There is conflicting evidence on the role of theta oscillations in episodic memories. While most studies employing surface EEG report increases in theta power, most iEEG studies report a memory induced theta power decrease. Herweg and colleagues (tics, 2020 xx) review this evidence and suggest that studies contrasting later remembered with later forgotten conflating domain-general cognitive processes such as attention and perception with memory specific processes. Because the former is assumed to lead to a spectral tilt (less low frequency power and more high frequency power) a narrow band theta power increase induced by memory might be overshadowed. [simons synch/desync].

To ameliorate this shortcoming researcher should not contrast successful memory with unsuccessful memory but instead should compare strength of memory (e.g., retrieval confidence, amount of detail in contextual retrieval, retrieved spatial distance to encoded location in a navigational task). The authors implicitly assume that task engagement, effort and perception/attention are binary processes, whereas memory strength is continuous. Although a valid concern, this assumption is not necessarily met. One way to test this hypothesis is to invert the focus from remembered episodes to forgotten episodes. If successful memory hinges on domain-general cognitive processes manifested in a spectral tilt and memory-specific narrowband theta increases, then later forgotten episodes should sometimes exhibit a spectral tilt without a narrowband theta peak if the point of failure was memory related and sometimes there should be neither spectral tilt, nor theta peak if unsuccessful memory was due to failure in attention et al. Importantly, a theta peak without a spectral tilt would falsify the theory.

Another reason how surface EEG might show a theta power increase although the LFP shows a decrease is if theta over larger areas synchronizes but decreases in amplitude. The decrease is truthfully reflected in the LFP, but activity on the scalp is integrated over larger areas and thus more synchroneous theta could lead to higher scalp theta power. Taken together these considerations imply theta activity as an integral part of memory processing and suggest that conflicting evidence arises due to different recording methods (EEEG/iEEG), memory contrasts (success vs success or vs failure9 and frequency ranges (broadband vs narrowband).

An open question remains if all theta is created equal. Compared to rodents human theta activity is slower (xx) (hippocampal?) and in the hippocampus split into slow (2-5 Hz) and fast theta (5-9 Hz) (xx). Contrary to what has been believed for a long time there are separate theta generators in the hippocampus (septum, xx) and the cortex (xx).

* Buzsaki STDP idea and more into phase precession in place cells

WHAT IS iEEG AND EPILEPSY? (Kastner Paper)

In 1929 Hans Berger published his seminal work where he recorded electric potentials on the human scalp using an electroencephalopgraph (german: Elektroenkephalogramm). He mostly observed oscillations between x Hz, which he therefore termed alpha oscillations.

Roughly 1% of the population suffers from epilepsy. In a third of these cases treatment and medication provide no remedy from seizures [Kwan, 2011; n Engl J med].

If the seizure onset is focial, i.e., spatially confined it is sometimes possible to resect the epileptic tissue which effectively cures the patient [engel 1996, n engl j med j].

The most prominent epilepsy patient was henry molaison, aka. Patient H.M. (xx) who after resection of both hippocampi and large parts of his MTL (? xx) lived seizure free. As a side effect of the surgery he developed a graded retrograde amnesia and a complete anterograde amnesia inspiring a new wave of research implicating the hippocampus and neighbouring structures in episodic memory processing. Nowadawys an extensive battery of tests is administered prior to resection with the aim to exclude as much healthy tissue as possible. One important procedure is the transcranial implantation of depth electrodes at suspected seizure onset zones (based on seizure characteristics, anatomical scans and long-term surface EEG recordings). While these electrodes are implanted, researchers perform experiments with willing patients granting insight into the neurophysiological underpinnings of various brain functions.

In the first chapter I presented evidence of single neurons in the human hippocampus that reinstate their (temporal) firing rate during the retrieval of specific episodes. These Episode Specific Neurons (ESNs) are distinct from neurons that are tuned to specific concepts (Concept Neurons) or reoccurring time points (Time Cells). There is preliminary evidence that these ESNs do not exist in the parahippocampus, although our coverage in that area is worse than in the hippocampus, and that ESNs are likely excitatory pyramidal neurons.

In chapter 2 we extended these findings to the HF band in the LFP. Although no consensus has been reached ikn the literature it is generally agreed upon that an increase in HFP reflects an increase in spontaneous neural firing. In parallel to our earlier findings we demonstrated that power in the high frequency band (40-200 Hz) is reinstated for specific episodes in a significant number of microwires. This finding was limited to later remembered episodes and did not crystalize for later forgotten episodes. Although we did find high frequency power (HFP) modulations akin to the firing rate increases in Concept Neurons, these HFP changes were not responsible for the HFP memory reinstatements.

Unexpectedly, the relative power increases in reinstated episodes extended past our frequency range of interest (10hz? For encoding and 15hz? For retrieval). Future studies should differentiate between a power offset, a 1/f shift and oscillatory drivers.

Based on influential theoretical work by Hasselmo and colleagues in the third chapter we expected single neurons and ESNs to lock onto different phases of theta. Recent work has shown that hippocampal theta in humans is divided between a slow (2-5 Hz) and fast (5-9 Hz) theta oscillation. Contrary to our hypothesis we did not find a significant phase preference during encoding or retrieval of episodic memories consistently over two independent datasets. We also di not find evidence for a theta phase offset between encoding and retrieval. This is in line with previous research showing that although neurons lock to a preferred phase of the ongoing theta oscillation this phase is not shared across neurons. Indeed, many neurons might not be involved in processing a given memory providing a possible reason for our findings. However, this does not hold true for ESNs which by definition code a specific memory. The absence of a theta phase effect in this case possibly lies within the low number of ESNs leading to insufficient power to detect an effect. [not sufficient periodic theta?].

To conclude, we found a single neuron basis of memory processing and extended/embedded these findings to activity in a greater population of neurons reflected by the local field potential. While there remain many exciting open questions we hope to have laid a foundation for future work.

Future studies

Although our research that culminated in compelling evidence for esns was inspired by what Teyler and DiScenna called *Index Neurons*, we did not call them such. This is because there are features ascribed to Index Neurons that we cannot test using the two available datasets.

Upon presentation of a partial input present at memory encoding the index neuron assembly in CA3 is pattern completed. As we lack the sufficient coverage to record multiple neurons of one assembly that codes an episode, we can not investigate this. Relatedly, pattern separation should allow the distinction of highly similar, but different episodes through allocation to different index neuron assemblies. We are unable to verify this using the current experiments because the images used in each episode do not overlap. If Index Neurons allow memory reinstatement they should reinstate their firing pattern on all subsequent retrievals (although some variance due to memory consolidation is to be expected). Patients in our studies retrieved every episode only once. We are currently running an experiments where each episode is retrieved multiple times, but will not have a complete dataset in the foreseeable future.

A central part of the indexing theory is that ongoing cortical activation is bound by neurons in the hippocampus which project back and reactivate the initial cortical pattern during successful retrieval. There are several hurdles in showing this empirically. One is a low spatial coverage of implanted electrodes that is on top of that different for each patient (why is that ba d xx). The number of ESNs per patient is low. It is not clear at which timepoint memories are reinstated in the hippocampus based on the firing of individual ESNs. These concerns should not deter the curious reader, but merely caution to the difficulty of the task.

Only future studies using other experimental designs and/or newer hardware will be able to ascertain whether ESNs are Index Neurons. Until then we have to be satisfied to see a reinstatement of neural firing as an indicator of memory processing.

Another interesting question is the stability of ESNs over time. Does the index reliably reinstate a memory a day after memory encoding? What about a week? Note, that it is a separate question as to whether the hippocampus in general stays involved in older memories (multiple trace xx) or not (systems consolidation/two stage xx). This is because it is conceivable that the initial memory trace is transformed during the consolidation period. In light of this, being able to record more single neurons or even multiple ESNs that reinstate the same episode would be especially insightful. Otherwise, one might falsely believe that a memory trace is being erased from the hippocampus when in reality just a part of the initial neuron assembly coding for an episode has been pruned off. This is where our finding that HFP is being reinstated / ESNs are reflected in HFP comes in handy [expand, make more formal].

A related question is if the index is being systematically reactivated during the consolidation period, especially longer periods. Recording assemblies would possibly allow identifying points of reinstatement by making it possible to differentiate background firing from memory reinstatement [can we look at spike locked HFP?? Possibly get different results if you have ESW that reinstate the same episode as ESN; maybe only works then. Look at bimodal or lopsided distribution]. Sleep should be a major time period of interest when looking at memory consolidation (Kolibius et al., 2021, xx others; generally expand on this].

As I am writing this Neuralynx is seeking CE and FDA approval for microwire stimulation in patients (personal communication). If successful, microwire stimulation could provide causal evidence for an ESN based memory code. If ESNs are allocated based on excitability stimulating the neurons in the vicinity of a microwire should increase the probability they are allocated to an episode. This would shed light on a mechanism of ESN allocation predicted by animal work and also increase the yield of ESNs per patient. Using this method one could test the hypothesis that CN develop from ESNs by stimulating on a microwire during multiple episodes that shara a common element (e.g., Jennifer Aniston in Pisa, Jennifer Aniston in Paris, …). If the stimulation causes coallocation of neurons to these episodes it is conceivable that some of the “tagged” neurons exhibit neural firing akin to Concept Neurons tuned to Jennifer Aniston (as she is the common element in these episodes).

An open question remains how CNs initially develop their tuning. One possibility is that over repeated reconsolidation CNs evolve from ESNs. Imagine you meet your best friend in a coffee shop. This coffee shop episode will initially be represented by an assembly of ESNs. A few days later you meet with the same friend in a park and you remember the last time you met in the coffee shop. This reactivates the ESNs coding for the coffee shop episode. Engram literature suggests that recently active and more excitable neurons are preferentially bound to a new episode (Josselyn and Frankland, 2018). This makes it likely that some of the ESNs that coded the coffee episode now also code the park episode. The shared content between those two episodes is your best friend. It is conceivable that over many such similar episodes a proportion of the ESNs that initially coded the coffee shop episode would become "semanticized" i.e., develop a tuning for your best friend. A Concept Neuron is born.

In this way ESNs can be likened to variables in a computer program to which arbitrary information is bound. In the case of episodic memory, this arbitrary information would be the complete set of features that make up an episode.

Overlapping content? In context of pattern separation.

O’Reilly & Rudy 2001 notes

The hippocampus automatically binds sensory elements into a conjunctive code which corresponds well with the definition of episodic memory. Complementary learning systems solve the conundrum that the brain needs to capture general patterns in the environment and at the same time the specifics of a unique episode/experience.

Fundamental trade-off between learning… (McClelland et al., 1995).

Invariant features over repeated episodes (Sherry & Shacter 1987) also propose complementary learning systems.

To this end the cortex learns more gradually over multiple exerpiences while the hippocampus rapidly encodes the specifics of individual episodes. The hippocampus keeps experiences separate and avoids interference through a sparse neural code where each event is “bound” or represented by a small assembly of neurons/highly selective neurons. Case studies from the seventies clearly showed that the hippocampus is necessary for episodic memory (Squire, 1992; Hirsh 1974, Nadel & o’Keefe, 1974 xxxx). The most prominent patient is H.M. with bilateral damage to the mediotemporal lobe. H.M. had difficulties retrieval all but old memories (graded retrograde amnesia) and could no longer form new ones (anterograde amnesia) (Milner 1966) -> declarative procedural.

Squire 1992: Hippocampus binds cortical sites + pattern completion at partial cue

The hippocampus ability to do so is grounded in two biological properties: a vast number of cortical areas converge onto the hippocampuswhich received highly processed information (Rolls, 1989) and neurons in CA3 are highly interconnected (what Marr (19xx) called the auto-associator). These excitatory recurrent synampses are thought to play an integral part in pattern completion. [sparse representation -> pattern separation; auto-associator -> pattern completion].

According to a model by O’Reilly and Rudy (2001) during encoding information from the cortex reaches the EC where two representations are generated. One is projected to the dentate gyrus and CA3 creating a sparse representation of the cortical activity pattern. At the same time activity from the EC flows to CA1 in an invertable manner (bilaterally?). because neurons in CA3 and CA1 are coactive their synaptic connections are strengthened. During retrieval a partial input of the original representation is sufficient to reactivate the representation in CA3 where the entire representation is pattern completed, which in turn reactivates the appropriate CA1 representation which can project back to the EC (because EC<->CA1 is invertible).

Cortex-EC: one to one connections

EC-> DG&CA3: perforant path (broad and diffuse)

DG->CA3: mossy fibre pathway (sparse, focused, topographic; ~70 synapses to each CA3 neuron in rats)

CA3 -> CA1: schaffer collaterals (diffuse and widespread)

EC<-> CA1: point-to-point, not diffuse like perforant (Tamamaki, 1991)

Episodic memories although originally defined as such, can implicitly considered conjunctive codes. Complementary learning systems: O’Keefe & Nadel (1978): taxon local | hirsh 1974 | McClelland et al. (1995)

Indexing Theory

The indexing theory has initially been proposed by Teyler & DiScenna more than 35 years ago (Teyler & DiScenna, 1989) and provides a framework of hippocampal function during episodic (at the time called experiental) memory encoding and retrieval in humans. According to the indexing theory during initial encoding the multiple elements that make up an episode instate a cortical activity pattern that is projected to the hippocampus. Subsequently a partial input reactivating a subset of the cortical pattern representing the initial experience is sufficient to drive the entire assembly of associated hippocampal neurons. These hippocampal neurons would then project back to the neocortex reinstating the entire experience. This process is called pattern completion.

In this sense the function of the hippocampus can be likened to that of a librarian. A librarian (the hippocampus) can point you towards the relevant books within the library (neocortex), but will not possess this knowledge itself. Arguably, the hippocampus does not contain semantic information and is content-free. Within this framework it is possible that the less plastic neurocortical trace is gradually strengthened by repeated reactivation of the hippocampal index cells making the latter redundant over time for memory retrieval. This process would be in line with Systems Consolidation (marr, xx). However, the indexing theory also works with Complementary Learning Systems in which case the index would persist over time. [quote: p 1167 the index provides a rapid and economical way to rapidly establish episode memories, meaning that it is not necessary to strengthen connection among the cortical ensembles and most of what is initially stored is of little importance and can be forgotten (cf. Marr)].

Teyler & Rudy 2007:

The hippocampus is part of the allocortex and can be divided into the dentate gyrus, hippocampus proper (CA1-CA3) and the subiculum. Bilateral & symmetrical, looks like a seahorse/hence the name. Highly processed information flows from prefrontal neorcortex, perihinal cortical areas and association cortices through the EC to the hippocampus. This cortical information is integrated with subcortical input from the amygdala and thalamus. Input flows generally DG-> CA3 -> CA1 -> Subiculum & return projects to the EC and subcortical areas that input to hippocampus. This positions the hippocampus uniquely to integrate cortical and subcortical information streams (Swanson & Mogenson, 1981 xx). Reciprocal connections to and from hippocampus necessary. The hippocampal index provides a cheap and transient snapshot of the cortical representation of an experience. As such if it provdes unimportant the initially strengthened synaptic connections can decay over time or fall victim to interference of other experiences [is that last bit a quote?].

Pattern separation refers to the complementary ability of the hippocampus to keep highly similar but distinct episodes separate. Without this capacity a large overlap in the cortical representation of different episodes would lead to the reactivation of both episodes.[expand].

Episodic memories:

Tulving & markowitch 1998)

Nadel & Moscovitch 1997: even highly overlapping episodes are all unique.

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At the very beginning of my PhD Simon Hanslmayr and Bernhard Staresina invited me to a meeting discussing which dataset should be used to investigate “Index Neurons”. I was unrecoverably lost which found its peak when Bernhard understood some implications before Simon finished his sentence. That was the only time I doubted myself.

I soon recovered my excitement for research although often stumbled on unseen ground. I am very grateful to Simon, my *Doktorvater* for his guidance and his trust in me even when I was hard stuck on a particular problem for weeks or head over heels down a rabbit hole. For me, Simon embodies coolness and a keen mind in equal parts. I would also like to thank my second supervisor Howard Bowman. I find your intuitive grasp on mathematics inspiring and thoroughly enjoy our long conversations about neuroscience and all other things.

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Plugging into memory

Human intracranial research

Ward and Thomas (1955) were the first to successfully record human single neurons. They did so in the posterior temporal lobe using glass micropipettes while surgeons tried to localize the epileptic focus and repair a bone defect in the patient’s skull. The type of microwire electrodes that are still in use today (Fried et al., 1999) have been described in the early 70s by Babb and colleagues (Babb et al., 1973; electroenc & clinic neurophysiol). They consist of a hollow-depth intracranial macroelectrode through which the microwire electrode is inserted. Microwires radially protrude at the tip and allow the recordings of multiple single neurons amalgamated with local field potentials.

These electrodes remain implemented for typically 1-2 weeks to gain an understanding which brain regions are responsible for the generation of epileptic seizures and will be resected. The clear advantage of intracranial electrophysiological recordings over traditionally used non-invasive methods is a spatially confined (vs. surface EEG) and well localized signal with a high temporal resolution (vs. fMRI). In contrast to invasive recordings in animals, humans can typically perform a task after minimal instructions and can provide comprehensible verbal feedback when prompted.

A severe disadvantage of intracranial recordings is a relatively limited coverage of the brain compared to traditionally used brain recording methods. This downside is exacerbated by the fact that the spatial position of the intracranial electrodes are determined by clinical need and not scientific experimentation. Furthermore, access to epileptic patients that are willing to participate in scientific research is limited. Finally, even if these hurdles are overcome, it is important to ascertain that pathologic epileptic activity does not influence the obtained results.

Concept Cells

Concept cells are neurons in the MTL that fire in response to specific concepts in an all-or-none way (Rey et al., 2018). They exhibit a high degree of multimodal invariance (i.e., they respond to Jennifer Aniston as an image or her spoken name) and context invariance (i.e., a concept neuron tuned to Jennifer Aniston would activate when you see her in a park or in a café) (xx).

Curiously, the latency of their firing rate is much later than would be required by simple sensory processing and object recognition, which is an indication of their involvement in memory processing (Mormann et al., 2008). This lines up with the observation that most concept neurons are tuned to personally relevant concepts and depend on the subjective and conscious perception rather than objective sensory properties (Quiroga et al., 2014, 2008).

These concept neurons are not topographically organized, i.e., spatially close concept neurons might code for vastly different concepts (Quiroga 2016?). This spatial organization benefits episodic memory processing as it allows association between any two concepts without connecting distant areas (plugging into memory xx). According to Quian Quiroga (Cell 2019; tics; 2012 paper) these CN are the building blocks of episodic memory formation and retrieval. If you met your best friend in your favourite café the concurrent activation of two assemblies of CN (one for your friend and one for the café) would represent the episode in the hippocampus. These assemblies would then project back to the neocortex reinstating the sensory activity pattern first induced during the formation of the episode. This back-projection parallels the one described in the indexing theory (Teyler 1 & 2 xx) with the important difference that the hippocampal representation consists of previously existing concept specific representations/assemblies.

A separate memory of the same friend in a park would in turn be represented by the simultaneous activity of the same assembly coding for your friend and another assembly representing the park.

Once implanted these electrodes yield typically around a dozen separate neurons per microwire bundle.

The indexing theory DONE

Episodic memory NOT SURE

The hippocampus KINDA

The LFP – theta and high gamma NOT DONE BUT HAVE A LOT OF NOTES AROUND IN A WORD DOCUMENT?

Describe Behnke fried (1999 paper, 9 month report or early MS version has a summary)

Include a figure showing the LFP with AP

We use the hilbert transform which assumes sinusoidality of the signal.

Other methods (e.g., linear interpolation methods: doi.org/10.1152/jn.00273.2019; empirical mode decomposition) do not have that assumption and might be more adequate.

During a spatial navigation task neural spiking locked to oscillations in the LFP of the microwire at which they were recorded, particularly at theta and gamma (josh 2007 paper). Locked to various phases in the theta range

A walk down memory lane

We experience our present / the world around us filtered through the lens of our experiences. Without memories we could not hold on to these experiences locking us perpetually in the present. It follows that memories are at the core of what makes us humans.

Episodic memories is the ability to encoding and later recollect experiences that contain a what, where and when. They are rich in detail, integrating information from multiple modalities, they are encoded automatically, require no repetitions, and can last an entire life. Remembering these autobiographical events is akin to mentally traveling back in time experiencing these events again.

An example for an episodic memory is when I was sitting in a small coffee shop in Sevilla in the company of my loved one. The sun had not yet reached its peak and was pleasantly warm. A mild breeze carried over the smell of freshly brewed coffee and bits of conversations from other patrons. It was a satisfying way to start the day, my body still exhilarated from the workout we just finished. The waiter brought over two coffees. On the way back to the kitchen he hesitated, turned on his heels and walked back over to our table. "Your PhD thesis was a fantastic read" he said with a slight Spanish accent, adding "but why was your example for episodic memories so long?".

Semantic memories on the other hand refer to factual knowledge and understanding of concepts (such as knowing that the very real coffee shop in the above story was called "La Nueva Peseta"). Together with episodic memories they belong to the subgroup of declarative memories. Sometimes declarative memories are termed explicit memory because they require explicit perception(??).

Semantic and episodic memories are usually treated as different subcategories of declarative memories. In reality the line separating the two can get blurry. For example..

Declarative memories can in turn be distinguished from non-declarative memories. This category contains procedural memory (e.g., knowing how to make a coffee) and priming, which refers to the phenomena that exposure to a stimulus influences the behaviour or response to a later stimulus (e.g., judging someone’s character as "warmer" after holding a warm coffee; 10.1126/science.1162548). These memories do not require conscious perception which is why they are also referred to as implicit memories.