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.

What is memory:

Memory can be thought of as the ability to store internal representations of experiences over time and to recall them later (Dudai 2007).

use H.M. as an example for memory where without it we are locked into the present.

If we can access past experiences we need an internal representation of them

Importantly, if CA1 neurons were silenced during training, stimulation of tagged DG neurons did not lead to freezing (10.1126/science.aaa5542). <- in line with information flow in indexing theory

Add rebuttal answer about ESN sparcity to my thesis discussion

As it stands our studies provide only observational support and not causal support.

Read Buzsakis 2018 paper

read anna shaprios modeling paper

Hebb has been very influential by proposing that concurrently active interconnected neurons strengthen their connection. Something that is often informally summarized as "neurons that fire together, wire together" (D. O. Hebb, The Organization of Behavior (Wiley, 1949).).

[the hippocampus encodes episodes as discrete events, thereby facilitating the recall of an unambiguous memory, rich in detail (Kirwan & Stark 2007, Leutgeb et al. 2007, Norman & O’Reilly 2003).]

Marr mentiones pattern separation.

Excitable neurons have a higher chance of becoming place cells (Lee et al., 2012; Rickgauer et al., 2014). There is more on place cells in the 2020 paper.

Maybe we don't have a theta phase effect because there is no narrowband theta on the microwires. Possibly a white matter referenced macrowire (see Herweg for why not a bipolar reference) would lead to SFC. However, Josh (2007) has used microwire LFP to detect SFC and spikes can couple to the low frequency field potential even in the absence of periodic activity (Bush & Burgess, 2020)

Include the Behrens suggested papers (I should have notes on those somewhere??)