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. Nowadays, 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.

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].

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.

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.

The recorded signal from the microwires can be divided into two components depending on their frequency. The first component is the local field potential (LFP), which reflects changes in the extracellular membrane potential and ranges until 300 Hz. Superimposed onto the LFP is the activity of individual neurons and multiunits in close proximity to the microwire.

Action potentials (or *spikes*) are characterized by a steep and transient amplitude increase in the signal. Spike detection and sorting can be implemented using a variety of existing toolboxes, with new ones being developed continuously that demonstrate promising results (10.1101/2023.01.07.523036). Here, we used the wave\_clus algorithm, which is described in detail in Chaure, Rey and Quian Quiroga (2018). The following is a brief synopsis of the processing steps performed by this algorithm.

The first step to detect these neural spikes is to filter the data so it only contains the spike-band which ranges from 300 Hz to 3000 Hz. Next, the data is segmented into smaller epochs of typically five minutes each, so artefacts occurring in one segment do not increase the threshold across the entire recording. Each one of these epochs is then individually thresholded using some form of deviation to a measure of central tendency (such as the mean or median). Points where the threshold is surpassed are stored as putative spikes. This spike detection is done separately for positive and negative deflections. Once a spike is identified, 64 data points around the maximum are extracted, which corresponds to a 2 ms window at a sampling rate of 32000 Hz. The spike peak is aligned to the 20th sampling point. In order to avoid misalignment of the spike the waveshape is first upsampled to 320 data points using cubic spline- interpolated waveforms and then downsampled again. Based on the extracted spike-waveform, features are computed using a four-scale multiresolution decomposition with a Haar wavelet. This results in 64-wavelet coefficients for each spike. The 10 most significant coefficients are identified using a Lilliefors test and used for the clustering procedure (Chaure et al., 2018).

Nonparametric clustering in the feature space is done using superparamagnetic clustering (SPC). SPC groups spike waves into clusters based on nearest-neighbour interactions (Blatt et al., 1996). Template-matching in Euclidian space is performed to assign unclassified waveforms to one of the identified clusters. The resulting clustering solution is then manually inspected and further optimized by rejecting artefact cluster, splitting clusters that represent multi-unit activity and merging clusters that likely stem from the same neural source.

The extracellularly recorded local field potential (LFP) represents synchronously active neurons that are spatially aligned. Synaptic activity is the largest contributor to the LFP, but transmembrane currents from soma, dendrites, spikes, and spike afterpotentials also impact the LFP.

The LFP can be divided into periodic (oscillatory) and aperiodic (fractal, non-oscillatory) components.

Aperiodic power is inversely related to the frequency and roughly follows a 1/f relationship (where f is the temporal frequency). This power-frequency relationship is likely due to dendrites acting as a low-pass filter [83, 99, 100] and because fewer neurons can be active in shorter cycle lengths of higher frequencies (10.1038/nrn3241).

In the past, the aperiodic part of the signal was often ignored or considered background noise (xx). However, more recent research has pointed to the steepness or tilt as well as the offset of the 1/f aperiodic component as an indicator for excitation (xx) and a proxy for neural firing (Manning).

The periodic part reflects true oscillatory activity (i.e., rhythmic activity in a circumscribed frequency range). Activity in these narrowband frequencies have been associated with a wide range of cognitive processes (xx) and states (xx). Analysing this oscillatory activity without consideration of the 1/f shape can be problematic (10.1016/j.neuroimage.2022.118929; herwig paper) as the shape of the 1/f can bias the oscillatory activity. Moreover, a tilt or change in offset can be erroneously interpreted as a change in oscillatory activity (Herwig paper).

There are multiple methods to separate the signal into periodic and aperiodic parts such as Irregular Resampling Auto-Spectral Analysis (IRASA) (10.1371/journal.pone.0024331) and Fitting Oscillations and One Over F (FOOOF; 0.1038/s41593-020-00744-x).

How neurons are allocated to a memory trace: evidence from animals

Over one hundred years ago Richard Semon proposed that a memory is represented by the long lasting physical changes in neural assemblies that encoded the initial experience. This memory trace is termed “engram” in the animal literature (Richard Semon, 1921; doi.org/10.1038/npp.2016.73 xx, doi.org/10.1038/nrn4000 xx).

Unlike Index Neurons, which are assumed to be in the hippocampus, the entire engram representing an experience spans multiple assemblies in various brain regions that are functionally connected (Roy and colleagues doi: 10.1101/668483).

Optogenetics and chemogenetics (used in humans? xx), which are not available in human research, have been especially beneficial to memory research in animals. Although findings from rodent brains do not by default translate to the human brain, there is enough overlap that (non-human) animal work can inform human research.

Experiments conducted on rodents revealed that neurons are **allocated to an engram** based on their excitability, with those having higher excitability more likely to be included (10.1038/npp.2014.234, doi.org/10.1503/jpn.100015 xx). Excitability is defined as the inclination of a neuron to fire an action potential in response to a signal (Dong et al. 2006). Rashid and colleagues (Rashid et al., 2016) showed that neurons **allocated to an engram** inhibit neighbouring neurons for about 6 hours through GABAergic interneurons. Without this inhibition, memories that occur close in time might be encoded by non-overlapping neurons.

**Neurons allocated to an engram** representing an event remain in a state of elevated excitability for over six hours. Consequently, some of the initial engram neurons are likely to be coallocated to events that occur within this timeframe (Cai et al., 2016; Rashid et al., 2016). After this period excitability drops making it less likely that these neurons are **allocated to engrams** representing temporally distant events (Frankland & Josselyn 2015; Silva et al., 2009).

Cai and colleagues (Cai et al., 2016) found evidence for this in CA1 of mice, that were presented with context A, followed by context B seven days later and then context C five hours later. Engrams representing the contexts separated by a shorter temporal gap were largely overlapping, while those with a larger time delay showed no such overlap. Rashid and colleagues (xx) extended these findings by optogenetically stimulating neurons in the lateral nucleus of the amygdala that were allocated to an event 24h before a second event took place (i.e., outside of the 6 hour window of increased excitability). Due to this artificially induced excitability the second event was coallocated to the same subset of neurons. A similar result was obtained when the remote memory was retrieved prior to acquisition of a related memory, suggesting a mechanism for integrating newer memories with relevant older memories (Rashid et al., 2016; Yokose et al., 2017: two distant memories show an overlap if they are co-retrieved).

This mechanism of coallocation is suspected to be responsible for false memories. Engram cells in the dentate gyrus active during the exploration of context A were optogenetically reactivated in context B, where the mice also received footshocks. Mice then showed fear reinstatement in context A (artificial fear memory) and B (natural fear memory), but not in a third neutral context (10.1126/science.1239073). Similarly Vetere and colleagues (10.1038/s41593-019-0389-0) tagged neurons in the olfactory bulb and synchronized it with either appetitive or aversive neural pathways. Subsequently mice showed attraction or aversion to the real odour giving credence to the idea that an artificial memory was created the absence of a real experience.

Engram neurons are necessary and sufficient for memory retrieval. After destroying a subset of neurons that were initially allocated to a fear memory mice suffered from a profound memory loss (Han et al., 2009 10.1126/science.1164139;). Importantly this loss-of-function was specific to the fear memory and new fear conditioning was possible. Ablating other neurons did not lead to a disruption in memory. Conversely, artificial reactivation of engram cells in the dentate gyrus reliably led to the retrieval of the memory even in the absence of external retrieval cues (10.1038/nature11028). In a neutral context mice did not freeze until the engram representing the fear memory was optogenetically reactivated. This represents a gain-of-function and cements engram cells as causally relevant for memory processing.