavelet coherence spectrogram averaged across pairs of putative pacemaker neurons recorded in urethane-anesthetized rats (time 0 corresponds to non-theta to theta transitions; sessions in which at least two putative pacemakers were co-recorded are included, $n = 25$ pairs).

8.6 Septal rhythmic cells contribute to hippocampal supra-theta oscillations

Recent studies have demonstrated that certain theta cycles carry beta and gamma components ("theta spectral components", tSC), that are overlooked if long recordings are not filtered specifically for them (Lopes-dos-Santos et al., [2018](#)). However, these short oscillations possibly reflect important operations dedicated to sensory information processing, coding and memory retrieval (e.g. the theta nested gamma waves emerges during navigation and memory reported by (Fernández-Ruiz et al., [2017](#))).

Recently, David Dupret and his colleagues applied single cycle spectral profiling to CA1 recordings to reveal transient operating modes of the hippocampal circuit during theta (Lopes-dos-Santos et al., [2018](#)). These beta (tSC1, 20-30 Hz), slow- (tSC2, 30-50 Hz) and mid-gamma (tSC3 and tSC4, 50-100 Hz) components would otherwise be averaged out if the analysis considered only the entire recording. The authors observed different firing modulations of the CA1 principal cells related to the type and strength of the tSC. While spikes were locked to the tSC troughs, tSCs preferred different phases of the ongoing theta. Investigations revealed functional partitioning within the network. Generalized linear models -trained on spikes from a proportion of the recording session- were able to predict the strength of different tSCs on the test proportion.

Investigations explored synaptic plasticity of cells firing together during the exploration of a maze. If the animal was in a non-familiar environment, co-firing in mid-gamma-dominated theta cycles substantially increased the probability of reactivation during a subsequent sleep/ rest period (Sharp Wave Ripple).

Finally, researchers put the animals in a crossword maze, where barrier locations were changed every day, requiring mice to update their spatial knowledge regularly. During the initial, learning phase of the task 80 Hz mid-gamma oscillation (tSC4) strength strongly increased. On the other hand, other tSCs were more prominent during the late, probe phase. Current source density analysis of CA1 pyramidal cells localized the mid-gamma component to the lacunosum moleculare layer (lml). Beta and slow-gamma components were associated with the stratum radiatum layer (srl). While lml receives highly processed sensory inputs from the enthorinal cortex (EC), srl is targeted by CA3 projections conveying mnemonic information (Hasselmo et al., [2002](#)). These findings suggested the cycle-by-cycle dynamical tuning of CA1 circuits, gradually shifting weights from coding to memory retrieval.

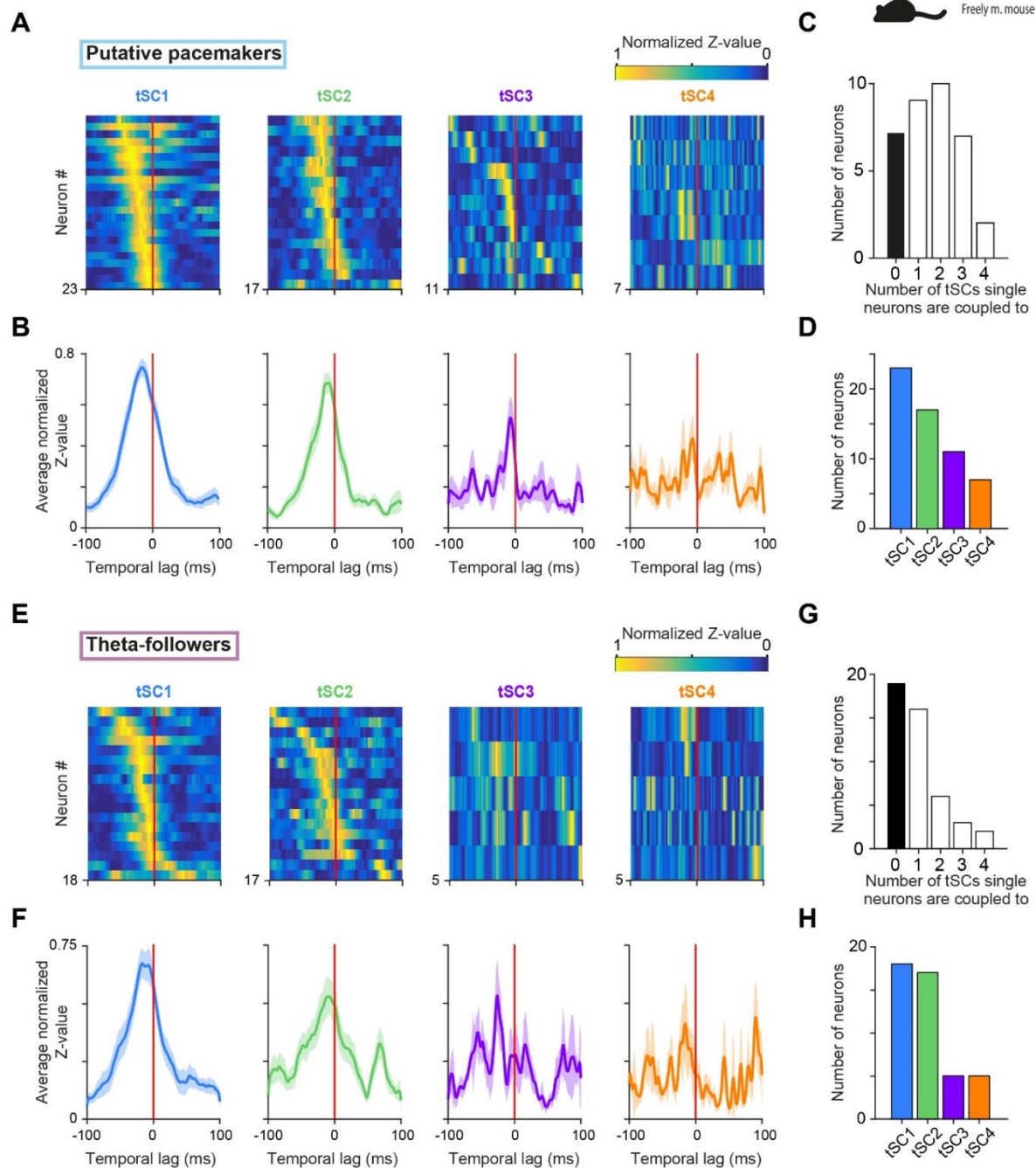
Since the MS has direct access to the hippocampus and contains a variety of rhythmic cells, our group proposed that it may also contribute to the generation of supra-theta oscillations. Indeed, my colleague, Bálint Király presented compelling evidence supporting the strong influence of the septum in this process (Király et al., [2023](#)).

Initially, the freely moving mouse dataset was analyzed (chronic mouse dataset was extended with 2 more mice; resulting in a total of 365 MS neurons from 6 mice). The tSC-detecting algorithm found that 30% of all theta cycles contained tSCs (*Figure 19*). These cycles were associated with higher MS firing rates, continuously increasing with tSC frequency. Although 82% of MS neurons were mostly active during tSC4 cycles, there was a small group exhibiting highest firing rates during tSC1. Additionally, tSC cycles induced tighter coupling to theta phase.

Rhythmicity based classification of MS neurons resulted in the identification of 36 putative pacemakers, 46 theta-followers and 11 tonically active cells in the extended dataset (including 1 pacemaker and 3 tonic cells from the two additional mice).

Interestingly, gamma-band tSCs were associated with increased firing rates across all rhythmicity groups. Intraburst firing rates of the theta coupled putative pacemakers and theta-follower group demonstrated a positive correlation with strong tSC cycles (*Figure 19*).

MS neurons anticipated subsequent changes, 81% of putative pacemakers preceded them (tSC1: 96%; tSC2: 71%; tSC3: 73%; tSC4: 71%). Theta-follower neurons displayed anticipation for tSC1 (83%) and tSC2 (65%).



20. Figure. Rhythmic septal cells predict tSCs. Figures are taken from (Király et al., 2023). (A) “Normalized Rayleigh’s Z-value as a function of temporal lag between hippocampal tSCs and MS spike trains”. Only putative pacemakers coupled to the given tSCs are shown. Majority of these cells exhibited strongest coupling with negative lag suggesting causal relationship with all tSCs. (Király et al./ Supplementary Figure 9./a). (B) “Average normalized Z-value of tSC-coupled putative pacemakers as a function of time lag. Error shade represents SEM”. (Király et al./ Supplementary Figure 9./c). (C)

“Histogram of the number of tSCs single putative pacemakers are coupled to”. (Kiraly et al./ Supplementary Figure 9./d). (D) “Number of putative pacemakers phase-coupled to each tSC”. (Kiraly et al./ Supplementary Figure 9./d). (E-H) Same as above for theta-follower neurons. This group predicted tSC1 and tSC2.

TSC analysis on the anesthetized rat and mouse datasets were less conclusive. Naturally, supra theta oscillations are less frequent when sensory input is switched off. Although the proportion of tSC cycles was lower both in rat (24%) and mice (24%), MS neurons still coupled to tSC phases.

TSC coupling of anatomically identified MS cells, laminar CSD profiling of tSC waves, and PV+ neuron targeting photostimulation evoked tSCs further supported the hypothesis that the MS plays a generator role beyond theta frequency (See Kiraly et al. for details (Király et al., [2023](#))).

This series of analyses demonstrated that theta rhythmicity based classification of neurons may also define functional classes across different frequency ranges. Putative pacemaker and theta-follower neurons exhibited increased firing rate and theta phase coupling in cycles with gamma-band tSCs, whereas tonically active cells also increased their firing rate (*Figure 19*). Majority of these neurons were coupled to tSC phases. Additionally, tSC-coupled putative pacemakers not only preceded all types of tSCs but also emerged as the earliest forecasters among all tSC-coupled cells.

9 Optotagging of MS neurons- Thesis group II.

To investigate the genetic and neurotransmitter identity of MS neurons, we performed optogenetic tagging in urethane-anesthetized mice in a separate set of experiments (*Figure 21, Figure 22*). Theta oscillation was induced by tail pinch, and we performed theta detection and rhythmicity-based classification of MS neurons as above. We performed optogenetic stimulation in PV-Cre (N = 2), VGAT-Cre (N = 2) or VGlut2-Cre (N = 3) mice transduced by a Cre-dependent Channelrhodopsin (ChR2) construct injected in the MS to identify parvalbumin-expressing, GABAergic and glutamatergic MS neurons, respectively (Gritti et al., [2006](#); Sotty et al., [2003](#)).

9.1 Methods

9.1.1 Surgery and optogenetic tagging protocol

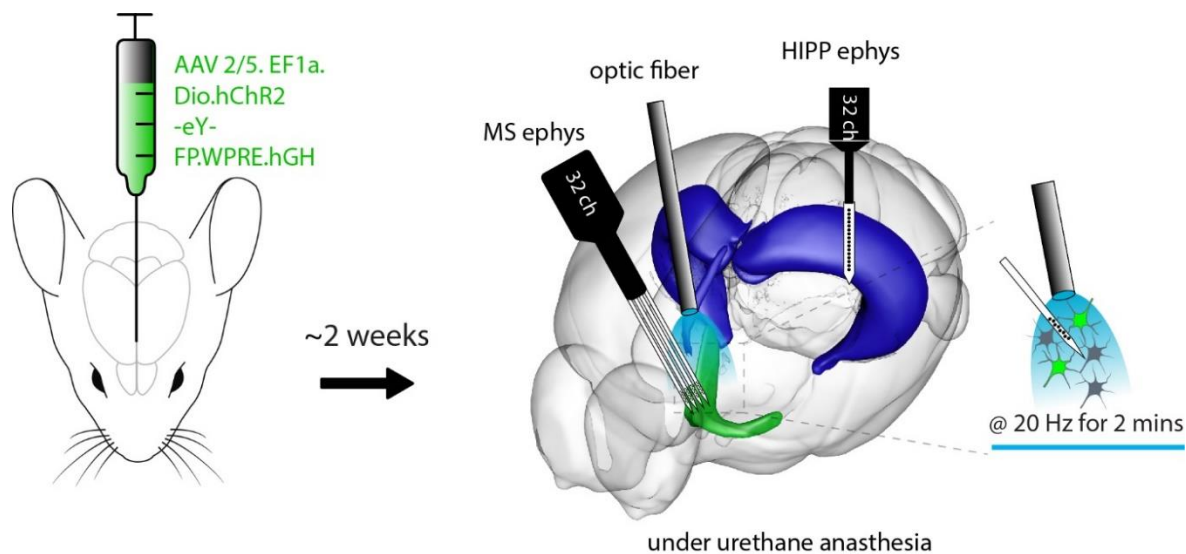
4 PV-IRES-Cre males (genetic background FVB/AntF_x), 4 VGAT-IRES-Cre males (genetic background Bl6F_x) and 5 Vglut2-IRES-Cre males and females (genetic background C57BL/6J) were used to assess the neurochemical nature of MS cells; 2 PV-Cre (n = 17, 1), 2 VGAT-Cre (n = 17, 3) and 3 VGLUT2-Cre (n = 15, 9, 6) mice yielded tagged neurons (numbers in brackets). Mice were anesthetized with an i.p. injection of ketamine-xylazine (0.166 and 0.006 mg/kg, respectively). After shaving and disinfecting (Betadine) the scalp, local anesthetic was applied (Lidocaine). Animals were positioned in the stereotaxic frame and the eyes were protected with eye ointment (Laboratories Thea). After opening the skin, the skull was cleaned and the head of the animal was leveled using Bregma, Lambda and a pair of lateral points equidistant from the sagittal suture.

A trephine hole was drilled in order to access the MS with a 10° lateral angle (MS 10°, antero-posterior +0.90 mm, lateral, 0.90 mm). An adeno-associated virus vector allowing Cre-dependent expression of channelrhodopsin2 [AAV 2/5. EF1a.Dio.hChR2(H134R)-eYFP.WPRE.hGH] was injected into the MS at 3.95, 4.45 and 5.25 mm depth from skull surface (200 nl at each depth, 100 nl at 25 nl s⁻¹ and 100 nl at 5 nl s⁻¹). After the viral injections, the skin was sutured and local antibiotics (Neomycin) and analgesics (Buprenorphine 0.1 mg kg⁻¹, s.c.) were applied.

Around two weeks after the virus injection, the animals were anesthetized with an i.p. injection of 20% urethane (Sigma-Aldrich, 0.007 ml g⁻¹ body weight). The depth of anesthesia was evaluated by pinching the paw, tail, or ear of the animal, and by checking the ocular reflex. When no reflexes

were elicited, the throat was shaved, and topical lidocaine was applied. A heating pad was used to keep constant body temperature of the animals. A tracheotomy was performed in order to sustain a constant airflow (Moldestad et al., [2009](#)). The animals were placed in a stereotaxic frame and, after opening the skin and leveling the skull, a cranial window was made above the MS (silicon probe MS 10°, antero-posterior, +0.90 mm, lateral, 0.90 mm; optic fiber MS 5° contralateral, antero-posterior, +0.90 mm, lateral, -0.50 mm), the hippocampus (silicon probe HPC, antero-posterior, -2.20 mm, lateral, 1.50 mm) and two above the cerebellum for reference electrode placement. A Neuronexus A1x32-6mm-50-177-CM32 silicon probe was placed in the hippocampus at 2.20 mm depth from skull surface. A Neuronexus Buzsaki32-H32_21 mm probe was lowered to the dorsal boundary of the MS at a 10° lateral angle (3.95 mm from skull surface). Reference electrodes for both probes were placed in the cerebellum, keeping around 5 mm distance between them, and a ground electrode was placed in the spinotrapezius muscle. A 200 µm core optic fiber (Thorlabs) was lowered 500 µm above the shanks of the MS probe. The MS probe and the optic fiber were lowered in consecutive recordings (100 µm steps for the probe; 50 µm steps for the optic fiber), spanning the entire depth of the MS. Extracellular data were collected by the Open Ephys data acquisition system, digitized at 30 kS/s. Each recording session consisted of an optical tagging period of two minutes, followed by a baseline period of five minutes of spontaneous activity. Three consecutive repetitions of one-minute tail pinch induced theta activity followed by one-minute control recording were applied, finishing the recording session with another two-minute-long optical tagging period. For optimizing the probability of finding tagged cells, we used the Online Peri-Event Time Histogram ([OPETH](#)) Open Ephys compatible plugin that allowed us to visualize the direct effect of the optogenetic activation at the cell population level. OPETH (Széll et al., [2020](#)) allowed us to reduce recording time by more efficient 'hunting' for light responsive neurons in the MS and to reduce light-triggered artifacts in our recordings, improving data quality and further analysis.

These experiments were performed by Sergio Martínez-Bellver (Lendület Laboratory of Systems Neuroscience, Institute of Experimental Medicine, 1083 Budapest, Hungary. And Department of Anatomy and Human Embryology, Faculty of Medicine and Odontology, University of Valencia, 46010 Valencia, Spain).



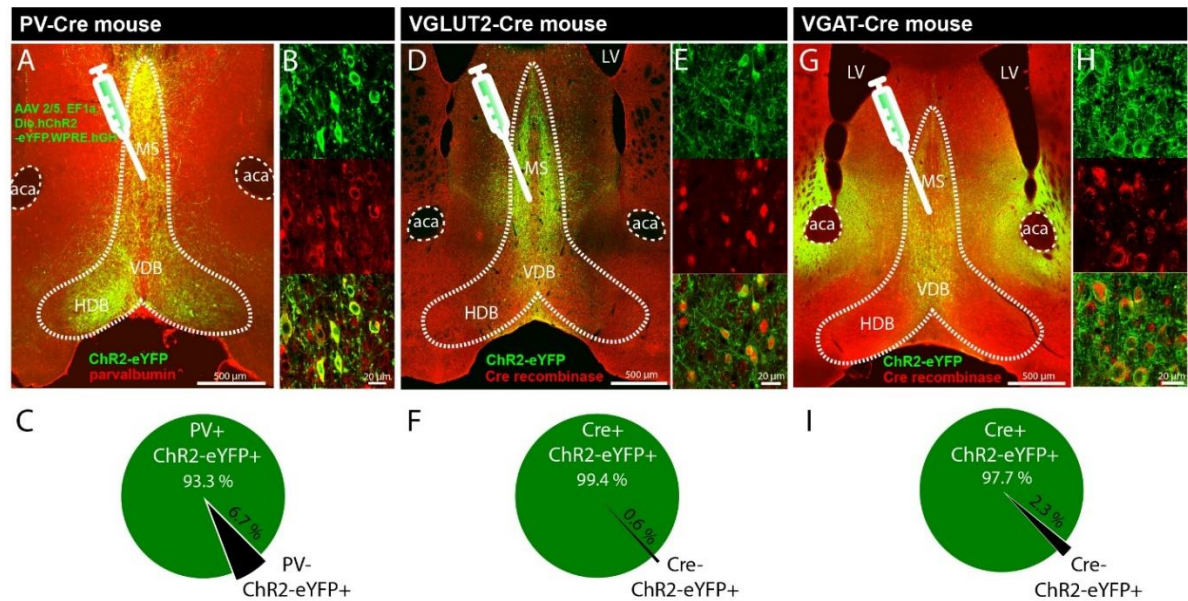
21. Figure. Optogenetic tagging of medial septal neurons. Schematic of the experiment. PV-IRES-Cre, VGLUT2-IRES-Cre and VGAT-IRES-Cre mice were injected with an adeno-associated virus vector allowing Cre-dependent expression of channelrhodopsin2 in the MS. Two weeks later mice were implanted with an optic fiber in the MS for laser stimulation and silicon probes in the MS and CA1 in acute anesthetized experiments. Three-dimensional mouse brain adopted from (Bakker et al., 2015).

9.1.2 Immunostaining

To verify the specificity of the ChR2 expression in targeted neuronal types in the optogenetic tagging experiments, 3 animals from each mouse strain (PV-Cre, VGAT-Cre, VGLUT2-Cre) were sacrificed 2-3 weeks after virus injection into the MS (see details in the “Surgery and optogenetic tagging protocol”, Figure 22). First, animals were anesthetized with an intraperitoneal injection of ketamine-xylazine (0.166 and 0.006 mg/kg, respectively), followed by transcardial perfusion with saline for 2 minutes and 4% para-formaldehyde (PFA) for 20 minutes. After sectioning 50 μ m thick slices of the brain tissue, sections containing the MS were washed in 0.1M phosphate buffer (PB) and tris-buffered saline (TBS), then incubated in blocking medium (1% human serum albumin + 0.1% Triton-X detergent) for 1 hour. Then, sections derived from PV-Cre mice were incubated in primary antibody against PV (PV 27, Swant, Switzerland), while sections from VGLUT2- and VGAT-Cre mice were incubated in primary antibody against Cre recombinase (Biologend, USA, cat#908002, 1:500) in each case mixed with primary antibody against GFP (Thermofisher Scientific, USA, cat#A10262, 1:1000) in TBS at 4°C for two days. After an extensive wash in TBS, the sections were incubated in a secondary antibody solution containing Alexa 488 conjugated goat anti-chicken (Thermofisher Scientific, USA, Cat#A11039, 1:1000), Alexa 594 conjugated donkey anti-rabbit (Jackson ImmunoResearch Europe Ltd., UK, cat#711585152, 1:500) or Alexa 647 conjugated donkey anti-

rabbit (Jackson ImmunoResearch Europe Ltd., UK, cat#711605152, 1:500) antibodies at 4°C overnight. Finally, sections were mounted on slides in aqua-Poly/Mount mounting medium (cat#18606, Polysciences, Inc., USA) and images were taken with a Nikon A1R confocal microscope.

Demonstrative experiments for *Figure 22* were performed by Dániel Schlingloff (Lendület Laboratory of Systems Neuroscience, Institute of Experimental Medicine, 1083 Budapest, Hungary).



22. Figure. Channelrhodospin-2 expression is confined to targeted PV+, VGLUT2+ and VGAT+ neuronal populations. (A) Confocal image of ChR2-eYFP (green) and PV (red) expression in the MS of an infected PV-Cre mouse. (B) High magnification images of ChR2-eYFP expression in the MS (top) along with PV expression (middle). Composite image shown on the bottom support strong specificity of ChR2 expression in PV+ cells. (C) 93.25 percent of cells expressing ChR2-eYFP were positive for PV ($n = 267$ cells from 3 animals). (D) Expression of ChR2-eYFP (green) and Cre recombinase (red) in the MS of an infected VGLUT2-Cre mouse. (E) High magnification images of ChR2-eYFP expression in the MS (top) along with Cre expression in VGLUT2-cre mouse line (middle). Composite image is shown on the bottom. (F) 99.43 percent of cells expressing eYFP were positive for Cre recombinase ($n = 529$ cells from 3 animals). (G) Image of ChR2-eYFP (green) and Cre recombinase (red) expression in the MS of an infected VGAT-Cre mouse. (H) High magnification images of ChR2-eYFP expression in the MS (top) along with Cre expression in VGAT-Cre mouse line (middle). Composite image is shown on the bottom. (I) 97.65 percent of cells expressing eYFP were positive for Cre recombinase ($n = 256$ cells from 3 animals), supporting the high specificity of the viral targeting of ChR2 in GABAergic cells. (Photos and Figure was made by Daniel Schlingloff.)

9.1.3 State detection and spike sorting

Hippocampal state detection was performed on a single channel from the stratum radiatum (~250 μm below the pyramidal layer). The LFP signal was resampled at 1 kHz. Theta and delta frequency band boundaries were determined based on spectral components (theta: 1.5-4 Hz; 1-4 and 1.5-6 Hz in 1-1 mice; delta: 0.5-1.5 Hz, 0.5-1 Hz in one mouse). Theta/ delta amplitude ratio was smoothed with a 5 second window and a 1.5 threshold (1 in one mouse) was applied for theta detection.

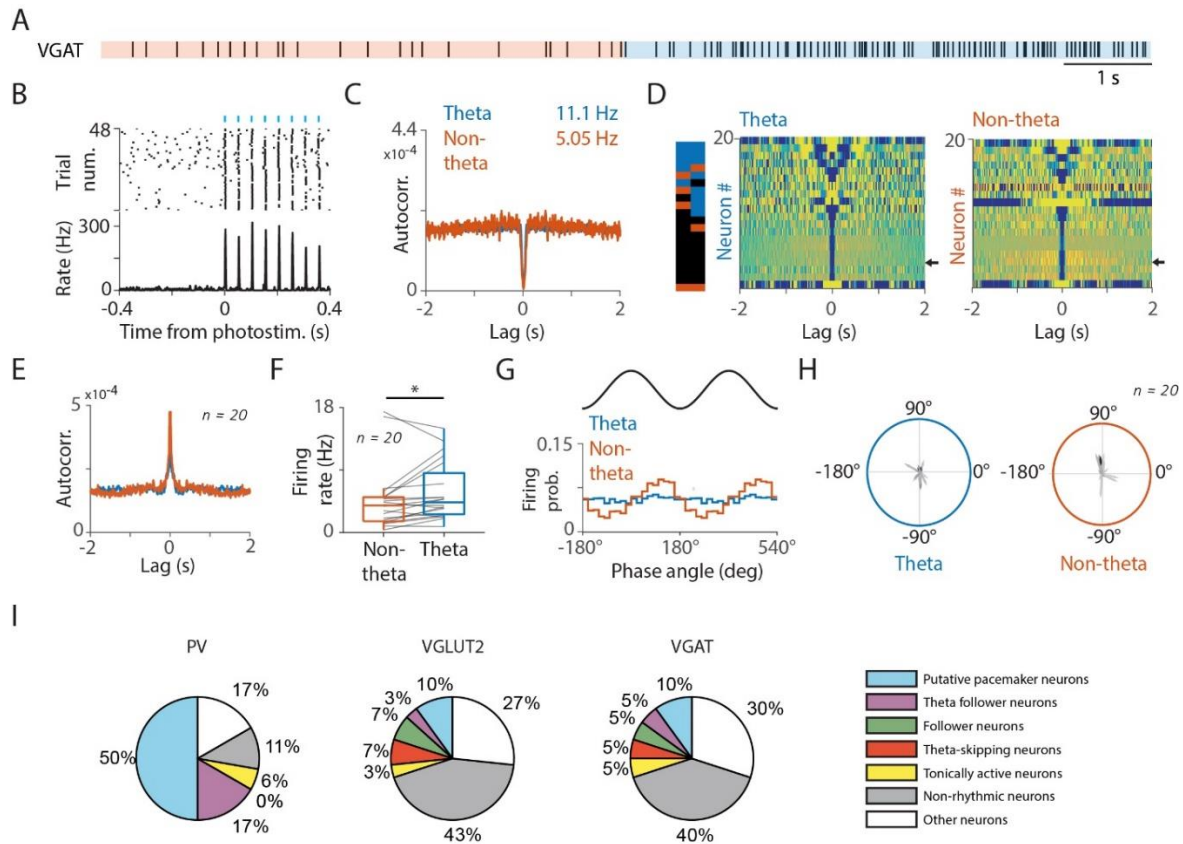
Additionally, theta amplitude was required to surpass the median value of the theta-filtered signal. Less than 5-second-long epochs were not considered as state transitions. In 8 recordings, only a part of the recording was analyzed due to electrical artifacts in other segments.

MS units were sorted in Kilosort as described above. MS neurons that had sufficient number of spikes (>500 in total and median interspike interval <500 ms) were further analyzed. Note that these spike number criteria were less stringent compared to other datasets (see above) due to generally shorter recordings. Significant photoactivation ($p < 0.01$) was determined using the stimulus-associated spike latency test ([SALT](#)) based on specific spike timing after light flashes (Kvitsiani et al., [2013](#)). After removing the phototagging segments from the recordings, rhythmicity indices and TBI (with [20,40] ms window) were computed as described above.

9.2 PV+ pacemaker cells synchronize their frequencies

We found that many PV-expressing neurons were theta rhythmic (*Figure 23A-H*), and $n = 9/18$ neurons were characterized as putative pacemakers (*Figure 23I*). Surprisingly, GABAergic neurons as a population contained few theta-rhythmic neurons; instead, most VGAT+ MS neurons were non-rhythmic (*Figure 24A-H, Figure 24I*; $n = 2/20$ putative pacemakers). Anatomical studies showed that a subset of GABAergic MS neurons express PV (Gritti et al., [2003](#); Kiss et al., [1990](#); Unal et al., [2015](#); Yang et al., [2017](#); Zaborszky et al., [1999](#), [2012](#)), suggesting that the subset of VGAT+ MS neurons that were rhythmic may have been PV expressing. These results suggest that PV expression marks the theta-generating population, confirming previous studies (Borhegyi et al., [2004](#); T. F. Freund, [1989](#); Varga et al., [2008](#)).

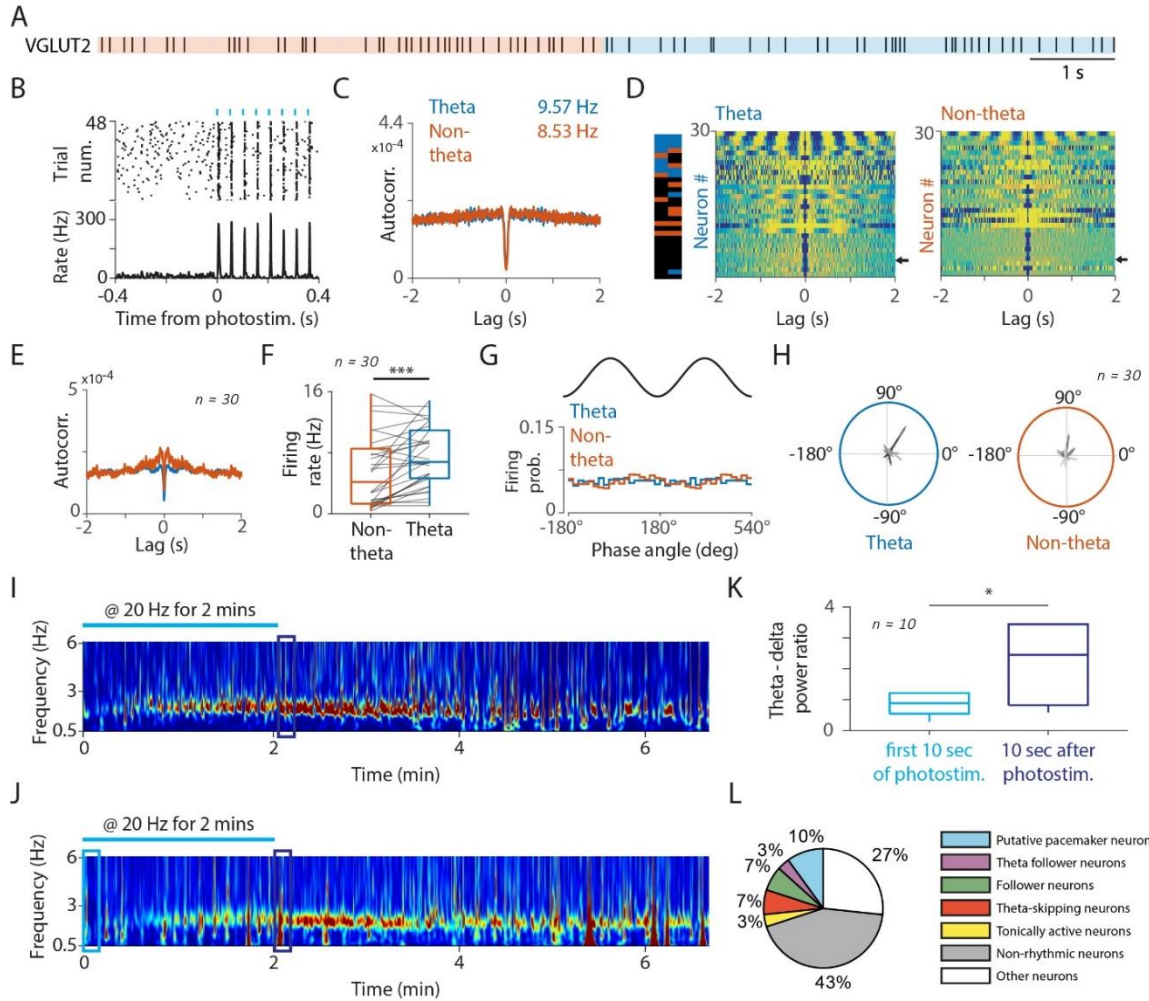
similar frequency synchronization as shown for unlabeled pairs of putative pacemakers in *Figure 18E* and for model pacemaker neurons in *Figure 28E*.



24. *Figure. Rhythmicity of GABAergic neurons. Proportion of rhythmicity types within identified cell populations. (A-H) Identical figure structure with Figure 23. (F) Firing rate was significantly higher during theta (* $p < 0.05$; $p = 3.66 \times 10^{-2}$, $W = 161$, $n = 20$). (I) Proportion of rhythmicity types within identified cell populations.*

9.3 Glutamatergic stimulation evokes theta

The majority of optogenetically identified MS glutamatergic neurons showed a strong increase in the firing rate (fold increase median $\pm$ standard error of the median, 1.42 ± 0.34) without any theta rhythmicity during hippocampal theta state (*Figure 25A-H*, *Figure S25L*). Few glutamatergic neurons were theta-rhythmic, with 3 of 30 characterized as pacemakers. This identifies the MS glutamatergic population as tonic theta ON neurons (Ford et al., [1989](#)).



25. Figure. Rhythmicity of glutamatergic neurons. 20 Hz stimulation of glutamatergic cells generates theta in the CA1. (A-H) Identical figure structure with Figure 23. (F) Firing rate was significantly higher during theta (** $p < 0.001$; $p = 8.94 \times 10^{-4}$, $W = 394$, $n = 30$). (I) Wavelet spectrogram of an example CA1 LFP segment during and after 20-Hz stimulation of MS glutamatergic neurons. The photostimulation induced lasting theta oscillation. (Note the lower frequency of theta typical under anesthesia). (J) Average of all recording sessions ($n = 10$) of 20 Hz glutamatergic stimulation. (K) Box-whisker plot showing significant increase in theta-delta ratio upon glutamatergic stimulation. Median, interquartile range and non-outlier range are shown (* $p < 0.05$; $p = 3.71 \times 10^{-2}$, $W = 7$, $n = 10$, Wilcoxon signed-rank test). (L) Proportion of rhythmicity types within 30 identified glutamatergic neurons.

Thus, local glutamatergic neurons may contribute to the increased excitatory drive to the MS pacemaker neurons during theta synchronization. To directly test this prediction, we analyzed CA1 LFP after 20 Hz stimulation of MS glutamatergic neurons in urethane-anesthetized VGLUT2-Cre mice (Figure 25I-K). We calculated the spectral power from the wavelet spectrograms for delta and theta frequency bands by averaging across within-band frequencies. Spectral power values were then averaged for the first 10 seconds of photostimulation and the first 10 seconds after photostimulation, and theta-delta power ratio was computed for both periods. Statistical testing of these power ratio distributions confirmed photostimulation evoked theta strengthening in CA1 LFP.

10 Model of the septal network- Thesis group III.

Our neural data suggested that increased tonic excitation led to higher firing rates and frequency synchronization in putative pacemakers that resulted in a strong theta-modulated output. To test if a simple network model of a homogeneous MS pacemaker population could produce these dynamics, we simulated MS neurons based on a minimalistic single-compartment conductance-based model constructed to produce fast spiking burst dynamics (Golomb et al., [2007](#)) (*Figure 26A*).

10.1 Methods

10.1.1 Septal pacemaker neuron model

Our model was implemented in NEURON (Carnevale & Hines, [2006](#)). We used a fixed time step of 0.025 ms. The neuron network parameters were defined, and the simulation results were processed by Matlab scripts.

We based our model on a fast spiking single compartment neuron model by Golomb et al. (Golomb et al., [2007](#)). This choice was motivated by the model's simplicity and its desirable firing properties, capable of high-frequency tonic firing but also rhythmic bursting, characteristic of MS pacemaker neurons. This model included a transient sodium channel (nas) that is necessary for action potential generation, the delayed rectifier potassium channel (kdr) for repolarization during fast spiking and the slowly inactivating d-type potassium channel (kd) for bursting behavior through controlling the duration of the after-hyperpolarization. We added the HCN-channel (hcn) responsible for the hyperpolarization-activated H-current, which was reported to be responsible for sag responses in MS neurons (Kocsis & Li, [2004](#); Morris et al., [2004](#); Sotty et al., [2003](#); Varga et al., [2008](#); Xu et al., [2004](#)). We could reproduce this sag response by including the H-current (*Figure 26C*); we note, however, that the presence of the H-current was not a prerequisite of rhythmic bursting in the present model. Further electrophysiology data and modeling should clarify the exact channel properties of MS pacemaker neurons. Nevertheless, the present model was capable of reproducing the characteristic rhythmic bursting of MS pacemaker neurons in the range of biologically plausible rhythmicity frequencies upon current injection, serving the modeling purposes of this study.

Potential change across the cell membrane was described by the following equation.

$$C \frac{dV}{dt} = -I_{Na}(V, m, h) - I_{Kdr}(V, n) - I_{Kd}(V, a, b) - I_H(V, x) - g_L(V - V_L) + I_{app}$$

where $C = 1\mu\text{F}/\text{cm}^2$ is the membrane capacitance, $g_L = 0.1 \text{ mS}/\text{cm}^2$ is the passive conductance, $V_L = -60 \text{ mV}$ is the equilibrium potential for leakage and I_{app} is the injected current in $\mu\text{A}/\text{cm}^2$. The lower g_L and higher V_L compared to the Golomb-model ($g_L = 0.25 \text{ mS}/\text{cm}^2$, $V_L = -70 \text{ mV}$) were introduced to facilitate the characteristic sag response mediated by the HCN channels. The total surface of the neuron was $5000 \mu\text{m}^2$. The applied point source input current amplitude varied between 40 and 80 pA in the network simulations (below).

Transient Na current I_{Na} was governed by the following equations.

$$I_{Na}(V, m, h) = g_{Na} m^3 h (V - V_{Na})$$

where the maximal conductance of the channels was $g_{Na} = 112.5 \text{ mS}/\text{cm}^2$, the reversal potential of sodium ion was $V_{Na} = 50 \text{ mV}$ and the dynamics of the three activation gates m and one inactivation gate h were given by

$$\frac{dm}{dt} = [m_\infty(V) - m]/\tau_m$$

$$\frac{dh}{dt} = [h_\infty(V) - h]/\tau_h(V)$$

The time constant of the m gate was $\tau_m = 0.01 \text{ ms}$ and the voltage-dependent steady-state activation and inactivation variables m_∞ , h_∞ and time constant of the h gate τ_h were

$$m_\infty(V) = \{1 + \exp[-(V - \theta_m)/\sigma_m]\}^{-1}$$

$$h_\infty(V) = \{1 + \exp[-(V - \theta_h)/\sigma_h]\}^{-1}$$

$$\tau_h(V) = 0.5 + 14 \times \{1 + \exp[-(V - \theta_{th})/\sigma_{th}]\}^{-1}$$

where $\theta_m = -24 \text{ mV}$, $\sigma_m = 11.5 \text{ mV}$, $\theta_h = -58.3 \text{ mV}$, $\sigma_h = -6.7 \text{ mV}$, $\theta_{th} = -60 \text{ mV}$ and $\sigma_{th} = -12 \text{ mV}$.

The delayed rectifier K current I_{Kdr} was governed by

$$I_{Kdr}(V, n) = g_{Kdr} n^2 (V - V_K)$$

where the maximal conductance of the channels was $g_{Kdr} = 225 \text{ mS}/\text{cm}^2$, the reversal potential of potassium ions was $V_K = -90 \text{ mV}$ and the dynamics of the two activation gates n were defined by

$$\frac{dn}{dt} = [n_{\infty}(V) - n]/\tau_n(V)$$

The voltage-dependent steady-state activation variable n_{∞} and time constant of the n gates τ_n were

$$\begin{aligned} n_{\infty}(V) &= \{1 + \exp[-(V - \theta_n)/\sigma_n]\}^{-1} \\ \tau_n(V) &= \left\{ 0.087 + 11.4 \times \left\{ 1 + \exp\left[\frac{V + 14.6}{8.6}\right] \right\}^{-1} \right\} \\ &\times \left\{ 0.087 + 11.4 \times \left\{ 1 + \exp\left[\frac{-(V - 1.3)}{18.7}\right] \right\}^{-1} \right\} \end{aligned}$$

where $\theta_n = -12.4$ mV, $\sigma_n = 6.8$ mV.

The slowly inactivating d-type K current I_{kd} was governed by

$$I_{kd}(V, a, b) = g_{kd} a^3 b (V - V_K)$$

where the maximal conductance of the channels was $g_{kd} = 1.8$ mS/cm² and the dynamics of the three activation gates a and one inactivation gate b were defined by

$$\begin{aligned} \frac{da}{dt} &= [a_{\infty}(V) - a]/\tau_a \\ \frac{db}{dt} &= [b_{\infty}(V) - b]/\tau_b \end{aligned}$$

The time constant of the activation gate was $\tau_a = 2$ ms and that of the inactivation gate was $\tau_b = 120$ ms. The voltage-dependent steady-state activation and inactivation variables a_{∞} and b_{∞} were

$$\begin{aligned} a_{\infty}(V) &= \{1 + \exp[-(V - \theta_a)/\sigma_a]\}^{-1} \\ b_{\infty}(V) &= \{1 + \exp[-(V - \theta_b)/\sigma_b]\}^{-1} \end{aligned}$$

where $\theta_a = -50$ mV, $\sigma_a = 20$ mV, $\theta_b = -60$ mV, $\sigma_b = -6$ mV.

We introduced smaller τ_b compared to the Golomb-model (where τ_b was 150 ms), which resulted in faster rhythmicity that was within the delta-theta frequency range (*Figure 26B*). We used a θ_b of -60 mV that enabled the characteristic sag response by the H-current.

To define the HCN channel, we started from a generic HCN model by Kali and Zemankovics (Káli & Zemankovics, [2012](#)) which used an alternative parameterization of the Hodgkin-Huxley type model as described by Borg-Graham (Borg-Graham, [1999](#)). Next, parameters of our model were tuned to

match the dynamical properties of the H-current in MS neurons (Migliore & Migliore, [2012](#); Xu et al., [2004](#)). The final I_H current was defined by

$$I_H(V, x) = g_H x (V - V_H)$$

where the maximal conductance of the channels was $g_H = 0.1$ mS/cm² and the reversal potential of the cations was $V_x = -30$ mV. The open probability of the activation gate x evolved as

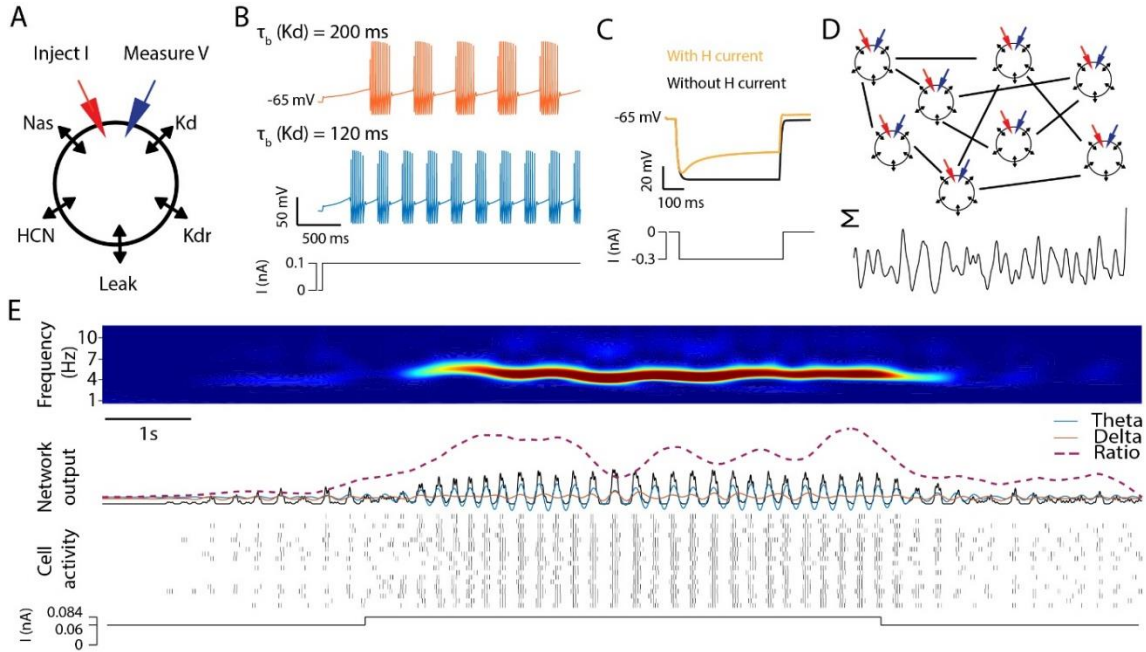
$$\frac{dx}{dt} = [x_\infty(V) - x] / \tau_x(V)$$

where the voltage-dependent steady-state activation variable x_∞ and time constant τ_x were

$$x_\infty(V) = \{1 + \exp[-(V - \theta_x) / \sigma_x]\}^{-1}$$

$$\tau_x(V) = \{G_x \exp\left[\frac{\gamma_x(V - \theta_x)}{\sigma_x}\right] + G_x \exp\left[\frac{(\gamma_x - 1)(V - \theta_x)}{\sigma_x}\right]\}^{-1} + \tau_{x0}$$

where rate coefficient was $G_x = 1.2353$ 1/ms, asymmetry parameter was $\gamma_x = 0.81$, half activation was $\theta_x = -98$ mV, $\sigma_x = -6.73$ mV, $\tau_{x0} = 130$ ms.



26. Figure. A simple conductance-based network model of the MS pacemaker circuit is capable of theta-synchronization upon tonic excitation. (A) Schematic of the single-compartment model neuron. The inhibitory neuron was equipped with transient sodium (Nas), slowly inactivating D-type potassium (Kd), delayed rectifier potassium (Kdr), HCN channels and passive leak channels. An electrode delivering current is attached to the cell. Adopted from (Golomb et al., [2007](#)). (B) Rhythmicity frequency of the model neuron can be controlled by the τ_b (Kd) inactivation time constant. Slower inactivation (200 ms) also increases burst length. (C) Adding H current caused a sag response to hyperpolarizing current, similar to MS GABAergic neurons reported in the literature (see e.g. (Xu et al., [2004](#), Figure 1: C). The moderate rebound effect did not induce rebound spikes. (D) Schematics of the network. Twenty model cells were connected with simulated GABA-A-

mediated inhibitory synapses. Spike trains were summed and convolved with a 50-ms Gaussian window to model network output. (E) Simulation of network behavior (60% connection rate; 7-ms synaptic delay, 3-nS mean synaptic strength; 2-ms synaptic decay; 10% variance for the latter three synaptic parameters; 60-pA mean baseline stimulation with 10% variance). Neurons synchronized in the theta frequency band in response to a tonic increase of stimulation and desynchronized when stimulation was reset to baseline. (Increased excitation was applied with jittered onset latency to avoid synchronous phase reset). Top: Wavelet spectrogram of network output. Middle: network output (black: raw; blue: filtered in the theta band; orange: filtered in the delta band; dashed: theta-delta ratio) and simulated spike raster (see Figure 8C for *in vivo* recording). Bottom: Injected current.

10.1.2 Modeling the septal pacemaker network

The neuron network parameters were defined, and the simulation results were processed in Matlab. In our network simulations, 20 inhibitory pacemaker neurons were connected at an average connection rate varied between 0 and 100% (randomly chosen connections were deleted from a fully connected graph). Inhibitory synapses were implemented with the built-in Netcon() and ExpSyn() point processes of the NEURON environment. Netcon() implements a presynaptic source object with threshold, delay and weight parameters. The threshold parameter was fixed at 0 mV. Synaptic delays between 1 and 15 ms (1, 4, 7, 11, 15 ms) were tested (Figure 27), fixed at 7 ms with 10% variance for simulations shown in Figure 26 and Figure 28. Expsyn() modelled the postsynaptic effect with a discontinuous change in conductance after each incoming spike event (which was initiated by Netcon() when the presynaptic membrane potential crossed the spike detection threshold), followed by an exponential decay with time constant τ :

$$I(t, V) = g(t) \times (V - e)$$

$$g(t) = weight \times \exp(-t/\tau)$$

where I (in nA) was the current transmitted to the postsynaptic cell, g (in μ S) was the actual conductance, $weight$ (in μ S) was the maximal conductance or synaptic strength, e (in mV) was the reversal potential, which was set to -70 mV and τ (in ms) was the exponential decay factor, which was set to 2 ms with 10% variance. We set these parameters to simulate GABA-A receptor kinetics, that triggered fast IPSCs.

All neurons received a non-rhythmic ('tonic') somatic excitatory current to mimic the changing excitatory drive to the septal pacemaker population. We used NEURONS's built-in IClamp() function, which simulated an electrode delivering current pulses of a given duration, amplitude and delay. Every neuron received three electrodes at their somata, delivering a sequence of three current pulses implementing weak, strong (1.4-fold), and weak tonic excitation in this order, with variable stimulus onset latency uniformly dispersed over a one-second-long interval to avoid

synchronous phase reset across the population. The extent of increase in excitation strength was based on the average firing rate increase of MS glutamatergic neurons (*Figure 25F*), the main excitatory input to MS GABAergic cells (Hajszan et al., [2004](#)), determined by our optogenetic tagging experiments. During each simulation, synaptic and stimulation parameters were drawn from normal distributions with given mean and variance.

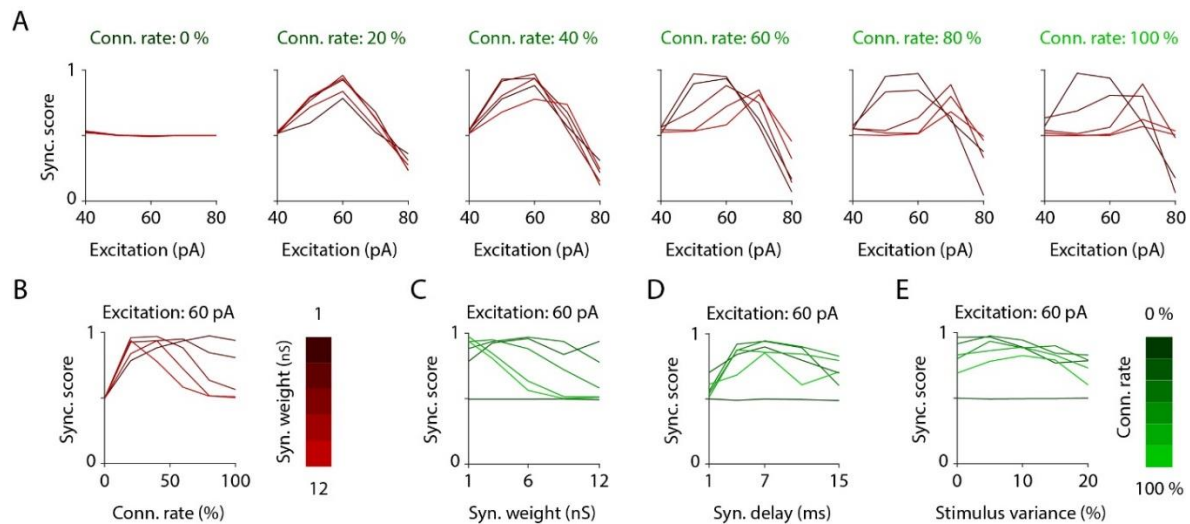
We modeled the theoretical output signal of the simulated pacemaker network as a proxy for the septal input to the hippocampus. Spike trains (i.e. the events when the simulated membrane potential reached the 0 mV spike generation threshold) were convolved with a 50 ms Gaussian window and averaged across all neurons. State detection was executed similarly as described for real data above with the following parameters: resampling rate, 1 kHz; theta band 4-6 Hz; delta band, 0.5-4 Hz; theta-delta ratio was smoothed, and short segments (<0.5 s) were handled as above; theta-delta ratio threshold, 2.

We found that, at low tonic excitation levels, the modelled septal output showed irregular activity with low levels of theta oscillation. Increasing the tonic drive resulted in a strong theta oscillatory output, which returned to the irregular activity when the tonic current was decreased (*Figure 26E*). Thus, the level of non-rhythmic excitation could toggle the model pacemaker network between theta and non-theta output, as suggested earlier (Bland et al., [1996](#); Hajszan et al., [2004](#)) and consistent with our neural recordings.

10.2 Exploring the parameter space of the pacemaker network model

To study the network dynamics and its dependence on key parameters, we performed a series of simulations. In each run, we simulated a 5-second-long baseline period, followed by a 10-second-long 'expected theta' period when a stronger excitatory current was injected to all pacemaker neurons (1.4-fold of baseline), followed by a 5-second-long 'expected non-theta' period when tonic excitation was reverted to baseline (with varied stimulus onset latency, see above). We systematically varied the connection rate (0-100% in increments of 20%), mean synaptic delay (1, 4, 7, 11, 15 ms), mean absolute synaptic strength (1, 3, 6, 9, 12 nS), mean (40-80 pA in increments of 10 pA) and variance (0-20% in increments of 5%) of baseline stimulation strength. The variance of synaptic weights, delays and decay times was kept at 10%.

We performed three sets of simulations. First, the variance of baseline stimulation was fixed at 10% and the synaptic delay at 7 ms, while all combinations of connection rates, stimulation strength and synaptic weight were tested (Figure 27A-C). Second, stimulation strength was fixed at 60 pA, synaptic weight at 3 nS and stimulation variance at 10%, while all possible combinations of connection rate and synaptic delay were tested (Figure 27D). Third, stimulation strength was fixed at 60 pA, synaptic weight at 3 nS and synaptic delay at 7 ms, while all possible combinations of connection rate and variance of stimulation strength were tested (Figure 27E). We repeated each simulation for a given parameter arrangement 10 times by redrawing parameters from the same distributions, performing 1800, 300 and 300 runs in the first, second and third set of simulations, respectively. We evaluated the simulated models by calculating a simple synchronization score, which quantified the ratio of the total simulation time the network spent in the expected state based on the state detection described above.



27. Figure. Parameter-dependence of the synchronization of the network model. (A) We systematically varied the parameters of the network model to explore the synchronization of the modelled pacemaker circuit with respect to the parameter space (connection rate, mean inhibitory synaptic strength, synaptic delay, mean baseline excitation level and its variance). The synchronization score quantified the proportional time the network spent in the expected network state (non-theta state during baseline excitation and theta state during increased excitation). By systematically varying mean excitation (variance fixed at 10%), connection rate and synaptic strength (synaptic delay was fixed to 7 ms), we found a discrete peak in synchronization score around 50-70 pA, largely independent of the connection rate. (B, C) Varying the connection rate and the synaptic weight indicated an inverse relationship, demonstrating that sparsely connected networks could only synchronize with stronger synapses, while densely connected networks required small inhibitory weights. (D) The model tolerated a range of synaptic delays, while very short delays did not result in stable synchrony. (E) The model was only relatively insensitive to the variance of tonic excitation strength, although high variance tended to destabilize the network. We used a moderate 10% variance in the final simulations.

Primarily, we found a discrete maximum of the model's synchronization capabilities at a mean baseline excitation of around 60 pA, which was largely independent of the connectivity rate.

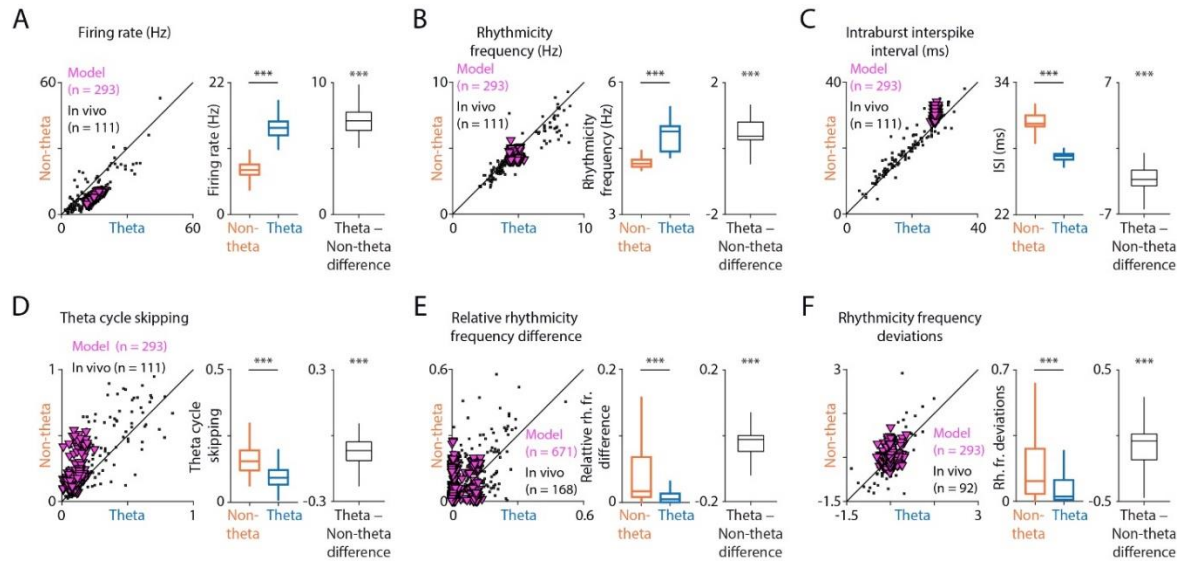
Interestingly, very strong baseline excitation could result in a mirrored activity (decreased theta synchronization upon increased excitation owing to switching to a continuously firing mode, indicated by a synchronization score <0.5), sometimes also observed in anesthetized preparations. Fixing the baseline tonic excitation at the optimum, the model network was capable of synchronizing at a range of mean synaptic strength levels and connection rates (*Figure 27C*).

Secondarily, we found an inverse relationship between the connection rate and synaptic strength, demonstrating that sparsely connected networks could only synchronize with stronger synapses, while densely connected networks required small inhibitory weights (*Figure 27C*).

Considering the most stable network behavior in terms of what is expected, parameters were fixed as follows: mean baseline excitation at 60 pA with 10% variance, connectivity rate at 60%, mean synaptic strength at 3 nS and mean synaptic delay at 7 ms. We performed a series of simulations ($n = 60$) of 60-second-long segments, with 20 seconds of baseline, followed by 20 seconds of increased excitation (with varied stimulus onset latency, see above), followed by 20 seconds of returning to baseline excitation levels to enable large scale analysis of pacemaker synchronization (*Figure 26E*, *Figure 28*). Rhythmicity indices, TBI (theta-burst interspike interval window, 20-40 ms), significant modulations, phase preference (with respect to the theoretical population output) and pacemaker synchronization were computed as described for the biological data.

10.3 Septal network model confirms Huygens-synchronization

This model allowed us to test whether a network of interconnected, minimalistic inhibitory MS units, without introducing specialized subpopulations and biased connectivity, exhibits the same frequency synchronization properties as we found in the septal network *in vivo*. To address this, we repeated the same battery of analyses on the model that we ran on the neural data (*Figure 28*). We found that model neurons increased their firing rate in theta state (*Figure 28A*), accompanied by a slight increase in rhythmicity frequency (*Figure 28B*) and a strong decrease in theta skipping (*Figure 28D*), with a consistent but relatively small change in burst properties (*Figure 28C*). When we compared pairwise differences in pacemaker frequencies, we found a significant theta-associated decrease (*Figure 28E*) accompanied by a tightening of the rhythmicity frequency distribution (*Figure 28F*), suggesting the presence of a frequency synchronization mechanism.

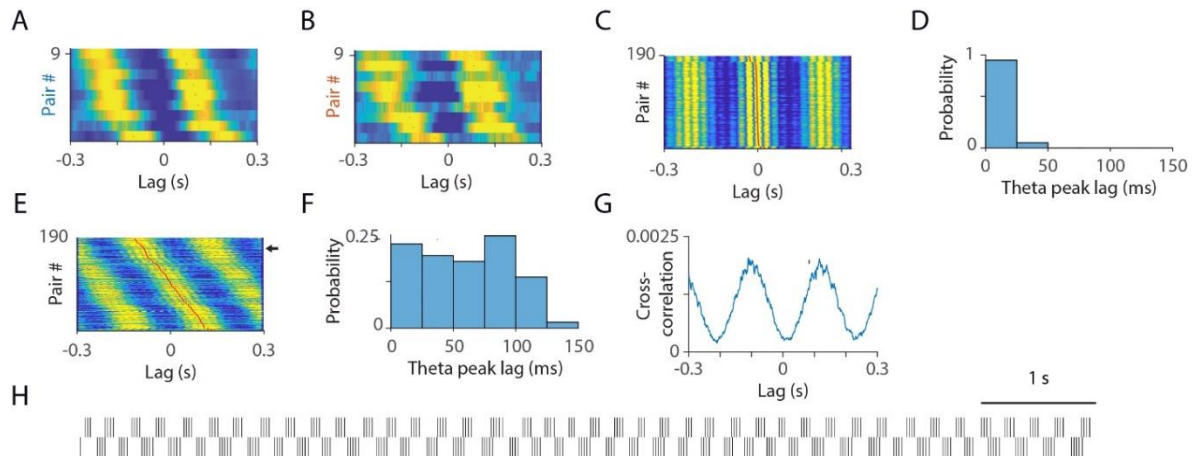


28. Figure. The pacemaker network model reproduces Huygens-synchronization properties of the MS neural circuit. Identical figure structure with Figure 25 (in vivo synchronization). (A) Firing rates of model pacemaker neurons were higher during theta oscillation than during non-theta segments. Left: real data in black (three data sets pooled), model data overlaid in magenta. Middle and right: box-whisker plot showing model statistics (***, $p < 0.001$; $p = 8.50 \times 10^{-50}$, $W = 43071$, $n = 293$, Wilcoxon signed-rank test). All box-whisker plots show median, interquartile range and non-outlier range in this figure. (B) Scatter plot of rhythmicity frequency measured by the time lag of the first autocorrelation peak in the theta band. Wilcoxon signed-rank test on model neuron data indicated higher rhythmicity frequency during theta (***, $p < 0.001$; $p = 6.35 \times 10^{-41}$, $W = 40489.5$, $n = 293$). (C) Scatter plot of average intraburst interspike intervals. Theta-associated decrease of interspike intervals in model neurons indicated a moderate elevation of intraburst frequency (***, $p < 0.001$; $p = 7.60 \times 10^{-50}$, $W = 0$, $n = 293$). (D) Scatter plot of the ratio of skipped theta cycles. Statistics indicated that model pacemaker neurons skipped more theta cycles during non-theta segments (***, $p < 0.001$; $p = 3.47 \times 10^{-45}$, $W = 1060$, $n = 293$). (E) Scatter plot of relative frequency difference of individual pacemaker neurons for simultaneously simulated pairs, normalized to the larger of the frequencies. Statistics indicated that individual model pacemakers became more similar in frequency during theta (***, $p < 0.001$; $p = 2.20 \times 10^{-30}$, $W = 51519$, $n = 671$). (F) Deviation from the simulation mean rhythmicity frequency during theta vs. non-theta segments for model pacemaker neurons. Statistics on pooled data indicated that the absolute deviation from the mean rhythmicity frequency was significantly larger during non-theta segments (***, $p < 0.001$; $p = 1.46 \times 10^{-13}$, $W = 10808$, $n = 293$).

Since a subset of putative pacemaker pairs showed stable anti-phasic firing patterns in urethane-anesthetized rats (Figure 29A-B), we tested whether the model also generated anti-phasic firing patterns. Accordingly, we tested the peak location distribution of pairwise cross-correlations between pacemaker neurons in the model, since anti-phasic firing results in the over-representation of cross-correlation peaks around half of the cycle length of theta. We ran a parameter search to detect such over-representations by defining an in-phase and an anti-phase sync score for each simulation. Crosscorrelogram peaks during the stronger tonic input period (6-15 s) were detected in the -300 to 300 ms range of lags, looking for peaks at least 166.7 ms apart (corresponding to maximal theta frequency). Crosscorrelogram 'offset' was defined as the lag corresponding to the peak that was closest to zero. Next, histograms of absolute offsets were calculated using a bin size of 25 ms (for offsets). The 'in-phase' score was defined as the value of

the first offset bin, while the ‘anti-phase’ value was defined as the fourth offset bin, corresponding to anti-phase crosscorrelation lags.

This analysis of pairwise crosscorrelograms showed that in-phase synchrony dominated in most of the parameter space (Figure 29C-D), whereas we also found examples of anti-phasic synchronization (Figure 29E-H). This suggests that anti-phasic synchronization can occur in the model, although it is not necessary for theta synchronization, in accordance with Huygens synchronization theory.



29. Figure. In-phase versus anti-phase synchronization in the rat medial septum and in the medial septal network model. (A) Pairs of putative pacemaker neurons recorded in anesthetized rats that show anti-phasic firing, based on the peak of their crosscorrelogram showing an offset above 50 ms during hippocampal theta (blue: low correlation; yellow: high correlation; each row corresponds to a pair of neurons). (B) Crosscorrelograms of the same pairs during non-theta segments. The similarity of crosscorrelograms across theta and non-theta segments indicates stable anti-phasic firing across hippocampal states. (C) Crosscorrelograms of pairs of putative pacemaker model neurons in a realization of the model that showed in-phase synchronization (blue: low correlation; yellow: high correlation; each row corresponds to a pair of model neurons). Parameters: CR, 60%; baseline excitation, 60 pA with 10% variance; synaptic delay, 7 ms; synaptic weight, 3 nS. (D) Histogram of lags corresponding to the crosscorrelogram peaks show that most crosscorrelograms peaked around zero, indicating in-phase synchrony. (E) Crosscorrelograms of pairs of putative pacemaker model neurons in a realization of the model where anti-phasic firing occurred. Parameters: CR, 20%; baseline excitation, 70 pA with 10% variance; synaptic delay, 7 ms; synaptic weight, 1 nS. (F) Histogram of lags corresponding to the crosscorrelogram peaks show an over-representation of peak lags around 100 ms, corresponding to half of the theta oscillation period time. (G) Crosscorrelogram of an example pair of putative pacemaker model neurons (E, arrow). (H) Spike raster of the example pair with stable anti-phasic spiking.

Thus, the model behaved similarly to the rodent theta-generating networks, confirming that Huygens-type frequency synchronization might be a general mechanism operating in brain networks, similar to many mechanical systems.

11 Discussion

We categorized medial septal neurons based on their rhythmic properties. This classification proved to define functional neuron classes in supra-theta oscillation generation as well. Putative pacemaker neurons showed constitutive theta rhythmic activity and synchronized their frequencies during hippocampal theta oscillations in different rodent theta model systems. This mechanism, known as Huygens synchronization, was reproduced by a network model of minimalistic theta-rhythmic inhibitory MS units, demonstrating that a homogeneous group of pacemakers can synchronize and desynchronize via inhibitory connections upon changing levels of tonic excitatory drive. Optogenetic tagging confirmed that pacemaker neurons are PV-expressing GABAergic cells, while non-PV GABAergic neurons likely do not participate in rhythm genesis. Glutamatergic septal neurons were of tonic theta ON type, which suggests that they contribute to the non-rhythmic excitatory control of the pacemaker rhythm generator network. In line with this prediction, optogenetic activation of MS glutamatergic neurons at 20 Hz induced theta oscillation in CA1.

We first performed an unbiased physiological characterization of MS units, extending previous electrophysiology studies (Apartis et al., [1998](#); Borhegyi et al., [2004](#); Duque et al., [2000](#); Ford et al., [1989](#); Hassani et al., [2009](#); A. P. Simon et al., [2006](#); Stewart & Fox, [1989](#); Varga et al., [2008](#)). Bland and colleagues characterized MS neurons as theta-on versus theta-off based on their firing rate changes, and phasic (theta-bursting) versus tonic (non-rhythmic) based on their firing patterns. Petsche et al. described A- and B-units, where B-units were phase locked to theta with a stable phase relationship (Petsche et al., [1962](#)). Many studies have since investigated B-units (Apartis et al., [1998](#); Borhegyi et al., [2004](#); Joshi et al., [2017](#); King et al., [1998](#); Stewart & Fox, [1989](#)), but A-units received less attention. Other studies indicated the presence of lower frequency rhythms, including “slow oscillations” and rhythmic activity related to breathing (Buzsaki et al., [1986](#); Tsanov, [2015](#); Tsanov et al., [2014](#); Wolansky et al., [2006](#)). In accordance, we also observed rhythmic activity in the delta frequency band, especially in urethane-anesthetized rats. Therefore, we characterized MS neurons based on their rhythmicity during hippocampal theta and non-theta episodes as non-rhythmic, delta-rhythmic or theta-rhythmic. While this resulted in nine theoretical combinations, most MS neurons belonged to a few characteristic types.

Stewart and Fox found that, after eliminating theta oscillation in the hippocampus of urethane-anesthetized rats using atropine, a subset of MS neurons remained theta rhythmic (Stewart & Fox,

[1989](#)). In another study, 15% of septal neurons were found phasic bursting even during non-theta epochs under anesthesia (Ford et al., [1989](#)). We identified putative pacemaker neurons that fired theta-rhythmic bursts regardless of whether theta oscillation was present in CA1. This group comprised 13% of MS neurons in freely moving mice; however, we found a lower percentage of rhythmic bursting neurons in anesthetized rodents, in line with some previous reports (King et al., [1998](#); Stewart & Fox, [1989](#)). The differences in percentage of pacemakers across reports may stem both from biased sampling, as the MS can be identified during recording based on the presence of theta-rhythmic activity, as well as from strictness of definitions for rhythmicity. We applied relatively conservative inclusion criteria for significant rhythmicity (*Figure 9*) to ensure data quality necessary for analyzing mechanisms of rhythmic synchronization, which may have resulted in a lower percentage of putative pacemakers in our datasets. These results also suggest that some MS neurons may be identified as putative pacemakers under awake but not in anesthetized conditions.

The expression of PV and HCN, the channel protein that underlies the H-current, has been associated with rhythmic pacemaking properties of MS GABAergic neurons (Borhegyi et al., [2004](#); Kocsis & Li, [2004](#); Varga et al., [2008](#); Xu et al., [2004](#)). However, other studies suggested that rhythmic MS glutamatergic or cholinergic neurons may act as pacemakers (Manseau et al., [2005](#); Mysin et al., [2015](#); Smythe et al., [1992](#); Ujfalussy & Kiss, [2006](#)), but see (Vandecasteele et al., [2014](#)). Here, we confirmed by optogenetic identification of multiple MS cell types that PV-expressing GABAergic neurons probably constitute most of the constitutive theta-rhythmic group. At the same time, we found that GABAergic neurons as a population contained only few theta-rhythmic neurons, suggesting that their subset that were rhythmic may have been PV expressing. We confirmed that septal pacemakers formed two groups with opposing phase preference with respect to the hippocampal theta oscillation in urethane-anesthetized rats, as reported before (Borhegyi et al., [2004](#); Joshi et al., [2017](#); Varga et al., [2008](#)).

We referred to MS neurons only showing theta-rhythmic bursting when hippocampal theta was present as follower neurons; their firing patterns tended to correspond with hippocampal network states. However, this property does not exclude them from participating in theta genesis. Indeed, these neurons tended to strongly synchronize with each other and putative pacemaker neurons both during theta and non-theta states, and optogenetic tagging experiments revealed an enrichment of both putative pacemaker and follower neurons in the PV+ GABAergic group (*Figure*

24I), suggesting that this functional distinction based on rhythmicity may occur within the anatomically defined PV-expressing group.

In the seventeenth century, Christiaan Huygens observed that two pendulum clocks, coupled through a house beam, tended to synchronize over time, which he referred to as “sympathy of two clocks” (Huygens, 1673; Oliveira & Melo, 2015; Ramirez et al., 2016; Willms et al., 2017). Such synchronization of coupled oscillators, where individual oscillators become closer to each other in their frequency and period time, has been found in many dynamical systems (Equihua & Ramirez, 2018; Ramirez et al., 2016). We identified this mechanism among MS pacemaker neurons, suggesting that a Huygens synchronization mechanism underlies the generation of a strong theta rhythmic output transmitted to the hippocampus. The two dominant oscillatory behaviors that emerge in coupled oscillators during Huygens synchronization are in-phase and anti-phase synchronization (Korteweg, 1906; Ramirez et al., 2014), and either one can sufficiently underlie frequency synchronization (Czolczynski et al., 2011; Ramirez et al., 2014, 2016). This may, at least in part, explain the observation of anti-phase firing in the MS of urethane-anesthetized rats. Experiments and modeling studies also observed less common modes of Huygens synchronization, including partial synchronization, when oscillators synchronize with a phase difference of less than 180 degrees; “quenching”, when the two oscillators suppress each other; “beating death”, in which one oscillator is suppressed but remains oscillatory owing to the influence of the other; and amplitude modulation, a consequence of mutual influence (Ramirez et al., 2014). It will be exciting to study whether and how the broad theory behind Huygens synchronization, often investigating limit behavior of complex non-linear ordinary differential equation systems, can be applied to neural circuits. For instance, “modulating” behavior can theoretically be related to forms of cross-frequency coupling (Buzsáki & Wang, 2012; Lisman & Jensen, 2013), whereas quenching and beating death can be viewed as synchronization failures, which may be relevant to oscillopathies, e.g. gamma oscillation failures in patients with schizophrenia (Hunt et al., 2017)(See chapter *“Oscillopathies: a rationale behind this study”*). Theoretical studies may explain how and why the output oscillation period may differ from the eigenperiods of the coupled individual oscillators (Dilão, 2009; Ramirez et al., 2016), also observed in the context of neuronal oscillations, possibly serving as a basis for phase precession (Geisler et al., 2007; O’Keefe & Recce, 1993; Zutshi et al., 2018).

Previous models of the septal pacemaker network either explored GABAergic (Denham & Borisyuk, [2000](#); Ujfalussy & Kiss, [2006](#); X.-J. Wang, [2002](#)) or glutamatergic (Ujfalussy & Kiss, [2006](#)) pacing mechanisms. These previous works already contained indirect reference to potential Huygens synchronization mechanisms. For instance, Wang suggested that desynchronized septal pacemaker units may oscillate at different frequencies (see Figure 4 in (X.-J. Wang, [2002](#))). Additionally, Ujfalussy et al. wrote that “blocking the GABAergic synapses in our ping-pong model causes desynchronization of these neurons but the cells remain theta periodic.” However, Huygens synchronization has neither been experimentally tested nor directly modelled, and previous models mostly focused on exploring the ways different oscillator networks may interplay, such as two GABAergic MS groups with opposing firing phase (Ujfalussy & Kiss, [2006](#)), MS and CA1 GABAergic groups (Denham & Borisyuk, [2000](#); X.-J. Wang, [2002](#); Zou et al., [2011](#)) or MS GABAergic and glutamatergic neurons (Mysin et al., [2015](#)). Thus, in previous ping pong models, the synchronization mechanism required the presence of at least two dedicated inhibitory groups, with biased, non-random connectivity between the groups. In contrast, we found that even a minimalistic, homogeneous network of MS GABAergic pacemakers was sufficient to generate coherent theta-rhythmic output upon increased tonic excitation. While desynchronization of the MS network was rarely addressed in previous theoretical work, we also found that our MS model network showed rapid spontaneous desynchronization when tonic excitation was decreasing. This MS model network could recapitulate multiple features of the in vivo synchronization process, including Huygens synchronization, increased firing rate, faster rhythmic firing, decreased theta skipping and increase in intra-burst firing frequency.

We found a substantial increase in the firing rates in MS pacemaker neurons upon theta onset. This finding is in line with previous studies suggesting that an increased tonic excitatory drive can switch the MS network into theta state (Korvasová et al., [2021](#); Lu et al., [2011](#); Müller & Remy, [2018](#); Oddie et al., [1996](#); Ujfalussy & Kiss, [2006](#)). Multiple cell types and pathways were proposed to contribute to this excitatory drive, including MS cholinergic, glutamatergic, and ascending brainstem inputs (Hajszan et al., [2004](#); Leranth & Frotscher, [1989](#); Müller & Remy, [2018](#); Oddie & Bland, [1998](#); Zaborszky et al., [2012](#)). We found that MS glutamatergic neurons strongly and non-rhythmically increased their firing rates at the onset of CA1 theta, suggesting they may be the dominant relay that conveys changing levels of tonic excitation to the MS pacemaker network, in agreement with anatomical findings showing that local excitatory neurons provide the majority of excitatory inputs to MS GABAergic neurons (Hajszan et al., [2004](#)).

In line with this, the optogenetic activation of MS glutamatergic neurons induced theta oscillation in the CA1. Importantly, we evoked theta rhythm by using a stimulation frequency of 20 Hz well above the theta range, demonstrating that VGLUT2-expressing MS neurons are capable of theta induction not only when stimulated at theta-range frequencies (Robinson et al., [2016](#)). These results are also consistent with the growing body of evidence showing that these neurons are involved in conveying locomotion-related activation to other cell types of the MS and beyond (Fuhrmann et al., [2015a](#); Justus et al., [2017](#); Korvasová et al., [2021](#); Oddie et al., [1996](#); Teitelbaum et al., [1975](#)).

Previous studies demonstrated theta-skipping behavior of rhythmic neurons both in the entorhinal cortex (EC) (Brandon et al., [2013](#); Jeffery et al., [1995](#)) and in the MS (K. Kay et al., [2020](#); King et al., [1998](#); Varga et al., [2008](#)). Theta skipping was characterized by rhythmic activity with one-half the frequency of ongoing hippocampal theta, by neurons firing rhythmically in every second theta cycle. It has been demonstrated that MS input was necessary for theta-skipping behavior in the EC in rats (Brandon et al., [2013](#)), and that theta-skipping behavior in the EC may rely on inhibitory rebound mechanisms, potentially crucial to the formation of characteristic grid cell firing fields (Hasselmo, [2014](#)). We confirmed the presence of theta-skipping neurons in the MS of urethane-anesthetized rats. While some of these neurons fired regularly in every second cycle, other neurons showed a less regular pattern, occasionally skipping more than one cycle. Interestingly, we found very few theta-skipping neurons in anesthetized and freely moving mice. Therefore, theta-skipping in the MS may not be necessary for grid pattern formation in mice.

We found a group of tonically active neurons both in rats and mice, which may be cholinergic, since (i) their firing patterns resemble cholinergic neurons in previous publications (Brazhnik & Fox, [1997](#); Mamad et al., [2015](#); Tsanov, [2015](#)), (ii) my colleagues identified cholinergic neurons with similar rhythmic and synchronization properties from other basal forebrain structures (Laszlovszky et al., [2020](#)), and (iii) rhythmic basal forebrain cholinergic neurons were not phase locked to hippocampal theta in a former study (M. G. Lee et al., [2005](#)), as we also found for the tonically active group. Theta-rhythmic cholinergic neurons may be more linked with a neocortical theta oscillation that can be recorded from the posterior cingulate cortex (Destrade & Ott, [1982](#); M. G. Lee et al., [2005](#)), and my colleagues have also reported behavior-specific synchronization of nucleus basalis cholinergic neurons with theta-band activity in the auditory cortex (Laszlovszky et al., [2020](#)). This would confirm that the role of MS cholinergic neurons in hippocampal theta generation is mostly

indirect through GABAergic neurons, controlling theta amplitude but not participating in rhythmic theta pacing (Dannenberg et al., [2015](#); M. G. Lee et al., [1994](#); Yang et al., [2014](#), [2017](#)). We expect that it will be one of the most exciting future directions to better understand how multiple theta rhythms interact dynamically in the brain, including synchronization with active sensing processes (Moore et al., [2013](#); Ranade et al., [2013](#); Semba & Komisaruk, [1984](#)), entraining local pacemaker groups (Manseau et al., [2008](#)) and interacting with cellular resonance properties (Zemankovics et al., [2010](#)).

Limitations of the study

Although we demonstrated that a homogeneous group of MS inhibitory neurons may be capable of pacing hippocampal theta, this does not rule out the possibility of other contributing neuronal populations including the hippocampo-septal feedback projection (Katona et al., [2017](#); Manseau et al., [2008](#); Toth et al., [1993](#); X.-J. Wang, [2002](#)) and subcortical areas such as the supramammillary nucleus (Farrell et al., [2021](#); Pan & McNaughton, [2002](#); R. P. Vertes & Kocsis, [1997](#)) and the nucleus incertus (S. Ma et al., [2009](#); Martínez-Bellver et al., [2015](#); Szőnyi et al., [2019](#)). Nevertheless, recent studies demonstrated that intraseptal connections are necessary for CA1 theta oscillations to emerge (Korvasová et al., [2021](#)), and that the nucleus incertus may not provide but rather receive theta-rhythmic signals from the MS (Trenk et al., [2022](#)).

An alternative mechanism to frequency synchronization is phase synchronization without concurrent change in rhythmicity frequency, defined generally as changes in the phase relationship of coupled oscillators (M. Rosenblum et al., [2001](#); M. G. Rosenblum et al., [1996](#)). Such mechanisms are known to operate between synchronizing brain regions and are thought to underlie changes in the efficacy of information transfer (Fell & Axmacher, [2011](#)). As a special case of phase synchronization, a decrease in phase difference between individual pacemaker units may lead to a larger amplitude rhythmic output. In contrast, we demonstrated a convergence of rhythmicity frequencies during synchronization. Although this change in frequencies can be accompanied by a change in relative firing phases, it is hard to interpret whether this is a necessary consequence of the frequency synchronization, or a parallel, separate phase synchronization process also takes place (M. G. Rosenblum et al., [1996](#)).

We found a strong consistency of rhythmic MS cell types and synchronization mechanisms across urethane-anesthetized rats, urethane-anesthetized mice and freely moving mice, while we did not obtain data from freely moving rats. This argues for common mechanisms of septo-hippocampal

theta-rhythmic synchronization. However, we also noted some differences. Part of them may stem from known distinctions of urethane- and atropine-sensitive theta oscillations (Kramis et al., [1975](#); S. Li et al., [2007](#)), with different underlying mechanisms (Losonczy et al., [2010](#); Mikulovic et al., [2018](#); Nicola & Clopath, [2019](#); Winterer et al., [2019](#)). Anesthetized rats showed strong hippocampal rhythmicity in the delta band during non-theta episodes, mostly absent in mice. In accordance, we found delta-rhythmic and theta-skipping MS neurons in rats but very few in mice. Tonically active neurons showed a theta-associated firing rate decrease in rats but increase in mice. While we speculated that this group might be cholinergic, the lack of optogenetic identification of cholinergic MS neurons is another limitation of this study.

In the optogenetic mouse experiments I identified PV+ putative pacemaker neurons and glutamatergic theta ON cells. However, other rhythmicity groups were not observed in sufficient numbers for detailed analysis. These included the “follower” (0 PV+, 2 glutamatergic and 1 GABAergic), “theta-follower” (3 PV+, 1 glutamatergic and 1 GABAergic) and “theta skipping” (0 PV+, 2 glutamatergic and 1 GABAergic) groups (see *Figure 24*). Therefore, a detailed description of these groups is lacking.

The cell and network model presented here incorporates several simplifications. It does not account for the effects of acetylcholine levels or the modulation of arousal levels, and it omits anatomically and biophysically relevant details. Consequently, it is not suitable for modelling variable membrane channel composition, spatially and temporally separated computations (e.g. in the hippocampus), travelling waves, dendritic action potentials and their specific effects. Furthermore, the model lacks dedicated neuronal populations or connectivity structure, does not include hippocampal-septal feedback (e.g. phase adjustment and frequency correction) and relies only on tonic -presumably glutamatergic- excitation as input, without any additional modulation. Nevertheless, the significance of this model lies in demonstrating that even a minimal network can generate theta oscillation through frequency synchronization.

Marder and colleagues observed that often the rhythmic firing activities are controlled and not the exact underlying ion channel constellations, leading to unexpected variability in channel abundance with stable oscillatory parameters (L. M. Alonso & Marder, [2019](#)). It is possible that, similar to this principle, the theta-rhythmic activity of the septo-hippocampal system is evolutionarily conserved, with a larger variance in the exact implementation (Payne et al., [2021](#)). Further experiments and modeling will help gauge the significance of this variability.

12 Conclusions and Outlook

In this dissertation, I investigated the network mechanisms underlying hippocampal theta oscillations, which are strongly associated with episodic learning and memory. By combining simultaneous recordings from the medial septum and hippocampus in both anesthetized and awake rodents with optogenetic identification and computational modeling, I showed that septal pacemaker neurons synchronize their individual rhythmic firing frequencies. This mechanism is analogous to the synchronization of weakly coupled oscillators, as originally described by Christiaan Huygens.

I further showed that these pacemaker neurons correspond predominantly to parvalbumin-expressing GABAergic cells, while glutamatergic septal neurons provide a tonic excitatory drive that is sufficient to induce theta oscillations. Consistent with these findings, a minimal network model revealed that modulation of tonic excitation can control transitions between theta and non-theta states via frequency synchronization of inhibitory pacemakers.

In addition, I identified distinct rhythmicity-based functional groups of medial septal neurons whose coupling to hippocampal activity depends on network state. Within these groups, supra-theta coupling emerged in a subset of neurons. This suggests a state-dependent organization of septal contributions to frequency-specific coordination within the classical theta band and beyond.

12.1 Future perspectives

One of the most intriguing open questions concerns the composition of rhythmicity groups: are we dealing with genetically distinct cell types, cells with different network connectivity, or state-dependent group transitions between groups?

For example, examination of the computer model revealed that, in certain cases, cells exhibiting follower-like behavior emerged, even though all elements of the network originated from the same pacemaker cell model. It is therefore plausible that the 'follower' property is also a function of a cell's embeddedness within the network, which may depend on either connectivity or state.

To investigate state dependence, chronic rodent experiments would be necessary: a series of recordings spanning sleep and wakefulness (active and inactive), and preferably including a final urethane anesthesia condition, would enable tracking of rhythmicity group stability across different

experimental states. However, it should be noted that, even with multi-channel recording, it is unlikely that all rhythmicity groups can be captured at a single recording depth.

From this perspective, the most valuable data would likely come from optotagging experiments. Recordings in rats are more likely to capture the full range of rhythmicity, including delta rhythmic activity. Additionally, identifying cholinergic cells would be particularly important.

Following the increase in recorded cell counts, analysis of firing metrics and waveforms of the identified rhythmic and optogenetically defined groups could provide further insight. Identification of hippocampal state-dependent groupings within the septal rhythmic populations based on alternative parameters would obviate the need for concurrent hippocampal LFP recordings. Establishing such a database would not only simplify the process and solve the problem of sometimes noisy hippocampal signals, but would also be advantageous due to the reduced invasiveness and lower disruption to the neural network.

However, as some firing metrics are state-dependent, it would be difficult to control for variability between experiments, for example that arising from different levels of anesthesia. If only septal recording were available, without knowledge of the dominant hippocampal activity and relative proportions of theta and non-theta (e.g. whether theta was successfully evoked by tail pinch), then one could only rely on the average septal population activity. In other words, a general classification scheme could not be proposed; instead, it would need to be derived separately for each recording or experimental session, which would in turn require a large number of simultaneously recorded cells.

In contrast, waveform-based clustering is less state-dependent. Furthermore, the existence of such clustering patterns may reflect differences in intrinsic properties, such as ion channel composition.

An exciting future research direction is the patch-seq approach, which combines electrophysiology, morphology and transcriptomics, although at present it is only limitedly applicable to large scale recordings.

My research does not include inhibition-controlled experiments. Optogenetic inhibition can significantly reduce hippocampal theta activity, making it less suitable for observing finer-scale, Huygens-type synchronization phenomena. It may therefore be preferable to use specific excitatory stimuli to demonstrate stronger causal relationships. For instance, in my co-authored paper, we describe 'whole-cell patch clamp' and acute optogenetic experiments conducted on awake mice

(Király et al., [2023](#)). These experiments demonstrate that hippocampal PV cells consistently respond to theta-modulated stimulation in the 22–80 Hz range. Future experiments of this type could provide more direct evidence for the mechanism described here.

An interesting direction for future research is the clarification of the role of glutamatergic cells in theta generation. For instance, it would be valuable to investigate whether theta oscillations generated by stimulation of septal glutamatergic cells differ in frequency, amplitude, or spatial characteristics from spontaneously occurring theta, or from theta evoked by nociceptive stimulation.

I have presented a minimal network model capable of generating theta waves through a frequency synchronization mechanism, consistent with in vivo findings. However, the biological system is likely to be considerably more complex, and specific aspects will therefore require more detailed modeling of the underlying phenomena. Future modelling directions could be the investigation of tSCs (theta spectral components), the incorporation of follower and theta-follower cell types, the inclusion of septal non-rhythmic but hippocampal theta phase linked cells as inputs. Further extensions could also examine the effects of hippocampal feedback and hippocampal phase precession.

Hippocampal theta activity is closely linked to certain behaviors, such as exploration and memory encoding. Although I analyzed sleep and wakefulness recordings, I did not have data derived from specific behavioral tasks. While such experiments could provide valuable insights, they are technically challenging and time-consuming to conduct. From a methodological perspective, two-electrode recordings, potentially combined with optogenetics, are difficult to implement reliably, even when the target areas are successfully accessed. Moreover, variability introduced by behavioral factors can further complicate the interpretation of data. It is also worth noting that, during behavior, analysis would primarily capture urethane-sensitive type 1 theta, which is associated with higher-frequency components. Nevertheless, conducting a medial septum-dependent working memory study would be highly valuable, ideally one that is dissociated from the navigational component (e.g. an adaptive associative learning paradigm).

I propose that the findings presented in this dissertation are at least indirectly relevant to the human context. Pathological animal models could be employed to investigate alterations in the composition, frequency and synchronization mechanisms of the cell groups identified here, both in chronic conditions and in relation to abnormal activity (e.g. seizures). Subsequently, human

electrophysiological data could be analyzed, either from tissue sections (in vitro) or from recordings obtained during surgery (in vivo). Data from both healthy and pathological tissue may be informative. Non-invasive human recordings may also be of interest; however, their spatial resolution is considerably lower than that of invasive methods. If certain lesion patterns could be identified, they might contribute to the currently limited toolkit available for the early diagnosis of conditions such as Alzheimer's disease.

Even more compelling results have emerged from mouse studies in recent years, as discussed in the "Oscillopathies" chapter of the dissertation. For instance, Etter et al. showed how, in a J20-APP AD model, supra-theta stimulation of PV+ cells in the medial septum can restore slow gamma amplitude and theta phase coupling in the hippocampus (Etter et al., [2019](#)). Notably, this intervention also rescued impaired memory traces despite substantial amyloid plaque accumulation.

The medial septum also appears to be a promising target for antiepileptic (Takeuchi et al., [2021](#)). There is evidence that certain epileptic seizures are preceded by alterations in hippocampal theta activity, and that induction of theta can exert antiepileptic effects. In optogenetic animal models of pathology, the effects of glutamatergic stimulation could be investigated in relation to seizure prevention, attenuation and postictal consequences such as behavioral hyperactivity. It is important to note, however, that such deep brain regions are difficult to access in humans, and that optogenetic techniques are currently limited to animal models. Nevertheless, sonogenetics may offer considerable therapeutic potential for neurodegenerative disorders (Fan et al., [2021](#)).

Furthermore, another intriguing idea is the interpretation of seizure-related synchronization mechanisms in the context of Huygens synchronization. For instance, the cessation of septo-hippocampal theta generation around seizures could be analogous to the 'quenching' ('amplitude death') phenomenon observed in physical systems, where the interaction of oscillators causes oscillations to cease. At the same time, the dynamics of intermittent ('modulatory') and partial synchronizations can provide a framework for describing state-dependent and unstable dynamics. Within this framework, parameters such as coupling strength, damping factor and cross-sectional parameters of the suspensions mentioned in the "The Sympathy of Clocks" section may be mapped onto biological features, including connection strength, excitatory/inhibitory balance, and the level of tonic input strength.

12.2 Thesis points

This dissertation rests on two pillars. In the article by Kocsis et al. we defined septal rhythmicity groups and investigated their synchronization mechanisms and their role in the generation of hippocampal theta frequency oscillations (Kocsis et al., [2022](#)). The research and results presented here are largely related to this first author article.

The second pillar is my co-authored paper with Kiraly et al. (Király et al., [2023](#)). This work studied the behavior of septal cells in relation to hippocampal theta spectral components (tSCs). The preprocessed data and classifier codes were partly derived from the first project. In Király et al. we reported the tSC-dependent behavior of septal rhythmicity groups (Kocsis et al., [2022](#)). The other results of this paper are not addressed in this dissertation.

The two papers are connected by the finding that the rhythmicity groups defined in the first paper were also distinct functional groups in the second paper. Therefore, the firing patterns of septal cells suggest that they play an active role in generating not only hippocampal theta but also gamma frequency oscillations.

12.2.1 Thesis group I.

Related to the hippocampal-state-dependent classification of medial septal rhythmic neurons and the exploration of their synchronization.

Thesis Ia. My semi-automatic method identifies functional neuron classes based on rhythmic firing properties.

Corresponding publications: Kocsis et al., [2022](#), Király et al., [2023](#).

I have developed a Matlab code package for the rhythmicity-based classification of neurons. Following some preprocessing steps and manual specification of the global variables corresponding to the examined rodent model, the software autonomously classifies cells and calculates group means, as well as intra- and intergroup synchronization measures.

First, hippocampal recordings are segmented into dominant theta and non-theta sections based on the amplitude ratio of theta to slower frequency bands. Next, the firing patterns of medial septal neurons are analyzed for theta-rhythmic, delta-rhythmic (or non-rhythmic) modulation in both

hippocampal states. Significant modulation is determined by a bootstrap permutation test to ensure unbiased classification.

I have observed four main categories of rhythmic behaviors in our experiments: pacemaker, theta follower/ follower, theta-skipping and tonically active neurons. I have characterized firing properties and phasic relations of these classes across all three datasets.

When septal rhythmic cells were examined in relation to hippocampal tSCs, significant firing modulation was observed. Putative pacemaker and theta-follower neurons exhibited increased firing rate and theta phase coupling in cycles with gamma-band tSCs, whereas tonically active cells also increased their firing rate. The majority of these neurons were coupled to specific tSC phases. Additionally, tSC-coupled putative pacemakers not only preceded all types of tSCs, but also emerged as the earliest forecasters among all tSC-coupled cells. Thus, my semi-automatic method identified functional neuron classes involved in rhythm genesis beyond theta frequency as well.

Thesis Ib. Pacemakers synchronize their burst frequencies.

Corresponding publication: Kocsis et al., [2022](#).

Crosscorrelation analysis of rhythmicity groups indicated the central role of putative pacemaker neurons in theta synchronization. Putative pacemakers fired theta rhythmic bursts of action potentials, irrespective of the hippocampal state, and exhibited hippocampal theta phase coupling.

To decipher the mechanisms of medial septal pacemaker synchronization I examined four alternatives, not excluding each other: tonic drive change, burst properties change, theta skipping and frequency synchronization. Applied metrics for these mechanisms revealed increased tonic drive, reduced cycle skipping and relatively stable burst properties during theta. Additionally, pacemakers synchronized their bursts frequencies in a manner similar to coupled pendulum clocks, a phenomenon known as Huygens synchronization.

12.2.2 Thesis group II.

Related to the optogenetic tagging of pharmacological neuron types in the medial septum.

To investigate the genetic and neurotransmitter identity of medial septal neurons, optogenetic tagging was performed in urethane-anesthetized mice. Following the successful tagging of PV+, GABAergic and glutamatergic neurons, I performed the same battery of the previously described

rhythmicity analyses on these recordings. Finally, I evaluated the proportions of rhythmicity classes in each tagged group.

Thesis IIa. PV expression marks the theta-generating septal population.

Corresponding publication: Kocsis et al., [2022](#).

I found the highest proportion of putative pacemaker cells in the PV-expressing group (n = 9/18 neurons), suggesting that PV expression marks the theta-generating population.

When I calculated the theta-associated change in relative frequency differences between pairs of putative pacemakers where at least one of the cells was tagged as PV+, I observed similar frequency synchronization ('Huygens synchronization') as shown for unlabeled pairs of putative pacemakers.

Thesis IIb. Stimulation of glutamatergic cells evokes theta in the hippocampus.

Corresponding publication: Kocsis et al., [2022](#).

The majority of glutamatergic neurons showed a strong increase in the firing rate -without any theta rhythmicity- during hippocampal theta state, suggesting their contribution to the increased tonic excitatory drive on pacemakers during theta synchronization. Indeed, I observed a significant increase in theta-band activity in the hippocampal frequency power distributions after the tagging protocol. Thus, photostimulation of glutamatergic cells induced hippocampal theta oscillations.

12.2.3 Thesis group III.

Related to the modeling of the medial septal theta generation.

The analysis of electrophysiological recordings suggested that increased tonic excitation induces frequency synchronization of septal pacemakers, leading to the generation of hippocampal theta oscillations. To deepen our understanding of theta synchronization, I have developed a minimalistic network model, allowing direct testing of in vivo findings.

Thesis III. My homogeneous tonically driven network model is sufficient for theta generation.

Corresponding publication: Kocsis et al., [2022](#).

I constructed a network model of pacemaker cells based on a single compartment, rhythmically bursting model neuron (Golomb et al., [2007](#)). I connected the members of this population randomly with inhibitory synapses without introducing network-level biases. All neurons received

controllable tonic excitation as the only input, allowing direct intervention to the network dynamics during simulation.

After optimizing static parameters for theta generation, I performed the same set of analyses for pacemaker synchronization as I did for the electrophysiological and optotagging data. I observed similar synchronization metrics, including frequency synchronization mechanism ('Huygens synchronization') of pacemaker cells. Thus, the model successfully reproduced several aspects of in vivo synchronization.

13 My contributions

I will now describe my contributions to the pillars of this dissertation (Király et al., [2023](#); Kocsis et al., [2022](#)). In addition to the following, I will indicate the contributions of other researchers along with their affiliations at the end of each relevant chapter.

Animal surgeries, electrophysiological **recordings** and **histological verifications** of the recording locations were performed by my colleagues Balazs Hangya, Richárd Fiáth, Andor Domonkos and Sergio Martínez-Bellver. **Immunostaining** for the verification of the specificity in optotagging experiments was conducted by Dániel Schlingloff. Detailed descriptions of these methods are included in this report for technical completeness.

Preprocessing of the recorded data entailed the selection of hippocampal channel with highest amplitude and spike sorting of septal neurons. These tasks were carried out by me, except for the acute rat dataset, spike sorted by Péter Barthó.

The identification of state dependent **rhythmicity classes** in the MS and **analysis** of their **synchronization** were entirely performed by me under the guidance of Balázs Hangya.

The septal rhythmic **cell model** was developed using an existing model (Golomb et al., [2007](#)) and was extended with the H current using an existing generic HCN model (Káli & Zemankovics, [2012](#)). For the sake of completeness, I will share the differential equations of the activation and inactivation gates that control transmembrane currents.

The construction of the **network** and the study of model synchronization were conducted entirely by me. The fine tuning of the Golomb model parameters and the network modelling were performed under the guidance of Szabolcs Káli and Balázs Hangya.

I declare that the analysis of the relationship between **tSCs** and MS spiking patterns was carried out mostly by Bálint Király. His tSC detection algorithm was adapted from (Lopes-dos-Santos et al., [2018](#)). The findings presented in (Király et al., [2023](#)) were incorporated into his dissertation submitted for PhD degree. My contributions to this co-authored publication were as follows: i) preprocessing of the datasets from freely moving mice, anesthetized mice, and anesthetized rats, ii) rhythmic labeling of MS neurons, iii) preparation of one of the figures included in the publication.

I did not participate in the experiments, nor did I contribute to the results related to the current source density profiling of tSC waves or anatomical observations on tSC-coupled MS neurons.

Data processing and the result analysis were carried out using self-developed Matlab codes (MATLAB 2016a and 2020a (Mathworks, Natick, US)). Model simulations were executed using NEURON software. Both the Matlab and NEURON software code have been deposited at Zenodo and is publicly available at <https://doi.org/10.5281/zenodo.6798310>. The GitHub repository of the code is available at https://github.com/hangyabalazs/ms_sync_analysis.

Declaration of LLM use

In some cases it is still not precisely defined where the borders of legal AI use are. Nevertheless, I hereby explicitly state that I used LLMs (Large Language Model) exclusively for purposes related to literature review and for improving academic style in the introductory chapters: *“Overview of the hippocampal theta oscillation”, “Role of theta oscillation”, “Oscillopathies: a rationale behind this study”*. In this context, I believe the primary concern may relate to unintentional plagiarism.

Since I could not identify any dedicated guidelines of the university to regulate the use of LLM, I adapted the prevailing consensus within the life sciences community, as reflected by the Nature standards published in November, 2024 (Porsdam Mann et al., [2024](#)).

In accordance with this consensus I disclose the specific purposes for which I used LLMs during the preparation of the manuscript (*Criterion 3: Acknowledgement and transparency*). LLM tools used include: Perplexity AI (Pro) (Perplexity, www.perplexity.ai, 2025), ChatGPT (OpenAI, www.chatgpt.com, 2025), Consensus (San Francisco, Consensus NLP 2025, www.consensus.app), DeepL (Cologne, Dr. Jaroslaw Kutylowski, www.deepl.com, 2026).

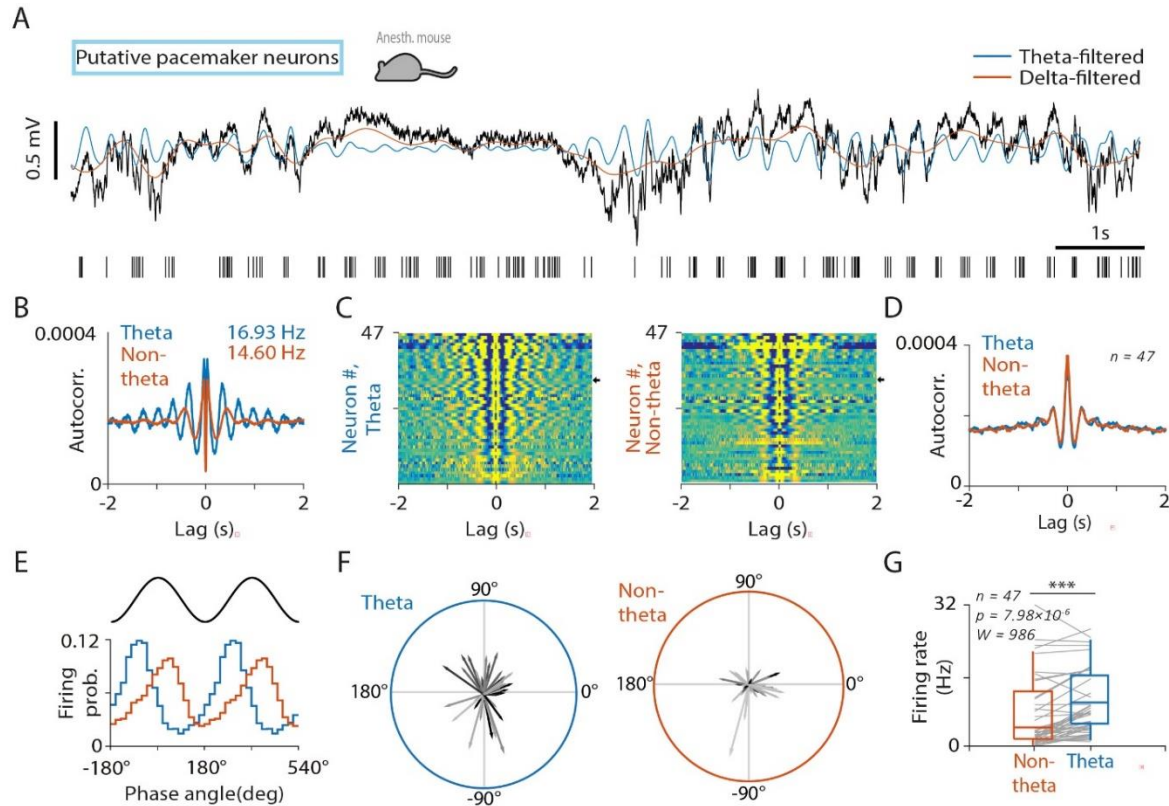
- Sentence synthesis from 13 articles in chapter *“Oscillopathies: a rationale behind this study”*: I used LLMs to paraphrase my notes, extracted mainly from 14 peer-reviewed articles (Broncel et al., [2018](#); Carrion et al., [2018](#); Chen et al., [2017](#); Dickerson et al., [2010](#); R. S. Fisher, [2015](#); H.-J. Freund et al., [2009](#); Hunt et al., [2017](#); H. Lee et al., [2012](#); Leung & Ma, [2022](#); Lv et al., [2018](#); Takeuchi et al., [2021](#); Tsanov, [2022](#); Uhlhaas & Singer, [2006](#); Vargas-Caballero et al., [2022](#)). General descriptions of the disorders were based on Takeuchi et al. (Takeuchi & Berényi, [2020](#)). Additional information (including other subchapters) was gathered from APA, NIMH, Wikipedia. This general information was

pooled and supervised, and was treated as common knowledge and therefore not cited individually. I emphasize that results and ideas of this chapter are not my own, but are included to provide the context of my research topic. Some citations are coming from the selected 14 articles, but their content were verified. Additionally, I enriched this chapter with more recent references to ensure academic quality, adhering to *“Criterion 1: about Human vetting and guaranteeing”*.

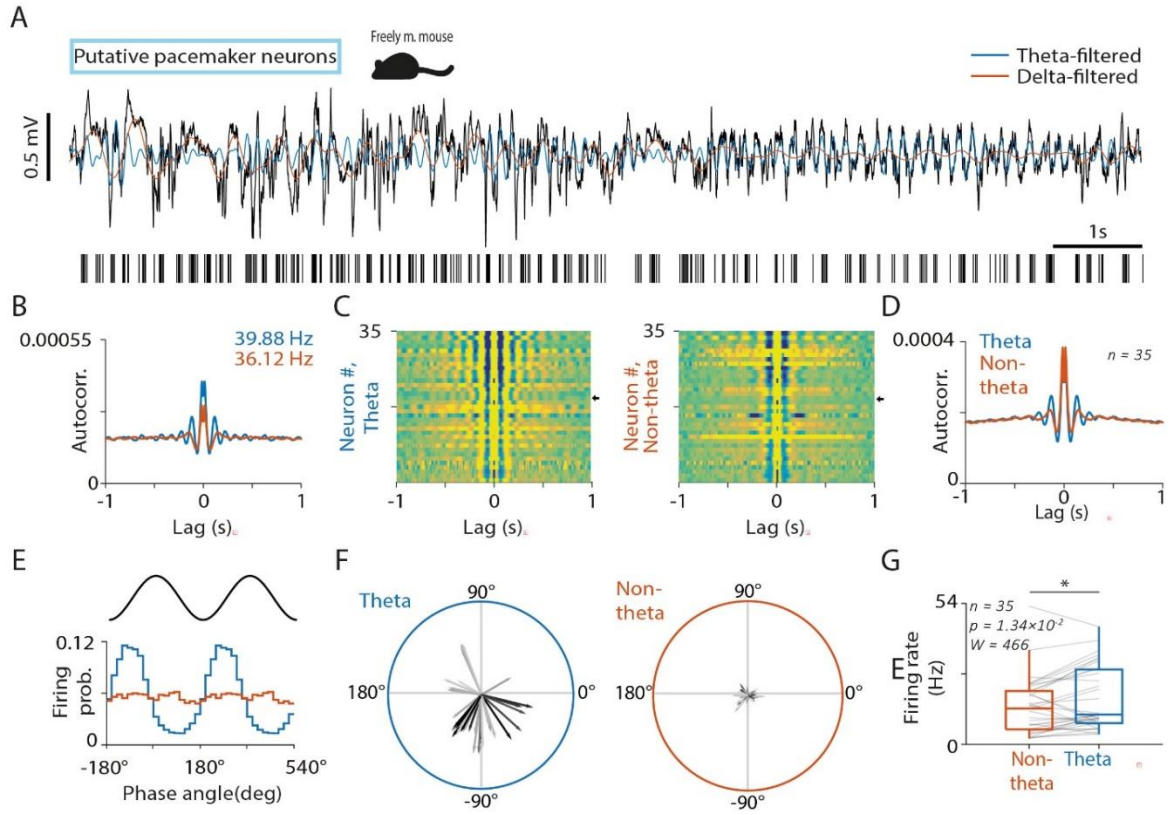
- Flag scientifically inappropriate claims: I used LLMs to identify possibly inaccurate statements. Contradictions and inaccuracies were inspected and reviewed carefully through human judgement, improving the overall quality of the processed manuscript.
- Paraphrasing and translation: In the introductory chapters (listed above) I used LLMs to paraphrase parts of my written manuscript to academic style. In the “Thesis outline” and “Conclusions and Outlook” sections I used LLMs to translate my notes.
- I employed LLMs to review grammar, spelling, punctuation, coherence and academic style.

I again emphasize that no LLM was used in the design of the research, data acquisition, analysis-interpretation and writing of the *“Discussion”* section (*“Criterion 2: Substantial human contribution”*). However, beyond these Methods, Result and Discussion chapters, I take full responsibility for the content of the Introductory chapters, in terms of tracking and tracing scientific content.

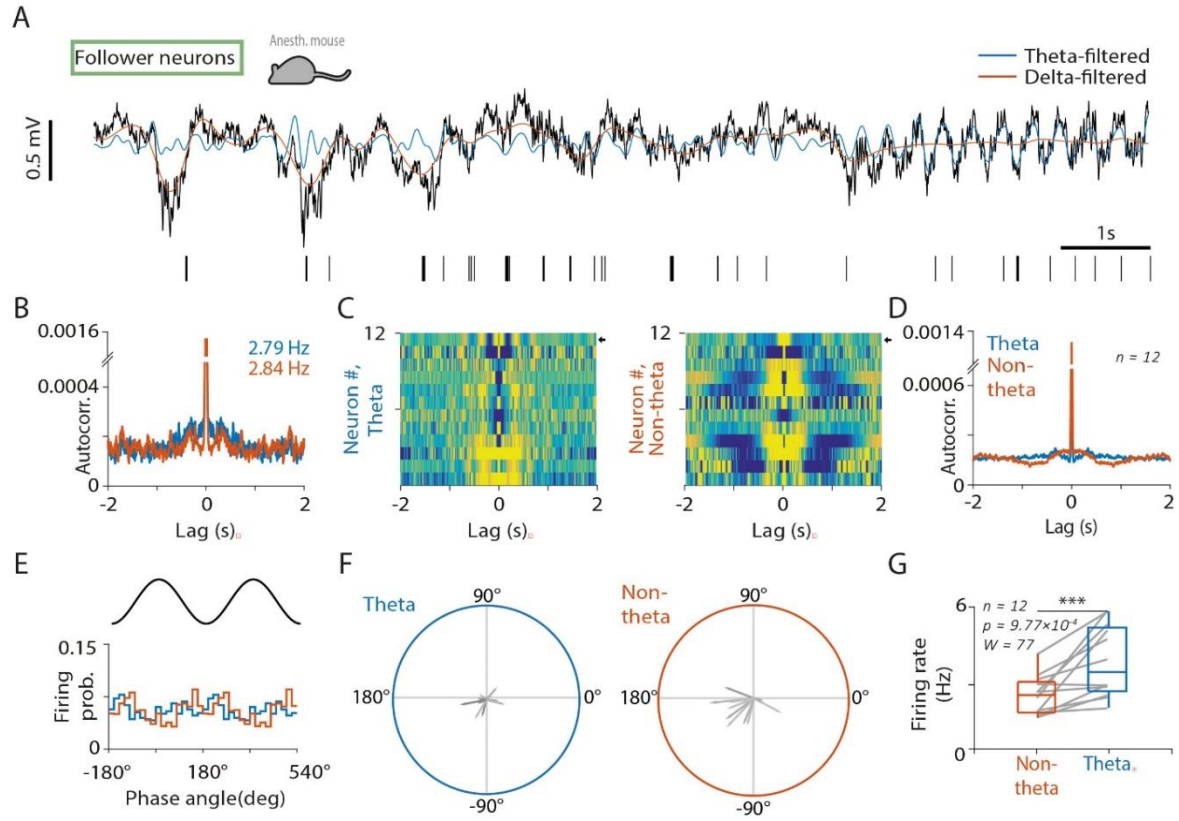
Supplementary Figures and Tables



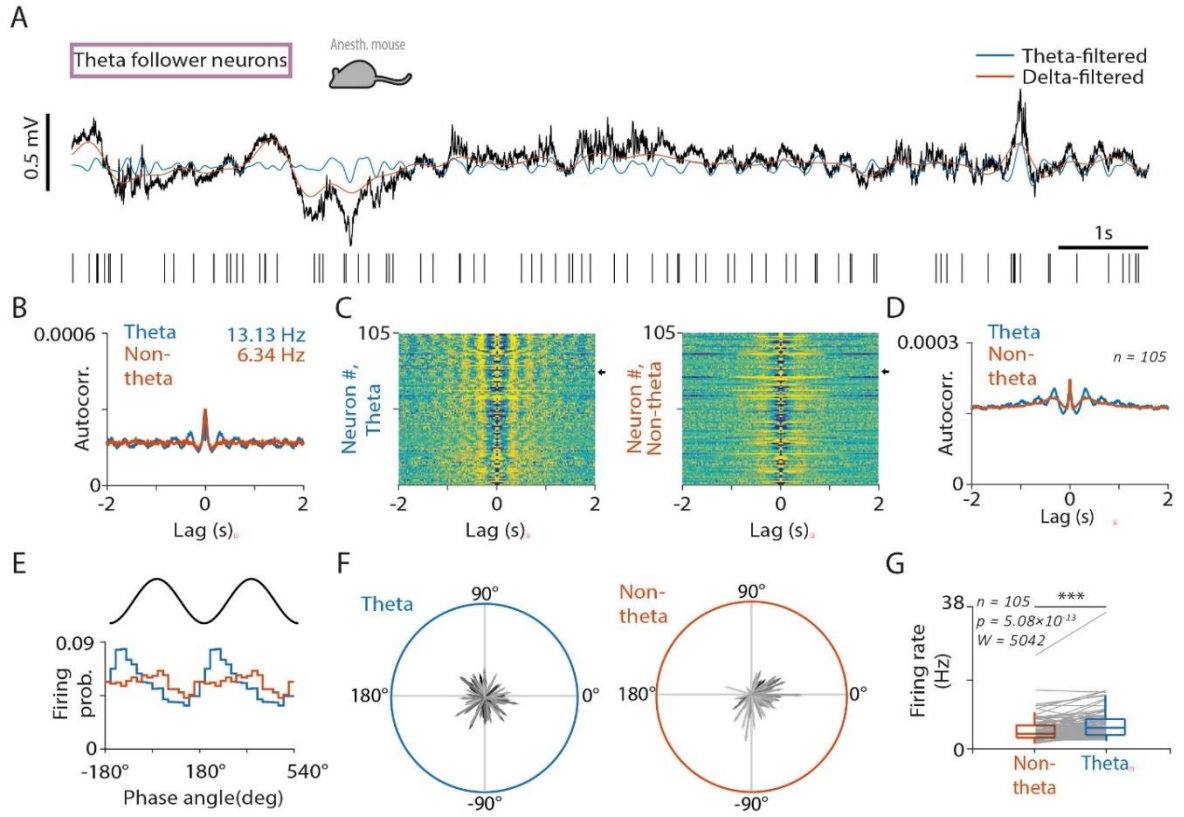
S1. Figure. Putative pacemaker neurons of the anaesthetized mouse. (A) Top: Raw LFP (black) from the CA1 shows a delta-to-theta state transition. Bottom: spike raster of an example putative pacemaker neuron from the same recording session. (B) Theta and non-theta state autocorrelograms of the neuron from panel A. Numbers indicate average firing rates. (C) Autocorrelograms of all putative pacemaker neurons during theta (left) and non-theta (right) segments. Arrows indicate the example neuron (panel A). (D) Average autocorrelogram of all putative pacemaker neurons. (E) Phase histogram of the example neuron spikes (panel A) relative to HPC delta (orange) and theta (blue) oscillations in non-theta and theta states, respectively. Two oscillatory cycles are shown. (F) Phase-locking of all putative pacemaker neurons to HPC theta (left) and delta (delta) oscillations in polar coordinates. Angle: circular phase; length: mean vector length; greyscale corresponds to average firing rate (black, higher firing rate). Phase-locking strength to delta oscillation was low for most putative pacemaker neurons. (G) Firing rates of putative pacemaker neurons during non-theta and theta segments. Boxes and whiskers represent interquartile ranges and non-outlier ranges, respectively. Lines correspond to individual neurons. Firing rate was significantly higher during theta (Wilcoxon signed-rank test). For two more example neurons see (Kocsis et al., 2022, Figure S3: B, F).



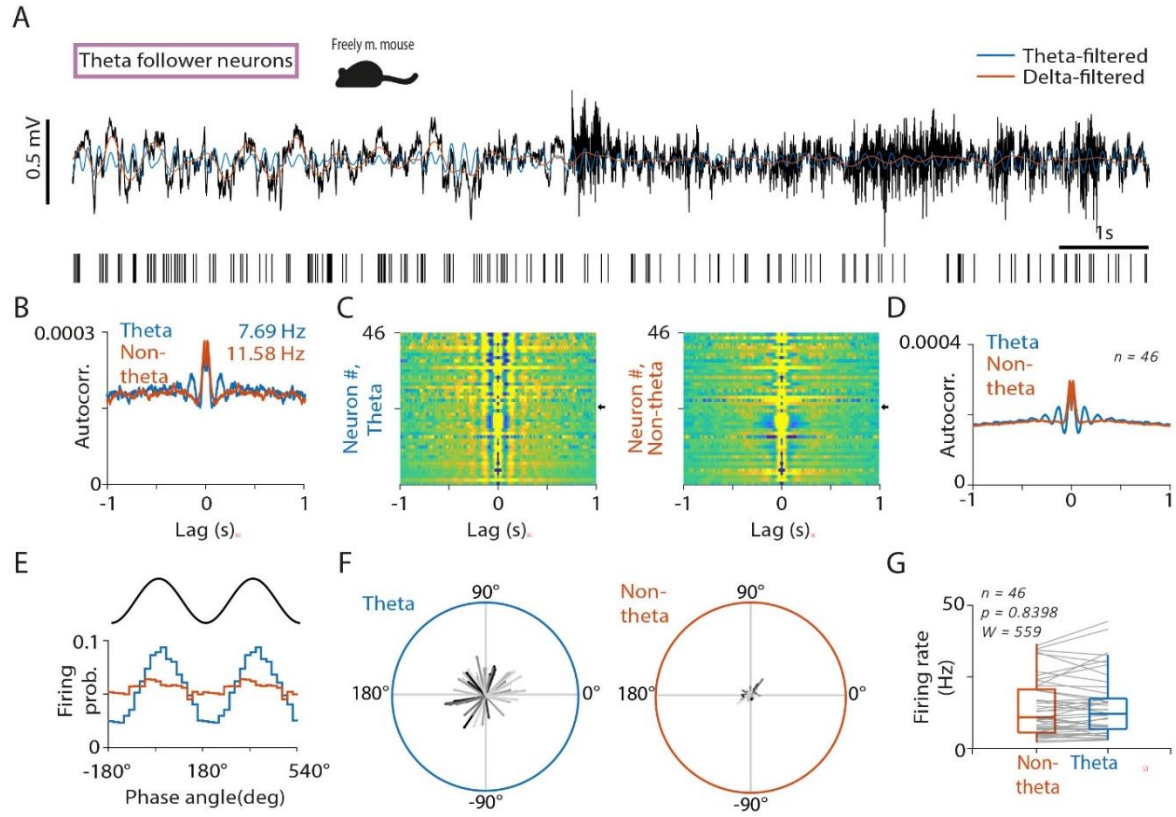
S2. Figure. Putative pacemaker neurons of the freely moving mouse. Identical figure structure with Figure S1. Phase-locking strength to delta oscillation was low for most putative pacemaker neurons. Firing rate was significantly higher during theta. For two more example neurons see (Kocsis et al., 2022, Figure S4: B, F).



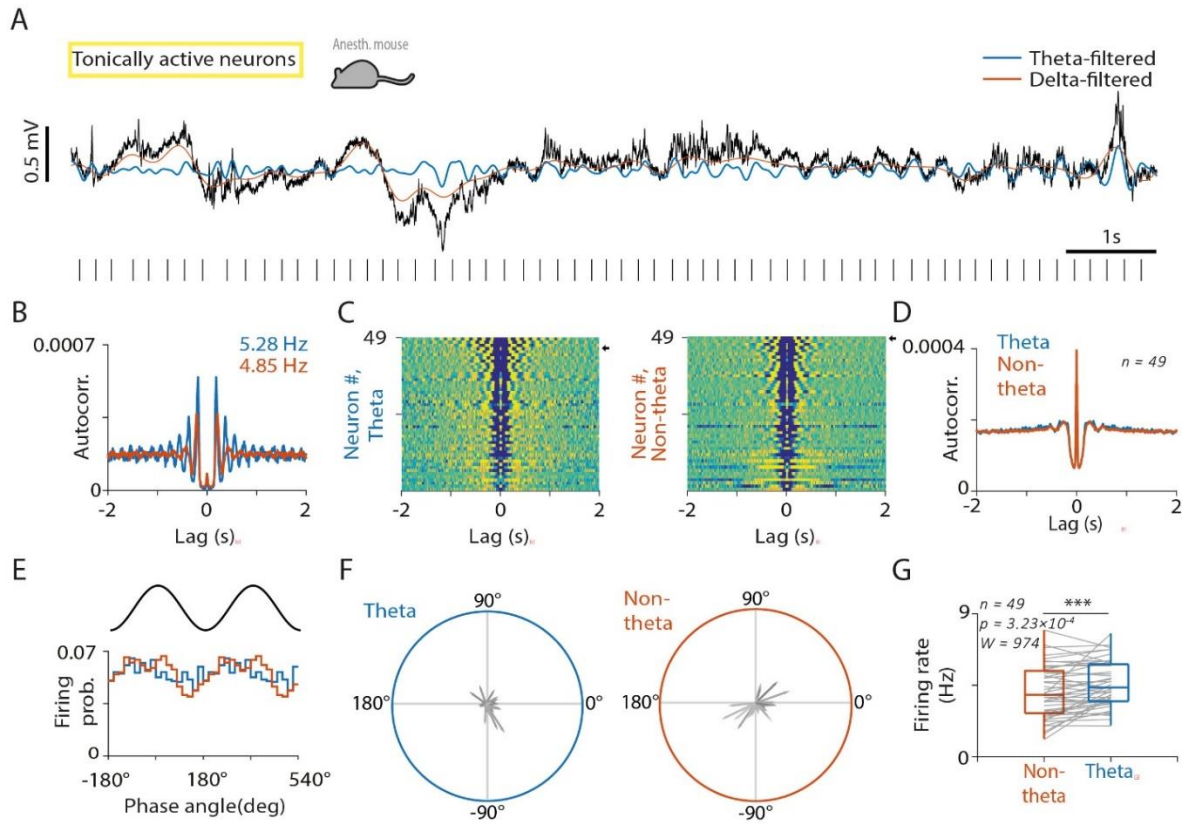
S3. Figure. Follower neurons of the anaesthetized mouse. Identical figure structure with Figure S1. For two more example neurons see (Kocsis et al., 2022, Figure S6: B, F).



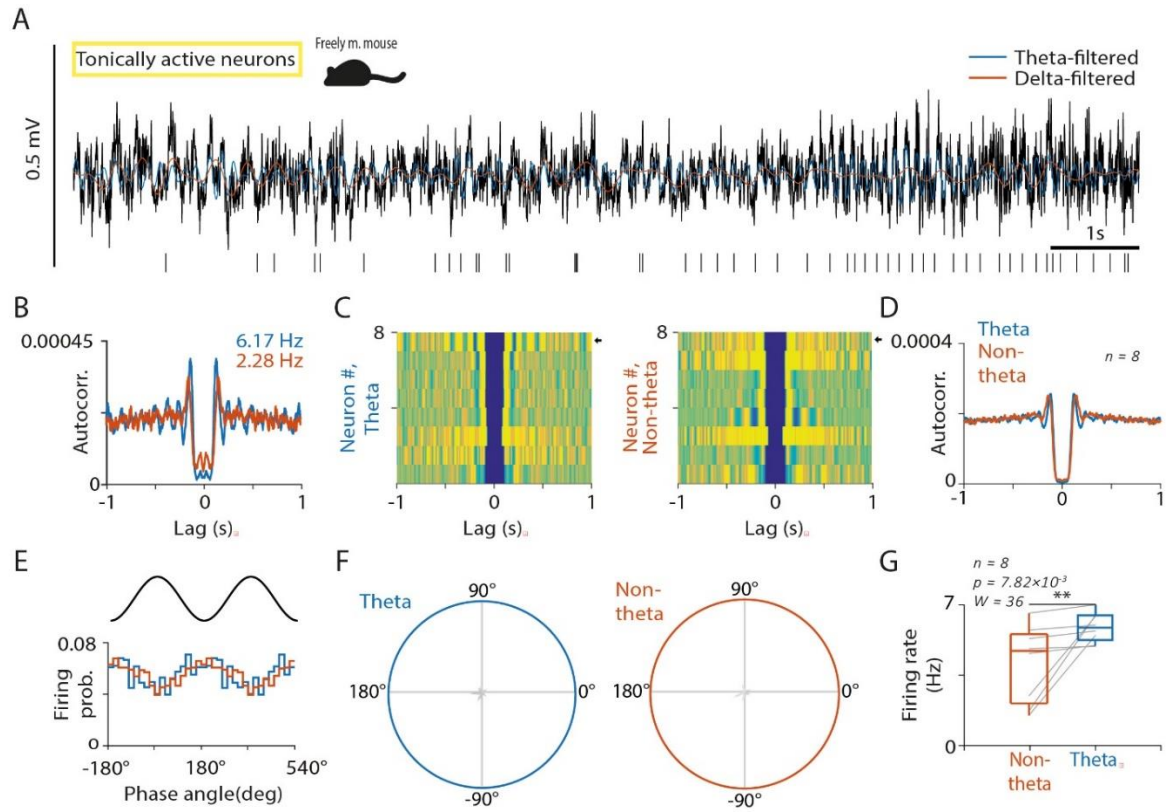
S4. Figure. Theta follower neurons of the anaesthetized mouse. Identical figure structure with Figure S1. For two more example neurons see (Kocsis et al., 2022, Figure S7: B, F).



S5. Figure. Theta follower neurons of the freely moving mouse. Identical figure structure with Figure S1. For two more example neurons see (Kocsis et al., 2022, Figure S8: B, F).



S6. Figure. Tonic activity of neurons in the anaesthetized mouse. Identical figure structure with Figure S1. These neurons did not show strong phase-locking to HPC oscillations. For two more example neurons see (Kocsis et al., 2022, Figure S11: B, F).



S730. Figure. Tonic active neurons of the freely moving mouse. Identical figure structure with Figure S1. These neurons did not show strong phase-locking to HPC oscillations. For two more example neurons see (Kocsis et al., 2022, Figure S12: B, F).

S1. Table. Major differences among rodent models of hippocampal theta oscillation.

urethane-anesthetized rats	urethane-anesthetized mice	freely moving mice
delta-rhythmic activity dominates in non-theta state	non-rhythmic activity dominates in non-theta state	non-rhythmic activity dominates in non-theta state
substantial number of theta- skipping neurons	few theta-skipping neurons	few theta-skipping neurons
tonically active neurons decrease their firing rate upon theta onset	tonically active neurons increase their firing rate upon theta onset	tonically active neurons increase their firing rate upon theta onset
statistically significant anti- phase groups within putative pacemakers	no strong support for two anti- phasic putative pacemaker groups	no strong support for two anti- phasic putative pacemaker groups

S2. Table. Number of neurons in different rhythmicity groups in the MS. Theta-rhythmic neurons were separated to theta-bursting MS neurons reported in previous studies (Figures 11, 12, S1, S2) and tonically active neurons that show rhythmic firing in the theta band but do not exhibit rhythmic bursting properties and show little synchrony with ongoing theta activity (Figures 11, 16, S6, S7). Follower neurons reflected theta versus non-theta state of the network (Figures 13, S3). For part of neurons, this type of activity was only confirmed statistically for either of these states (theta followers (Figures 14, S4, S5) and delta followers). Neurons that were delta-rhythmic during theta oscillation were identified as theta-skipping neurons (Figure 15 focuses on those cells that were delta-rhythmic during both states). Neurons that were theta-rhythmic during non-theta segments but found non-rhythmic during theta segments may be part of the pacemaker group, where the amount of data (number of spikes and length of identified theta segments) may have been insufficient for statistical detection of rhythmicity during theta. It is theoretically possible that some MS neurons would be theta-rhythmic in non-theta state but delta-rhythmic in theta state. However, this group was negligible in all three data sets.

Activity during theta	Activity during non-theta	Anesth. rat (#,%)		Anesth. mouse (#,%)		Freely m. mouse (#,%)		
theta-rhythmic	theta-rhythmic	29	7.0%	47	7.6%	35	13.2%	Putative pacemakers (theta-bursting)
		18	4.3%	49	7.9%	8	3.0%	Tonically active neurons
	delta-rhythmic	35	8.4%	12	1.9%	0	0.0%	Follower neurons
	non-rhythmic	67	16.1%	105	17.0%	46	17.4%	Theta follower neurons
delta-rhythmic	theta-rhythmic	6	1.4%	2	0.3%	1	0.4%	Hypothetical 'inverse' neurons
	delta-rhythmic	48	11.5%	4	0.6%	1	0.4%	Theta-skipping neurons
	non-rhythmic	31	7.5%	12	1.9%	5	1.9%	
non-rhythmic	theta-rhythmic	21	5.0%	36	5.8%	2	0.8%	Probably part of the pacemaker circuit
	delta-rhythmic	36	8.7%	14	2.3%	12	4.5%	Delta follower neurons
	non-rhythmic	125	30.0%	336	54.5%	155	58.5%	Non-rhythmic neurons
Total		416	100.0%	617	100.0%	265	100.0%	

S3. Table. Statistics for synchronization analysis in individual data sets. Since all three data sets showed similar results, Figure 18 displays pooled results. This table provides *p*-values (two-sided Mann-Whitney U-test for unpaired samples and two-sided Wilcoxon signed-rank test for paired samples) for the three data sets separately and pooled. Corresponding statistical tests on simulated data are also indicated (Figure 28).

	Anesth. rat	Anesth. mouse	Freely m. mouse	Pooled	Figure	Model
Firing rate (Hz)	1.04×10^{-4}	7.98×10^{-6}	1.34×10^{-2}	1.40×10^{-9}	Fig. 4A	8.50×10^{-50}
Rhythmicity frequency (Hz)	1.37×10^{-3}	1.53×10^{-1}	2.21×10^{-5}	2.64×10^{-7}	Fig. 4B	6.35×10^{-41}
Intraburst interspike interval (ms)	2.95×10^{-3}	3.30×10^{-1}	1.95×10^{-4}	7.34×10^{-5}	Fig. 4C	7.60×10^{-50}
Theta cycle skipping	2.06×10^{-3}	4.41×10^{-5}	4.61×10^{-1}	3.02×10^{-6}	Fig. 4D	3.47×10^{-45}
Relative rhythmicity frequency difference	4.53×10^{-3}	5.61×10^{-2}	1.48×10^{-5}	3.17×10^{-6}	Fig. 4E	2.20×10^{-30}
Rhythmicity frequency deviations	3.70×10^{-3}	4.61×10^{-1}	2.47×10^{-3}	4.19×10^{-4}	Fig. 4F	1.46×10^{-13}

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